Total Asymmetric Syntheses of Iminosugars

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

by

Aude L. A. Figuccia

New College
Oxford

Trinity Term
2015

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2011 until June 2015, 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.

Aude L. A. Figuccia

June 2015

Abstract

Aude L. A. Figuccia D.Phil. Thesis

New College Trinity Term 2015

This thesis is concerned with the development of ring-closing iodoamination and ring-expansion methodology and its subsequent application to the asymmetric syntheses of pyrrolidine and piperidine iminosugars.

Chapter 1 highlights the remarkable biological properties displayed by iminosugars and introduces methods for the formation of the pyrrolidine and piperidine sub-classes.

Chapter 2 describes investigations into the ring-closing iodoamination of bishomoallylic amines which occurs with concomitant *N*-debenzylation to give an iodomethyl pyrrolidine scaffold. Conversion to the corresponding aziridinium species followed by its regioselective intermolecular ring-opening by H_2O enabled the synthesis of (+)-2,5-dideoxy-2,5-imino-D-glucitol (DGDP). A protocol for the preparation of its 1-deoxy-1-amino analogue (+)-ADGDP was also developed.

Chapter 3 details studies into the ring-expansion of iodomethyl pyrrolidine scaffolds via the trapping of CO_2 (from $NaHCO_3$) to produce cyclic carbonates as single diastereoisomers. Subsequent deprotection of these piperidines allowed the syntheses of (−)-1-deoxymannojirimycin (DMJ) and (+)-1-deoxyallonojirimycin (DANJ) to be completed.

Chapter 4 delineates investigations into the trapping of alternative "X=C=Y" electrophiles, via the ring-expansion methodology developed in Chapter 3, initially utilising a model system. These studies culminated in the development of the trapping of *p*-TsNCO and the application of this methodology in the total asymmetric syntheses of (−)-ADMJ and (+)-ADANJ, the 2-deoxy-2-amino analogues of (−)-DMJ and (+)-DANJ, respectively.

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

Acknowledgements

Firstly, I would like to thank my supervisor, Professor Steve Davies, for allowing me the privilege of working in his research group, providing me with funding and for all the opportunities he has given me over the past four years. His guidance and support has enabled me to pursue this interesting and challenging project to the full.

I would also like to thank New College and in particular the New College Development Fund for providing me with additional financial support during the fourth year of my D.Phil studies.

My gratitude to the SGD post-docs Dr. Ai Fletcher, Dr. Paul Roberts and Dr. Jim Thomson for all their advice over the years and, more recently, for their efforts in proof-reading and polishing this thesis. Jim, thank you so much for your encouragements during writing-up; Paul, thank you for all the discussions we had on this project and Ai, thank you for your sharp eyes at proof-reading my numbering and experimental. I am also indebted to Dr Jim Thomson and Dr. Ai Fletcher for the colourful X-ray crystal structures in this thesis.

Very many thanks to Anne Tennant-Eyles for all her help and the fantastic NMR and MS teams and support staff that keeps the CRL running. A huge thank you must go to Prof. Tim Claridge and Dr. Barbara Odell, not only for the multiple nOe experiments or VT NMRs, but for always finding time for me when I came downstairs with some characterisation issues. In addition, I would like to thank the workshop staff, particularly Alan Roper, for being so helpful with anything we ask for.

A very big thank you to everyone that I have had the pleasure of working with during my time in the group. My fellow G9 people: thanks to Ian for being so upbeat and positive, David for your personalised fumehood/wall drawings that cheered me up and Marta for bringing a Mediterranean atmosphere in the lab. The G10 neighbours: thanks to Aileen for being the group baker, Alex for taking care of breakfast, Matt for keeping the peace and Kristína for being the mummy of the group. Thank you also to the several Part II/visiting students that made the group even more friendly.

Last but not least, thank you to my friend Charlotte. I am so glad that we had each other to share this journey from day one. Through the ups and downs, thank you for everything and for your patience listening to my chemistry issues. In the future, we shall meet for dinner but not go back to the lab! Thank you also to Méabh and Ai for your friendship and support from the very beginning.

My mentor and friend, Dr. Chi Ming Cheung, deserves a special mention for instilling his enthusiasm for chemistry into me and always supporting me.

Finally, thank you to my family for always being there for me. Un immense merci à mes parents pour leur confiance inconditionnelle, pour leur soutien de tous les instants et pour leurs encouragements quelque soit ce que j'entreprends. Merci de m'avoir permis de réaliser mes rêves, merci pour tout.

Abbreviations

~	Approximately
(±)	Racemic
$[\alpha]_D$	Specific rotation
Å	Angstroms
Ac	Acetyl
acac	Acetylacetonate
ADANJ	2-Amino-1,2,5-trideoxy-1,5-imino-D-allose
ADGDP	1,2,5-Trideoxy-1-amino-2,5-imino-D-glucitol
ADMDP	1,2,5-Trideoxy-1-amino-2,5-imino-D-mannitol
ADMJ	2-Amino-1,2,5-trideoxy-1,5-imino-D-mannose
app	Apparent
aq	Aqueous
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflectance
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
br	Broad
Bu	Butyl
Bz	Benzoyl
c	Concentration
C	Celsius
^{13}C	Carbon-13
CAN	Ceric ammonium nitrate
cat.	Catalytic
Cbz	Carboxylbenzyl
CDI	1,1'-Carbonyldiimidazole
cm	Centimetres
cm^{-1}	Wavenumber
conc	Concentrated
COSY	Correlated spectroscopy
CSA	Camphorsulfonic acid
CSI	Chlorosulfonyl isocyanate
CSO	Camphorsulfonyloxaziridine
d	Doublet
DAB	1,4-Dideoxy-1,4-imino-D-arabinitol
DANJ	1-Deoxyallonojirimycin
DBB	Di-*tert*-butyl biphenyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
deg	Degrees
DGDP	2,5-Dideoxy-2,5-imino-D-glucitol
$(DHQD)_2PHAL$	Hydroquinidine-1,4-phthalazinediyl diether
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine

DMDP	2,5-Dideoxy-2,5-imino-D-mannitol
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMJ	1-Deoxymannojirimycin
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DNJ	1-Deoxynojirimycin
dr	Diastereoisomeric ratio
δ_H	Proton (^{1}H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
(*E*)	Entgegen
Edn.	Edition
EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess
er	Enantiomeric ratio
ent	Enantiomer
epi	Epimer
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FDA	Food and drug administration
FGI	Functional group interconversion
FI	Field ionisation
FT	Fourier transform
g	Grams
Grubbs I	Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium
h	Hours
^{1}H	Proton
HIV	Human immunodeficiency virus
HMBC	Heteronuclear multiple bond correlation
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
i	Ipso
^{i}	Iso
IBX	2-Iodoxybenzoic acid
^{i}Pr	Isopropyl
IR	Infra-red
J	Coupling constant
^3J	Vicinal coupling constant
K	Kelvin
L	Litres
LC	Liquid chromatography
lit.	Literature
LRMS	Low resolution mass spectrometry
Ltd	Limited company
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
NJ	Nojirimycin
nm	Nanometres
Nu	Nucleophile
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
o	Ortho
Oxone®	Potassium peroxymonosulfate
p	Para
PCC	Pyridinium chlorochromate
Ph	Phenyl
PhMe-d_8	Deuterated toluene
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
Pr	Propyl
q	Quartet
quant	Quantitative
R	Alkyl
(*R*)	Rectus
Red-Al®	Sodium bis(2-methoxyethoxy)aluminum hydride
ref.	Reference
rt	Room temperature
s	Singlet
(*S*)	Sinister
Satd	Saturated
S_N1	Substitution, nucleophilic, unimolecular
S_N2	Substitution, nucleophilic, bimolecular
^{t}Bu	*tert*-Butyl
^{t}, *tert*	Tertiary
t	Triplet
T	Temperature

TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
tet	Tetrahedral
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMG	Tetramethylguanidine
TMP	Tetramethylpiperidide
TMS	Trimethylsilyl
ToF	Time of flight
Ts	*para*-Toluenesulfonyl
U.K.	United Kingdom
UV	Ultra-violet
ν_{max}	Infra-red absorption maximum
v	Volume
w	Weight
(*Z*)	Zusammen

Contents

Chapter 1: Introduction

This thesis describes investigations into the total asymmetric syntheses of iminosugar natural products and analogues using a ring-closing iodoamination and a ring-expansion reaction as the key steps.

1.1. Iminosugars and their biological activity

Iminosugars are sugars in which the endocyclic oxygen atom has formally been replaced by a basic nitrogen atom [e.g., nojirimycin (NJ) **2** is the iminosugar analogue of glucose **1**]. This apparently simple substitution raises many synthetic challenges and opens the way to remarkable biological properties. As such, iminosugars have become and remain the most attractive class of carbohydrate mimics used in therapeutic applications.[1] Iminosugars are widely found in Nature, with currently more than one hundred having been isolated from a variety of plants and microorganisms.[1a,2] The iminosugar motif is present in several classes of monocyclic and bicyclic compounds, leading to a large and structurally diverse class of molecules. These compounds fall into one of five main categories: polyhydroxylated piperidines [e.g., (–)-1-deoxynojirimycin (DNJ) **3**], pyrrolidines [e.g., (+)-2,5-dideoxy-2,5-imino-D-mannitol (DMDP) **4**], indolizidines [e.g., (+)-castanospermine **5**], pyrrolizidines [e.g., (+)-casuarine **6**] and nortropanes [e.g., (–)-calystegine A3 **7**] (Figure 1). Nojirimycin (NJ) **2** was the first naturally occurring iminosugar to be identified (in 1966), being isolated by Inouye *et al.* from both *Streptomyces roseochromogenes* and *S. lavendulae*, and was described as an antibiotic.[3] The same year, Paulsen *et al.* reported the first synthesis[4] of the reduced and more stable[5] analogue of NJ **2**, DNJ **3**, well before its later isolation as a natural product from the roots of mulberry trees[6] and from various bacterial cultures.[7] The subsequent discovery (in 1976) of its biological activity as an α-glucosidase inhibitor rendered DNJ **3** the flagship compound of the increasingly desirable iminosugar class of molecules.[8]

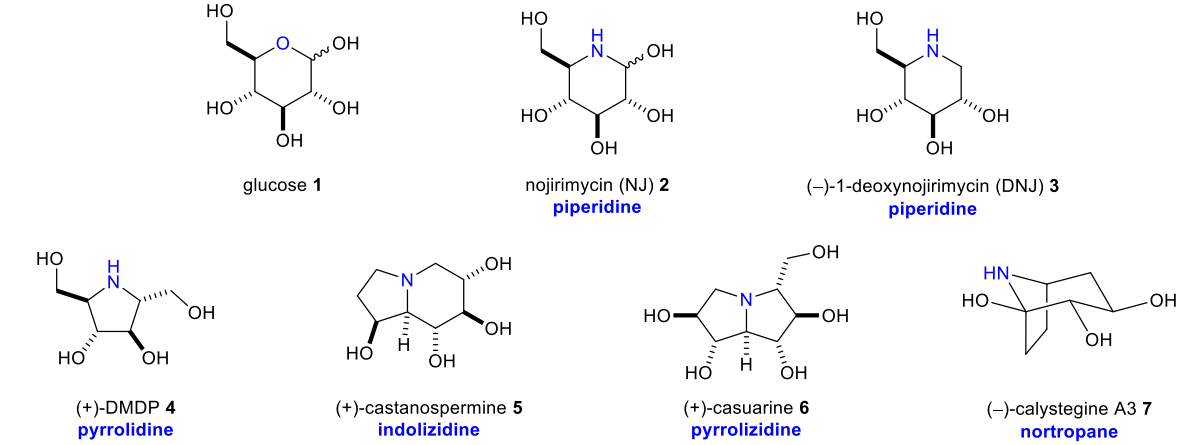


Figure 1. Glucose **1** and representative examples of the structural classes of naturally occurring iminosugars **2**–**7**.

The most significant biological mode of action of iminosugars is that of inhibition of glycosidases (glycoside hydrolases), and the exploitation of this activity underpins the therapeutic rationale behind the treatments of most disease targets. Glycosidases are enzymes which catalyse the cleavage of the glycosidic bonds within polysaccharides. The transition states involved in the mechanisms[9] of the glycosidic bond hydrolysis all possess significant oxocarbenium ion character, such as that seen for **8**, thus rendering the ammonium forms of iminosugars (which are protonated at physiological pH), such as DNJ **3**, ideal competitive inhibitors of these enzymes due to their structural resemblance to the sugar moiety (Figure 2).

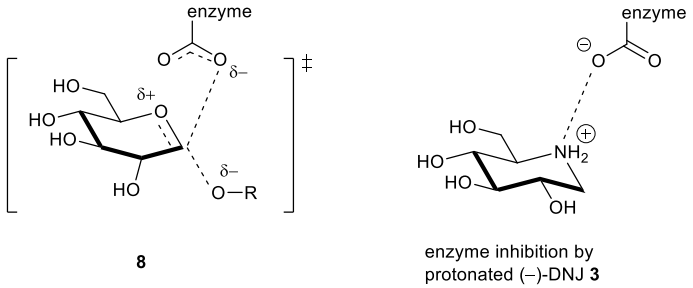


Figure 2. Protonated (–)-DNJ **3** as a transition state mimic for glycosidation.

Glycosidases play a vital role in a host of biological functions, including intestinal digestion, post-translational processing of glycoproteins or the lysosomal catabolism of glycoconjugates.[10] As such, iminosugars have proven to be effective therapeutic agents for the treatment of various diseases including diabetes,[11] viral infections,[12] lysosomal storage disorder,[13] Gaucher's disease[14] and cancer.[15] For example, Glyset® **9** and Zavesca® **10** are closely related to (–)-DNJ **3**, and are FDA approved drugs for the treatment of type II diabetes and Gaucher's disease, respectively.[16] (–)-1-Deoxymannojirimycin (DMJ) **11** has been shown to potently inhibit α-D-mannosidase, α-D-glucosidase and α-L-fucosidase,[17] and Celgosivir®

12, an ester prodrug of (+)-castanospermine **5**, is the most advanced clinical stage antiviral iminosugar being used to target the hepatitis C virus.[18] In addition, pyrrolidine iminosugars, such as (+)-1,4-dideoxy-1,4-imino-D-arabinitol (DAB) **13** and (+)-2,5-dideoxy-2,5-imino-D-glucitol (DGDP) **14** have also been well documented as highly promising candidates for the treatments of diabetes, cancer and HIV (Figure 3).[19]

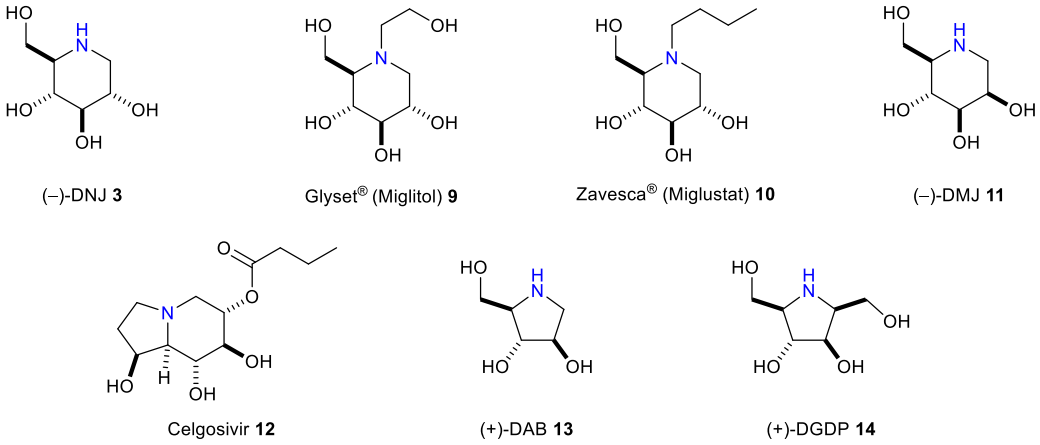


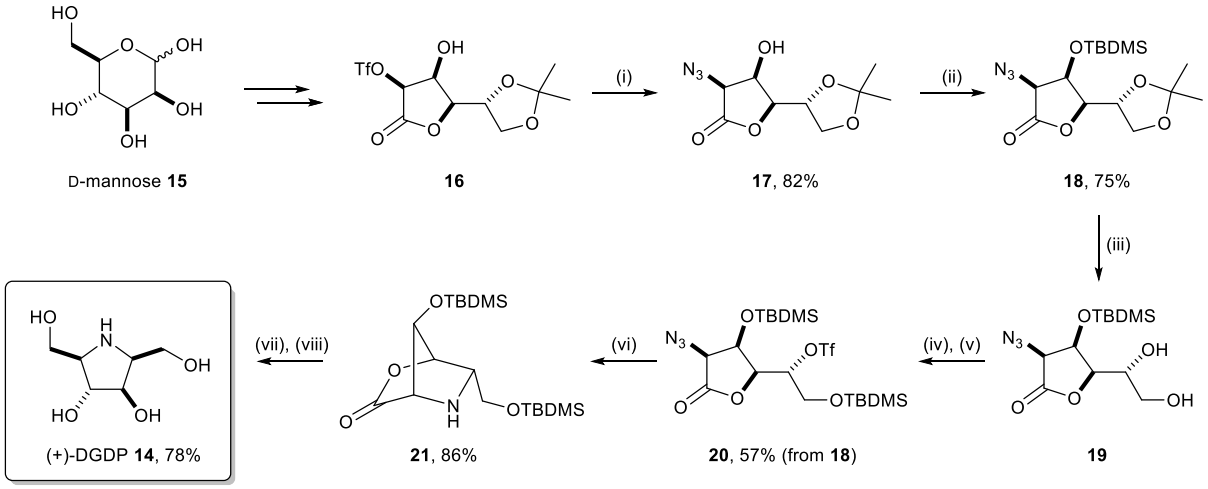
Figure 3. Selected biologically active iminosugars and therapeutic agents.

As a result, the development of improved methodology to access iminosugars and synthetic analogues (e.g., deoxy-amino analogues of natural products), along with the biological evaluation of these compounds, is a research priority. Most of the synthetic strategies reported so far for the synthesis of iminosugars concern the elaboration of readily available carbohydrate precursors. In contrast, relatively few *de novo* asymmetric approaches have been reported. Selected representative examples of these procedures for the synthesis of pyrrolidine and piperidine scaffolds, the two largest sub-classes of iminosugars, are described below.

1.2. Synthesis of pyrrolidine iminosugars

Most of the strategies for the synthesis of enantiopure pyrrolidine iminosugars involve the use of precursors derived from carbohydrates, tartaric acid, and α-amino acids.[20] (+)-DGDP **14**, for example, was isolated from the leaves of the legume *Derris elliptica* in 1976.[21] It is known to be a selective inhibitor of α-galactosidase, and exhibits broad-spectrum inhibition against α- and β-glucosidases and α-mannosidases.[22] In 1998, Fleet *et al.* reported a synthesis of (+)-DGDP **14** starting from 2-*O*-triflyl γ-lactone **16**, which is readily accessible from D-mannose **15**.[23] Displacement of the triflate group within **16** using NaN_3 in DMF for 40 h gave **17** in 82% yield (with overall retention of configuration as a result of S_N2-type displacement followed by epimerisation).[24] Treatment of **17** with TBDMSOTf and pyridine

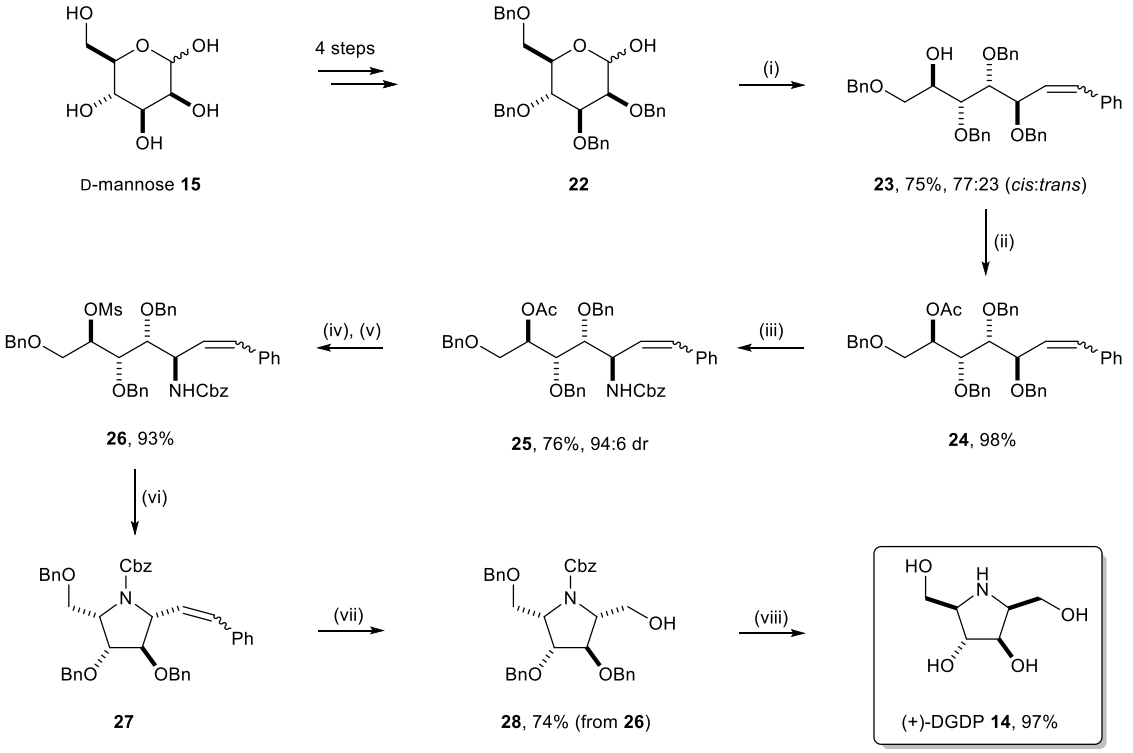
resulted in the formation of **18** in 75% yield, which was then converted into the corresponding diol **19** upon treatment with AcOH and H_2O. Subsequent selective protection of the primary hydroxyl group within **19** using TBDMSCl and imidazole followed by triflation of the remaining hydroxyl group gave triflate **20** in 57% yield over three steps from **18**. Reduction of azide **20** upon treatment with H_2 and Pd-black produced the corresponding amine, which underwent cyclisation upon displacement of the triflate moiety to give bicyclic lactone **21** in 86% yield. Finally, reduction of **21** with $LiHBEt_3$ followed by *O*-desilylation of the corresponding polyhydroxylated pyrrolidine afforded (+)-DGDP **14** in 78% yield. Overall, **14** was prepared in 24% yield over eight steps from γ-lactone **16** (Scheme 1).



Scheme 1. *Reagents and conditions:* (i) NaN_3, DMF, 40 h; (ii) TBDMSOTf, pyridine, CH_2Cl_2; (iii) AcOH/H_2O (4:1); (iv) TBDMSCl, imidazole, DMF; (v) Tf_2O, pyridine, CH_2Cl_2; (vi) H_2, Pd-black, EtOAc, then NaOAc, MeCN; (vii) $LiHBEt_3$, THF; (viii) HCl in MeOH (1%).

Jung *et al.* utilised their methodology involving a chlorosulfonyl isocyanate (CSI)-mediated regio- and stereoselective amination[25] of polybenzyl ether **24** and intramolecular cyclisation to form the pyrrolidine ring within (+)-DGDP **14**.[26] Wittig olefination of 2,3,4,6-tetra-*O*-benzyl-D-mannose **22** (which was prepared from commercially available D-mannose **15** in four steps)[27] was achieved using the dimsyl anion in THF at 60 °C and olefin **23** was obtained in 75% yield as a 77:23 mixture of *cis*- and *trans*-olefin isomers, which were carried through the rest of the synthesis. Subsequent acetylation of **23** gave **24** in 98% yield, which underwent reaction with CSI involving neighbouring group participation to furnish **25** in 76% yield and 94:6 dr at the *N*-bearing stereogenic centre, with overall retention of configuration for the major product. Methanolysis of **25** followed by treatment with MsCl and Et_3N delivered **26** in 93% yield. Cyclisation was promoted upon treatment of **26** with KO^tBu and the corresponding olefin **27** was subjected to a tandem ozonolysis/reduction protocol to give

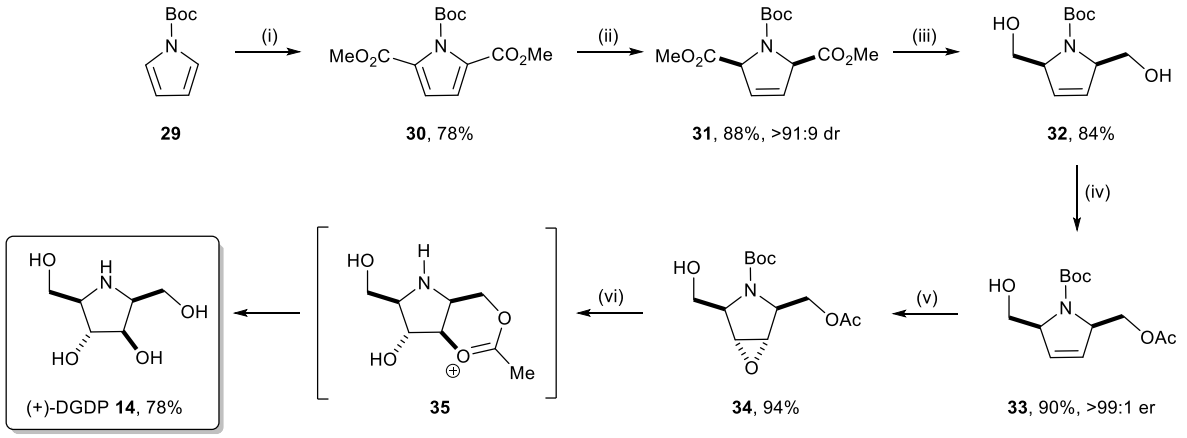
pyrrolidine **28** in 74% yield over two steps (from **26**). Finally, catalytic hydrogenolysis of **28** afforded (+)-DGDP **14** in 97% yield. Overall, **14** was prepared in 37% yield over eight steps from 2,3,4,6-tetra-*O*-benzyl-D-mannose **22** (Scheme 2).



Scheme 2. *Reagents and conditions:* (i) NaH, DMSO, $BnPPh_3Cl$, THF, 60 °C, 3 h; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 3 h; (iii) CSI, Na_2CO_3, PhMe, 0 °C, 24 h, then Na_2SO_3, rt, 24 h; (iv) K_2CO_3, MeOH, rt, 2 h; (v) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; (vi) KO^{t}Bu, THF, 0 °C, 2 h; (vii) O_3, CH_2Cl_2/MeOH (1:1), −78 °C, 1 h, then $NaBH_4$, 0 °C, 1 h; (viii) 10% Pd/C, H_2, HCl (10 M in EtOH), EtOH, rt, 12 h.

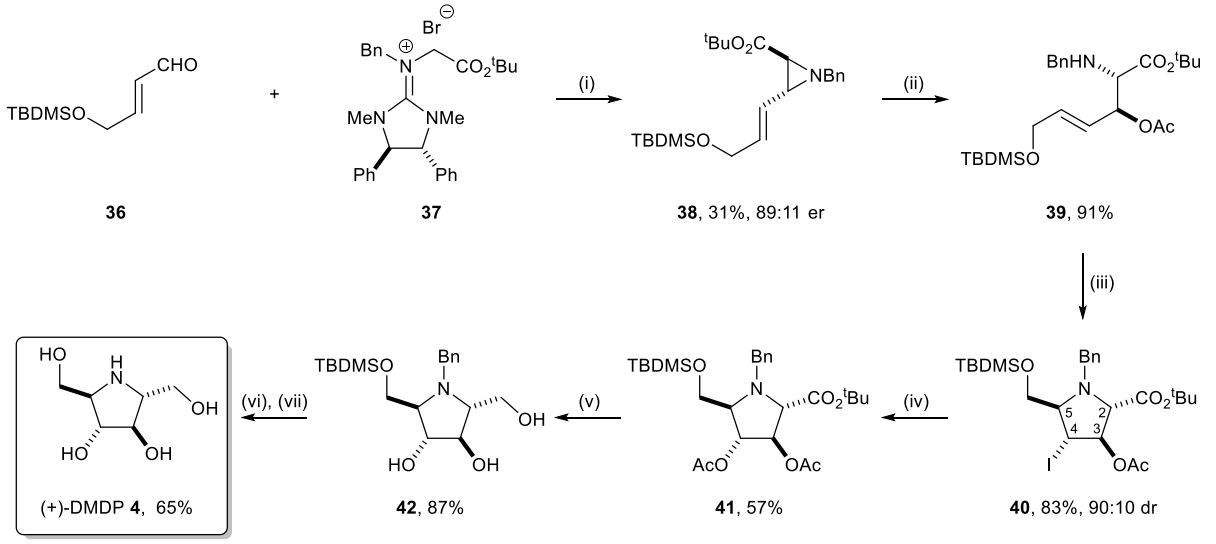
Although most syntheses of (+)-DGDP **14** have been achieved by the elaboration of readily available carbohydrate precursors, Donohoe *et al.* reported a concise asymmetric synthesis of **14** using the partial reduction of an electron deficient pyrrole and an epoxidation/ring-opening approach as the key steps.[28] Double deprotonation of *N*-Boc pyrrole **29** with LiTMP followed by reaction with methyl chloroformate resulted in the formation of diester **30** in 78% yield. Subsequent diastereoselective reduction under ammonia-free conditions (i.e., Li, catalytic DBB, THF) using 2,6-di-*tert*-butylphenol as the proton source gave *cis*-dihydropyrrole **31** in 88% yield and >91:9 dr. Reduction of the ester moieties within **31** was performed upon treatment with Red-Al® to give *cis*-diol **32** in 84% yield. Enantioselective desymmetrization of diol **32** was then achieved using lipoprotein lipase from *Pseudomonas* species, which effected esterification with vinyl acetate in THF to afford monoacetylated pyrrolidine **33** in 90% yield and >99:1 er. Oxidation of dihydropyrrole **33** was achieved with high diastereoselectivity using an *in situ* generated dioxirane reagent which gave epoxide **34** in

94% yield as a single diastereoisomer. Treatment of **34** with BF_3·OEt resulted in regioselective epoxide ring-opening via anchimeric assistance by the acetate group within **34**; concomitant cleavage of the *N*-Boc protecting group under the reaction conditions produced intermediate **35**. Subsequent addition of MeOH successfully cleaved the acetate-derived protecting group *in situ* to give (+)-DGDP **14** in 78% yield. Overall, **14** was prepared in 38% yield over six steps from *N*-Boc pyrrole **29** (Scheme 3).



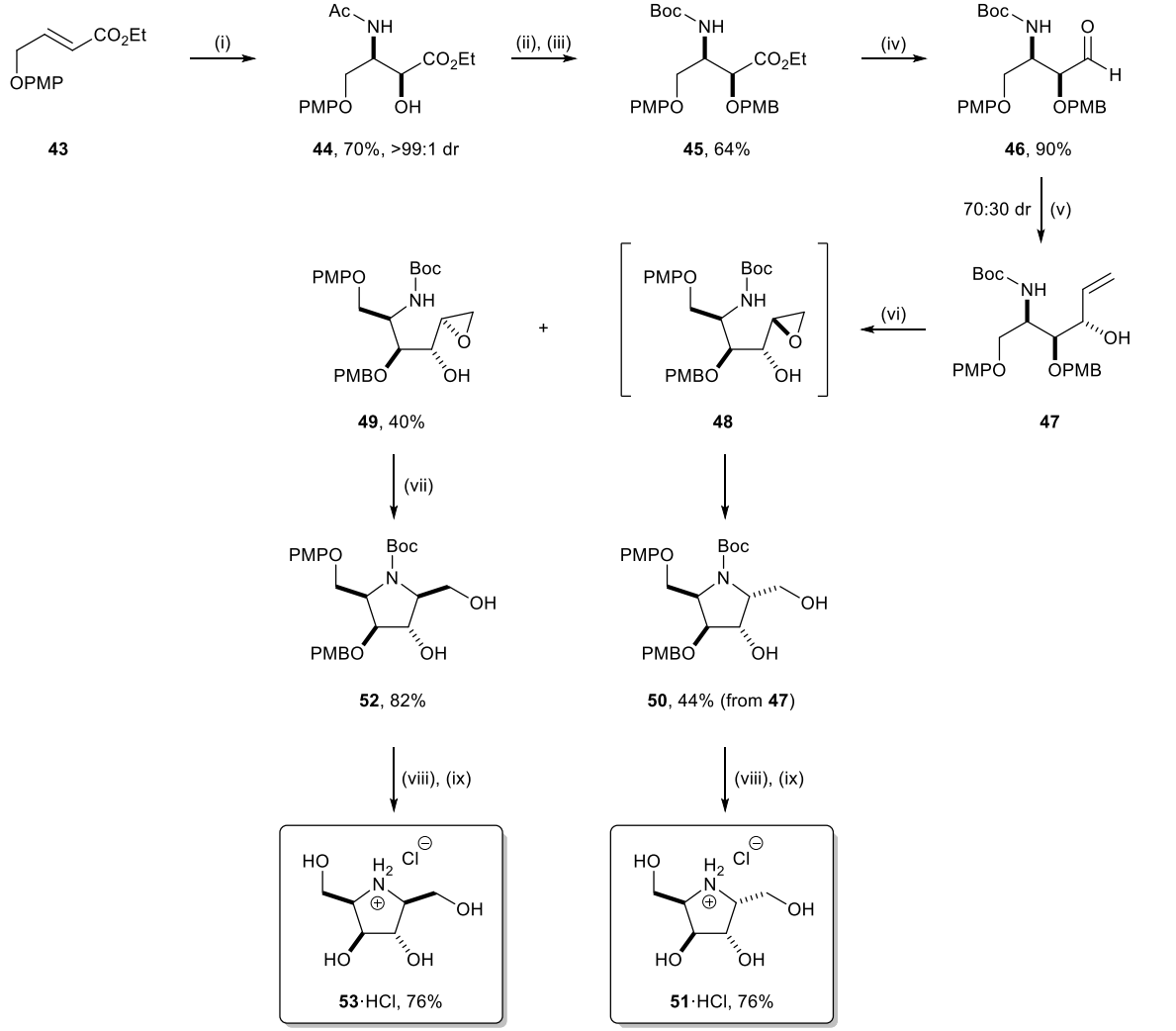
Scheme 3. *Reagents and conditions:* (i) LiTMP then MeOCOCl, THF, −78 °C, 3.5 h; (ii) Li, DBB (cat.), THF, then 2,6-di-*tert*-butylphenol, −78 °C, 2.5 h; (iii) Red-Al®, THF, 0 °C, 2 h; (iv) Lipase, THF, vinyl acetate, 37 °C, 30 h; (v) Oxone®, 4.10^{-4} M aq Na_2EDTA, 1,1,1-trifluoroacetone, $NaHCO_3$, MeCN, 0 °C, 2 h; (vi) BF_3·OEt_2, CH_2Cl_2, 0 °C to rt, 4 h, then MeOH, rt, 12 h.

(+)-DMDP **4**, a powerful inhibitor of both β-glucosidases and β-galactosidases,[29] is one of the most widely found iminosugars in Nature.[2a] Ishikawa *et al.* reported an enantioselective synthesis of (+)-DMDP **4** using an asymmetric aziridination and a 5-*endo*-*trig*[30] iodoamination as the key steps.[31] Treatment of aldehyde **36**[32] with guanidinium bromide **37** in the presence of tetramethylguanidine (TMG) followed by reaction with Ac_2O delivered *trans*-**38** in 31% yield and 89:11 er.[33] Regioselective aziridinium ring-opening of **38** upon treatment with AcOH gave **39** in 91% yield. Iodoamination of **39** produced pyrrolidine **40** as the major product (90:10 dr), which underwent Prévost displacement upon treatment with AgOAc to give pyrrolidine **41**, with overall retention of configuration at C(4), in 57% yield as single diastereoisomer. Subsequent reduction of the *tert*-butyl ester moiety within **41** and concomitant *O*-acetyl deprotection upon treatment with $LiBH_4$ gave **42** in 87% yield. Finally, treatment of **42** with TBAF followed by catalytic hydrogenolysis afforded (+)-DMDP **4** in 65% yield over two steps. Overall, **4** was prepared in 5.7% yield over nine steps from the commercially available starting material (*Z*)-1,4-dihydroxybut-2-ene (Scheme 4).



Scheme 4. *Reagents and conditions:* (i) TMG, THF, rt, 17 h, then Ac_2O, MeCN, rt, 1 h; (ii) AcOH, rt, 1.5 h; (iii) I_2, K_2CO_3, EtOAc, −40 °C, 1 h; (iv) AgOAc, AcOH, 40 °C, 15 h; (v) $LiBH_4$, THF, reflux, 10 h; (vi) TBAF, THF, rt, 30 min; (vii) H_2, $Pd(OH)_2/C$, MeOH, HCl, rt, 1 h, then ion-exchange resin.

In 2003, Han *et al.* developed an asymmetric approach[34] towards polyhydroxylated pyrrolidines **51** and **53** starting from a readily available α,β-unsaturated ester **43**.[35,36] Their strategy included the regioselective asymmetric aminohydroxylation of **43** and the epoxidation/intramolecular cyclisation of allylic alcohol **47** as the key steps. Aminohydroxylation of **43** was achieved using $(DHQD)_2PHAL$ and *N*-bromoacetamide to give *syn*-amino alcohol **44** in 70% yield and >99:1 dr. Treatment of **44** with NaH and PMBCl followed by *N*-Boc protection and subsequent hydrazinolysis of the *N*-acetyl group resulted in the formation of **45**. Partial reduction of the ester functionality within **45** gave aldehyde **46**, which underwent reaction with vinylmagnesium bromide to give a separable 70:30 mixture of allylic alcohols.[37] Epoxidation of the major diastereoisomer **47** upon treatment with $VO(acac)_2$ and TBHP gave a mixture of epoxides **48** and **49**; the former undergoing concomitant intramolecular cyclisation to form pyrrolidine **50** in 44% isolated yield. Epoxide **49** was isolated in 40% yield and its intramolecular cyclisation was promoted in the presence of TFA to give the epimeric pyrrolidine **52**, which was isolated in 82% yield. Finally, treatment of **50** and **52** with CAN followed by hydrolysis of the corresponding triols delivered unnatural pyrrolidine iminosugars **51** and **53**, which were isolated as the corresponding hydrochloride salts, in 76% yield in both cases (Scheme 5).

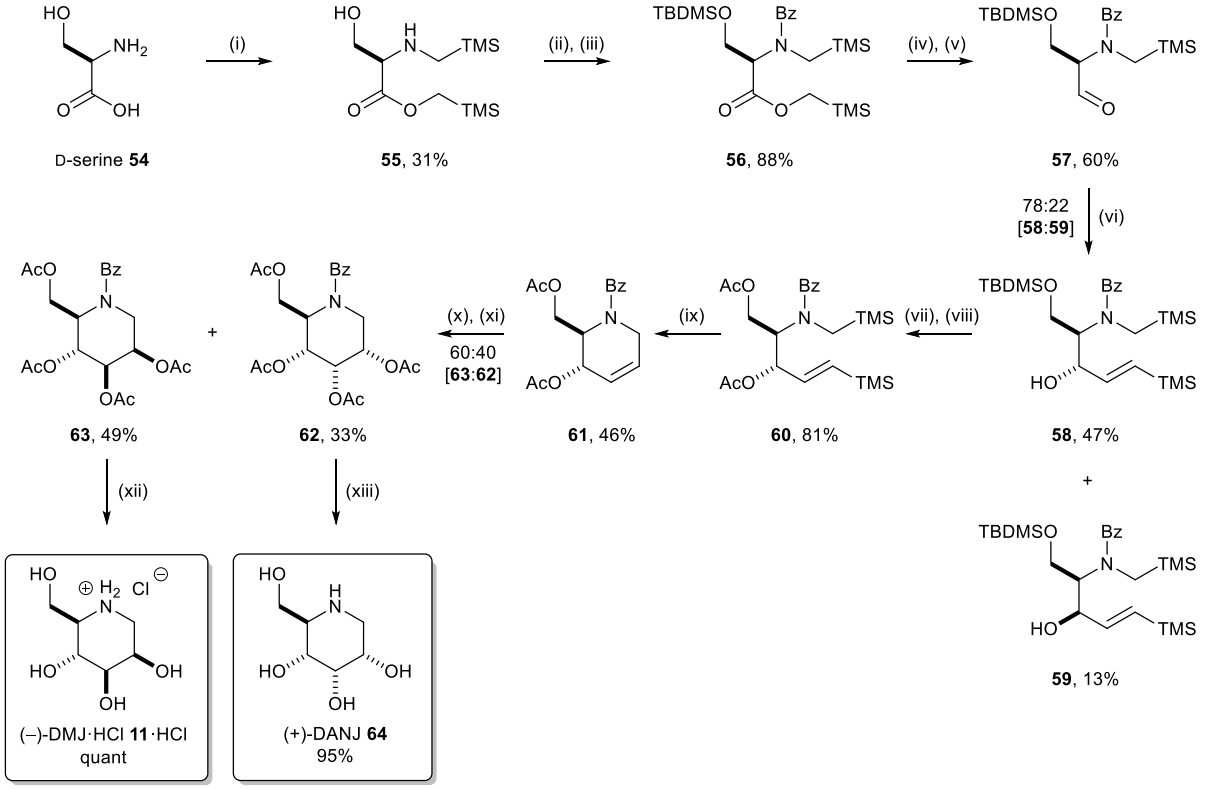


Scheme 5. *Reagents and conditions:* (i) $K_2OsO_4{\cdot}2H_2O$, $(DHQD)_2PHAL$, LiOH, *N*-bromoacetamide, $^tBuOH/H_2O$ (2:1), 4 °C, 8 h; (ii) NaH, PMBCl, DMF, 0 °C, 10 h; (iii) $(Boc)_2O$, DMAP, THF, reflux, 4 h, then N_2H_4, MeOH, 4 h; (iv) DIBAL-H, CH_2Cl_2, −78 °C, 3 h; (v) CH_2=CHMgBr, THF, −50 °C, 1 h, then rt, 1 h; (vi) $VO(acac)_2$, TBHP, PhMe, rt, 16 h; (vii) TFA, CH_2Cl_2, 4 °C, 3 h; (viii) CAN, $MeCN/H_2O$ (4:1), 4 °C, 10 min; (ix) 3.0 M aq HCl, 3 h.

1.3. Synthesis of piperidine iminosugars

(–)-DMJ **11**, which was isolated from *Lonchocarpus sericeus* in 1979,[38] and (+)-1-deoxyallonojirimycin [(+)-DANJ] **64**, which was isolated from the leaves and twigs of *Connarus ferrugineus*,[39] have been the targets of much synthetic endeavour within the piperidine sub-class of iminosugars. Mariano *et al.* achieved the syntheses of both (–)-DMJ **11** and (+)-DANJ **64** from D-serine **54** by utilising an oxidative Mannich cyclisation process.[40] D-Serine **54** was first converted into **55** in 31% yield using K_2CO_3 and $TMSCH_2I$.[41] Treatment of **55** with TBDMSCl and imidazole followed by *N*-benzoylation upon treatment with BzCl and Et_3N gave **56** in 88% yield over two steps. Reduction of the ester moiety within **56** led to the corresponding primary alcohol, which was subjected to Swern oxidation conditions to deliver aldehyde **57** in 60% yield over two steps. Reaction of **57** with

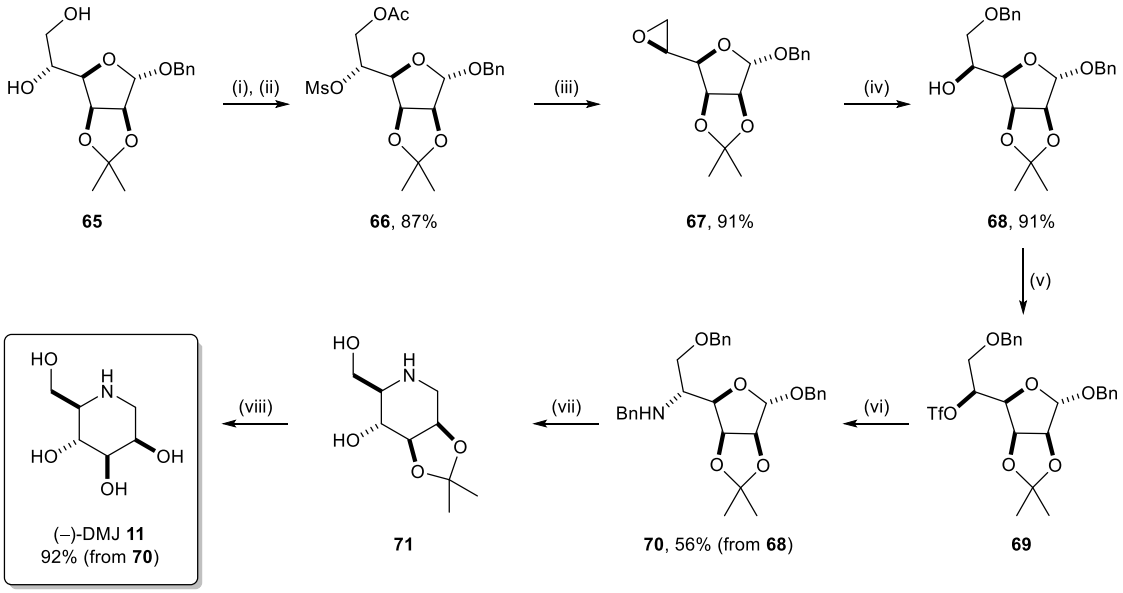
(*E*)-TMS(CH)$_2$Li produced a 78:22 mixture of epimeric alcohols **58** and **59**, respectively, from which **58** was isolated in 47% yield and **59** was isolated in 13% yield. The major diastereoisomer **58** was then transformed into diacetate **60**, which underwent oxidative Mannich cyclisation upon treatment with CAN (*in situ* promotion of the corresponding *N*-alkyl iminium cation) to give tetrahydropyridine **61** in 46% yield. Subsequent dihydroxylation of **61** using Upjohn conditions[42] and peracetylation of the resultant diols furnished a 60:40 mixture of tetraacetates **63** and **62**, which were isolated in 49 and 33% yield, respectively. Global deprotection of **63** using 6.0 M aq HCl afforded (–)-DMJ hydrochloride **11**·HCl in quantitative yield. Similarly, (+)-DANJ **64** was obtained in 95% yield from **62** after deprotection and purification by ion-exchange chromatography (Scheme 6).



Scheme 6. *Reagents and conditions:* (i) TMSCH$_2$I, K$_2$CO$_3$, DMF, 100 °C, 17 h; (ii) TBDMSCl, imidazole, DMF, rt, 18 h; (iii) BzCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 15 min; (iv) NaBH$_4$, EtOH, rt, 6 h; (v) DMSO, (COCl)$_2$, CH$_2$Cl$_2$, −78 °C, 3.5 h, then Et$_3$N, −78 °C to rt, 2.5 h; (vi) (*E*)-TMS(CH)$_2$SnBu$_3$, BuLi, THF, −78 °C, 2 h, then rt, 30 min; (vii) HF·H$_2$O (48%), MeCN, rt, 30 min; (viii) Ac$_2$O, DMAP, pyridine, rt, 17 h; (ix) CAN, MeCN, 40 °C, 20 h; (x) OsO$_4$, NMO, acetone/H$_2$O (10:1), 0 °C, 17 h; (xi) Ac$_2$O, DMAP, pyridine, rt, 17 h; (xii) 6.0 M aq HCl, reflux, 5 h; (xiii) 6.0 M aq HCl, reflux, 5 h, then ion-exchange resin.

In 1988, Van Boom *et al.* reported[43] the synthesis of (–)-DMJ **11** from the readily available carbohydrate precursor benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside **65**,[44] which was obtained in three steps from D-mannose **15**. Mesylation of **65** followed by substitution of the

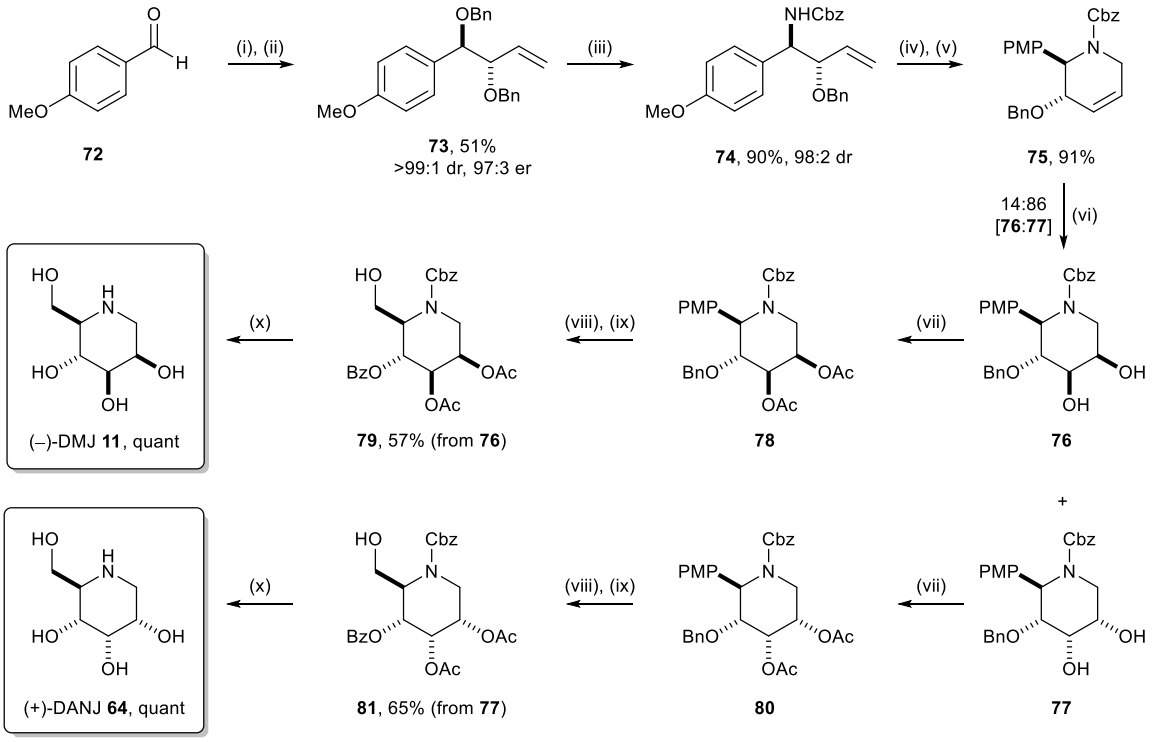
primary mesylate moiety with KOAc led to the isolation of **66** in 87% yield over two steps. Under optimised conditions, treatment of **66** with KO^{t}Bu in DMF resulted in the formation of epoxide **67** in 91% yield. Regioselective ring-opening of the epoxide moiety within **67** upon treatment with NaH and BnOH gave alcohol **68** in 91% yield. Subsequent triflation of **68** with Tf_2O and pyridine gave **69**, which underwent nucleophilic substitution upon treatment with $BnNH_2$ in PhMe to deliver **70** in 56% yield over two steps. Finally, hydrogenolysis of **70** resulted in the formation of piperidine acetonide **71**, which was subjected to acidic hydrolysis to afford (–)-DMJ **11** in 92% yield over two steps (Scheme 7).



Scheme 7. *Reagents and conditions:* (i) MsCl, pyridine, 0 °C to 5 °C, 16 h; (ii) KOAc, 18-crown-6, MeCN, reflux, 20 h; (iii) KO^{t}Bu, DMF, 0 °C, 30 min; (iv) NaH, BnOH, DMF, 0 °C, 16 h; (v) Tf_2O, CH_2Cl_2, pyridine, −20 °C, 1 h; (vi) $BnNH_2$, PhMe, rt, 14 days; (vii) $Pd(OH)_2/C$, H_2, EtOH/H_2O/AcOH (5:1:1), rt, 48 h; (viii) conc HCl, H_2O, rt, 48 h, then Amberlite IRA-400 ($OH^–$).

Jung *et al.* reported the total asymmetric syntheses of both (–)-DMJ **11** and (+)-DANJ **64** via the diastereoselective dihydroxylation of the common intermediate tetrahydropyridine **75**.[45] Commercially available *p*-anisaldehyde **72** was first subjected to Brown's asymmetric aldol reaction[46] and subsequent perbenzylation to give *anti*-**73** in 51% yield (over two steps), >99:1 dr and 97:3 er. Regio- and stereoselective CSI-mediated amination of **73** proceeded with high diastereoselectivity to produce the protected vicinal amino alcohol *anti*-**74** in 90% yield and 98:2 dr. Treatment of **74** with NaH and allyl bromide gave the corresponding *N*-allylic derivative, which underwent ring-closing metathesis upon treatment with Grubbs catalyst to afford **75** in 91% yield over two steps. Under optimised conditions, Upjohn dihydroxylation of **75** produced a separable 14:86 mixture of diols **76** and **77**, respectively, in 75% total yield.[47] Peracetylation of **76** followed by oxidation of the PMP moiety within **78**,

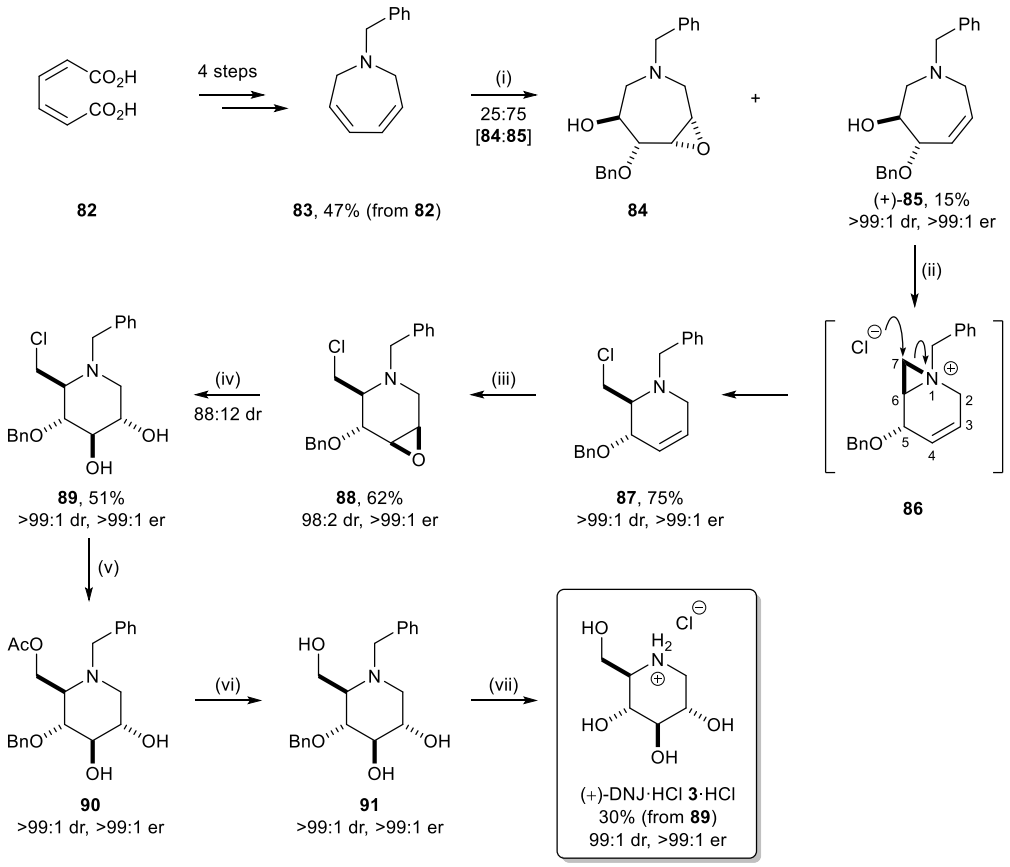
upon treatment with $RuCl_3$ and $NaIO_4$, led to the formation of the corresponding carboxylic acid, with concomitant oxidation of the benzyl group to a benzoate moiety. Subsequent reduction with BH_3·THF delivered primary alcohol **79** in 57% yield over three steps from **76**. Finally, treatment of **79** with 6.0 M aq HCl and subsequent purification on Dowex resin afforded (–)-DMJ **11** in quantitative yield. Diol **77** underwent the same sequence of reactions to deliver (+)-DANJ **64** in 65% yield over four steps (Scheme 8).



Scheme 8. *Reagents and conditions:* (i) allyl(diisopropylamino)dimethylsilane, BuLi, TMEDA, (−)-*B*-methoxydiisopinocamphenylborane, BF_3·OEt_2, Et_2O, −78 °C, 3 h, then KF, $KHCO_3$, H_2O_2 (30%), THF, MeOH, rt, 20 h; (ii) NaH, BnBr, THF, DMF, rt, 11 h; (iii) CSI, Na_2CO_3, PhMe, −78 °C, 24 h, then Na_2SO_3 (25%), rt, 24 h; (iv) NaH, allyl bromide, THF, DMF, rt, 2 h; (v) Grubbs I, CH_2Cl_2, rt, 4 h; (vi) OsO_4, NMO, acetone/H_2O (5:1), rt, 8 h; (vii) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 3 h; (viii) $RuCl_3$, $NaIO_4$, H_2O/MeCN/EtOAc (2:1:1), rt, 4 h; (ix) BH_3·THF, THF, 0 °C, 24 h; (x) 6.0 M aq HCl, MeOH, reflux, 14 h, then Dowex 50WX8 (H^+ form).

The total asymmetric synthesis of (+)-DNJ **3** was achieved by Davies *et al.* using an oxidation/ring-contraction approach coupled with a resolution protocol.[48] Under optimised conditions, treatment of azepine **83** (which was prepared in 47% yield over four steps from *cis,cis*-muconic acid **82**)[49] with 1.5 equiv of *m*-CPBA in the presence of HBF_4·OEt_2 and BnOH gave a 25:75 mixture of epoxide (±)-**84** and allylic amine (±)-**85**. Purification and resolution of (±)-**85** via preparative chiral HPLC gave (+)-**85** in 15% yield, >99:1 dr and >99:1 er.[50] The mechanism of this transformation involved epoxidation of the double bond with subsequent regioselective ring-opening by BnOH to give (±)-**85** [further

diastereoselective oxidation of (±)-**85** was responsible for the formation of epoxide (±)-**84**]. Ring-contraction of (+)-**85** upon treatment with MsCl proceeded via aziridinium **86** to produce piperidine **87** in 75% yield and >99:1 dr. Subsequent oxidation of the olefin within **87** using a mixture of F_3CCO_3H and F_3CCO_2H afforded epoxide **88** in 62% isolated yield (98:2 dr). Regioselective ring-opening of epoxide **88** with Cl_3CCO_2H and subsequent hydrolysis of the trichloroacetate ester delivered diol **89** in 51% yield and >99:1 dr, after chromatographic purification. Conversion of the primary chloride moiety into the corresponding acetate **90** was achieved upon treatment with AgOAc. Finally, sequential methanolysis and hydrogenolysis of **90** afforded (+)-DNJ hydrochloride **3**·HCl in 30% yield (over three steps from **89**) and 99:1 dr (Scheme 9).



Scheme 9. *Reagents and conditions:* (i) *m*-CPBA, $HBF_4{\cdot}OEt_2$, CH_2Cl_2, BnOH, rt, 24 h, then preparative chiral HPLC (Chiralpak AD-H column); (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 2.0 M aq NaOH; (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 conc aq HCl.

1.4. Synthesis of deoxy-amino analogues

The formal replacement of an exocyclic oxygen atom for nitrogen in iminosugars to form polyamines has been shown to lead to compounds with interesting and useful biological activities. For example, (+)-ADMDP **92**, the synthetic 1-deoxy-1-amino analogue of (+)-DMDP **4**, and *N*(1)-substituted derivatives have been reported to display significantly enhanced selectivity and potency towards the inhibition of glucosidases than the parent iminosugar **4**.[51] In addition, 2-deoxy-2-acetamidonojirimycin **93** has been investigated as a potent inhibitor of *N*-acetylglucosaminidases[52] and 1,2-dideoxy-2-acetamidonojirimycin **94** has been shown to be one of the most powerful reversible inhibitors of hexosaminidases[53] reported to date (Figure 4). However, relatively few syntheses of deoxy-amino analogues of naturally occurring iminosugars have been documented in the literature.

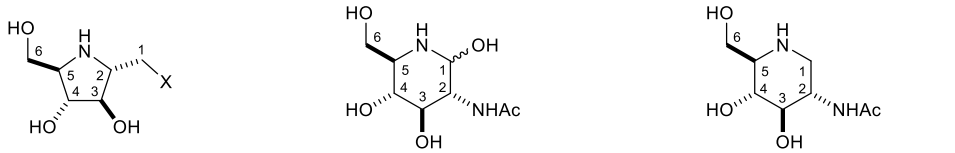
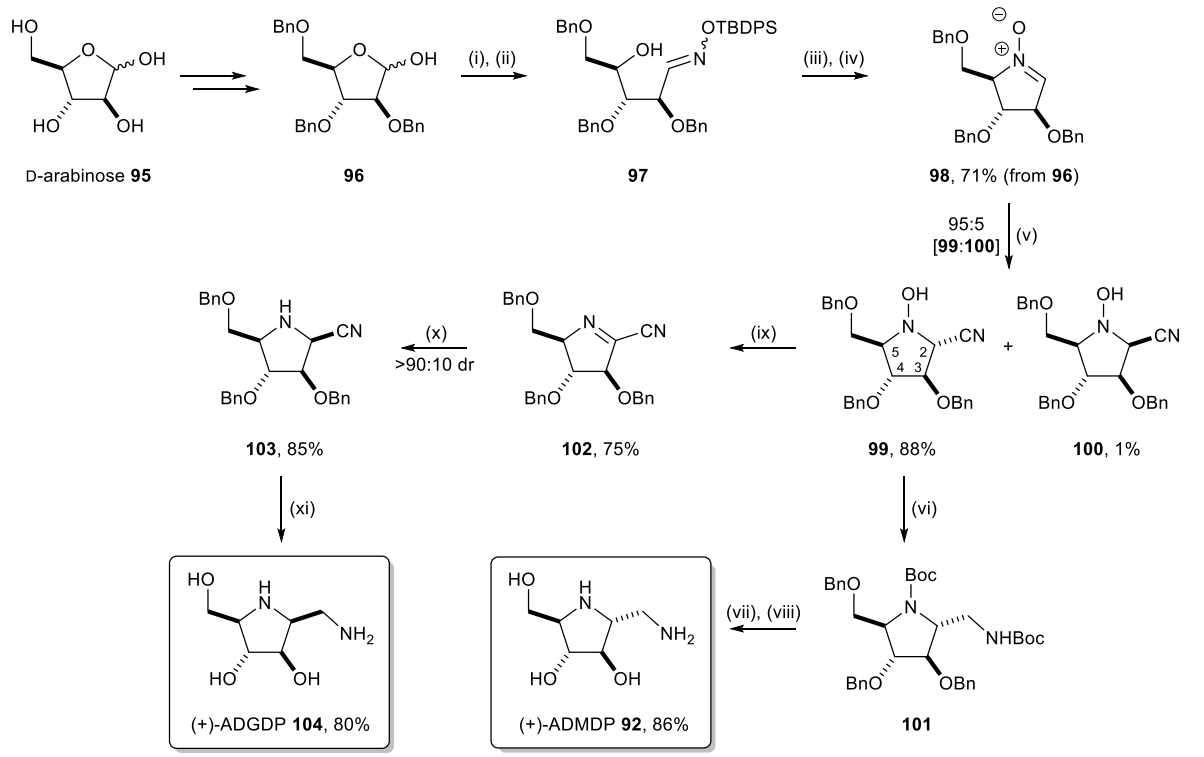


Figure 4. Selected biologically active deoxy-amino analogues of naturally occurring iminosugars.

Cheng *et al.* reported the syntheses of (+)-ADMDP **92** and (+)-ADGDP **104** [the 1-deoxy-1-amino analogue of (+)-DGDP **14**] via a common cyclic nitrone precursor **98**.[54] Treatment of **96** (which is readily available from D-arabinose **95**)[55] with $NH_2OH{\cdot}HCl$ followed by *O*-protection upon treatment with TBDPSCl and imidazole afforded *O*-protected oxime **97**. Subsequent iodination and *O*-silyl deprotection with TBAF resulted in the formation of cyclic nitrone **98** in 71% yield over four steps. Addition of TMSCN to **98** proceeded with high diastereoselectivity to give **99** in 88% isolated yield. Reduction of both the hydroxylamine and nitrile moieties within **99** was achieved using Raney Ni and H_2 in the presence of Boc_2O to deliver *N*,*N*'-di-Boc protected diamine **101**. Subsequent hydrogenolysis and hydrolysis of **101** afforded (+)-ADMDP **92** in 86% yield from **99** (i.e., 75% from cyclic nitrone **98**). Inversion of configuration at the C(2)-position within **99** was performed upon mesylation of the diastereoisomeric mixture of **99** and **100**, followed by regioselective elimination under the basic reaction conditions to give iminonitrile **102**. Subsequent diastereoselective reduction of **102** upon treatment with $NaBH_4$ afforded nitrile **103** in >90:10 dr and 85% isolated yield.

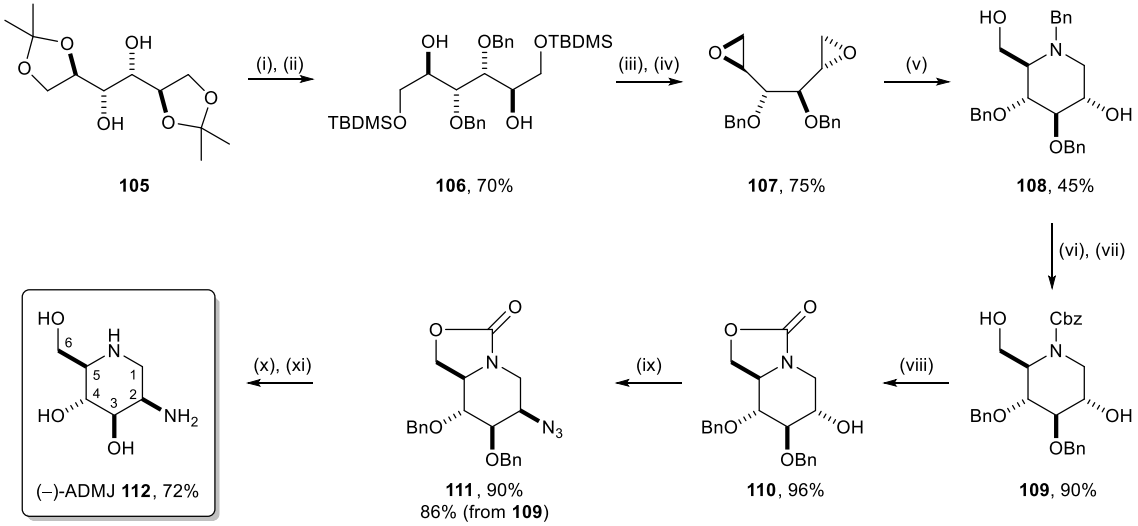
Finally, catalytic reduction/hydrogenolysis of **103** gave (+)-ADGDP **104** in 80% yield (i.e., 51% from cyclic nitrone **98**) (Scheme 10).



Scheme 10. *Reagents and conditions:* (i) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, 5 h; (ii) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 h; (iii) I_2, PPh_3, imidazole, PhMe, reflux, 1 h; (iv) TBAF, PhMe, reflux, 30 min; (v) TMSCN, MeOH, 50 °C, 8 h; (vi) Raney Ni, H_2 (1 atm), Boc_2O, MeOH, rt, 4 h; (vii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 10 h; (viii) TFA, CH_2Cl_2, 0 °C, 30 min; (ix) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; (x) $NaBH_4$, MeOH, 0 °C, 5 h; (xi) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, AcOH, rt, 48 h.

In 1997, Le Merrer *et al.* reported the only known synthesis of (–)-ADMJ **112**, the 2-deoxy-2-amino analogue of (–)-DMJ **11**. Their strategy involved the ring-opening of enantiopure C_2 symmetric bis-epoxide **107** by $BnNH_2$.[56] The total synthesis started from the commercially available 1,2:5,6-di-*O*-isopropylidene-D-mannitol **105**, which gave access to the *O*-silyl and *O*-benzyl protected derivative **106** in 70% yield over two steps.[57] Mesylation of the 2,5-hydroxyl groups within **106** followed by *O*-silyl deprotection upon treatment with HCl resulted in the formation of bis-epoxide **107** (after treatment with NaOH) in 75% yield over two steps. Subsequent treatment of **107** with $BnNH_2$ led to the regioselective ring-opening of one epoxy moiety, which underwent *in situ* aminocyclisation to afford polyhydroxylated piperidine **108** in 45% isolated yield.[58] Conversion of **108** into the corresponding carbamate **109** was achieved in 90% yield by selective hydrogenation followed by reaction with benzyl chloroformate. Methanolysis of **109** gave oxazolidinone **110**, which underwent substitution under Mitsunobu conditions to deliver azide **111** in 86% yield over two steps. Finally,

methanolysis and hydrogenolysis of **111** afforded (–)-ADMJ **112** in 72% yield over two steps. Overall, **112** was prepared in 13% yield over eleven steps from 1,2:5,6-di-*O*-isopropylidene-D-mannitol **105** (Scheme 11).



Scheme 11. *Reagents and conditions:* (i) NaH, BnBr, Bu_4NI, THF, 0 °C, 1 h, then AcOH, H_2O, 50 °C, 2 h; (ii) TBDMSCl, imidazole, DMF, 0 °C, 2 h; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min; (iv) HCl, MeOH, rt, 2 h, then KOH (20% in H_2O), 0 °C to rt, 3 h; (v) $BnNH_2$, $CHCl_3$, reflux, 48 h; (vi) H_2, $Pd(OH)_2$/C, EtOH, 2.5 h; (vii) CbzCl, K_2CO_3, DMF, 0 °C, 30 min; (viii) MeOH, K_2CO_3, rt, 45 min; (ix) Ph_3P, DEAD, HN_3, THF, 0 °C, 1 h, then rt, 2 h; (x) MeOH, K_2CO_3, rt, 45 min; (xi) H_2, Pd-black, AcOH, rt, 18 h.

1.5. Thesis aims

This thesis describes investigations into the total asymmetric syntheses of pyrrolidine and piperidine iminosugars via the regioselective ring-opening of a common aziridinium intermediate **118**. It was envisaged that diastereoselective aminohydroxylation of protected γ-hydroxy-α,β-unsaturated ester **113** followed by FGI and addition of vinylmagnesium bromide to the corresponding aldehyde **115** would result in the formation of the diastereoisomeric bishomoallylic amines **116**. Subsequent ring-closing iodoamination was anticipated to produce iodomethyl pyrrolidines **117**, which could then be converted into the corresponding aziridinium species **118**. Nucleophilic ring-opening of **118** at the C(6)-position would allow access to pyrrolidine iminosugars **119** and their 1-deoxy-1-amino analogues **120**. Alternatively, ring-opening of **118** at the C(5)-position would allow the preparation of piperidine iminosugars **121** and their 2-deoxy-2-amino analogues **122** (Figure 5).

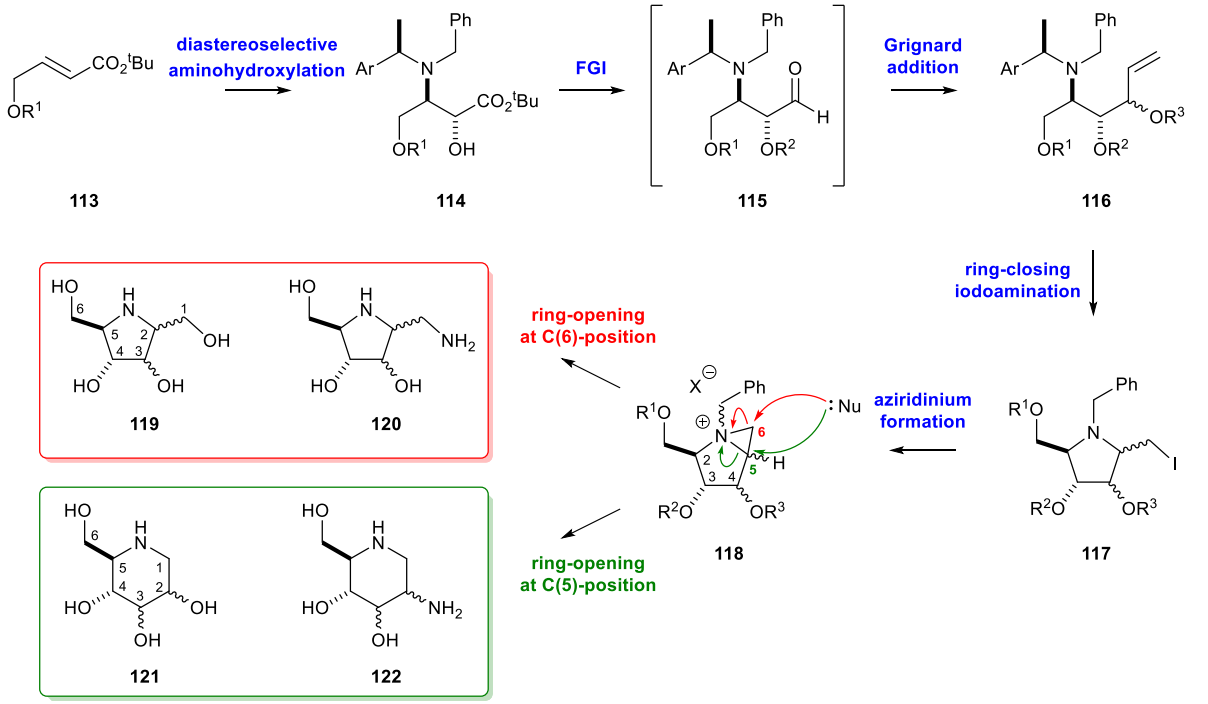


Figure 5. Proposed synthetic route to pyrrolidine and piperidine iminosugars **119**–**122**.

1.6. References and notes

[1] (a) Compain, P.; Martin, O. R. *Iminosugars: From synthesis to therapeutic applications*; Wiley-VCH: Weinheim, 2007. (b) Winchester, B. G.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (c) Winchester, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645.

[2] (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.

[3] (a) Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiot.* **1966**, *19*, 288. (b) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125.

[4] (a) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 495. (b) Paulsen, H.; Todt, K. *Chem. Ber.* **1967**, *100*, 3385.

[5] Nojirimycin **2** is quite unstable due to its hemiaminal functionality and thus is usually stored as the bisulfite adduct.

[6] Yagi, M.; Kouno, T.; Aoyagi, Y.; Murai, H. *Nippon Nougei Kagaku Kaishi* **1976**, *50*, 571.

[7] (a) Schmidt, D. D.; Frommer, W.; Muller, L.; Truscheit, E. *Naturwissenschaften* **1979**, *66*, 584. (b) Murao, S.; Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219. (c) Ezure, Y.; Maruo, S.; Miyazaki, K.; Kawamata, M. *Agric. Biol. Chem.* **1985**, *49*, 1119.

[8] Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1998.

[9] The hydrolysis of the glycosidic bond can occur with either retention or inversion of configuration at the anomeric centre, and these outcomes serve to distinguish glycosidases into the mechanistically distinct classes of "retaining" or "inverting" enzymes; see: (a) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171. (b) Zechel, D. L.; Withers, S. G. *Acc. Chem. Res.* **2000**, *33*, 11.

[10] (a) Sansom, C.; Markman, O. *Glycobiology*; Scion Publishing Ltd: Banbury, 2007. (b) Stick, R. V.; Williams, S. J. *Carbohydrates: The Essential Molecules of Life*; 2nd Edn.; Elsevier, 2009.

[11] (a) Ichikawa, Y.; Igarashi, M.; Suhara, Y. *J. Am. Chem. Soc*. **1998**, *120*, 3007. (b) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C. H.; Liu, P. S. *J. Org. Chem*. **1989**, *54*, 2539.

[12] Von Itzstein, M.; Wu, W. Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Phan, T. V.; Smythe, M. L.; White, H. F.; Oliver, H. S. W.; Colman, P. M.; Varghese, J. N.; Ryan, D. M.; Woods, J. M.; Bethell, R. C.; Hothman, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418.

[13] (a) Alper, J. *Science* **2001**, *291*, 2338. (b) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev*. **2000**, *100*, 4683. (c) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119.

[14] Butters, T. D.; Dwek, R. A.; Platt, F. M. *Curr. Top. Med. Chem*. **2003**, *3*, 561.

[15] Elbein, A. D.; Molyneux, R. D. Inbibitors of Glycoprotein Processing. In *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stütz, A. E. Wiley-VCH: Weinheim, 1998, pp 216.

[16] Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer R. *Drug Discovery Today* **2011**, *16*, 1359.

[17] Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953.

[18] Sorbera, L. A.; Castaner, J.; Garcia-Capdevila, L. *Drugs of the Future* **2005**, *30*, 545.

[19] Dwek, R. A.; Butters, T. D.; Platt, F. M.; Zitzmann, N. *Nat. Rev. Drug Discovery* **2002**, *1*, 65.

[20] For example, see: (a) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927. (b) Yoda, H.; Shimojo, T.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 1335. (c) Izquierdo, I.; Plaza, M. T.; Robles, R.; Franco, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2481. (d) Yoda, H. *Current Org. Chem.* **2002**, *6*, 223. (e) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1581. (f) Verma, S. K.; Atanes, M. N.; Busto, J. H.; Thai, D. L.; Rapoprt, H. *J. Org. Chem.* **2002**, *67*, 1314. (g) Davis, B. G.; Maughan, M. A. T.; Chapman, T. M.; Villard, R.; Courtney, S. *Org Lett.* **2002**, *4*, 1026. (h) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903. (i) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron: Asymmetry* **2004**, *15*, 1465. (j) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901. (k) Gautier-Lefebvre, I.; Behr, J.-B.; Guillerm, G.; Muzard, M. *Euro. J. Med. Chem.* **2005**, *40*, 1255. (l) García-Moreno, M. I.; Aguilar, M.; Ortiz Mellet, C.; García Fernández, J. M. *Org. Lett.* **2006**, *8*, 297. (m) Izquierdo, I.; Plaza, M. T.; Rodríguez, M.; Tamayo, J. A.; Martos, A. *Tetrahedron* **2006**, *62*, 2693. (n) Kumar, V.; Ramesh, N. G. *Tetrahedron* **2006**, *62*, 1877. (o) Izquierdo, I.; Plaza

M. T.; Yánez, V. *Tetrahedron* **2007**, *63*, 1440. (p) Doyagüez, E. G.; Calderon, F.; Sánchez, F.; Fernández-Mayoralas, A. *J. Org. Chem.* **2007**, *72*, 9353. (q) Vyavahare, V. P.; Chattopadhyay, S.; Puranik, V. G.; Dhavale, D. D. *Synlett* **2007**, 559. (r) Malle, B. M.; Lundt, I.; Wrodnigg, T. M. *Org. Biomol. Chem.* **2008**, *6*, 1779. (s) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929. (t) Blanco, O.; Pato, C.; Ruiz, M.; Ojea, V. *Org. Biomol. Chem.* **2008**, *6*, 3967. (u) Ayers, B. J.; Ngo, N.; Jenkinson, S. F.; Martínez, R. F.; Shimada, Y.; Adachi, I.; Weymouth-Wilson, A. C.; Kato, A.; Fleet, G. W. J. *J. Org. Chem.* **2012**, *77*, 7777.

[21] Welter, A.; Jadot, J.; Dardenne, G.; Marlier, M.; Casimir, J. *Phytochemistry* **1976**, *15*, 747.

[22] (a) Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 8146. (b) Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6280.

[23] Long, D. D.; Frederiksen, S. M.; Marquess, D. G.; Lane, A. L.; Watkin, D. J.; Winkler, D. A.; Fleet, G.W. J. *Tetrahedron Lett.* **1998**, *39*, 6091.

[24] Krulle, T. M.; Davis, B.; Ardron, H.; Long, D. D.; Hindle, N. A.; Smith, C.; Brown, D.; Lane, A. L.; Watkin, D. J.; Marquess, D. G.; Fleet, G. W. J. *Chem. Commun.* **1996**, *11*, 1271.

[25] For selected examples, see: (a) Kim, J. D.; Kim, I. S.; Hua, J. C.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2005**, *46*, 1079. (b) Jung, Y. H.; Kim, J. D. *Arch. Pharm. Res.* **2005**, *28*, 382. (c) Kim, J. D.; Zee, O. P.; Jung, Y. H. *J. Org. Chem.* **2003**, *68*, 3721. (d) Kim, J. D.; Han, G.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2003**, *44*, 733.

[26] Kim, I. S.; Kim, S.-J.; Lee, J. K.; Li, Q.-R; Jung, Y.-H. *Carbohydrate Res.* **2007**, *342*, 1502.

[27] Koto, S.; Morishima, N.; Miyata, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2639.

[28] (a) Donohoe, T. J.; Cheeseman, M. D.; O'Riordan, T. J. C.; Kershaw, J. A. *Org. Biomol. Chem*. **2008**, *6*, 3896. (b) Donohoe, T. J.; Rigby, C. L.; Thomas, R. E.; Nieuwenhuys, W. F.; Bhatti, F. L.; Cowley, A. R.; Bhalay, G.; Linney, I. D. *J. Org. Chem.* **2006**, *71*, 6298. (c) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, T. J. *Org. Lett*. **2003**, *5*, 999.

[29] Best, D.; Wang, C.; Weymouth-Wilson, A. C.; Clarkson, R. A.; Wilson, F. X.; Nash, R. J.; Miyauchi, S.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2010**, *21*, 311.

[30] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.

[31] Kondo, Y.; Suzuki, N.; Takahashi, M.; Kumamoto, T.; Masu, H.; Ishikawa, T. *J. Org. Chem.* **2012**, *77*, 7988.

[32] Aldehyde **36** was obtained from commercially available (*Z*)-1,4-dihydroxybut-2-ene in 76% yield over two steps (via treatment with TBDMSCl in THF followed by oxidative isomerisation with PCC).

[33] The corresponding *cis*-isomer was also isolated in 33% yield and 93:7 er.

[34] Singh, S.; Chikkanna, D.; Singh, O. V.; Han, H. *Synlett* **2003**, 1279.

[35] Singh, O. V.; Han, H. *Tetrahedron Lett.* **2003**, *44*, 2387.

[36] Singh, S.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 6349.

[37] The diastereoisomeric allylic alcohols were obtained in 88% total yield. Isolated yields for the separated diastereoisomers were not reported in the original publication; see: Ref. 36.

[38] Fellow, L. E.; Bell, E. A.; Lynn, D. G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1979**, 977.

[39] Asano, N.; Yamauchi, T.; Kagamifuchi, K.; Shimizu, N.; Takahashi, S.; Takatsuka, H.; Ikeda, K.; Kizu, H.; Chuakul, W.; Kettawan, A.; Okamoto, T. *J. Nat. Prod.* **2005**, *68*, 1238.

[40] Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841.

[41] Attempts to improve the reaction yield (i.e., by employing alternative bases, solvents, alkylating agents etc) proved unsuccessful.

[42] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

[43] Broxterman, H. J. G.; Neefjes, J. J.; Van der Marel, G. A.; Ploegh, H. L.; Van Boom, J. H. *J. Carbohydr. Chem.* **1988**, *7*, 593.

[44] Legler, G.; Jülich, E. *Carbohydr. Res.* **1984**, *128*, 61.

[45] Kim, I. S.; Lee, H. Y.; Jung, Y. H. *Heterocycles* **2007**, *71*, 1787.

[46] Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2005**, *7*, 4025.

[47] Isolated yields for diols **76** and **77** were not reported in the original publication; see: Ref. 45.

[48] Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 8133.

[49] Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2010**, *12*, 136.

[50] Allylic amine (–)-**85** was also obtained after preparative chiral HPLC in 13% yield, >99:1 dr and >99:1 er.

[51] Wrodnigg, T. M.; Diness, F.; Gruber, C.; Hausler, H.; Lundt, I.; Rupitz, K.; Steiner, A. J.; Stütz, A. E.; Tarling, C. A.; Withers, S. G.; Wolfler, H. *Bioorg. Med. Chem.* **2004**, *12*, 3485.

[52] Kappes, E.; Legler, G. *J. Carbohydr. Res.* **1989**, *8*, 371.

[53] Gradnig, G.; Legler, G.; Stutz, A. E. *Carbohydr. Res.* **1996**, *287*, 49.

[54] Tsou, E.-L.; Yeh, Y.-T.; Liang, P.-H.; Cheng, W.-C. *Tetrahedron* **2009**, *65*, 93.

[55] Barker, R.; Fletcher, H. G. *J. Org. Chem.* **1961**, *26*, 4605.

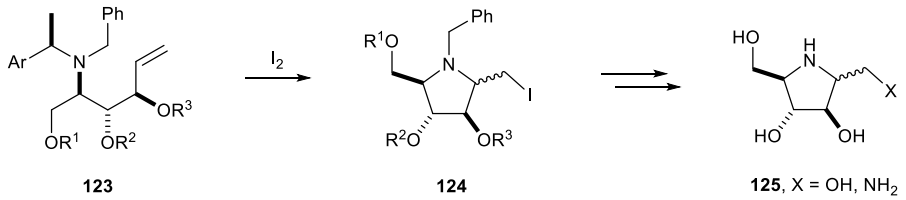
[56] Le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg. Med. Chem.* **1997**, *5*, 519.

[57] Jurczak, J.; Bauer, T.; Chmielewski, M. *Carbohydr. Res.* **1987**, *164*, 493.

[58] The corresponding azepane (which was formed via a 7-*endo*-*tet* process) was also isolated in 33% yield after column chromatography.

Chapter 2: Asymmetric Syntheses of (+)-DGDP and (+)-ADGDP via a Ring-Closing Iodoamination

This chapter describes investigations into the ring-closing iodoamination of bishomoallylic amines **123** in the synthesis of iodomethyl pyrrolidines **124** and their application in the asymmetric synthesis of pyrrolidine iminosugars and analogues **125** (Figure 6).

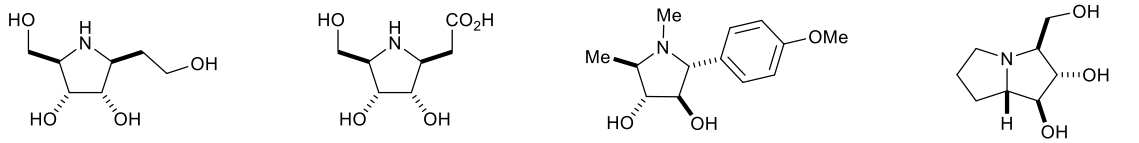


123 **124** **125**, X = OH, NH_2

Figure 6. Ring-closing iodoamination as a strategy to access pyrrolidine iminosugars and analogues **125**.

2.1. Iodoamination reactions

Davies *et al.* have previously reported a stereoselective iodine-mediated ring-closing iodoamination reaction of an unsaturated amine that proceeds with concomitant *N*-debenzylation to generate pyrrolidine and pyrrolizidine scaffolds. This methodology has been successfully employed in the asymmetric syntheses of polyhydroxylated pyrrolidines **126** and **127**,[1] the pyrrolidine alkaloid (−)-codonopsinine **128**[2] and the pyrrolizidine (−)-hyacinthacine A2 **129**[3] (Figure 7).

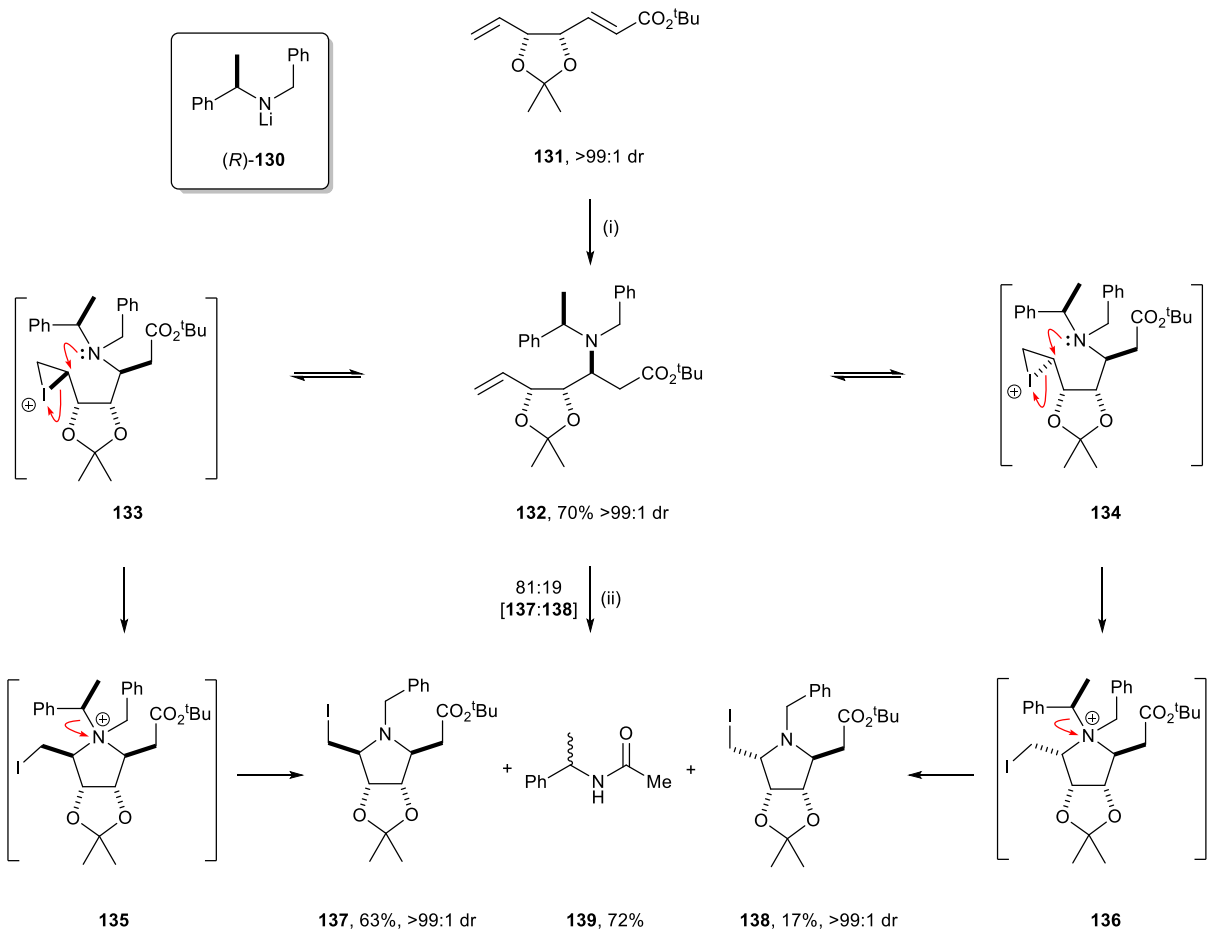


126 **127** (–)-codonopsinine **128** (–)-hyacinthacine A2 **129**

Figure 7. Polysubstituted nitrogen-containing heterocycles synthesised by Davies *et al.* using the iodoamination methodology.

These asymmetric syntheses also use Davies' diastereoselective conjugate addition of enantiopure secondary lithium amides to α,β-unsaturated esters for the synthesis of β-amino esters as a key step.[4] For example, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**130** to α,β-unsaturated ester **131** (which was synthesised in four steps and 45% overall yield from D-ribose) gave β-amino ester **132** in 70% yield and >99:1 dr.[5] Subsequent treatment of **132** with I_2 in MeCN in the presence of $NaHCO_3$ gave a chromatographically separable 81:19 mixture of iodomethyl pyrrolidines **137** and **138**, in 63 and 17% isolated yield, respectively, and as single diastereoisomers in each case (>99:1 dr),

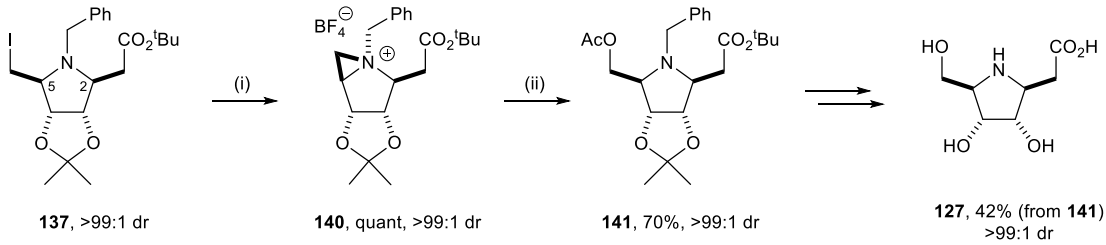
in addition to racemic α-methylbenzyl acetamide (*RS*)-**139**, which was isolated in 72% yield. The mechanism of this transformation was proposed to involve reversible formation of iodonium ions **133** and **134**, followed by preferential cyclisation of **133** to give ammonium **135**. Chemoselective S_N1-type loss of the *N*-α-methylbenzyl group (in preference to the *N*-benzyl group) from the sterically congested nitrogen atom within **135** gives the major diastereoisomer **137**. Presumably, the minor diastereoisomer **138** is formed from cyclisation of the epimeric iodonium intermediate **134**. Trapping of the α-methylbenzyl cation by MeCN and interception by H_2O in a Ritter reaction is consistent with the formation of **139** (Scheme 12).



Scheme 12. *Reagents and conditions:* (i) (*R*)-**130**, THF, −78 °C, 2 h, then satd aq NH_4Cl; (ii) I_2, $NaHCO_3$, MeCN, −20 °C to rt, 20 h.

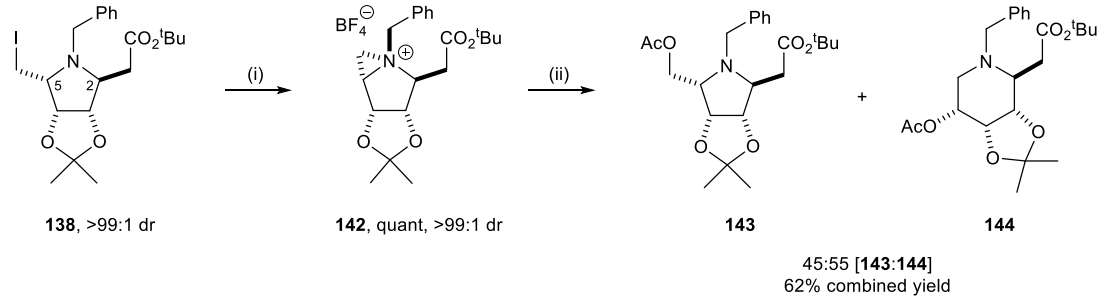
Elaboration of iodomethyl pyrrolidine scaffolds **137** and **138** to polyhydroxylated pyrrolidines, via functional group manipulation and deprotection, was also investigated. Treatment of 2,5-*cis*-iodomethyl pyrrolidine **137** with $AgBF_4$ gave the isolable aziridinium **140** in quantitative yield. Subsequent ring-opening of **140** upon treatment with NaOAc in PhMe proceeded with complete regioselectivity to give **141** in 70% yield and >99:1 dr.

Deprotection of **141** furnished polyhydroxylated pyrrolidine **127** in 42% overall yield from **141** (Scheme 13).



Scheme 13. *Reagents and conditions:* (i) $AgBF_4$, CH_2Cl_2, rt, 2 h; (ii) NaOAc, PhMe, rt, 2 h.

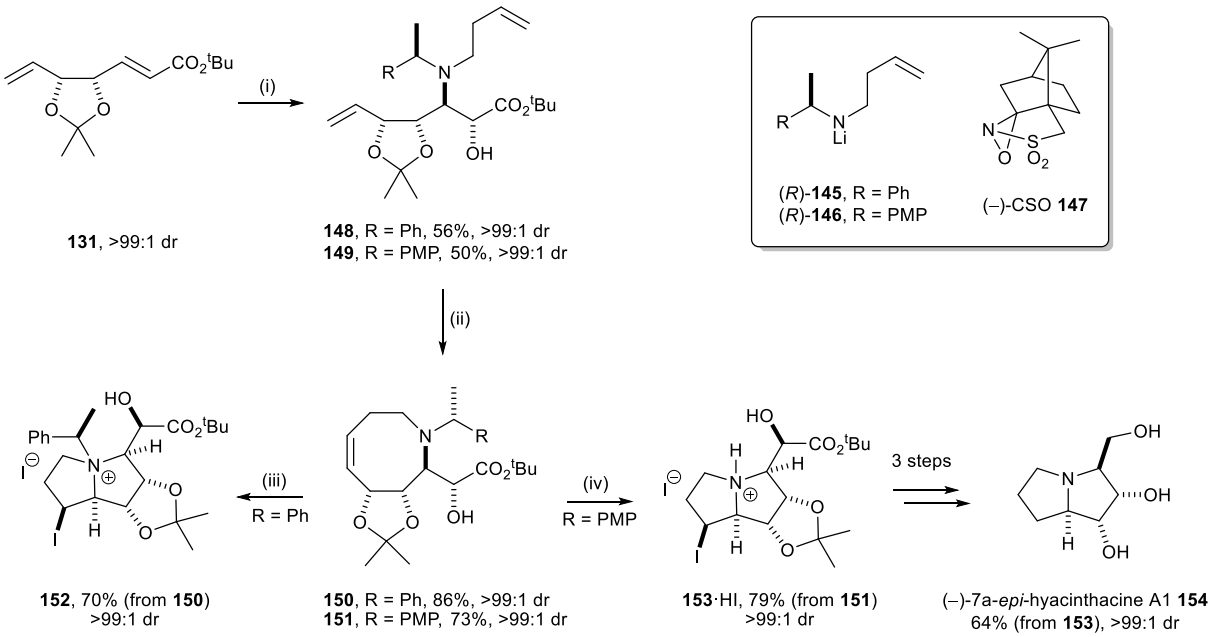
Similarly, treatment of the epimeric 2,5-*trans*-iodomethyl pyrrolidine **138** with $AgBF_4$ gave aziridinium **142** in quantitative yield. However, when aziridinium **142** was treated with NaOAc in PhMe, an inseparable 45:55 mixture of the pyrrolidine **143** and piperidine **144**, respectively, was obtained in 62% combined yield, indicating that the ring-opening of aziridinium **142** does not proceed in a regioselective manner. Mechanistic studies in the literature regarding the ring-opening of related aziridinium ions (i.e., [3.1.0] bicyclic systems) have shown that the regioselectivity of aziridinium ring-opening is highly dependent upon the nature of both the nucleophile[6] and solvent,[7] and that steric and electronic substituent effects[8] are involved in determining the reaction outcome (Scheme 14).



Scheme 14. *Reagents and conditions:* (i) $AgBF_4$, CH_2Cl_2, rt, 2 h; (ii) NaOAc, PhMe, rt, 2 h.

During the course of their studies on conjugate addition/iodoamination reactions, Davies *et al.* have noted that the nature of the *N*-protecting groups can have a dramatic effect on the reaction outcome.[2,9] For example, in the total synthesis of (−)-7a-*epi*-hyacinthacine A1 **154**, iodoamination of hexahydroazocines **150** and **151** were investigated in order to promote a transannular cyclisation with concomitant deprotection of either the *N*-α-methylbenzyl or *N*-(α-methyl-*p*-methoxy)benzyl groups to form the pyrrolizidine skeleton.[10] The doubly diastereoselective "matched"[11] conjugate addition of lithium (*R*)-*N*-(but-3-enyl)-*N*-(α-methylbenzyl)amide (*R*)-**145** and lithium (*R*)-*N*-(but-3-enyl)-*N*-(α-methyl-*p*-

methoxybenzyl)amide (*R*)-**146** to α,β-unsaturated ester **131**, followed by *in situ* oxidation of the intermediate lithium (*Z*)-β-amino enolate[12] with (−)-camphorsulfonyloxaziridine [(−)-CSO] **147**, gave α-hydroxy-β-amino esters **148** and **149**, in 56 and 50% yield, respectively, and >99:1 dr in each case. Subsequent ring-closing metatheses of **148** and **149** upon treatment with Grubbs I catalyst in CH_2Cl_2 resulted in the formation of hexahydroazocines **150** and **151** as single diastereoisomers (>99:1 dr), in 86 and 73% yield, respectively. Treatment of **150** with I_2 in $CHCl_3$ gave ammonium salt **152**, which was isolated in 70% yield and >99:1 dr. However, when hexahydroazocine **151** was submitted to iodoamination (under optimised conditions), cyclisation was accompanied by concomitant loss of the *N*-α-methyl-*p*-methoxybenzyl group to generate pyrrolizidine **153**, which was isolated as the corresponding hydroiodide salt, in 79% yield and >99:1 dr. This observation is supported by an increase in the stability of the carbocation (i.e., the α-methyl-*p*-methoxybenzyl cation is more stable than the α-methylbenzyl cation),[13] which promotes the desired *N*-debenzylation via an S_N1-type reaction pathway. Furthermore, it was discovered that use of CH_2Cl_2 stabilised by EtOH facilitated the purification of **153** as α-methyl-*p*-methoxybenzyl ethyl ether was produced as the sole side-product of the reaction (consistent with trapping of the α-methyl-*p*-methoxybenzyl cation by the EtOH stabilizer). Pyrrolizidine **153** was then elaborated to (−)-7a-*epi*-hyacinthacine A1 **154** in 64% overall yield over three steps (Scheme 15).[10]



Scheme 15. *Reagents and conditions:* (i) (*R*)-**145** or (*R*)-**146**, THF, −78 °C, 2 h then (−)-CSO **147**, −78 °C to rt, 12 h; (ii) Grubbs I catalyst (10 mol%), CH_2Cl_2, 30 °C, 12 h; (iii) I_2, $NaHCO_3$, $CHCl_3$, rt, 12 h; (iv) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h.

2.2. Chapter aims: proposed route to the pyrrolidine scaffold

Building on these investigations, it was anticipated that the ring-closing iodoamination methodology could be applied in the synthesis of polyhydroxylated pyrrolidines **119** and **120** using the iodine-mediated cyclisation of a bishomoallylic amine **116**, which was expected to proceed with concomitant *N*-debenzylation.[14] It was envisaged that the requisite bishomoallylic amines **116** required for this study could be readily prepared by aminohydroxylation of an α,β-unsaturated ester **113** followed by FGI of α-hydroxy-β-amino esters **114** and addition of vinylmagnesium bromide to the corresponding aldehydes **115**. Treatment of bishomoallylic amines **116** with I_2 was predicted to result in 5-exo cyclisation[15] with concomitant loss of the *N*-α-methylaryl protecting group to form the corresponding iodomethyl pyrrolidines **117**. Subsequent conversion of **117** to the corresponding aziridinium species **118**, followed by nucleophilic attack may result in ring-opening at the least hindered C(6) position[5] to furnish polysubstituted pyrrolidines **155**. This system could then undergo global deprotection to access polyhydroxylated pyrrolidine natural products and analogues **119** and **120** (Figure 8).

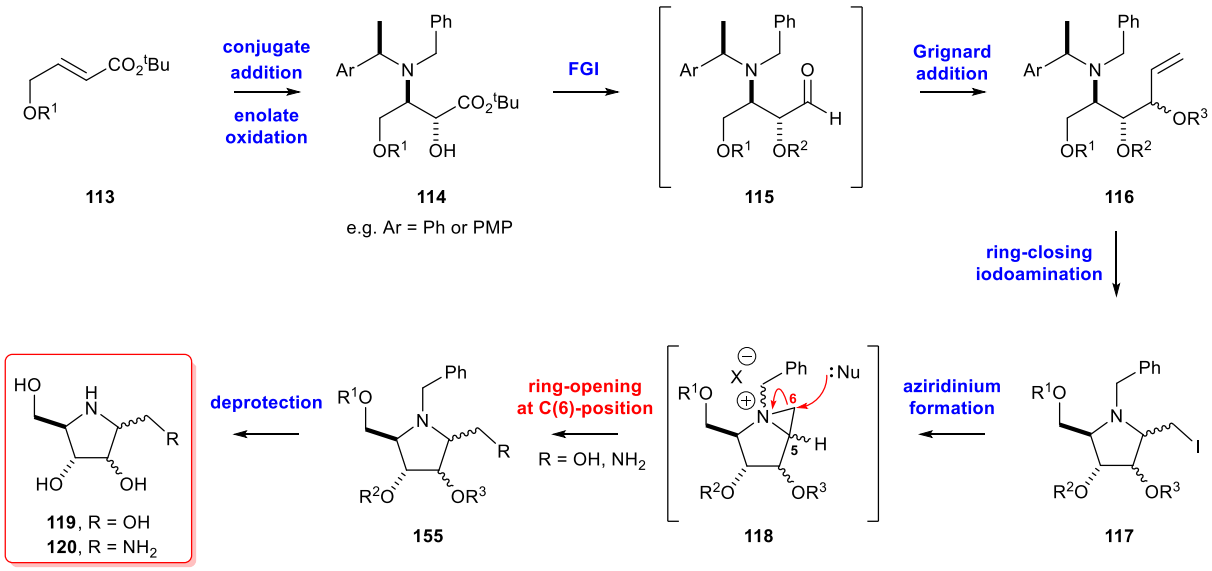
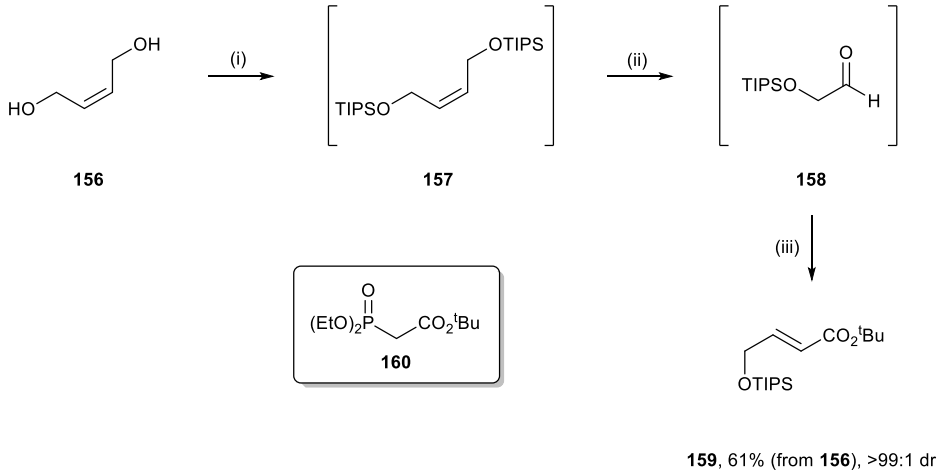


Figure 8. Proposed route to polyhydroxylated pyrrolidine natural products and analogues **119** and **120**.

2.3. Preparation of the requisite bishomoallylic amines

Previous investigations by Davies *et al.* have demonstrated that use of γ-silyloxy-α,β-unsaturated esters was compatible with the lithium amide conjugate addition methodology with *O*-TIPS as a protecting group showing more robustness or being higher yielding than *O*-TBDMS- or *O*-TBDPS-protected substrates when the corresponding α-hydroxy-β-amino esters were subjected to subsequent reductive steps.[16,17] The requisite α,β-unsaturated ester

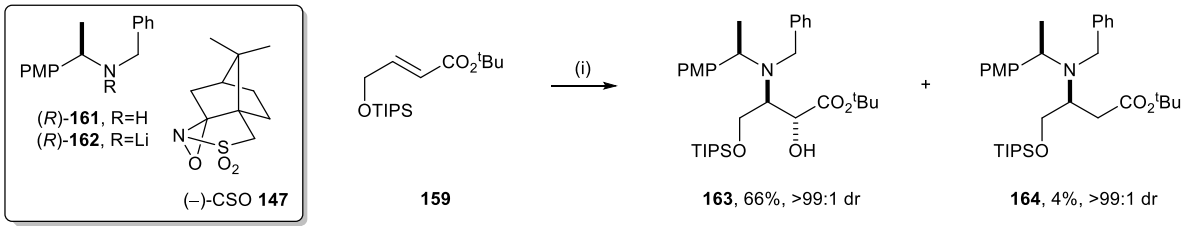
159 was thus prepared following the previously reported procedure.[16] Bis-*O*-protection of diol **156** was achieved by treatment with TIPSCl, imidazole and DMAP in CH_2Cl_2 to give **157**. Ozonolysis of **157** gave aldehyde **158**, which underwent a Masamune-Roush reaction[18] with *tert*-butyl diethylphosphonoacetate **160**, LiCl and Hünig's base to give **159** as a single diastereoisomer (>99:1 dr) in three steps and 61% overall yield from commercially available diol **156** (Scheme 16).



Scheme 16. *Reagents and conditions:* (i) TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 16 h; (ii) O_3, CH_2Cl_2, −78 °C, then DMS, −78 °C to rt, 16 h; (iii) **160**, LiCl, $^{i}Pr_2NEt$, MeCN, rt, 72 h.

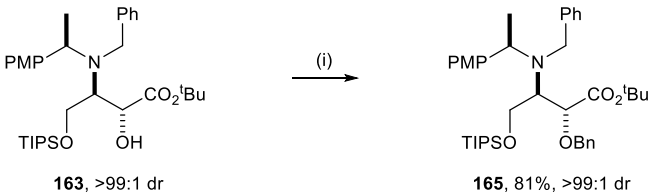
As previously mentioned in the synthesis of (−)-7a-*epi*-hyacinthacine A1 **154**, Davies *et al.* have developed a method for the *in situ* oxidation of lithium (*Z*)-β-amino enolates (formed from α,β-unsaturated esters upon conjugate addition of lithium amides) using CSO **147** as the oxidant, which results in the diastereoselective formation of an *anti*-α-hydroxy-β-amino ester.[12] In light of the aforementioned observations made on *N*-debenzylation during the iodoamination step,[10] conjugate addition of (*R*)-**162** to α,β-unsaturated ester **159** was first investigated. Although the stereochemical outcome in the oxidation procedure is usually under the dominant stereocontrol of the lithium (*Z*)-β-amino enolate (i.e., the substrate), with the formation of the corresponding *anti*-α-hydroxy-β-amino ester being favoured, a slight dependency on the configuration of CSO **147** (i.e., the reagent) is observed.[19] Lithium amide (*R*)-**162** is conventionally paired with (−)-CSO **147**, whilst (*S*)-**162** is paired with (+)-CSO **147**, upon conjugate addition to achiral α,β-unsaturated esters.[12] Following this precedent, conjugate addition of 2.0 equiv[20] of (*R*)-**162**[21] to α,β-unsaturated ester **159** in THF at −78 °C followed by treatment with (−)-CSO **147**[22] gave α-hydroxy-β-amino ester **163** in 66% yield and >99:1 dr, and β-amino ester **164** in 4% yield and >99:1 dr, after chromatographic

separation (Scheme 17). The configuration of the newly formed C(3)-stereogenic centre within **163** and **164** was initially assigned by reference to the transition state mnemonic of Davies *et al.* that has been used to rationalise and reliably predict the stereochemical outcome of this class of conjugate addition reaction.[23] In addition, the relative *anti*-configuration of the C(2)- and C(3)-stereogenic centres within **163** was assigned by reference to the well-established stereochemical outcome of this aminohydroxylation process.[24] This procedure could reliably be used for the production of **163** in >10 g batches.



Scheme 17. *Reagents and conditions:* (i) (*R*)-**161**, BuLi, THF, −78 °C, 2 h then (−)-CSO **147**, −78 °C to rt, 16 h.

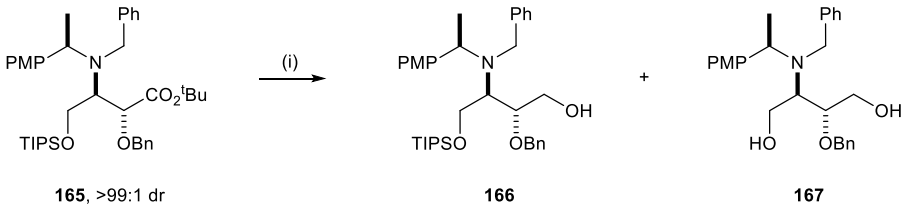
The free hydroxyl moiety within **163** was subsequently protected with an *O*-benzyl group, as attempted *O*-silyl protection of a similar system had proven unsuccessful.[17] Treatment of **163** with NaH, 15-crown-5 and BnBr delivered α-benzyloxy-β-amino ester **165** in 81% yield and >99:1 dr (Scheme 18).



Scheme 18. *Reagents and conditions:* (i) NaH, THF, 0 °C to rt, 1 h, then BnBr, 15-crown-5, rt, 16 h.

Subsequent reduction of **165** to the corresponding primary alcohol **166** was investigated next. Treatment of **165** with $LiAlH_4$ (2.0 equiv) in THF at 0 °C resulted in reduction of the ester and concomitant desilylation, giving a 46:54 mixture of **166** and **167**, respectively, which were isolated as single diastereoisomers in 29 and 36% yield, after chromatographic purification. The use of DIBAL-H to effect reduction of the ester without promoting desilylation was next probed.[16a] However, treatment of **165** with DIBAL-H (2.0 equiv) in THF at 0 °C returned starting material and repetition of the reaction using DIBAL-H (2.0 equiv) in CH_2Cl_2 gave a 40:60 mixture of starting material **165** and alcohol **166**. Increasing the number of equivalents of DIBAL-H (to 4.0 equiv) resulted in full reduction of **165** but some desilylation was also observed after 4 h; thus it was envisaged to perform the addition of

DIBAL-H at −78 °C. Treatment of **165** with DIBAL-H (4.0 equiv) in CH_2Cl_2 at −78 °C (allowing the reaction to slowly warm to rt)[25] gave a 98:2 mixture of **166** and **167**, respectively, from which alcohol **166** was isolated in 98% yield and >99:1 dr, after chromatographic purification (Scheme 19).

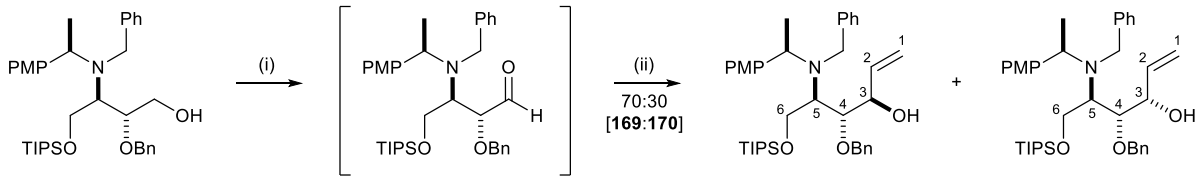


165, >99:1 dr **166** **167**

reducing agent	solvent	equiv of reducing agent	temperature	time (h)	crude ratio [165:166:167]	isolated yield of 166 [% (dr)]	isolated yield of 167 [% (dr)]
$LiAlH_4$	THF	2	0 °C to rt	16	0:46:54	29 (>99:1)	36 (>99:1)
DIBAL-H	THF	2	0 °C to rt	16	100:0:0	-	-
DIBAL-H	CH_2Cl_2	2	0 °C to rt	16	40:60:0	-	-
DIBAL-H	CH_2Cl_2	4	0 °C to rt	4	0:73:27	-	-
DIBAL-H	CH_2Cl_2	4	–78 °C to rt	2	0:98:2	98 (>99:1)	-

Scheme 19. *Reagents and conditions:* (i) $LiAlH_4$ or DIBAL-H (1.0 M in solvent), see table.

With this substrate in hand, attention was next turned to the preparation of bishomollylic amines **169** and **170**. Oxidation of **166** under Swern conditions, followed by treatment of the intermediate aldehyde **168** with commercially available vinylmagnesium bromide gave a 70:30 mixture of the diastereoisomeric bishomoallylic amines **169** and **170**.[26] Chromatographic purification delivered **169** in 55% yield and >99:1 dr (i.e., 29% overall yield from α,β-unsaturated ester **159**) and **170** in 5% yield and >99:1 dr (i.e., 3% overall yield from α,β-unsaturated ester **159**) (Scheme 20). Attempts to obtain crystalline salts of **169** and **170** (in order to perform single crystal X-ray diffraction analysis) were unsuccessful; therefore the configurations of **169** and **170** were tentatively assigned by analogy to the outcome of the addition of vinylmagnesium bromide to a closely related substrate (being an *N*-α-methylbenzyl group rather than an *N*-α-methyl-*p*-methoxybenzyl group) and these assignments were supported by ^{1}H NMR ^3J coupling constant analyses between the C(3)*H* and C(4)*H* protons (*vide infra*).



166, >99:1 dr **168**, >99:1 dr **169**, 55%, >99:1 dr 29% (from **159**, 5 steps) **170**, 5%, >99:1 dr 3% (from **159**, 5 steps)

Scheme 20. *Reagents and conditions:* (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 40 min, then Et_3N, −78 °C to rt, 1 h; (ii) CH_2=CHMgBr, THF, 0 °C to rt, 16 h.

The stereochemical outcome of this Grignard addition can be rationalised using Felkin-Anh models. In a first model, where the *O*-benzyl group acts as the "large" group on stereoelectronic grounds, the favoured pathway for nucleophilic attack occurs on the substrate in conformation **171A**, as this results in the least hindered trajectory for the nucleophile, to give **170**. However, when chelation with magnesium[27] is involved, attack of **171B** along the least hindered pathway leads to **169** being favoured. Therefore, the incomplete diastereocontrol observed in the Grignard addition in favour of bishomoallylic amine **169**, is indicative of chelation playing a major but not completely dominant role in this reaction (Figure 9).

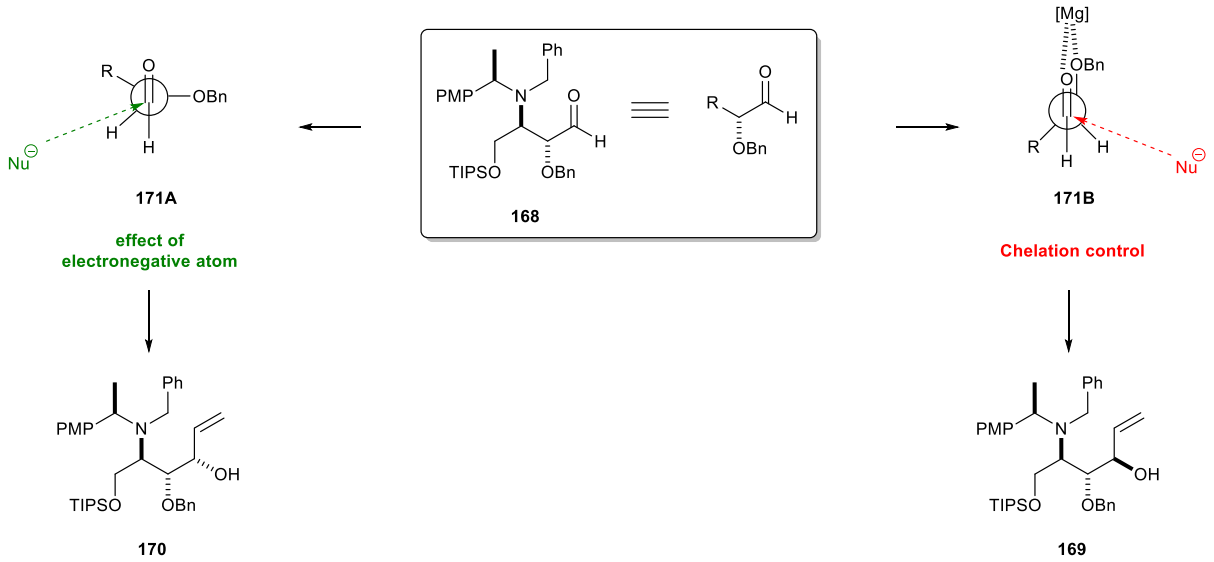
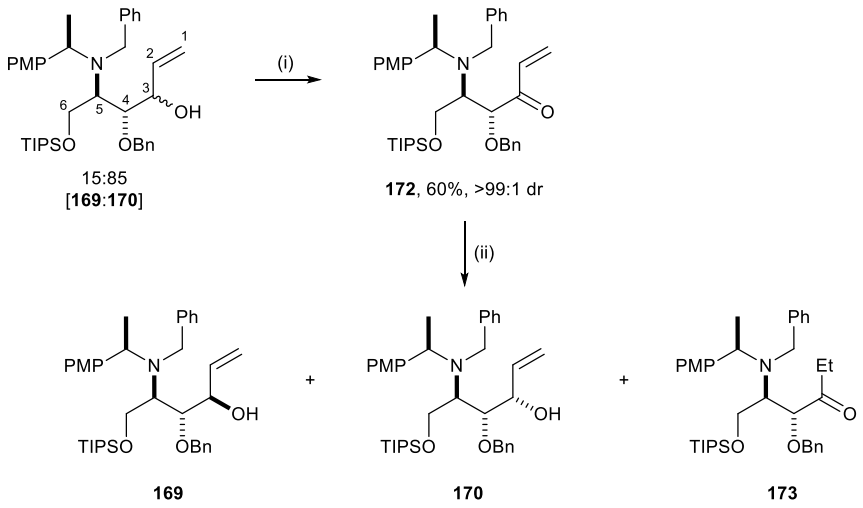


Figure 9. Felkin-Anh models to rationalise the diastereoselectivity in the addition of vinylmagnesium bromide to **168**.

Following these observations, an alternative route to bishomoallylic amines **169** or **170** involving a chemo- and diastereoselective reduction of enone **172** was investigated. In order to ascertain its synthetic utility, enone **172** was first prepared by oxidation of a 15:85 diastereoisomeric mixture of bishomoallylic amines **169** and **170** (which was obtained as a fraction upon purification of **169** and **170** by flash column chromatography) using IBX in DMSO:[17] this furnished **172** in 60% yield and >99:1 dr; thereby proving that **169** and **170** are epimers at the C(3)-stereogenic centre. A range of reducing agents, solvents, reaction times and reaction temperatures were investigated in the hope of favouring a chelation controlled pathway which could provide a diastereoisomerically pure sample of **169** or **170**. Treatment of enone **172** with DIBAL-H in THF,[28] returned starting material. Similarly, the use of $NaBH(OAc)_3$ or $LiAl(O^tBu)_3H$ failed to effect reduction of **172**, and starting material **172** was

recovered in both cases. Enone **172** was next subjected to Luche reduction conditions using $NaBH_4$ and $CeCl_3$ in MeOH, which proceeded with essentially a complete reversal of the Grignard diastereoselective outcome (i.e., 37:63 mixture of **169** and **170**, respectively). In addition, Evans *et al.* have reported a procedure for the chemo- and diastereoselective reduction of enones to the corresponding unsaturated alcohols using $Zn(BH_4)_2$ in THF.[29] Treatment of **172** with $Zn(BH_4)_2$ (prepared with $NaBH_4$ and $ZnCl_2$ using a literature procedure)[30] in THF at −20 °C resulted in the sole formation of ketone **173**. Repetition of the reaction at −78 °C for 3 h returned starting material; thus the reaction was next performed at −50 °C, however ketone **173** was observed in the crude reaction mixture after 15 min with no evidence of bishomoallylic amines **169** or **170** being formed (Scheme 21). Following these results, this route was abandoned and the Grignard addition to aldehyde **168** was chosen as the preferred strategy for the production of bishomoallylic amines **169** and **170** on multigram scales.



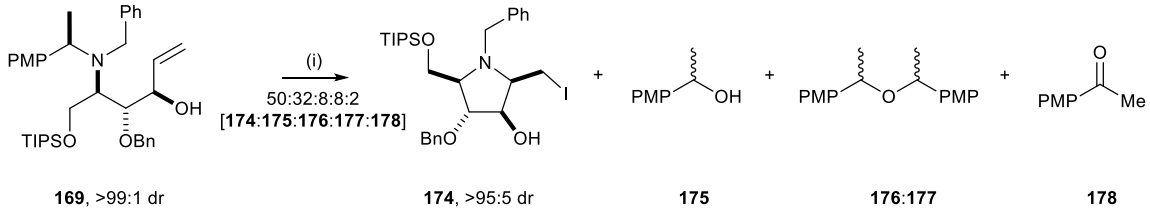
reducing agent	solvent	temperature	time	conversion (%)	crude ratio [169:170:173]
DIBAL-H	THF	–78 °C to rt	16 h	0	-
$NaBH(OAc)_3$	MeOH	–20 °C to rt	16 h	0	-
$LiAl(O^tBu)_3H$	THF	–78 °C to rt	16 h	0	-
$NaBH_4$, $CeCl_3$	MeOH	0 °C to rt	16 h	100	37:63:0
$Zn(BH_4)_2$	THF	–20 °C	16 h	100	0:0:100
$Zn(BH_4)_2$	THF	–78 °C	3 h	0	-
$Zn(BH_4)_2$	THF	–50 °C	15 min	14	0:0:100

Scheme 21. *Reagents and conditions:* (i) IBX, DMSO, rt, 16 h; (ii) see table.

2.4. Iodoamination of bishomoallylic amines

Initially, the iodoamination of bishomoallylic amine **169** (i.e., the major product of the vinylmagnesium bromide addition to aldehyde **168**) was attempted under the conditions previously reported by Davies *et al.* in their investigations into the synthesis of pyrrolidine

scaffolds:[5] treatment of **169** with 3.0 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in MeCN at −20 °C resulted in the formation of iodomethyl pyrrolidine **174** (>95:5 dr), plus various other species, which were identified as alcohol **175**,[31] ethers (*RS*,*RS*)-**176** and (*RS*,*SR*)-**177**,[32] (presumably derived from the intermediate α-methyl-*p*-methoxybenzyl cation formed in the anticipated *N*-debenzylation step) and ketone **178**.[33] In addition, upon integration of the ^{1}H NMR spectrum of the crude reaction mixture, it was apparent that iodomethyl pyrrolidine **174** and the total sum of the PMP-containing species were obtained in a 50:50 ratio. Attempts to isolate an analytically pure sample of **174** proved unsuccessful by column chromatography; however an impure fraction of **174** (which contained **176**, **177** and **178**) could be used to tentatively assign the relative configuration within **174** (Scheme 22).



Scheme 22. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, −20 °C to rt, 20 h.

Davies *et al.* have previously reported that the chemical shift of the carbon directly bonded to iodine in the ^{13}C NMR spectrum of iodomethyl pyrrolidine products is diagnostic of their relative configuration.[5b] For example, for pyrrolidines **179** in which the iodomethyl group at C(2) and the *O*-protected substituent at C(3) have a *cis*-relationship, the signal appears at between 1.9 and 3.2 ppm, while for pyrrolidines **180**, in which the two groups have a *trans*-relationship, the signal appears at between 10.1 and 11.4 ppm. The chemical shift of ICH_2 in iodomethyl pyrrolidine **174** was observed at 3.4 ppm, suggesting a *cis*-relationship between the C(4) and C(5) substituents (Figure 10). These observations are also consistent with ^{13}C NMR spectral data reported in the literature by Yoshida *et al.* in related systems.[34] The relative configuration within **174** assigned herein was later supported by ^{1}H NMR nOe analysis of a pure sample (*vide infra*).

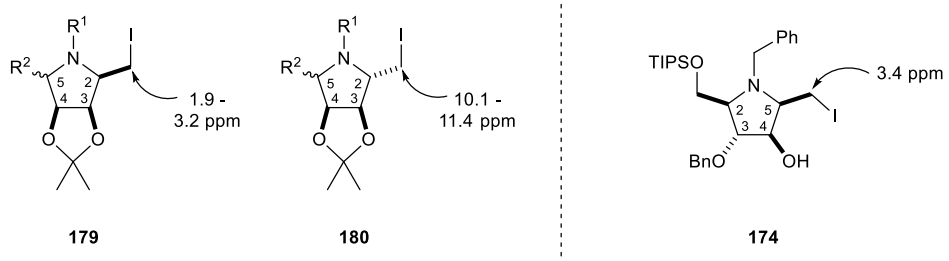
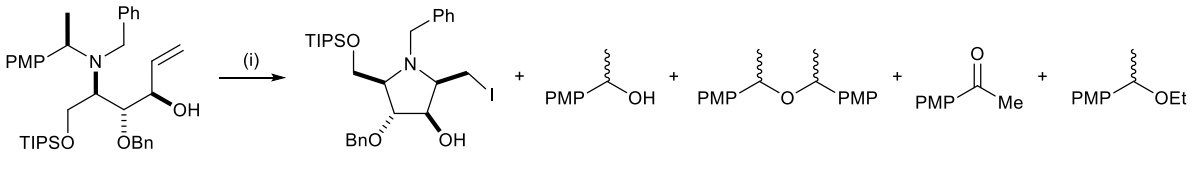


Figure 10. Diagnostic ^{13}C NMR chemical shifts for iodomethyl pyrrolidines.

In light of these results, it was decided to investigate if an alternative solvent system in which the iodoamination could be carried out would enable efficient scavenging of the α-methyl-*p*-methoxybenzyl cation to give a sole PMP-containing by-product, and consequently facilitate the purification of iodomethyl pyrrolidine **174**. In their aforementioned synthesis of pyrrolizidine scaffolds via an iodoamination strategy, Davies *et al.* have efficiently scavenged the α-methyl-*p*-methoxybenzyl cation by EtOH (present as the stabilizer within the CH_2Cl_2 solvent) to give α-methyl-*p*-methoxybenzyl ether **181**, which was readily separated from the desired pyrrolizidine product by crystallisation: ether **181** remained in the mother liquor.[35] Thus, treatment of **169** with I_2 and $NaHCO_3$ in CH_2Cl_2 (EtOH stabilised) resulted in the formation of two PMP-containing species (ether **181**[36] and ketone **178**); however the conversion to iodomethyl pyrrolidine **174** appeared to be low using this solvent system. In fact, although the ^{1}H NMR spectrum of the crude reaction mixture was found to be extremely complex (thus rendering the quantitative analysis of the reaction mixture problematic), starting material could be clearly observed. Employing CH_2Cl_2 as the solvent of the reaction was discarded and attention next turned to the use of MeCN in combination with EtOH. Repetition of the reaction in MeCN at −20 °C in the presence of 3.0 equiv of EtOH resulted in the formation of **174**, together with ether **181**, alcohol **175** and ketone **178**. Unfortunately, attempts to isolate **174** were again unsuccessful. In addition, it was also proposed to vary the temperature of the original iodoamination conditions[5] to assess its effect on the outcome of the reaction. Treatment of **169** in MeCN at rt gave a similar mixture of **174** and the various PMP-containing species (i.e., **175**, **176**, **177** and **178**) to when the reaction was performed at −20 °C; therefore, all subsequent attempts at iodoamination reactions were performed at rt (Scheme 23).

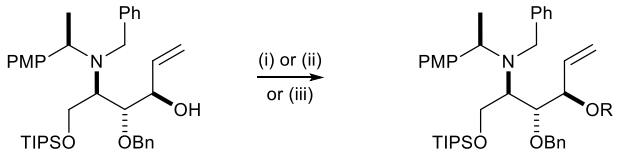


169, >99:1 dr | **174**, >95:5 dr | **175** | **176**:**177** | **178** | **181**

solvent	conditions	PMP-containing species observed in the ^{1}H NMR spectrum of the crude reaction mixture
CH_2Cl_2 (EtOH stabilised)	rt, 16 h	**181** (major) and **178**
MeCN, EtOH	–20 °C to rt, 16 h	**181** (major), **175** and **178**
MeCN	rt, 16 h	**175** (major), **176**, **177** and **178**

Scheme 23. *Reagents and conditions:* (i) I_2, $NaHCO_3$, see table for solvent and conditions.

It was next envisaged that a globally protected pyrrolidine would show a significant difference in polarity compared to **174**, thus making it more amenable to purification. Therefore, *O*-protection of **169** was investigated in order to subject the corresponding bishomoallylic amines to the iodoamination conditions. While attempts to protect **169** with either *O*-TIPS or *O*-MOM groups showed no or low conversion to products **182** and **183**, treatment of **169** with NaH and BnBr gave 88% conversion to bishomoallylic amine **184**, and chromatographic purification furnished **184** in 60% yield and >99:1 dr (Scheme 24).



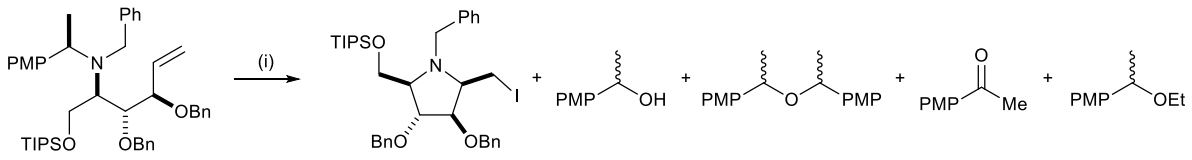
169, >99:1 dr

182, R = TIPS
183, R = MOM
184, R = Bn, 60%

R	conditions	conversion (%)	isolated yield (%)
TIPS	(i)	0	-
MOM	(ii)	35	-
Bn	(iii)	88	60

Scheme 24. *Reagents and conditions:* (i) TIPSCl, imidazole, DMAP, rt, 16 h; (ii) MOMCl, DIPEA, CH_2Cl_2, rt, 16 h; (iii) NaH, THF, 0 °C to rt, 1 h, then BnBr, 15-crown-5, rt, 16 h.

Iodoamination of **184** in MeCN at rt resulted in the formation of the corresponding pyrrolidine **185**, together with alcohol **175**, ethers **176** and **177**, and ketone **178**. The ^{1}H NMR spectrum of the crude reaction mixture was again complex and a significant amount of starting material was observed. Although chromatographic purification proved successful in this case, pyrrolidine **185** was only obtained in 6% isolated yield. Repetition of the reaction in CH_2Cl_2 (EtOH stabilised) returned mainly starting material with only traces of pyrrolidine **185** present, as determined from inspection of the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 25).



184, >99:1 dr

185, >95:5 dr

175

176:**177**

178

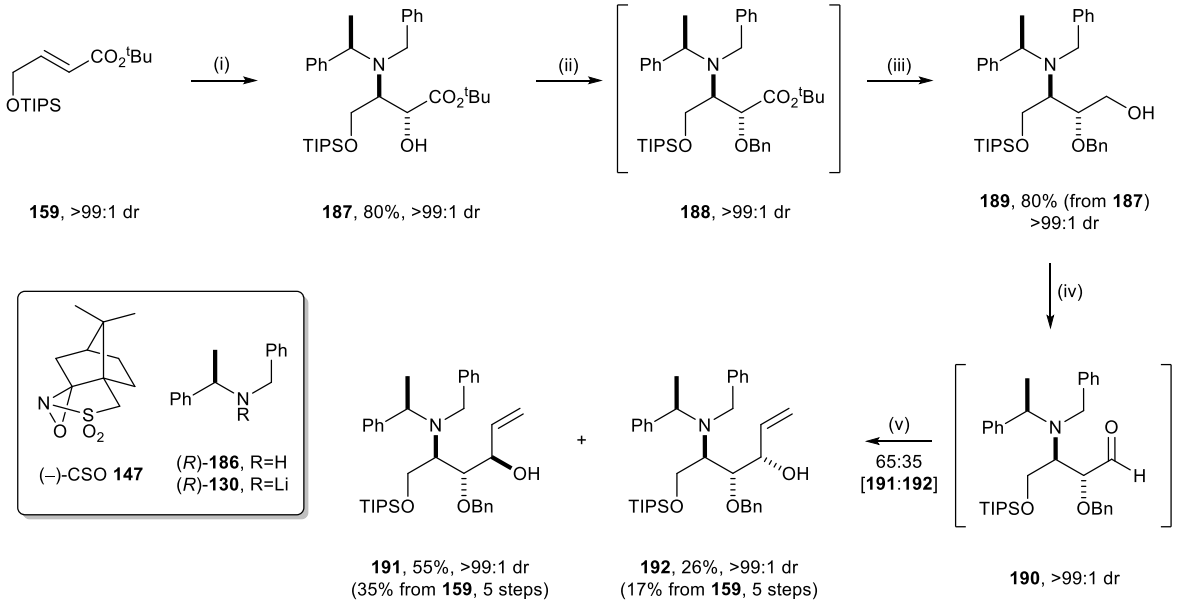
181

solvent	PMP-containing species observed in the ^{1}H NMR spectrum of the crude reaction mixture	isolated yield of 185 (%)
MeCN	**175** (major), **176**, **177** and **178**	6
CH_2Cl_2 (EtOH stabilised)	**181** (major), **175** and **178**	-

Scheme 25. *Reagents and conditions:* (i) I_2, $NaHCO_3$, solvent (see table), rt, 16 h.

2.5. Alternative *N*-protecting groups: preparation of *N*-benzyl-*N*-α-methylbenzyl protected bishomoallylic amines

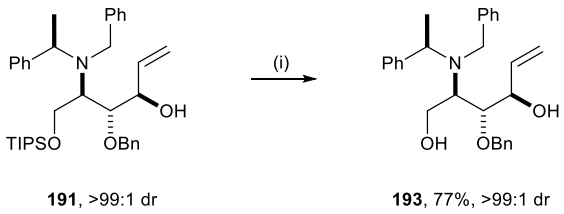
The formation of the various PMP-containing species during the iodoamination of **169** rendered **174** unamenable to purification; thus attention was turned to the iodoamination of the corresponding *N*-benzyl-*N*-α-methylbenzyl protected bishomoallylic amine **191**. The synthesis of **191** was achieved using the optimised conditions developed for the synthesis of bishomoallylic amine **169**. Conjugate addition of lithium amide (*R*)-**130**[37] to α,β-unsaturated ester **159** followed by *in situ* enolate oxidation with (−)-CSO **147** gave the known α-hydroxy-β-amino ester **187**[38] in 80% yield and >99:1 dr. Treatment of **187** with NaH and BnBr furnished **188** and subsequent reduction of the ester moiety within **188** using DIBAL-H at −78 °C gave alcohol **189** in 80% overall yield (from **187**) and >99:1 dr. Oxidation of the primary hydroxyl functionality within **189** under Swern conditions followed by treatment of the resultant aldehyde **190** with vinylmagnesium bromide gave a 65:35 mixture of bishomoallylic amines **191** and **192**, respectively.[26] Chromatographic purification of the crude reaction mixture delivered **191** in 55% yield (35% overall yield from **159**) and **192** in 26% yield (17% overall yield from **159**), as single diastereoisomers (>99:1 dr) in each case (Scheme 26).



Scheme 26. *Reagents and conditions:* (i) (*R*)-**186**, BuLi, THF, −78 °C, 2 h then (−)-CSO **147**, −78 °C to rt, 16 h; (ii) NaH, THF, 0 °C to rt, 1 h, then BnBr, 15-crown-5, rt, 16 h; (iii) DIBAL-H, −78 °C to rt, 2 h; (iv) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 40 min, then Et_3N, −78 °C to rt, 1 h; (v) CH_2=CHMgBr, THF, 0 °C to rt, 16 h.

Deprotection of the *O*-silyl group within the major diastereoisomer **191** was achieved using TBAF in THF, and gave diol **193** in 77% yield and >99:1 dr (Scheme 27). The relative

configuration within **193** was unambiguously established by single crystal X-ray diffraction analysis,[39] with the absolute (*R*,*R*,*R*,*R*)-configuration within **193** being assigned from the known (*R*)-configuration of the *N*-α-methylbenzyl fragment (Figure 11). This analysis also unambiguously established the absolute configurations within the synthetic precursors **187**−**191** and the epimeric bishomoallylic amine **192**.



191, >99:1 dr **193**, 77%, >99:1 dr

Scheme 27. *Reagents and conditions:* (i) TBAF, THF, 0 °C to rt, 16 h.

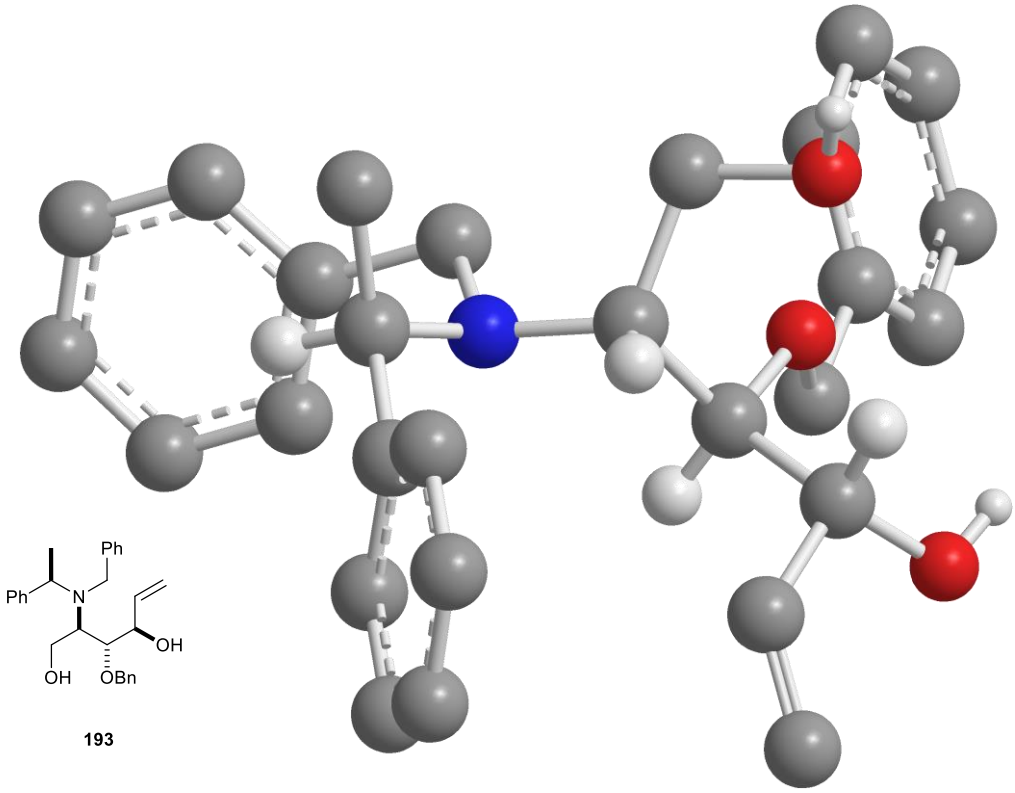


Figure 11. X-Ray crystal structure of (*R*,*R*,*R*,*R*)-**193** (selected H atoms have been omitted for clarity).

In addition, the configurations of the *N*-α-methyl-*p*-methoxybenzyl analogues **169** and **170** were supported by ^{1}H NMR ^{3}J coupling constant analyses. A comparison of the two sets of ^{1}H NMR $^{3}J_{3,4}$ coupling constants for **191** and **169** (major products) and for **192** and **170** (minor products) showed diagnostic values for both the major and the minor diastereoisomers. A $^{3}J_{3,4}$ value of 2.3 Hz was observed between the C(3)*H* and C(4)*H* protons for bishomoallylic amine **191**, while a $^{3}J_{3,4}$ value of 2.4 Hz was distinguished for bishomoallylic amine **169**. Similarly, the ^{1}H NMR spectrum of the minor diastereoisomer **192** showed a $^{3}J_{3,4}$

value of 4.4 Hz, while the ^{1}H NMR spectrum of **170** displayed a $^3J_{3,4}$ value of 4.8 Hz (Figure 12).

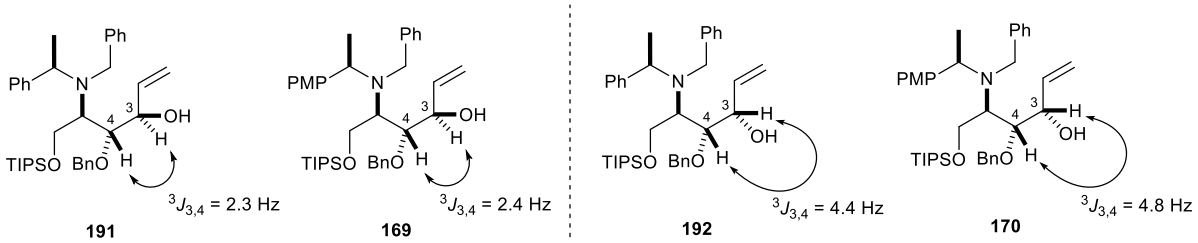
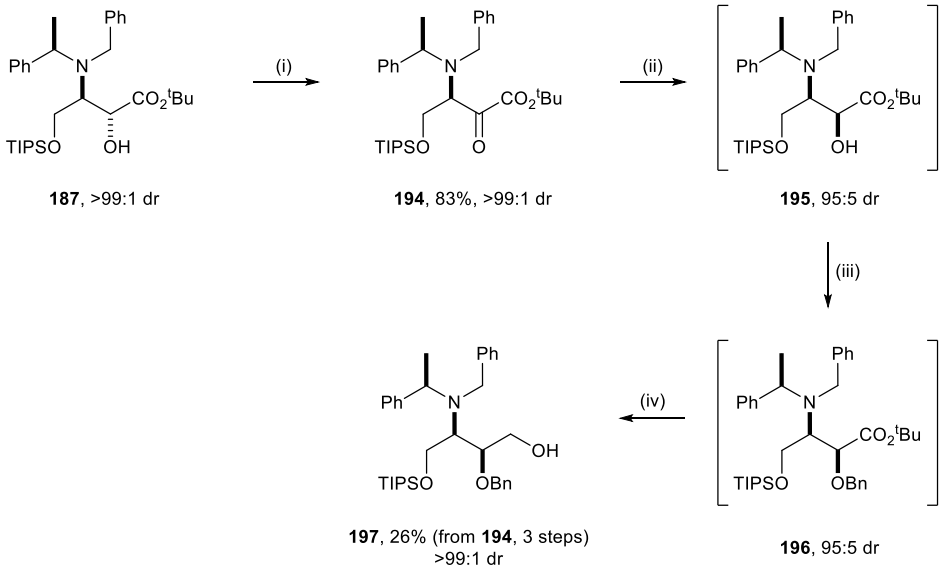


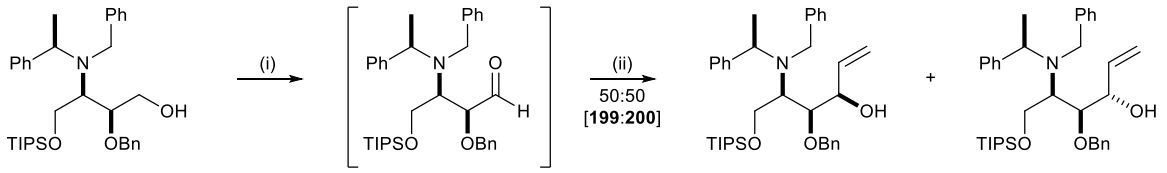
Figure 12. ^{1}H NMR $^3J_{3,4}$ coupling constant correlations between bishomoallylic amines **191** and **169**, and **192** and **170**.

The synthesis of the C(2)-epimeric alcohol **197** was next investigated, in the hope that the addition of vinylmagnesium bromide to the corresponding aldehyde would proceed with superior diastereoselectivity. Following an established procedure,[40] oxidation of the hydroxyl moiety within **187** under Swern conditions gave ketone **194** in 83% yield and >99:1 dr. Subsequent treatment of **194** with $NaBH_4$ at −20 °C resulted in the diastereoselective reduction of the ketone group to give α-hydroxy ester **195** in 95:5 dr. *O*-Benzyl protection of **195**, followed by reduction of the ester moiety within **196** furnished primary alcohol **197** in 26% overall yield (in three steps from **194**) and >99:1 dr, after chromatographic purification (Scheme 28).



Scheme 28. *Reagents and conditions:* (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 40 min, then Et_3N, −78 °C to rt, 1 h; (ii) $NaBH_4$, MeOH, −20 °C, 2 h; (iii) NaH, THF, 0 °C to rt, 1 h, then BnBr, 15-crown-5, rt, 16 h; (iv) DIBAL-H, −78 °C to rt, 2 h.

Unfortunately, oxidation of **197** under Swern conditions followed by reaction of the corresponding aldehyde **198** with vinylmagnesium bromide gave a 50:50 mixture of bishomoallylic amines **199** and **200** (Scheme 29). Following this result, the route employing the C(2)-epimer **197** was abandoned and **191** was next chosen to assess the iodoamination reaction of *N*-benzyl-*N*-α-methylbenzyl protected bishomoallylic amines.



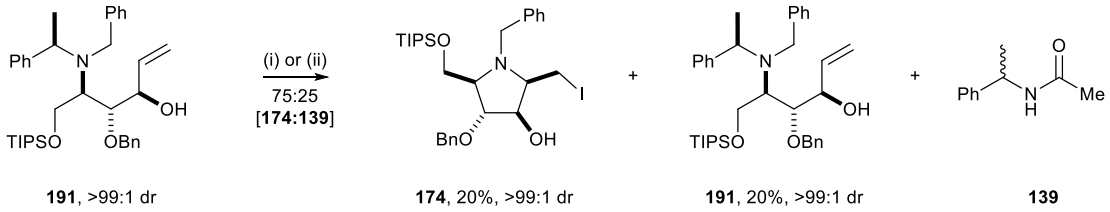
197, >99:1 dr **198**, >99:1 dr **199** **200**

Scheme 29. *Reagents and conditions:* (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 40 min, then Et_3N, −78 °C to rt, 1 h; (ii) CH_2=CHMgBr, THF, 0 °C to rt, 16 h.

2.6. Iodoamination of *N*-benzyl-*N*-α-methylbenzyl protected bishomoallylic amine

Under the previously optimised conditions (developed for *N*-benzyl-*N*-α-methyl-*p*-methoxybenzyl protected bishomoallylic amine **169**), treatment of **191** with 3.0 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in MeCN at rt gave a 75:25 mixture of iodomethyl pyrrolidine **174** and *N*-α-methylbenzyl acetamide **139**[5] as the sole species derived from the α-methylbenzyl cation resulting from a Ritter-type reaction. After chromatographic purification of the crude reaction mixture, iodomethyl pyrrolidine **174** was isolated in 20% yield and >99:1 dr. Surprisingly, bishomoallylic amine **191** was also recovered after purification in 20% yield, while no evidence of **191** could be gleaned from the ^{1}H NMR spectrum of the crude reaction mixture (in $CDCl_3$). Attempts to leave the reaction running for longer (~24 h) also resulted in the isolation of iodomethyl pyrrolidine **174** in 20% yield (Scheme 30). Investigations into the recovery of starting material were initiated next. It was envisaged that the formation of ammonium salts of **191** under the reaction conditions could be responsible for the recovery of **191** after column chromatography. Thus, in an attempt to provide some evidence of the presence of ammonium salts in the crude reaction mixture, the ^{1}H NMR spectrum of the reaction mixture was recorded at several intervals over a period of 16 h. As the reaction progressed, diagnostic peaks corresponding to iodomethyl pyrrolidine **174** were observed, however the 4.5−6.5 ppm region (diagnostic of unsaturated compounds) remained complex after 16 h (in $CDCl_3$). Work-up of the reaction mixture with $Na_2S_2O_3$ resolved the complex mixture into a clean ^{1}H NMR spectrum devoid of any resonances in the olefinic region.

In addition, the ^{1}H NMR spectrum of the crude reaction mixture in MeOH-d_4 was even more complex. Based on these data, it was hypothesised that an unidentified ammonium species was responsible for the isolation of starting material after purification.



191, >99:1 dr **174**, 20%, >99:1 dr **191**, 20%, >99:1 dr **139**

Scheme 30. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) I_2, $NaHCO_3$, MeCN, rt, 24 h.

The relative configuration within **174**, which had already been tentatively assigned (*vide supra*), was next supported by ^{1}H NMR nOe analysis of this analytically pure sample. Irradiation of the protons around the pyrrolidine ring within **174** resulted in a series of enhancements linking the C(2)*H*, C(4)*H*, C(5)*H* and OC*H*$_2$Ph protons, which suggested that they occupy the same face of the pyrrolidine ring. In addition, a reciprocal interaction between the C(3)*H* and O*H* protons was also observed, along with a reciprocal enhancements of the C(3)*H* and C(2)C*H*$_2$ protons, supporting the proposed 2,3-*anti*-3,4-*anti*-4,5-*syn*-configuration within **174**. This allowed the absolute (2*R*,3*R*,4*R*,5*R*)-configuration within **174** to be assigned from the known absolute configurations of the C(2), C(3) and C(4)-stereogenic centres. This stereochemical outcome is also consistent with the previous observations made by Davies *et al.* concerning this class of ring-closing iodoamination reaction.[5b] The formation of **174** can be rationalised by the reaction taking place through an envelope transition state, where the C(2)-silyloxymethyl and the C(5)-iodonium groups occupy pseudo-equatorial positions. Subsequent loss of the *N*-α-methylbenzyl group from the corresponding ammonium species would then generate **174** (Figure 13).

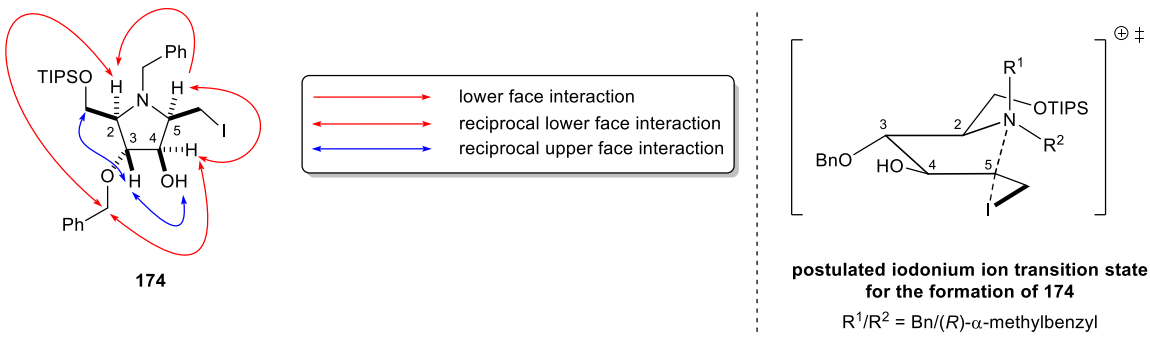
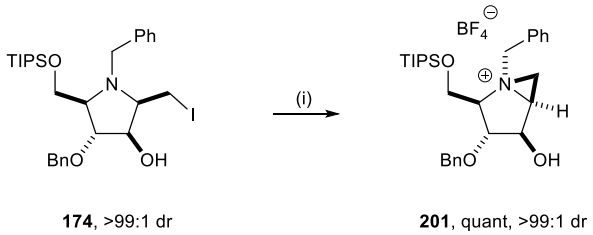


Figure 13. ^{1}H NMR nOe correlations within iodomethyl pyrrolidine **174** and a postulated iodonium ion transition state for its formation.

2.7. Aziridinium ring-opening by H_2O

Having isolated an analytically pure sample of iodomethyl pyrrolidine **174**, attention next turned to its conversion into the corresponding aziridinium species **201**. Treatment of **174** with $AgBF_4$ in CH_2Cl_2 resulted in the formation of aziridinium ion **201** in quantitative yield and >99:1 dr.[41] Full NMR spectroscopic analysis of **201**, including a ^1H–^{13}C HMBC study, was consistent with the assigned bicyclic system (Scheme 31).[42]



Scheme 31. *Reagents and conditions:* (i) $AgBF_4$, CH_2Cl_2, rt, 1 h.

The relative configuration within **201** was supported by ^1H NMR NOESY analysis. Correlations were observed between the C(2)C*H*$_2$, C(3)*H*, C(6)*H*$_A$ and C(6)*H*$_B$ protons, which suggested that they occupy the same face of the bicyclic system. In addition, a reciprocal correlation between the C(4)*H* and C(5)*H* protons was also observed, along with reciprocal enhancements between the C(4)*H* and C(2)*H* protons, suggesting that these protons also occupy the same face. This allowed the relative configuration within **201**, and consequently the absolute (1*S*,2*R*,3*R*,4*R*,5*S*)-configuration of **201** to be established, following from the known configurations of the stereocentres at C(2), C(3) and C(4) (Figure 14).

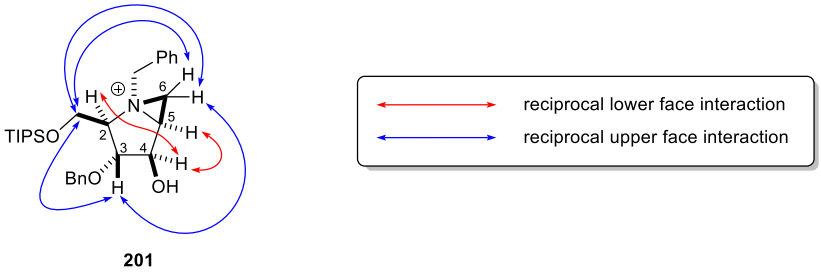
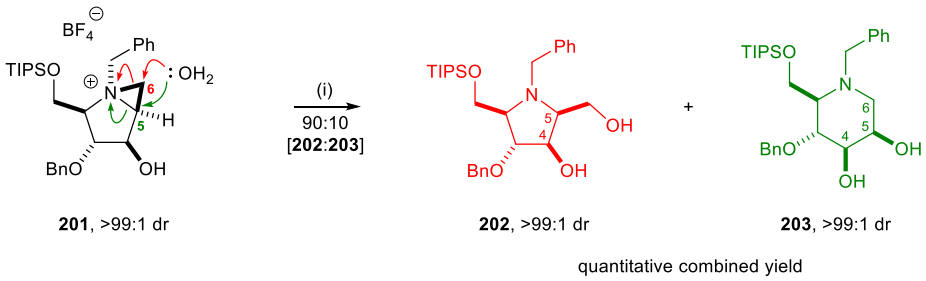


Figure 14. ^1H NOESY correlations within aziridinium **201** (the formal BF_4^- counterion has been omitted for clarity).

It was next envisaged that attack of aziridinium **201** by H_2O would produce pyrrolidine **202** preferentially, as a result of ring-opening at the least hindered C(6)-position. Thus, treatment of **201** with a 3:1 mixture of dioxane and H_2O resulted in the formation of a 90:10 mixture of pyrrolidine **202** and piperidine **203**, respectively, both in >99:1 dr (Scheme 32). The relative configuration within pyrrolidine **202** was initially assigned on the basis that substitution

occurs at C(6) [with the configuration at C(5) being unchanged] and this assignment was later confirmed unambiguously via single crystal X-ray diffraction analysis of a derivative (*vide infra*). The ring-opening of aziridinium **201** by H_2O at the most hindered C(5)-position [with inversion of configuration at C(5)] is responsible for the formation of piperidine **203**, as the minor regioisomer. From full NMR spectroscopic analysis of **203**, including ^{1}H NMR nOe and ^3J coupling constant analyses (*vide infra*, Chapter 3), it was concluded that the C(4)*H* and C(5)*H* protons have a *cis*-relationship; and this relative configuration was subsequently confirmed unambiguously by single crystal X-ray diffraction analysis of a derivative. The possibility of producing pyrrolidine **202** in a one-pot reaction, directly from bishomoallylic amine **191**, was next investigated. However, treatment of **191** with I_2 in dioxane/H_2O (3:1) for 1 h, followed by addition of $AgBF_4$, gave a complex mixture of products. Although pyrrolidine **202** was observed in the ^{1}H NMR spectrum of the crude reaction mixture, the stepwise process proved more efficacious. Attempts to separate pyrrolidine **202** and piperidine **203** by column chromatography were unsuccessful; therefore the crude reaction mixture was used directly in the next step as it was anticipated that subsequent repetition of this reaction and global deprotection of the pyrrolidine scaffold would allow separation and facilitate the synthesis of the iminosugar natural product (+)-DGDP **14**.

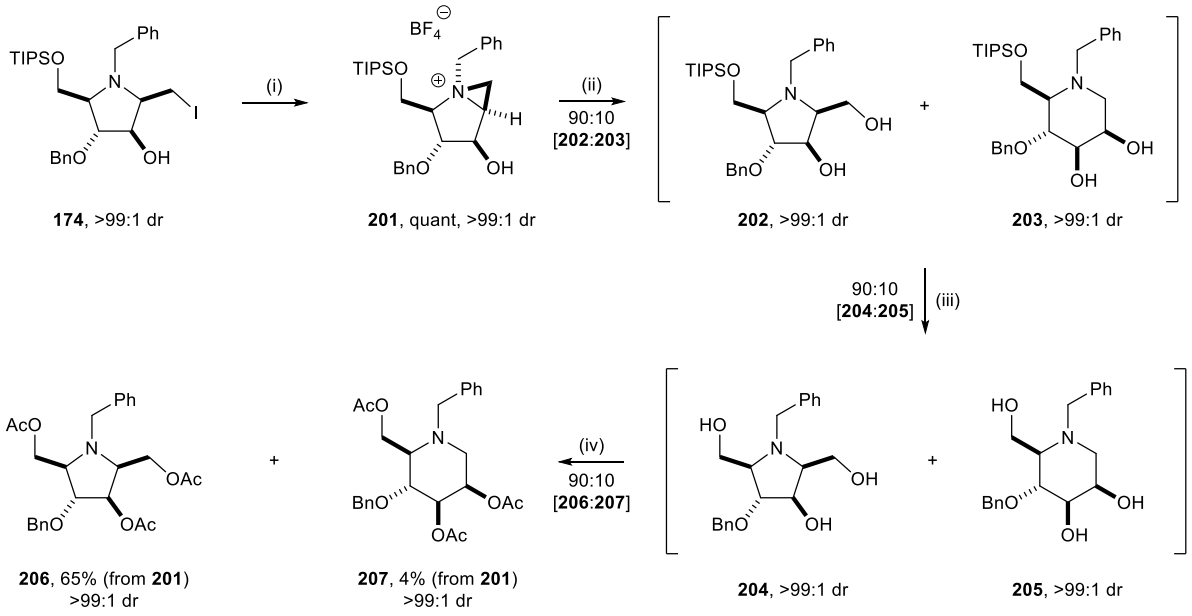


Scheme 32. *Reagents and conditions:* (i) dioxane/H_2O (3:1), rt, 16 h.

2.8. Elaboration to (+)-DGDP

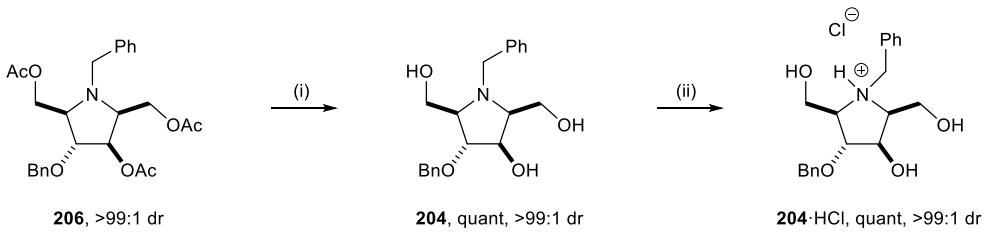
Following the ring-opening of aziridinium **201** with H_2O, treatment of the crude reaction mixture of pyrrolidine **202** and piperidine **203** with HF·pyridine in THF gave a 90:10 mixture of triols **204** and **205**. Subsequent peracetylation (for ease of purification) furnished a 90:10 mixture of **206** and **207**, which facilitated the isolation of both pyrrolidine **206** and piperidine **207** in 65 and 4% yield (from **201**), respectively, as single diastereoisomers (>99:1 dr) in each case. Analysis of the ^{1}H NMR ^3J coupling constants for piperidine **207**, as well as the

synthesis of an authentic sample of **207**,[43] confirmed the assigned configurations within **207**, **205** and **203** (Scheme 33).



Scheme 33. *Reagents and conditions:* (i) $AgBF_4$, CH_2Cl_2, rt, 1 h; (ii) dioxane/H_2O (3:1), rt, 16 h; (iii) HF·pyridine, THF, 0 °C to rt, 16 h; (iv) Ac_2O, DMAP, pyridine, 0 °C to rt, 16 h.

Transesterification of pyrrolidine **206** upon treatment with K_2CO_3 in MeOH delivered a pure sample of triol **204** in quantitative yield and >99:1 dr. Subsequent conversion of **204** to the corresponding hydrochloride salt **204**·HCl (Scheme 34), followed by X-ray diffraction analysis[39] of **204**·HCl allowed the relative configuration within **204** to be established unambiguously (Figure 15). Furthermore, the determination of a Flack *x* parameter[44] of −0.057(13) for the crystal structure of **204**·HCl·H_2O allowed the assigned absolute (2*R*,3*R*,4*R*,5*S*)-configuration of **204** to be confirmed. This analysis also unambiguously established the absolute configurations within pyrrolidines **206** and **202** and these stereochemistries were entirely supportive of the proposed mechanism.



Scheme 34. *Reagents and conditions:* (i) K_2CO_3, MeOH, rt, 16 h; (ii) HCl (2.0 M in Et_2O), rt, 10 min.

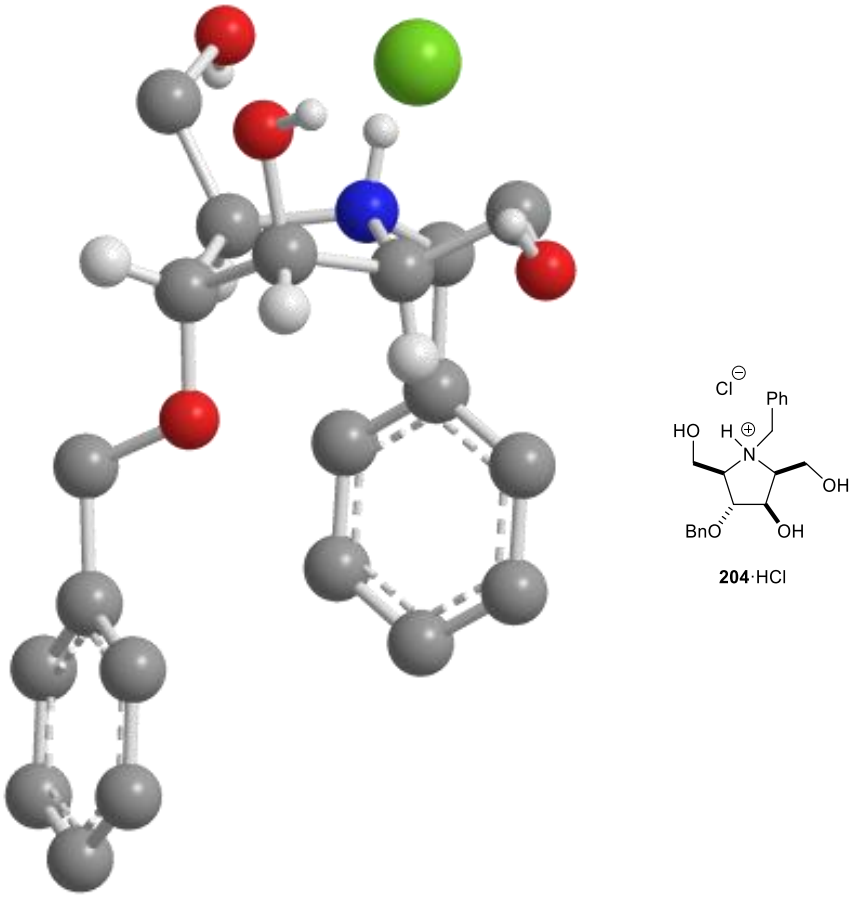
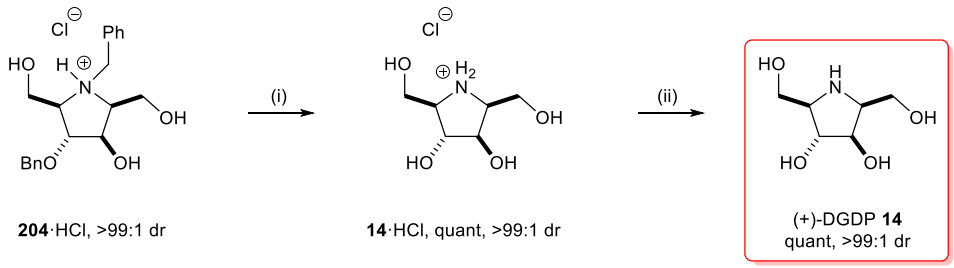


Figure 15. X-Ray crystal structure of (2*R*,3*R*,4*R*,5*S*)-**204**·HCl·H_2O (H_2O and selected H atoms have been omitted for clarity).

Subsequent treatment of **204**·HCl with Pearlman's catalyst [$Pd(OH)_2$/C] under an atmosphere of H_2 (5 atm) resulted in hydrogenolytic *N*- and *O*-debenzylation to give **14**·HCl in quantitative yield and >99:1 dr. Purification of this sample by ion exchange chromatography on Dowex 50WX8 (H^+ form) resin afforded (+)-DGDP **14** in quantitative yield and as single diastereoisomer (Scheme 35).[45,46,47]



Scheme 35. *Reagents and conditions:* (i) $Pd(OH)_2$/C, H_2 (5 atm), MeOH, rt, 48 h; (ii) Dowex 50WX8 (H^+ form).

The melting point, specific rotation, and ^{1}H and ^{13}C NMR spectra of this sample of (+)-DGDP **14** were in excellent agreement with the values previously reported in the literature (Tables 1, 2 and 3).

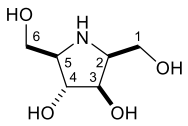
^{1}H NMR data for (+)-DGDP **14** 					
H	Asano *et al.*[45a] δ_H (500 MHz, D_2O) (isolation)	Donohoe *et al.*[46j] δ_H (400 MHz, D_2O)	Behr *et al.*[46e] δ_H (250 MHz, D_2O)	Somfai *et al.*[46f] δ_H (500 MHz, D_2O)	This study δ_H (400 MHz, D_2O)
C(1)H_A	3.71 dd *J* 11.3, 4.9	3.61 dd *J* 6.4, 3.0	3.50-3.80 m -	3.63-3.79 m -	3.60-3.67 m -
C(1)H_B	3.82 dd *J* 11.3, 6.0	3.72 dd *J* 11.4, 6.1	3.50-3.80 m -	3.63-3.79 m -	3.70-3.78 m -
C(2)*H*	3.38 ddd *J* 6.0, 4.9, 2.9	3.26 q *J* 6.2	3.32 q *J* 5.0	3.31 app q *J* 5.5	3.30 app q *J* 5.5
C(3)*H*	4.14 dd *J* 5.2, 2.9	4.05 dd *J* 5.1, 2.8	4.06 dd *J* 4.4, 2.1	4.14 dd *J* 4.9, 3.0	4.08 dd *J* 5.5, 2.8
C(4)*H*	3.90 dd *J* 5.2, 2.9	3.80 dd *J* 5.2, 2.8	3.82 dd *J* 3.6, 2.1	3.87 dd *J* 5.2, 3.0	3.84 dd *J* 5.2, 2.8
C(5)*H*	3.08 ddd *J* 4.9, 4.4, 2.9	2.96 q *J* 5.2	3.02 dd -	2.99 app q *J* 5.2	2.99 app q *J* 5.2
C(6)H_A	3.69 dd *J* 11.5, 4.4	3.58 dd *J* 6.6, 3.3	3.50-3.80 m -	3.63-3.79 m -	3.60-3.67 m -
C(6)H_B	3.77 dd *J* 11.5, 4.9	3.67 dd *J* 11.5, 4.9	3.50-3.80 m -	3.63-3.79 m -	3.70-3.78 m -

Table 1. Comparison of ^{1}H NMR data for the sample of (+)-DGDP **14** prepared in this study with representative examples from the literature [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

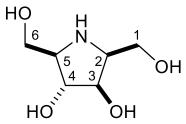
^{13}C NMR data for (+)-DGDP **14** 					
C	Asano et al.[45a] δ_C (125 MHz, D_2O) (isolation)	Donohoe *et al.*[46j] δ_C (100 MHz, D_2O)	Behr *et al.*[46e] δ_H (62.5 MHz, D_2O)	Somfai *et al.*[46f] δ_H (500 MHz, D_2O)	This study δ_C (100 MHz, D_2O)
C(1)	62.8	60.2	62.2	61.2	59.9
C(2)	63.7	61.2	63.6	61.5	60.8
C(3)	80.0	77.5	79.4	79.4	77.2
C(4)	81.8	79.2	81.2	81.2	78.9
C(5)	67.7	65.2	67.6	67.6	64.8
C(6)	64.9	62.3	64.3	64.3	62.1

Table 2. Comparison of ^{13}C NMR data for the sample of (+)-DGDP **14** prepared in this study with representative examples from the literature [chemical shifts (δ_C) are reported in ppm].

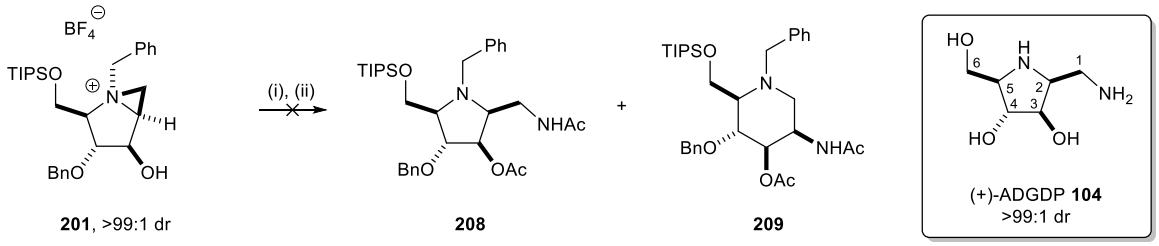
Selected physical data for (+)-DGDP **14**		
	Specific rotation (H_2O)	Melting point (°C)
Asano *et al.*[45a] (isolation)	$[\alpha]_D$ +26.1 (*c* 0.84)	127-130
Donohoe *et al.*[46j]	$[\alpha]_D^{25}$ +24.8 (*c* 1.0)	139-141
Ojea *et al.*[46i]	$[\alpha]_D^{22}$ +24.2 (*c* 0.7)	136-138
Ramesh *et al.*[46g]	$[\alpha]_D^{28}$ +22.7 (*c* 0.14)	-
Jung *et al.*[46h]	$[\alpha]_D^{22}$ +24.1 (*c* 1.0)	-
Behr *et al.*[46e]	$[\alpha]_D$ +22.7 (*c* 0.77)	-
This study	$[\alpha]_D^{20}$ +22.2 (*c* 0.5)	124-127

Table 3. Comparison of the specific rotation and melting point of (+)-DGDP **14**.

2.9. Synthesis of the 1-deoxy-1-amino analogue: (+)-ADGDP

2.9.1. Attempted aziridinium ring-opening with nitrogen-centred nucleophiles

It was next envisaged that ring-opening of aziridinium **201** with nitrogen-centred nucleophiles, followed by global deprotection of the corresponding pyrrolidine scaffold, would allow the asymmetric synthesis of (+)-ADGDP **104**, the 1-deoxy-1-amino analogue of (+)-DGDP **14**. Treatment of **201** with NH_3, followed by acetylation (to ease purification), resulted in low mass return, and the ^{1}H NMR spectrum of the crude reaction mixture was broad and complex (Scheme 36).

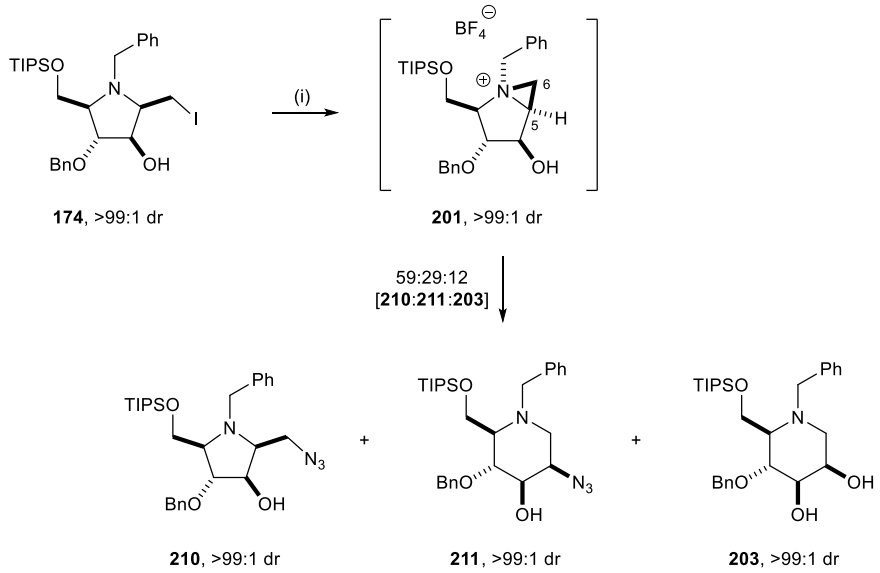


201, >99:1 dr **208** **209**

Scheme 36. *Reagents and conditions:* (i) NH_3 (0.5 M in dioxane), rt, 16 h; (ii) Ac_2O, DMAP, pyridine, 0 °C to rt, 16 h.

The use of NaN_3 was investigated next. Thus, conversion of **174** to aziridinium **201** with $AgBF_4$, followed by addition of NaN_3 to the reaction mixture, gave a 59:29:12 mixture of pyrrolidine **210**, piperidine **211** and piperidine diol **203**. The ring-opening reaction of aziridinium **201** with azide proceeded with low regioselectivity (67:33, [**210**:**211**]), and the formation of piperidine **203** as a single diastereoisomer was in contrast to the production of a 90:10 mixture of **202** and **203** when aziridinium **201** was subjected to dioxane/H_2O (3:1). This result suggested that **203** was presumably formed upon ring-opening of unreacted **201** with H_2O when performing the work-up of the reaction. Furthermore, the regioselectivity of ring-opening by H_2O (under the work-up conditions) could be rationalised by the formation of an intermolecular hydrogen bond between the hydroxyl moiety within **201** and H_2O, which may direct the ring-opening of aziridinium **201** at the C(5)-position (i.e., a tethered nucleophile), to give piperidine **203**. The relative configuration within pyrrolidine **210** was tentatively assigned on the basis that substitution occurs at C(6) [with the configuration at C(5) being unchanged], while the ring-opening of **201** at the most hindered C(5)-position proceeds with inversion of configuration to give piperidines **211** and **203**. Attempts to purify this mixture by column chromatography proved unsuccessful at this stage; however ^{1}H NMR ^3J coupling

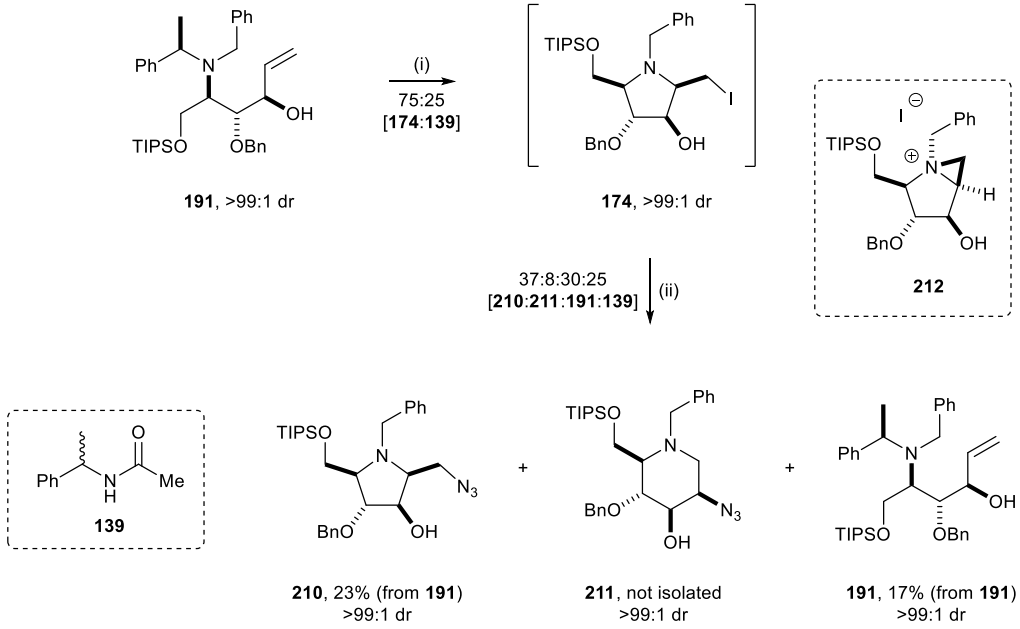
constant and NOESY analyses of an enriched sample of piperidine **211** (77:23, [**211**:**210**]) were consistent with the assigned configuration of **211** (Scheme 37).



Scheme 37. *Reagents and conditions:* (i) $AgBF_4$, CH_2Cl_2, rt, 1 h, then NaN_3, rt, 3 h.

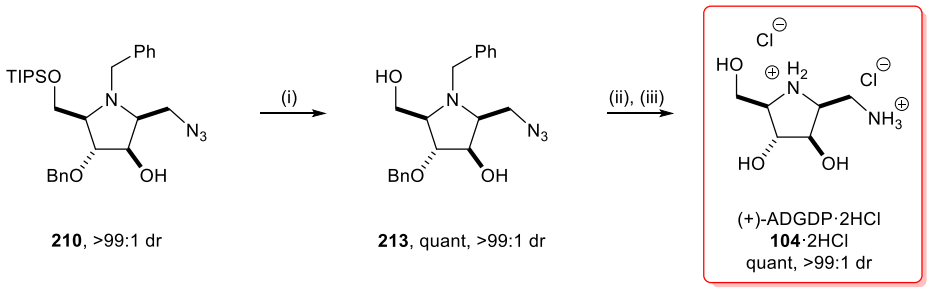
2.9.2. Optimised route to (+)-ADGDP

Following these results, it was envisaged that pyrrolidine **210** could alternatively be synthesised by subjecting iodomethyl pyrrolidine **174** to S_N2-type substitution conditions upon treatment with NaN_3. Thus, iodoamination of bishomoallylic amine **191**, followed by immediate treatment of the crude reaction mixture with NaN_3 in DMF, gave a 37:8:30:25 mixture of pyrrolidine **210**, piperidine **211**, returned starting material **191** and *N*-α-methylbenzyl acetamide **139**, respectively. Although this reaction must proceed via competing pathways (with the formation of aziridinium **212** being responsible for the synthesis of piperidine **211**), reaction in favour of the formation of pyrrolidine **210** (83:17, [**210**:**211**]), proved more efficacious than ring-opening of aziridinium **201** with azide. Chromatographic purification of this mixture delivered pyrrolidine **210** in 23% isolated yield (in two steps from **191**) and >99:1 dr, along with bishomoallylic amine **191** in 17% yield (in two steps from **191**) and >99:1 dr, which was then recycled (Scheme 38).



Scheme 38. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) NaN_3, DMF, 80 °C, 16 h.

Treatment of **210** with HF·pyridine resulted in *O*-silyl deprotection to give diol **213** in quantitative yield and >99:1 dr. Subsequent tandem hydrogenolysis/reduction of **213** upon treatment with Pearlman's catalyst [$Pd(OH)_2/C$] under an atmosphere of H_2 (5 atm), followed by purification of this sample by ion exchange chromatography on Dowex 50WX8 (H^+ form) resin gave (+)-ADGDP **104**, which was isolated as the corresponding dihydrochloride salt **104**·2HCl in quantitative yield and >99:1 dr (Scheme 39).[48,49]



Scheme 39. *Reagents and conditions:* (i) HF·pyridine, THF, 0 °C to rt, 16 h; (ii) $Pd(OH)_2/C$, HCl (2.0 M in Et_2O), H_2 (5 atm), MeOH, rt, 48 h, then Dowex 50WX8 (H^+ form); (iii) HCl (2.0 M in Et_2O), rt, 5 min.

Only one previous synthesis of (+)-ADGDP dihydrochloride **104**·2HCl has been reported in the literature.[48a] Comparison of the ^1H and ^{13}C NMR data for this synthetic sample of **104**·2HCl showed excellent agreement with the data previously reported by Merino *et al.* (Tables 4 and 5). The specific rotation and melting point of this synthetic sample of **104**·2HCl {mp >170 °C; $[\alpha]_D^{20}$ +33.2 (*c* 0.6 in H_2O)} were also consistent with the data reported in the literature {lit.[48a] >150 °C; lit.[48a] $[\alpha]_D^{25}$ +43 (*c* 1.43 in H_2O)}.

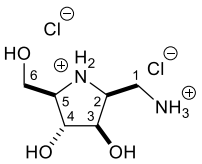
^{1}H NMR data for (+)-ADGDP dihydrochloride **104**·2HCl 		
H	Merino *et al.*[48a] δ_H (400 MHz, D_2O)	This study δ_H (400 MHz, D_2O)
C(1)H_A	3.54 dd *J* 13.9, 6.2	3.46 dd *J* 13.9, 6.0
C(1)H_B	3.54 dd *J* 13.9, 6.8	3.58 dd *J* 13.9, 7.0
C(2)*H*	4.02 dt *J* 6.6, 3.6	4.05 app td *J* 6.5, 3.6
C(3)*H*	4.27 dd *J* 3.5, 1.4	4.29-4.32 m -
C(4)*H*	4.05 dd *J* 2.7, 1.7	4.08-4.11 m -
C(5)*H*	3.62 ddd *J* 8.8, 4.9, 2.4	3.64-3.68 m -
C(6)H_A	3.76 dd *J* 12.1, 8.8	3.81 dd *J* 12.1, 9.0
C(6)H_B	3.90 dd *J* 12.1, 4.8	3.94 dd *J* 12.1, 4.7

Table 4. Comparison of ^{1}H NMR data of (+)-ADGDP dihydrochloride **104**·2HCl [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

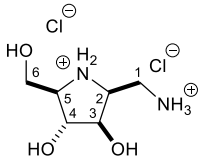
^{13}C NMR data for (+)-ADGDP dihydrochloride **104**·2HCl		
C	Merino *et al.*[48a] δ_C (100 MHz, D_2O)	This study δ_C (100 MHz, D_2O)
C(1)	35.4	35.4
C(2)	58.7	58.7
C(3)	74.5	74.5
C(4)	75.6	75.6
C(5)	68.3	68.3
C(6)	59.3	59.3

Table 5. Comparison of ^{13}C NMR data of (+)-ADGDP dihydrochloride **104**·2HCl [chemical shifts (δ_C) are reported in ppm].

2.10. Summary

Bishomoallylic amine **191** was obtained in five steps and 35% overall yield from γ-silyloxy-α,β-unsaturated ester **159** using the Davies diastereoselective aminohydroxylation procedure followed by reduction and reaction with vinylmagnesium bromide. Ring-closing iodoamination of **191** resulted in 5-*exo* cyclisation with concomitant loss of the *N*-α-methylbenzyl group to form iodomethyl pyrrolidine **174**, which was isolated in 20% yield after chromatographic purification. Conversion of **174** to the corresponding aziridinium species **201**, followed by its ring-opening with H_2O at the least hindered C(6)-position delivered pyrrolidine **202**, which underwent *O*-silyl deprotection and peracetylation to furnish **206** in 65% isolated yield (from **174**). Finally, tandem methanolysis/hydrogenolysis of **206** afforded (+)-DGDP **14** in 2.8% overall yield (over fifteen steps) from commercially available starting materials. In addition, direct treatment of the crude reaction mixture of **174** with NaN_3 gave azide **210**, which underwent *O*-silyl deprotection and tandem hydrogenolysis/reduction to give (+)-ADGDP dihydrochloride **104**·2HCl in 4.9% overall yield (over twelve steps) from commercially available starting materials (Figure 16).[47]

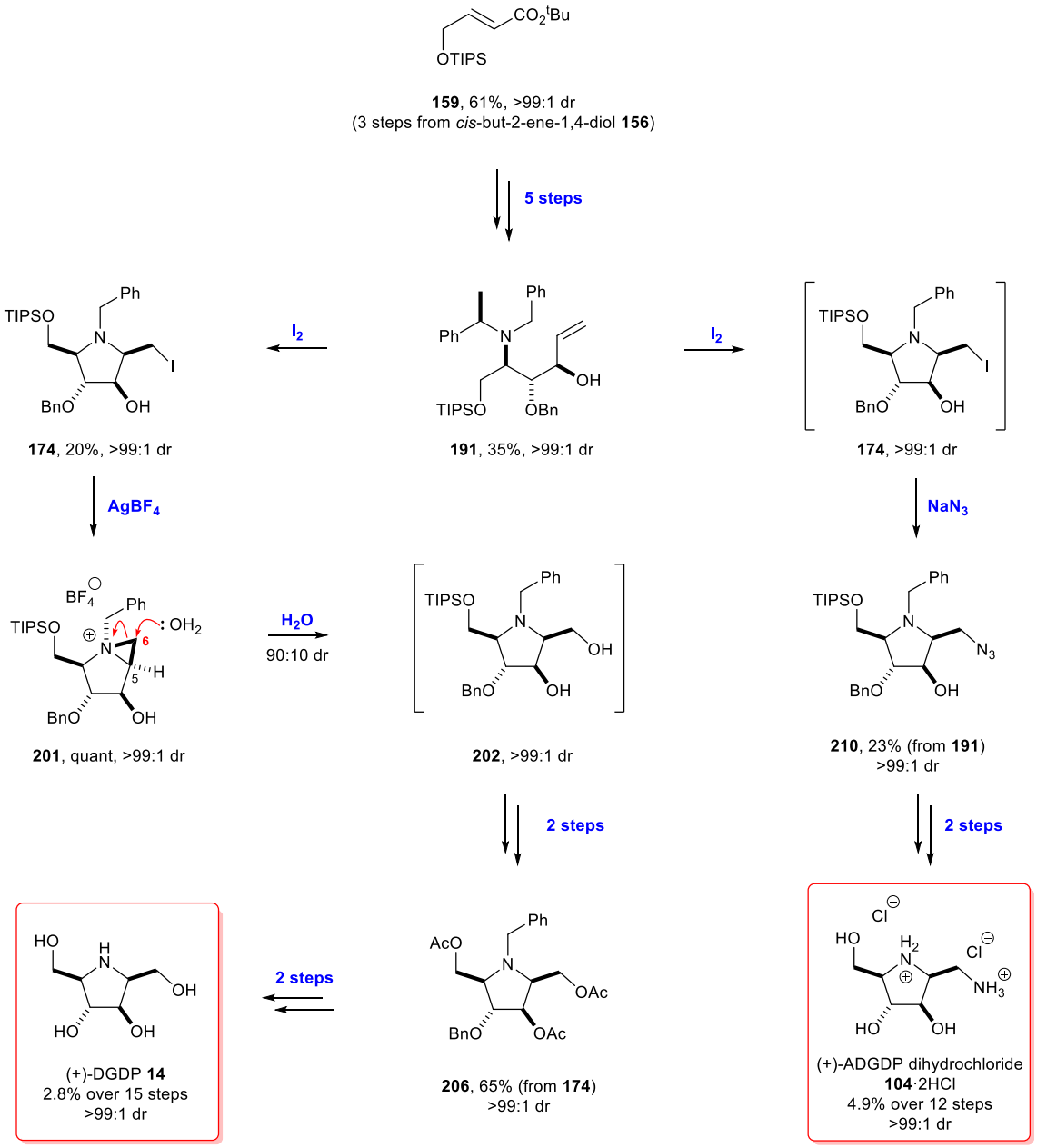


Figure 16. The total asymmetric syntheses of (+)-DGDP **14** and (+)-ADGDP dihydrochloride **104**·2HCl via a ring-closing iodoamination strategy.

2.11. References and notes

[1] Price, P. D. *D.Phil. Thesis*, University of Oxford, **2005**.

[2] (a) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron* **2012**, *68*, 4302. (b) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron Lett.* **2011**, *52*, 6477.

[3] Brock, E. A.; Davies, S. G.; Lee, J. A; Roberts, P. M.; Thomson, J. E. *Org. Biomol. Chem.* **2013**, *11*, 3187.

[4] (a) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833. (b) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.

[5] (a) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901. (b) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Russell, A. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758.

[6] (a) Weber, K.; Kuklinski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647. (b) Nagle, A. S.; Salvatore, R. N.; Chong, B.-D.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 3011. (c) Graham, M. A.; Wadsworth, A. H.; Thornton-Pett, M.; Rayner, C. M. *Chem. Commun.* **2001**, 966.

[7] Abbaspour Tehrani, K.; Van Syngel, K.; Boelens, M.; Contreras, J.; De Kimpe, N.; Knight, D. W. *Tetrahedron Lett.* **2000**, *41*, 2507.

[8] (a) O'Brien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304. (b) Richardson, P. F.; Nelson, L. T. J.; Sharpless, K. B. *Tetrahedron Lett.* **1995**, *36*, 9241. (c) Liu, Q.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511. (d) de Sousa, S. E.; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483.

[9] (a) Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567. (b) Davies, S. G.; Fletcher, A. M.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Tetrahedron* **2011**, *67*, 9975.

[10] Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594.

[11] (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5953.

[12] (a) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375. (b) Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2373. (c) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2385.

[13] Richard, J. P. *Tetrahedron* **1995**, *51*, 1535.

[14] See Ref. 2, 5 and 10.

[15] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738.

[16] (a) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. (b) Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510.

[17] Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665.

[18] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

[19] Foster, E. M. *D.Phil. Thesis*, University of Oxford, **2012**.

[20] Reaction conditions were first optimised upon reaction of (*R*)-**162** with α,β-unsaturated ester **159** followed by the addition of satd aq NH_4Cl to give β-amino ester **164**. Treatment of **159** with 1.6 equiv of (*R*)-**162** followed by satd aq NH_4Cl addition resulted in 48% conversion to β-amino ester **164**, whereas treatment of **159** with 1.6 equiv of (*R*)-**130** has previously been reported to reach completion to give the corresponding *N*-benzyl-*N*-α-methylbenzyl protected β-amino ester; see: Ref. 17. Upon repetition of the reaction using 2.0 equiv of (*R*)-**162**, 100% conversion to β-amino ester **164** (>99:1 dr) was observed.

[21] Amine (*R*)-**161** was synthesised on >20g scale in 96% yield from the reaction of benzaldehyde and commercially available (*R*)-(+)-α-methyl-*p*-methoxybenzylamine under previously reported conditions, see Thomson, J. E. *D.Phil. Thesis*, University of Oxford, **2007**.

[22] (−)-CSO **147** was successfully prepared in 80% yield on >200 g scale from (1*R*)-(−)-10-camphorsulfonic acid [(−)-CSA] under modified literature conditions, see: Davis, F. A.; Tousson, J. C.; Weismiller, M. C.; Cal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *25*, 8477.

[23] Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *10*, 1999.

[24] For previous examples of this aminohydroxylation protocol, see: Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 3708. See also Ref. 16.

[25] It was noted that reaction needs to reach rt to go to completion.

[26] A similar diastereoselectivity (70:30 dr) was observed by Han *et al.* for the addition of vinylmagnesium bromide to a related aldehyde (Chapter 1); see: Singh, S.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 6349.

[27] For selected examples of magnesium used in a chelation-controlled Grignard addition, see: (a) Kim, T. H.; Kim, Y.-H.; Yang, Z.; Jung, J. W.; Jeong, L. S.; Kim, H. D. *Synlett* **2014**, 251. (b) Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2004**, *69*, 9143. (c) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968. (d) Kornienko, A.; D'Alarcao, H. *Tetrahedron Lett.* **1997**, *38*, 6497. (e) Clayden, J.; McCarthy, C.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1363.

[28] Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021.

[29] Evans, D. A.; Welch, D. S.; Speed, A. W. H.; Moniz, G. A.; Reichelt, A.; Ho, S. *J. Am. Chem. Soc.* **2009**, *131*, 3840.

[30] Yoon, N. M.; Lee, H. J.; Kim, H. K.; Kang, J. *J. Korean Chem. Soc.* **1976**, *20*, 59.

[31] For data of alcohol **175**, see: Cao, L.; Ding, J.; Gao, M.; Wang, Z.; Li, J.; Wu, A. *Org. Lett.* **2009**, *11*, 3810.

[32] An authentic racemic sample of ethers **176** and **177** was synthesised in 32% yield following a literature procedure; see: Noji, M.; Konno, Y.; Ishii, K. *J. Org. Chem.* **2007**, *72*, 5161.

[33] Buchwald, S. L.; Watson, B. T.; Lum, R. T.; Nugent, W. A. *J. Am. Chem. Soc.* **1987**, *109*, 7137.

[34] (a) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett*. **1984**, *25*, 1063. (b) Palmer, A. M.; Jäger, V. *Synlett* **2000**, 1405.

[35] Brock, E. A. *D.Phil. Thesis*, University of Oxford, **2012**.

[36] An authentic racemic sample of ether **181** was synthesised in 86% yield following a literature procedure; see: Srihari, P.; Bhunia, D. C.; Sreedhar, P.; Yadav, J. S. *Synlett* **2008**, 1045.

[37] Amine (*R*)-**186** was synthesised on >20g scale in 78% yield from the reaction of benzaldehyde and commercially available (*R*)-(+)-α-methylbenzylamine under previously reported conditions, see: Ref. 19.

[38] For spectroscopic data for *ent*-**187**, see: Ref. 17.

[39] X-Ray crystal structure determination was performed by Dr. J. E. Thomson and Dr. A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[40] (a) Davies, S. G.; Fletcher, A. M; Foster, E. M; Lee, J. A; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 2500. (b) Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8885.

[41] Degradation of an isolated sample of aziridinium **201** was observed after 24 h.

[42] The sp^2 character of *C*(6) within aziridinium **201** and presumably the $J_{C\text{-}H}$ coupling constants for C(6)H_A and C(6)H_B made the C(6)H_2 protons appear as if they were supported by different carbons in the HSQC spectrum. I would like to thank Prof. Tim Claridge for the discussion.

[43] An authentic sample of **207** was synthesised from **205** (obtained via another route in Chapter 3) upon treatment with Ac_2O and DMAP in pyridine, in quantitative yield and >99:1 dr.

[44] (a) Flack, H. D. *Acta. Crystallogr., Sect. A* **1983**, *39*, 876. (b) Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908. (c) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.

[45] For details concerning the isolation of (+)-DGDP **14** from natural sources, see: (a) Asano, N.; Yamauchi, T.; Kagamifuchi, K.; Shimizu, N.; Takahashi, S.; Takatsuka, H.; Ikeda, K.; Kizu, H.; Chuakul, W.; Kettawan, A.; Okamoto, T. *J. Nat. Prod.* **2005**, *68*, 1238. (b) Minami, Y.; Kuriyama, C.; Ikeda, K.; Kato, A.; Takebayashi, K.; Adachi, I.; Fleet, G. W. J.; Kettawan, A.; Okamoto, T.; Asano, N. *Bioorg. Med. Chem.* **2008**, *16*, 2734.

[46] For selected previous syntheses of (+)-DGDP **14**, see: (a) Legler, G.; Korth, A.; Berger, A.; Ekhart, C.; Gradnig, G.; Stütz, A. E. *Carbohydrate Res.* **1993**, *250*, 67. (b) Gyeong, L. S.; Yong-Jin, Y.; Chul, S. S.; Yong, L. B.; Su-Dong, C.; Kyu, K. S.; Ji-Hyun, L. *Heterocycles* **1997**, *45*, 701. (c) Long, D. D.; Frederiksen, S. M.; Marquess, D. G.; Lane, A. L.; Watkin, D. J.; Winkler, D. A.; Fleet, G. W. J. *Tetrahedron Lett.* **1998**, *39*, 6091. (d) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203. (e) Gautier-Lefebvre, I.; Behr, J.-B.; Guillerm, G.; Muzard, M. *Euro. J. Med. Chem.* **2005**, *40*, 1255. (f) Restorp, P.; Fischer, A.; Somfai, P. *J. Am. Chem. Soc.* **2006**, *128*, 12646. (g) Kumar, V.; Ramesh, N. G. *Tetrahedron* **2006**, *62*, 1877. (h) Kim, I.-S.; Kim, S.-J.; Lee, J. K.; Li, Q.-R; Jung, Y.-H. *Carbohydrate Res.* **2007**, *342*, 1502. (i) Blanco, O.; Pato, C.; Ruiz, M.; Ojea, V. *Org. Biomol. Chem.* **2008**, *6*, 3967. (j) Donohoe, T. J.; Cheeseman, M. D.; O'Riordan, T. J. C.; Kershaw, J. A. *Org. Biomol. Chem.* **2008**, *6*, 3896. (k) Tsou, E.-L.; Yeh, Y.-T.; Liang, P.-H.; Cheng, W.-C. *Tetrahedron* **2009**, *65*, 93.

[47] Part of this work has been published; see: (a) Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, *15*, 2042. (b) Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 3601.

[48] For previous syntheses of (+)-ADGDP **104**, see: (a) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929. (b) Ref. 46k.

[49] Part of this work has been published; see: Ref. 47b.

Chapter 3: Asymmetric Syntheses of (–)-1-Deoxymannojirimycin and (+)-1-Deoxyallonojirimycin via a Ring-Expansion Approach

This chapter describes investigations into the ring-expansion of iodomethyl pyrrolidines **214** in the synthesis of cyclic carbonates **215** and the application of this methodology in the asymmetric syntheses of piperidine iminosugars **121** of the deoxynojirimycin class (Figure 17).

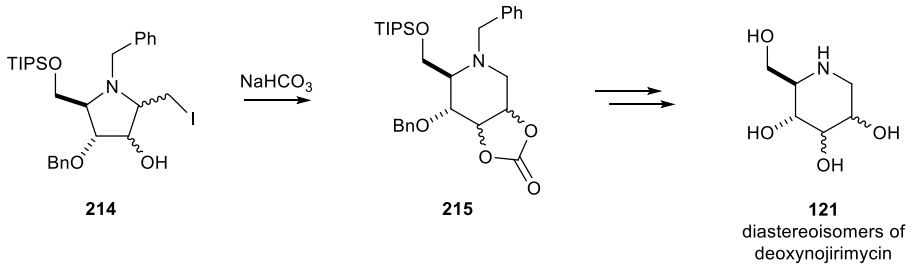
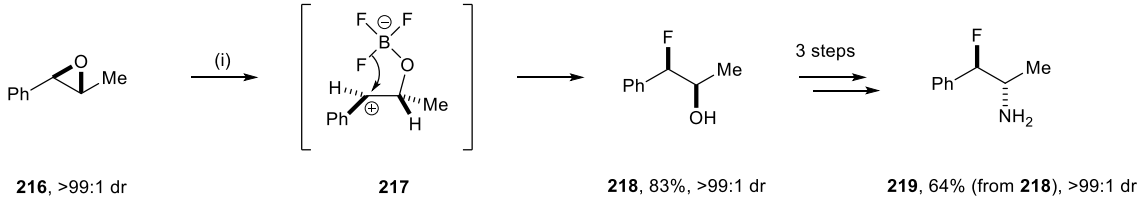


Figure 17. Strategy for the ring-expansion of iodomethyl pyrrolidines **214** to piperidine iminosugars **121**.

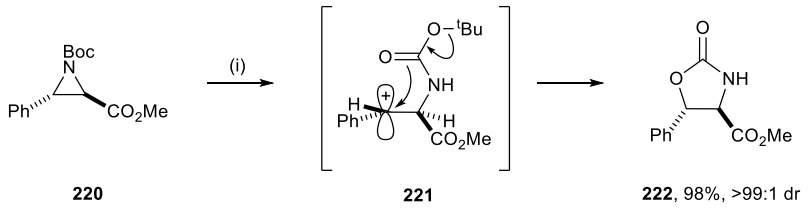
3.1. Tethered nucleophile strategies

A tethered nucleophile strategy is commonly used in organic synthesis to effect regio- and stereoselective transformations. For example, Davies *et al.* have recently reported an efficient ring-opening hydrofluorination of aryl epoxides which gave the corresponding *syn*-fluorohydrins via a tethered transfer of fluoride.[1] Treatment of racemic (*E*)-*β*-methylstyrene oxide **216** with 0.33 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −20 °C for 5 min gave fluorohydrin **218** in 83% yield and >99:1 dr, after chromatographic purification. The mechanism of this transformation was proposed to involve the formation of benzylic carbocation **217** (by co-ordination of BF_3 to the oxirane oxygen and subsequent rupture of the C−O bond), followed by intramolecular fluoride transfer[2] and work-up. Subsequent elaboration of **218** furnished *anti*-β-fluoroamphetamine **219** in 64% yield over three steps and >99:1 dr (Scheme 40).



Scheme 40. *Reagents and conditions:* (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C, 5 min.

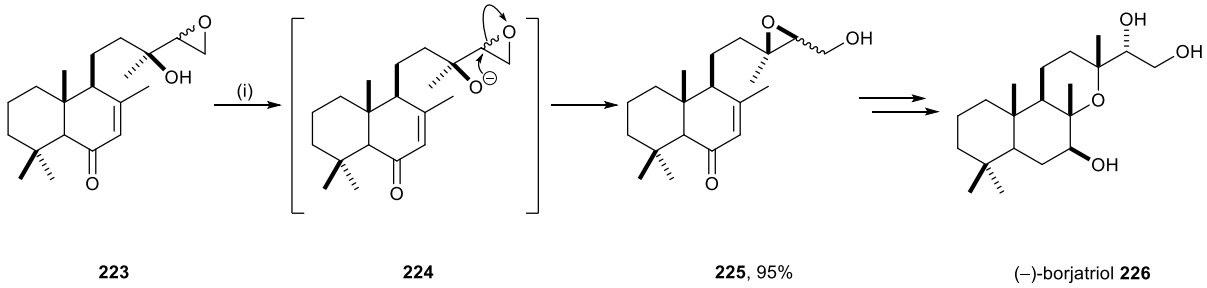
Similarly, during the course of their studies on the regioselective ring-opening of aziridines, Tomasini *et al.* have reported another reaction which relied on the delivery of a tethered nucleophile to a carbocationic centre.[3] Treatment of *trans*-aziridine **220** with $BF_3 \cdot 2H_2O$ resulted in the formation of the corresponding benzylic carbocation **221** (via an S_N1-type ring-opening of **220**), which underwent rapid intramolecular reaction with the carbamate moiety and concomitant loss of the *tert*-butyl group to form *trans*-oxazolidin-2-one **222** in 98% yield (Scheme 41).



220 **221** **222**, 98%, >99:1 dr

Scheme 41. *Reagents and conditions:* (i) $BF_3 \cdot 2H_2O$, CH_2Cl_2, rt, 30 min.

In addition, several well-known reactions involve the intramolecular attack of a nucleophile to an sp^3 hybridised centre as the key step. In their synthesis of (–)-borjatriol **226**, a diterpene which presents anti-inflammatory properties, Khuong-Huu *et al.* used the Payne rearrangement to good effect.[4] Treatment of a mixture of epimeric epoxides **223** with 0.5 M aq NaOH in a mixture of ^{t}BuOH and H_2O promoted the formation of alkoxide **224**, which underwent Payne rearrangement to give **225** in 95% yield. The diastereoisomeric mixture of rearranged epoxides **225** was subsequently elaborated to (–)-borjatriol **226** (Scheme 42).

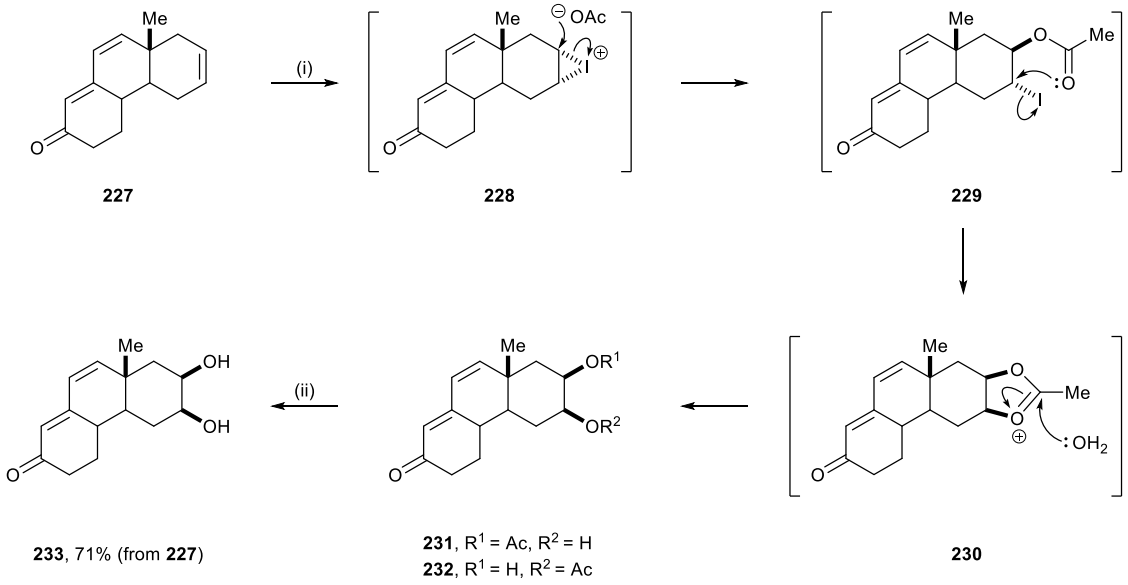


223 **224** **225**, 95% (–)-borjatriol **226**

Scheme 42. *Reagents and conditions:* (i) 0.5 M aq NaOH, ^{t}BuOH, H_2O, rt, 3 h.

In 1958, Woodward *et al.* developed a modification of the Prévost reaction to synthesise *syn*-diols from alkenes.[5] Treatment of **227** with I_2 and AgOAc in a mixture of AcOH and H_2O at 95 °C for 3 h was reported to lead to the formation of a mixture of monoacetylated diols **231** and **232**. By analogy to the Prévost reaction, initial addition of iodine resulted in the formation of iodonium ion **228**, which was ring-opened with acetate. Intramolecular S_N2-type nucleophilic substitution of the iodide within **229** by the tethered acetoxy moiety gave cyclic

acetoxonium ion **230**, which underwent hydrolysis to give the mixture of monoacetylated diols **231** and **232**. Subsequent hydrolysis of this mixture upon treatment with KOH gave *syn*-diol **233** in 71% overall yield from **227** (Scheme 43).



Scheme 43. *Reagents and conditions:* (i) AgOAc, I_2, AcOH, H_2O, 95 °C, 3 h; (ii) aq KOH.

Following this precedent, it was envisaged that the free hydroxyl moiety within aziridinium **201** could be used as a synthetic handle to tether a nucleophile that would consequently direct ring-opening at the C(5)-position within **235** (i.e., a ring-expansion reaction) to give a piperidine scaffold **236** as opposed to ring-opening occurring at the C(6)-position to give pyrrolidine scaffold **234**, as seen previously. It was also expected that reaction of the tethered nucleophile (intramolecular process) within **235** would be faster than the corresponding reaction with any external nucleophiles (intermolecular process) present in the reaction mixture (Figure 18).

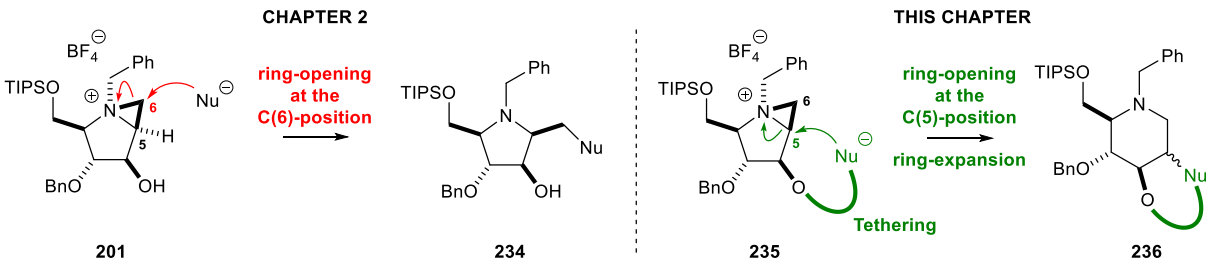
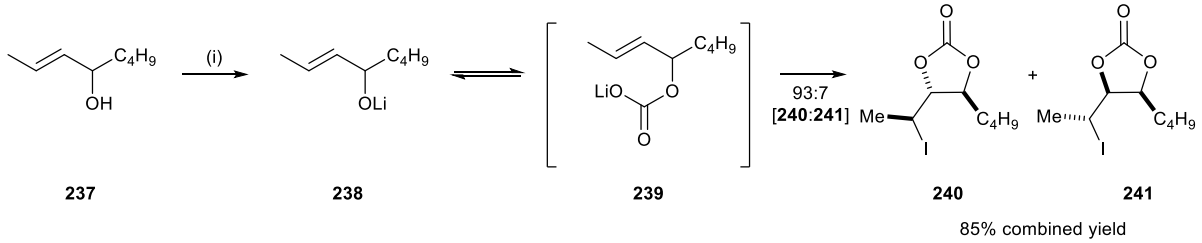


Figure 18. Aziridinium **201** and **235** ring-opening to pyrrolidines **234** and piperidines **236**.

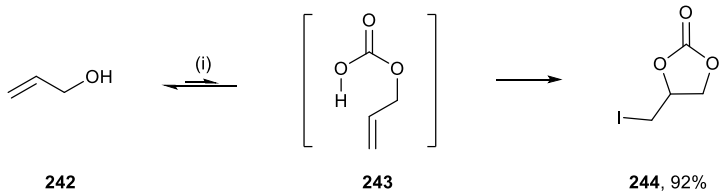
3.2. Ring-expansion via the trapping of CO_2

The trapping of CO_2 by allylic alcohols to form 5-membered ring iodocarbonates is one of the best known examples of the application of the iodolactonisation reaction in the production of a carbonate moiety. For example, Cardillo *et al.* reported the iodocyclisation of lithium alkenyl carbonate **239**, which was readily synthesised by bubbling CO_2 into a solution of lithium alkoxide **238** in THF.[6] Treatment of **239** with I_2 in THF at rt afforded iodocarbonates **240** and **241** in 85% combined yield and in 93:7 dr, respectively (Scheme 44).



Scheme 44. *Reagents and conditions:* (i) CO_2 (1 atm), BuLi (1.8 M in hexane), THF, 0 °C to rt, 1 h, then I_2, THF, rt, 12 h.

While this reaction requires a strong base for the generation of alkoxide **238**, Minakata *et al.* reported more recently an extremely mild procedure for the fixation of CO_2 to allylic alcohols.[7] Treatment of allylic alcohol **242** with ^{t}BuOI in THF under an atmosphere of CO_2 (1 atm) resulted in the formation of iodocarbonate **244** in 92% yield. This transformation proceeded via the formation of alkylcarbonic acid **243** (generated spontaneously by the reaction of CO_2 with allylic alcohol **242**), followed by subsequent iodocyclisation using the iodinating reagent ^{t}BuOI (with the liberation of the relatively weak acid ^{t}BuOH) to afford iodocarbonate **244** (Scheme 45).



Scheme 45. *Reagents and conditions:* (i) CO_2 (1 atm), ^{t}BuOI, THF, −20 °C, 12 h.

Building on this precedent, it was envisaged that the trapping of CO_2 by the hydroxyl moiety within aziridinium **201** may result in the formation of alkyl carbonic acid half ester **245**, which could then undergo intramolecular cyclisation by ring-opening the aziridinium **245** at the C(5)-position [i.e., via attack of the tethered nucleophile with inversion of configuration at C(5)], to give cyclic carbonate **246**. The use of CO_2 as a synthetic handle for the tethering

strategy also allows incorporation of an oxygen atom at the C(5)-position of the piperidine ring within **246**, and consequently renders cyclic carbonate **246** a useful precursor for the synthesis of deoxyiminosugars such as (–)-1-deoxymannojirimycin **11** (Figure 19).

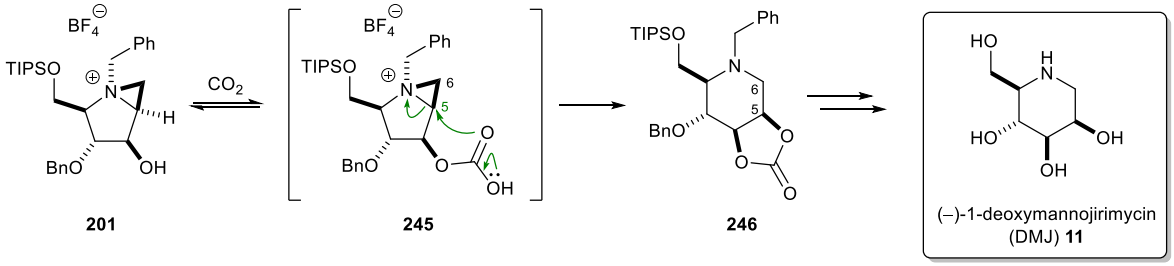
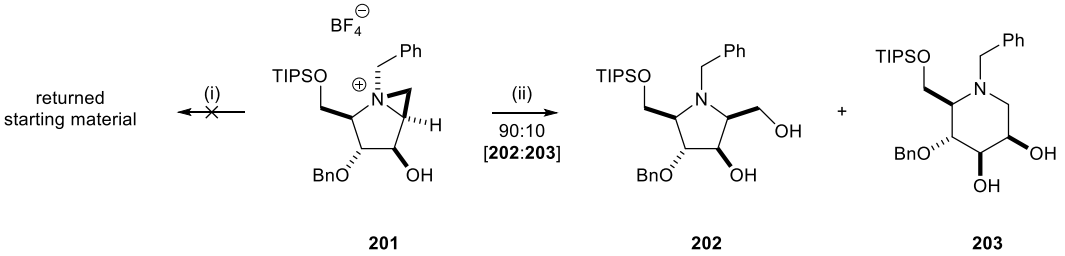


Figure 19. Ring-expansion strategy via the trapping of CO_2 by the hydroxyl moiety within aziridinium **201**.

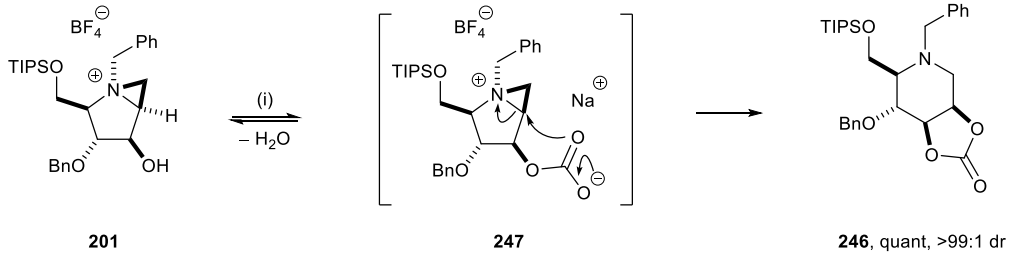
Aziridinium **201** was subjected to an atmosphere of CO_2 (1 atm) in CH_2Cl_2 at rt; however, no conversion to cyclic carbonate **246** was observed and the reaction only returned starting material. As the solubility of CO_2 in the solvent was assumed to play a major role in the reaction outcome, it was next proposed to add aziridinium **201** to a mixture of dioxane/H_2O (3:1), which was pre-saturated with CO_2. Unfortunately, the trapping of CO_2 also proved unsuccessful, and aziridinium **201** was instead ring-opened by H_2O (i.e., intermolecular nucleophilic attack) to give a 90:10 mixture of the known pyrrolidine **202** and piperidine **203**, respectively (Scheme 46). These results were consistent with observations made in the literature that basic conditions were required for the trapping of CO_2 to proceed and it was next envisaged that bicarbonate salts could be employed as an alternative source of CO_2.



Scheme 46. *Reagents and conditions:* (i) CO_2 (1 atm), CH_2Cl_2, rt, 16 h; (ii) CO_2 (1 atm), dioxane/H_2O (3:1), rt, 16 h.

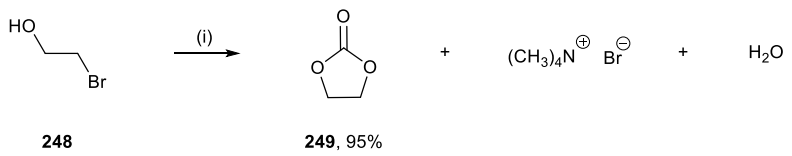
It was anticipated that carrying out the reaction in a mixture of dioxane/H_2O (3:1) would facilitate the dissolution of both bicarbonate salts and starting material **201** in the solvent, and this would therefore provide a high concentration of HCO_3^- in the solution. Thus, treatment of **201** with 3.0 equiv of $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) delivered cyclic carbonate **246** in quantitative yield and >99:1 dr. Full ^1H and ^{13}C NMR spectroscopic analyses of **246**, including an HMBC study, were consistent with the assigned structure of **246**; furthermore

the IR spectrum of the crude reaction mixture confirmed the presence of a carbonate moiety with a diagnostic C=O absorbance at 1810 cm^{-1}. The configuration of the newly formed C(5)-stereogenic centre within **246** was initially assigned on the basis that substitution occurs with inversion of configuration, and this assignment was later confirmed unambiguously via single crystal X-ray diffraction analysis of a derivative (*vide infra*). The mechanism of this transformation was proposed to involve reversible alkyl carbonate formation from **201** followed by intramolecular cyclisation of **247** to give carbonate **246**. It was interesting to note that neither pyrrolidine **202** nor piperidine **203** could be observed in the ^{1}H NMR spectrum of the crude reaction mixture, thereby supporting the prediction that the intramolecular pathway proceeds much faster in this case than the intermolecular ring-opening of **201** by H_2O (Scheme 47).



Scheme 47. *Reagents and conditions:* (i) $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h.

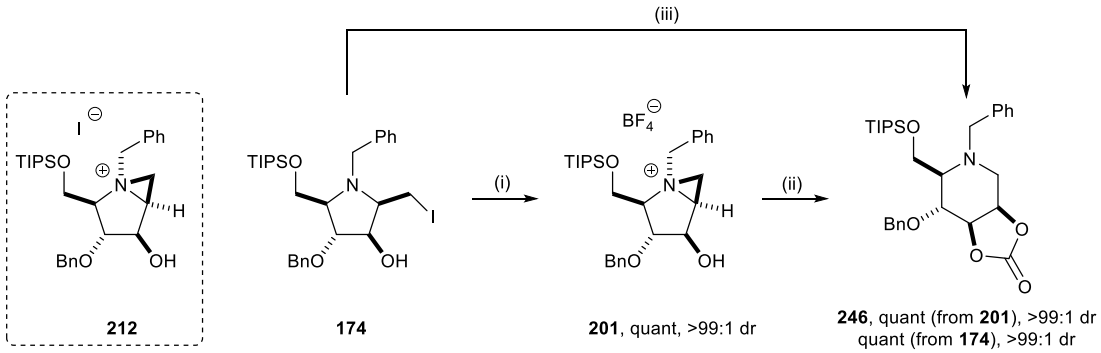
Venturello *et al.* previously reported the incorporation of CO_2 from Me_4NHCO_3, even though the reaction was preferentially performed under an atmosphere of CO_2.[8] Treatment of halohydrin **248** with Me_4NHCO_3 in MeCN (readily prepared by saturating tetramethylammonium hydroxide in methanol with CO_2) under an atmosphere of CO_2 was reported to give carbonate **249** in 95% yield, along with tetramethylammonium bromide, which was filtered off and isolated in quantitative yield. Although a variety of ammonium hydrogen carbonate salts (*viz.* tetraethyl-, tetrabutyl-, and benzyltrimethyl-) were employed in place of tetramethylammonium hydrogen carbonate, alkali metal hydrogen carbonates were reported to be virtually unreactive under the reaction conditions (Scheme 48). The incorporation of CO_2 from $NaHCO_3$ in the ring-expansion of aziridinium **201** is consequently unprecedented.



Scheme 48. *Reagents and conditions:* (i) Me_4NHCO_3, CO_2 (1 atm), MeCN, 20 °C, 10 min.

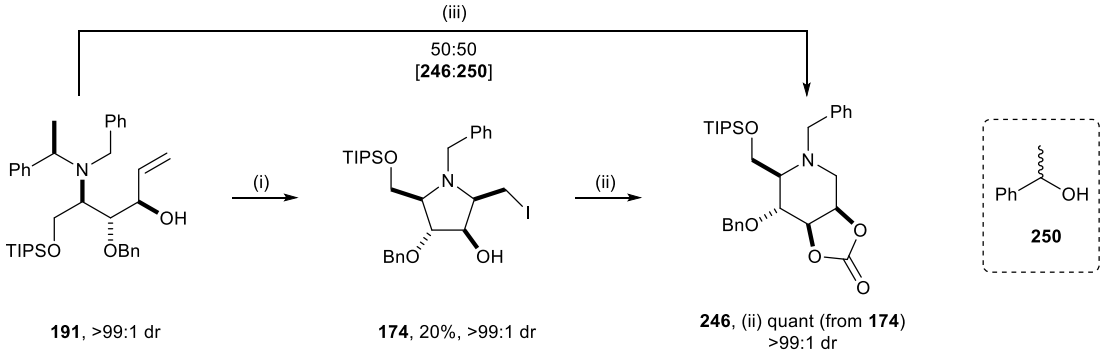
3.3. Development of a one-pot reaction to cyclic carbonate

Having successfully synthesised cyclic carbonate **246** from aziridinium **201**, attention next turned to the development of a one-pot procedure from either iodomethyl pyrrolidine **174** or bishomoallylic amine **191**, to give carbonate **246** directly. Treatment of iodomethyl pyrrolidine **174** with 3.0 equiv of $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) resulted in the formation of cyclic carbonate **246** in quantitative yield and >99:1 dr. This result suggested that formation of aziridinium **212** was spontaneously promoted under the mildly basic reaction conditions. Subjecting iodomethyl pyrrolidine **174** to a 3:1 mixture of dioxane/H_2O (i.e., omitting the addition of $NaHCO_3$) returned only starting material (Scheme 49).



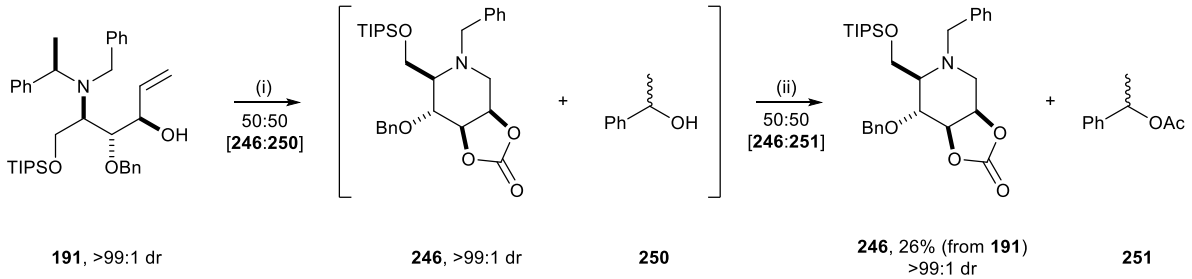
Scheme 49. *Reagents and conditions:* (i) $AgBF_4$, CH_2Cl_2, rt, 1 h; (ii) $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (iii) $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h.

Iodoamination of bishomoallylic amine **191** upon treatment with 3.0 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in MeCN gave iodomethyl pyrrolidine **174** in 20% yield, after chromatographic purification (*vide supra*). Since $NaHCO_3$ was already employed in these reaction conditions, it was next anticipated that substituting MeCN for a mixture of dioxane/H_2O (3:1) would promote the *in situ* generation of aziridinium **212** and the subsequent formation of cyclic carbonate **246**, via the trapping of CO_2 from $NaHCO_3$. Indeed, treatment of **191** with 3.0 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) resulted in the formation of a 50:50 mixture of cyclic carbonate **246** and the known α-methylbenzyl alcohol **250**[9] (derived from the S_N1-type loss of the α-methylbenzyl cation during the ring-closing iodoamination step). Unfortunately, attempts to separate **246** and **250** by flash column chromatography proved unsuccessful (Scheme 50).



Scheme 50. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (iii) I_2, $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h.

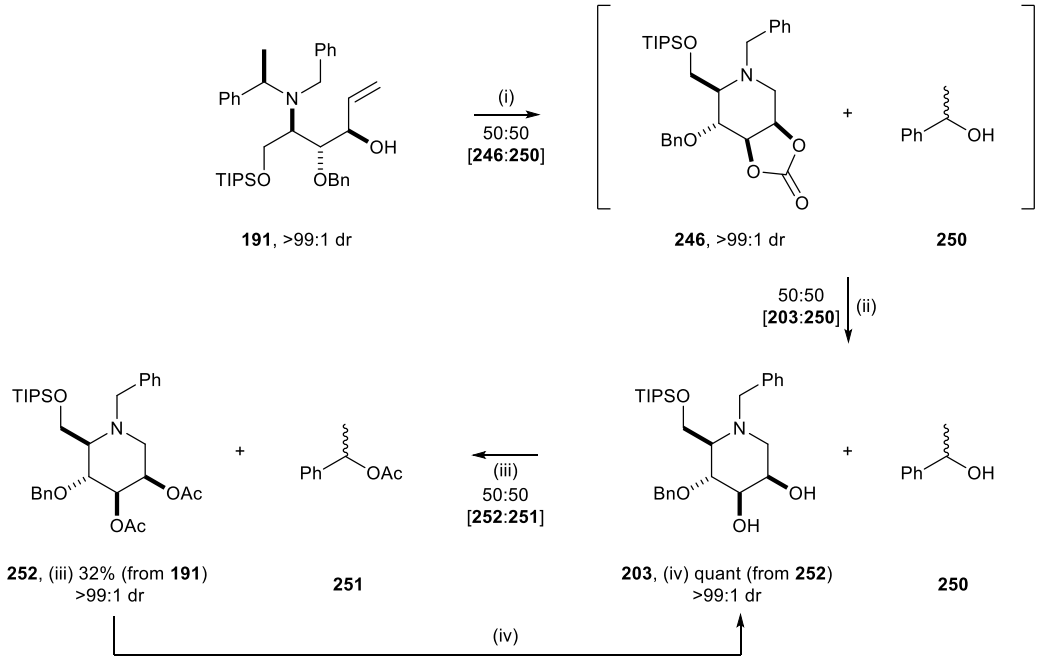
Direct acetylation of the crude reaction mixture of cyclic carbonate **246** and α-methylbenzyl alcohol **250** upon treatment with Ac_2O and pyridine facilitated the separation of **246** from α-methylbenzyl acetate **251**[10] by flash column chromatography, giving cyclic carbonate **246** in 26% isolated yield (over two steps from **191**) and >99:1 dr (Scheme 51).



Scheme 51. *Reagents and conditions:* (i) I_2, $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (ii) Ac_2O, pyridine, DMAP, 0 °C to rt, 16 h.

3.4. Optimised route to the piperidine scaffold

Building on this result, it was next anticipated that the purification of an alternatively protected piperidine would prove to be higher yielding than the isolation of cyclic carbonate **246**; therefore the development of a telescoped process for the synthesis of the corresponding diacetate **252** was investigated. Iodoamination of **191** upon treatment with I_2 and $NaHCO_3$ in a mixture of dioxane/H_2O (3:1), followed by direct methanolysis of the 50:50 mixture of **246** and **250** upon treatment with K_2CO_3 in MeOH furnished a 50:50 mixture of diol **203** and α-methylbenzyl alcohol **250**. Subsequent treatment of the crude reaction mixture with Ac_2O and pyridine afforded a 50:50 mixture of diacetate **252** and α-methylbenzyl acetate **251**, from which **252** was isolated in 32% yield over three steps (from **191**) as single diastereoisomer (>99:1 dr). Transesterification of **252** (isolated sample) upon treatment with K_2CO_3 in MeOH also allowed the synthesis of an authentic sample of diol **203** in quantitative yield and >99:1 dr (Scheme 52).



Scheme 52. *Reagents and conditions:* (i) I_2, $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (ii) K_2CO_3, MeOH, rt, 6 h; (iii) Ac_2O, pyridine, DMAP, 0 °C to rt, 16 h; (iv) K_2CO_3, MeOH, rt, 6 h.

A study of the relative configurations within piperidines **203** and **252** involving ^{1}H NMR ^3J coupling constant and ^{1}H NMR nOe analyses was initiated next. Following from the known configurations of the C(2), C(3) and C(4) stereogenic centres within **203**, it was envisaged that **203** would preferentially adopt conformation **203A**, where the C(2)-silyloxymethyl, C(3)-benzyloxy and C(4)-hydroxyl groups all occupy equatorial positions. In fact, although the $^3J_{2,3}$ and $^3J_{3,4}$ values of 8.1 Hz within **203** were found to be lower than expected,[11] they were still entirely diagnostic of the C(2)*H*, C(3)*H* and C(4)*H* protons occupying axial positions. A $^3J_{4,5}$ value of 3.3 Hz for **203**, along with a $^3J_{5,6ax}$ value of 4.6 Hz and a $^3J_{5,6eq}$ value of less than 2 Hz were all consistent with an axial-equatorial or equatorial-equatorial vicinal coupling, therefore suggesting that the C(4)*H* and C(5)*H* protons have a *cis*-relationship. Furthermore, ^{1}H NMR nOe analysis of **203** was consistent with the assigned relative configuration. Irradiation of the protons around the piperidine ring within **203** resulted in a series of reciprocal enhancements linking the C(2)*H*, C(4)*H*, C(5)*H*, C(6)H_{ax} and OCH_2Ph protons, which suggested that they occupy the same face of the piperidine ring. Similarly, analysis of the ^{1}H NMR ^3J coupling constants within **252** supported a *cis*-relationship between the C(4)*H* and C(5)*H* protons. The $^3J_{4,5}$ value of 3.2 Hz and the $^3J_{5,6ax}$ value of 6.2 Hz were consistent with axial-equatorial vicinal couplings, along with $^3J_{5,6eq}$ value of 2.6 Hz being consistent with an equatorial-equatorial vicinal coupling. In addition, reciprocal ^{1}H NMR nOe enhancements linking the C(2)*H*, C(4)*H*, C(5)*H*, C(6)H_{ax} and OCH_2Ph protons

were observed, suggesting that these protons also occupy the same face of the piperidine ring (Figure 20). Thus, these studies allowed confident assignment of the relative configurations within **203** and **252**, and also that within the synthetic precursor **246**; these assignments were later confirmed unambiguously via single crystal diffraction analysis of a derivative (*vide infra*).

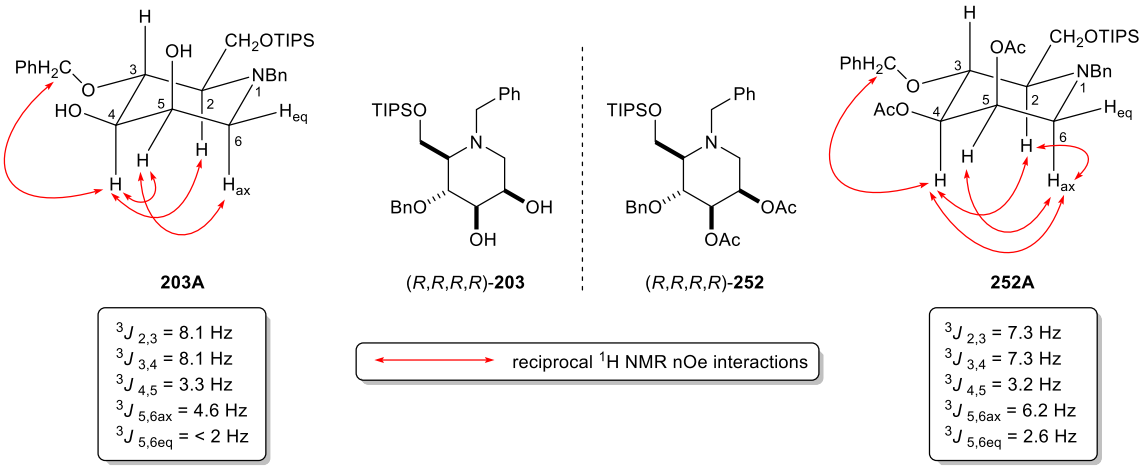
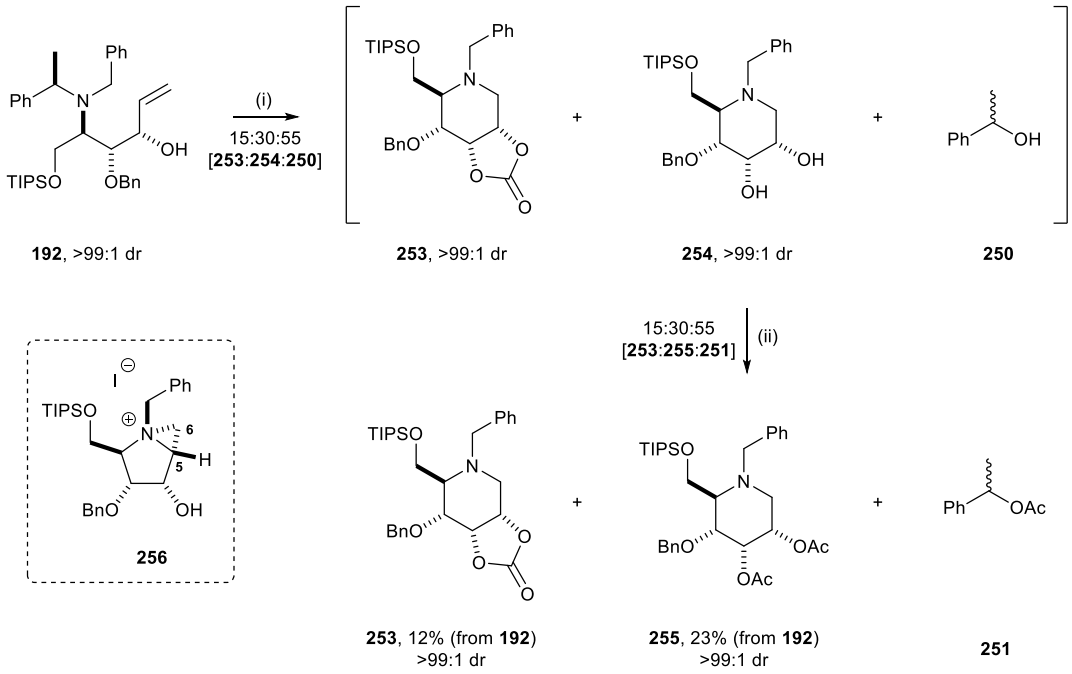


Figure 20. ^{1}H NMR ^{3}J coupling constant and ^{1}H NMR nOe analyses of **203** and **252**.

3.5. Ring-closing iodoamination/ring-expansion of epimeric bishomoallylic amine

It was next anticipated that the methodology developed on the ring-closing iodoamination/ring-expansion of bishomoallylic amine **191** could be applied to the epimeric substrate **192**, which was obtained as the minor diastereoisomer upon addition of vinylmagnesium bromide to aldehyde **190** (*vide supra*, Chapter 2). Thus, treatment of bishomoallylic amine **192** with I_2 and $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) gave a 15:30:55 mixture of cyclic carbonate **253**, diol **254** and α-methylbenzyl alcohol **250**. Subsequent acetylation of the crude reaction mixture to facilitate purification afforded a 15:30:55 mixture of **253**, **255** and **251**, respectively, from which cyclic carbonate **253** was isolated in 12% yield and >99:1 dr and diacetate **255** was isolated in 23% yield and >99:1 dr (Scheme 53). Full ^{1}H and ^{13}C NMR spectroscopic analyses of **253**, including an HMBC study, confirmed the connectivity within the bicyclic system; furthermore the IR spectrum of **253** displayed a diagnostic (ν_{max} = 1804 cm^{-1}) absorbance for the C=O bond of the carbonate moiety. The (*S*)-configuration of the newly formed C(5)-stereogenic centre within **253** was initially assigned by analogy to the stereochemical outcome of the ring-closing iodoamination and subsequent ring-expansion of **191**, and was later confirmed by single crystal X-ray diffraction analysis of a derivative (*vide infra*). The mixture of cyclic carbonate **253** and diol

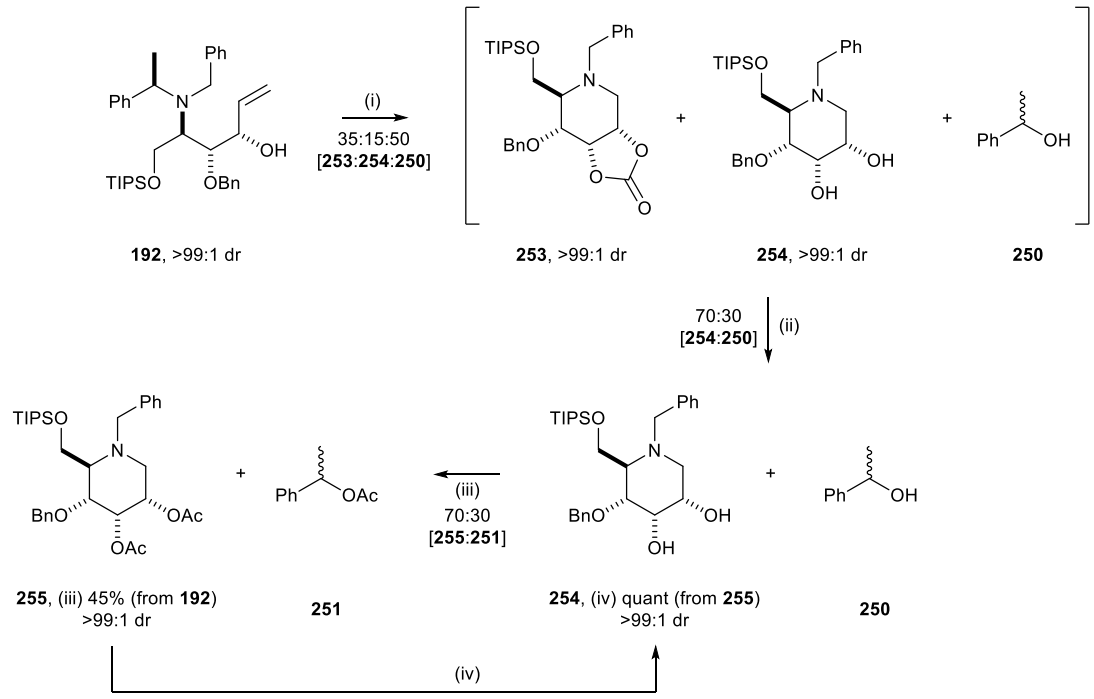
254 (33:67, [**253**:**254**]) produced during the one-pot ring-closing iodoamination/ring-expansion of **192** was in contrast with the sole formation of carbonate **246** when bishomoallylic amine **191** was treated under the same reaction conditions. The formation of diol **254** could be rationalised by either regioselective ring-opening of aziridinium **256** (which was produced *in situ* under the reaction conditions) by adventitious H_2O at the C(5)-position or partial hydrolysis of carbonate **253** upon work-up or a mixture of both pathways. The observation that **253** and **254** were obtained in different ratios upon repetition of the reaction is inconsistent with the ring-opening of **256** by H_2O (i.e., the first pathway) being responsible for the production of **254** alone (*vide infra*).



Scheme 53. *Reagents and conditions:* (i) I_2, $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (ii) Ac_2O, pyridine, DMAP, 0 °C to rt, 16 h.

By analogy to the isolation of diacetate **252**, it was next envisaged that the development of a telescoped process for the synthesis and purification of diacetate **255** would prove to be more efficacious. Iodoamination of **192** under the optimised reaction conditions, followed by methanolysis of the crude reaction mixture upon treatment with K_2CO_3 in MeOH furnished diol **254** as single diastereoisomer (along with by-product **250**), thereby confirming the homochirality of **253** and **254**. Subsequent acetylation of the mixture of **254** and **250** upon reaction with Ac_2O and pyridine gave a 70:30 mixture of **255** and **251**, from which diacetate **255** was isolated in 45% yield over three steps (from **192**) and >99:1 dr. An authentic sample

of diol **254** (>99:1 dr) was then obtained in quantitative yield upon transesterification of **255** with K_2CO_3 in MeOH (Scheme 54).



Scheme 54. *Reagents and conditions:* (i) I_2, $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (ii) K_2CO_3, MeOH, rt, 6 h; (iii) Ac_2O, pyridine, DMAP, 0 °C to rt, 16 h; (iv) K_2CO_3, MeOH, rt, 6 h.

Whilst most of the ^{1}H NMR ^3J coupling constants within diol **254** could not be determined due to the peaks in the ^{1}H NMR spectrum of **254** being broad, ^{1}H NMR ^3J coupling constant analysis of diacetate **255** allowed its relative configuration to be assigned. In fact, the $^3J_{2,3}$ value of 9.6 Hz (diagnostic of an axial-axial vicinal coupling), along with the $^3J_{3,4}$ value of 2.2 Hz (consistent with an axial-equatorial ^3J coupling) were consistent with **255** adopting chair conformation **255A**, where the C(2)-silyloxymethyl, C(3)-benzyloxy and C(5)-acetoxy groups all occupy equatorial positions. Although the $^3J_{4,5}$ and $^3J_{5.6eq}$ coupling constants could not be resolved, the $^3J_{5,6ax}$ value of 10.9 Hz was diagnostic of the C(5)*H* proton occupying an axial position, and therefore indicative of the C(4)*H* and C(5)*H* protons displaying a *cis*-relationship. Furthermore, ^{1}H NMR nOe analysis of **255** showed a series of enhancements linking the C(2)*H*, OCH_2Ph and OCO*Me* protons, suggesting that they all occupy the lower face of the piperidine ring. Similarly, a series of enhancements linking the C(3)*H*, C(4)*H*, C(5)*H* and C(6)H_{eq} protons were consistent with these protons all occupying the upper face of the piperidine ring (Figure 21). This study therefore confirmed the assigned relative configuration within **255**, and hence those within the synthetic precursors **254** and **253**; the absolute configurations of these compounds were assigned by reference to the known

configurations of the C(2), C(3) and C(4) stereogenic centres, and these assignments were later established unambiguously by single crystal X-ray diffraction analysis of a derivative (*vide infra*).

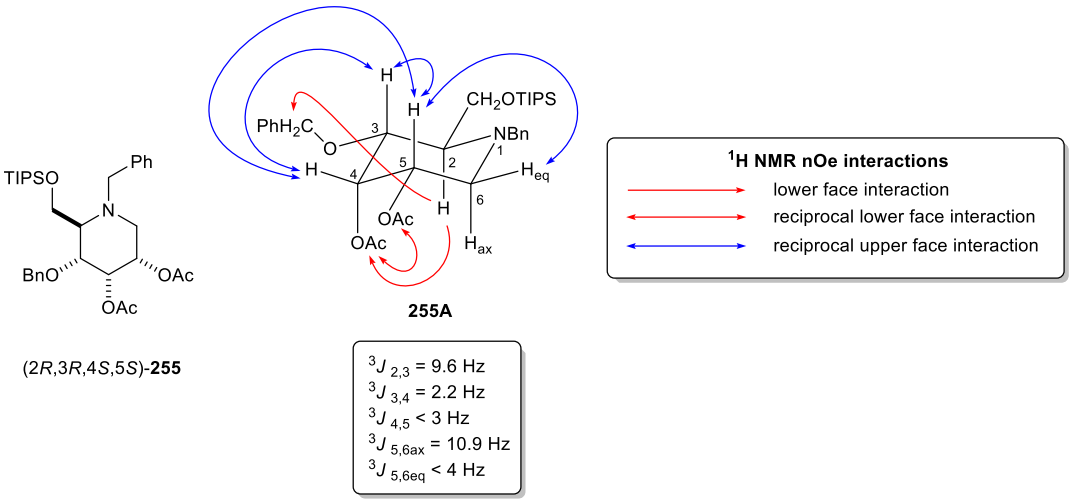
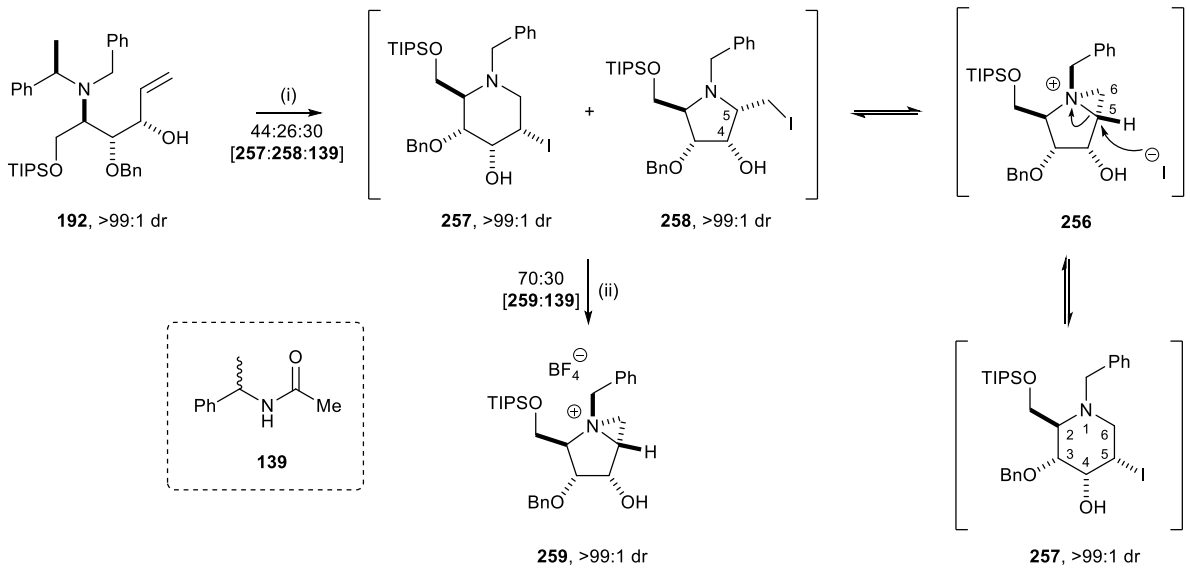


Figure 21. ^{1}H NMR ^{3}J coupling constant and ^{1}H NMR nOe analyses of **255**.

Interestingly, iodoamination of **192** using 3.0 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in MeCN resulted in the formation of a 44:26:30 mixture of piperidine **257**, pyrrolidine **258** and *N*-α-methylbenzyl acetamide **139**, respectively, as determined by inspection of the ^{1}H NMR spectrum of the crude reaction mixture in $CDCl_3$ (Scheme 55). This result was in contrast to the sole formation of iodomethyl pyrrolidine **174** (and acetamide **139**) when the epimeric bishomoallylic amine **191** was subjected to the same iodoamination conditions (*vide supra*, Chapter 2). Attempts to isolate piperidine **257** or pyrrolidine **258** upon purification by flash column chromatography were unsuccessful and led to degradation of the sample; therefore full ^{1}H and ^{13}C NMR spectroscopic analyses of the crude reaction mixture (which was obtained in 80% mass return) was utilised to support the identity and relative configurations of **257** and **258**. The (*S*)-configuration of the newly formed C(5)-stereogenic centre within pyrrolidine **258** was initially assigned by analogy to the stereochemical outcome of the ring-closing iodoamination of **191**, and this assignment was confirmed by the ^{13}C NMR value of the signal for the *C*H_2I carbon (δ_C = 3.4 ppm) being diagnostic of a *cis*-relationship between the C(4) and C(5) substituents (Figure 22).[12] The chemical shift of the carbon directly bonded to iodine in the ^{13}C NMR spectrum is diagnostic of the iodine being supported by a *C*H_2I carbon (i.e., a pyrrolidine scaffold) or a *C*HI carbon (i.e., a piperidine scaffold).[13] Whilst a value of 3.4 ppm was displayed for this carbon in iodomethyl pyrrolidine **258**, a value of 27.5 ppm was observed for this carbon in piperidine **257**. The predominant formation of piperidine

257 could be rationalised by the spontaneous conversion of pyrrolidine **258** to the corresponding aziridinium iodide **256** and its subsequent ring-opening with I^- at the C(5)-position with inversion of configuration. It was envisaged that the kinetic products of the reaction (i.e., a 63:37 mixture of **257** and **258**, respectively) could be driven to a thermodynamic product distribution by employing a more polar solvent (which would encourage the formation of **256**) to analyse the ^{1}H NMR spectrum of the crude reaction mixture. Indeed, recording the ^{1}H NMR spectrum in MeCN-d_3 led to the sole observation of piperidine **257**, thereby supporting the hypothesis that piperidine **257** and pyrrolidine **258** share a common origin. This latter spectrum of **257** allowed a full ^{1}H NMR ^3J coupling constant analysis of the piperidine **257** to be conduced, in support of the assigned *cis*-relationship between the C(4)*H* and C(5)*H* protons. The $^3J_{2,3}$ value of 9.8 Hz, the $^3J_{3,4}$ value of 2.7 Hz and the $^3J_{5,6ax}$ value of 11.3 Hz were all consistent with **257** adopting chair conformation **257A**, where the C(2)-silyloxymethyl, C(3)-benzyloxy and C(5)-iodo groups all occupy equatorial positions. Although the $^3J_{4,5}$ coupling constant could not be resolved, the $^3J_{5,6ax}$ value of 11.3 Hz was diagnostic of the C(5)*H* proton occupying an axial position; thereby allowing the relative configuration within **257** to be assigned (Figure 22). Subsequently, treatment of the 63:37 mixture of **257** and **258** with $AgBF_4$ promoted the sole formation of aziridinium **259** (which was obtained in quantitative mass return and characterised by NMR),[14] which again confirmed that piperidine **257** and pyrrolidine **258** share a common origin (Scheme 55).



Scheme 55. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) $AgBF_4$, CH_2Cl_2, rt, 1 h.

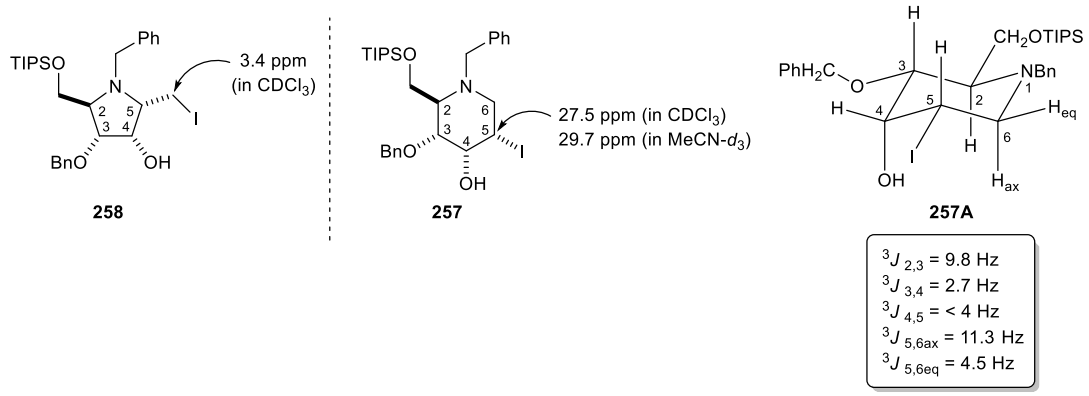
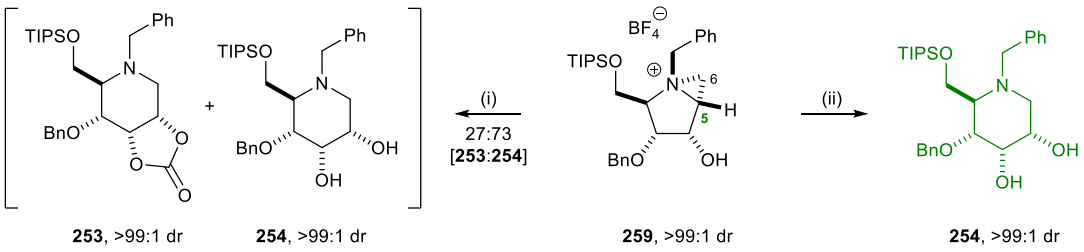


Figure 22. Diagnostic ^{13}C NMR chemical shifts for **257** and **258** and ^{1}H NMR ^{3}J coupling constant analysis of piperidine **257**.

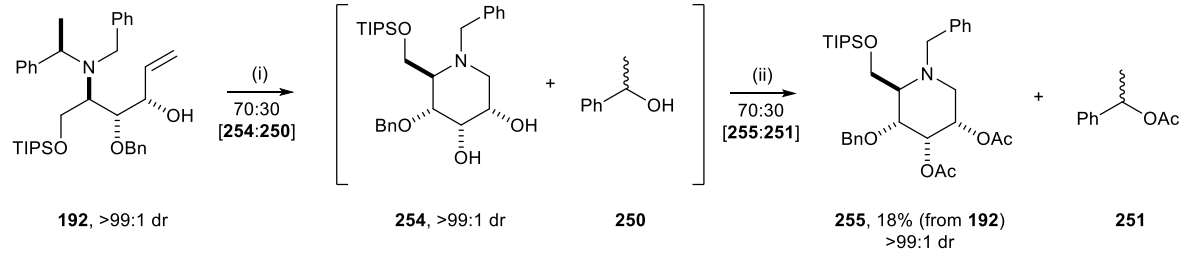
Subjection of the crude reaction mixture of aziridinium **259**[15] to the ring-expansion conditions upon treatment with $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) gave a mixture of carbonate **253** and diol **254**, as expected, this time in a 27:73 ratio. However, when aziridinium **259** was treated with a 3:1 mixture of dioxane/H_2O (i.e., omitting $NaHCO_3$), the intermolecular ring-opening of **259** by H_2O occurred at the C(5)-position to give piperidine **254** as single diastereoisomer (Scheme 56).[16] It is interesting to note that the regioselectivity of this ring-opening was in direct contrast with the regioselectivity of the ring-opening of epimeric aziridinium **201** by H_2O which occurred with high regioselectivity (90:10 ratio) at the C(6)-position to produce pyrrolidine **202** (*vide supra*, Chapter 2). This result could be rationalised by the formation of an intermolecular hydrogen bond between the hydroxyl moiety within **259** and H_2O, which may direct the ring-opening of aziridinium **259** at the C(5)-position (i.e., a tethered nucleophile), to give piperidine **254**.



Scheme 56. *Reagents and conditions:* (i) $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (ii) dioxane/H_2O (3:1), rt, 16 h.

It was next anticipated that the regioselective ring-opening of **259** by H_2O could be utilised to develop a one-pot procedure for the formation of piperidine **254** directly from bishomoallylic amine **192**. Thus, treatment of **192** with I_2 in a mixture of dioxane/H_2O (3:1) gave a 70:30 mixture of piperidine **254** and α-methylbenzyl alcohol **250**. Subsequent acetylation of the crude reaction mixture (for ease of purification) afforded a 70:30 mixture of diacetate **255** and α-methylbenzyl acetate **251** (Scheme 57). Unfortunately, diacetate **255** was isolated in only

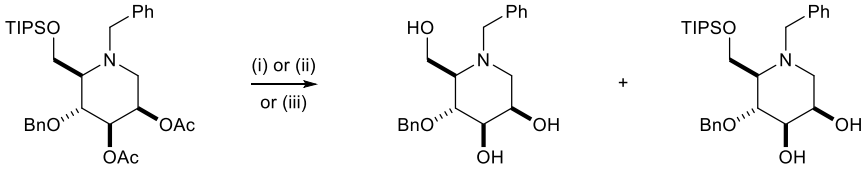
18% yield (from **192**) after column chromatography; therefore this approach was abandoned and the higher yielding protocol for the production of diacetate **255**, using the ring-expansion methodology (i.e., 45% yield from **192**) was therefore the preferred strategy.



Scheme 57. *Reagents and conditions:* (i) I_2, dioxane/H_2O (3:1), rt, 16 h; (ii) Ac_2O, pyridine, DMAP, 0 °C to rt, 16 h.

3.6. Deprotection towards iminosugars

With diacetates **252** and **255** in hand, attention next turned to the deprotection of the polyhydroxylated piperidine scaffold to give the corresponding triols. In the first instance, treatment of **252** with 3.0 M aq HCl at 50 °C for 3 h, followed by direct methanolysis of the residue upon treatment with K_2CO_3 in MeOH, resulted in the formation of a 70:30 mixture of triol **205** and diol **203**, respectively. Although subjection of **252** to 6.0 M aq HCl at 50 °C for 3 h led to incomplete *O*-desilylation (95:5, [**205**:**203**]), repetition of these conditions for 16 h allowed the reaction to reach completion to give triol **205** in 52% isolated yield and >99:1 dr, after chromatographic purification (Scheme 58).

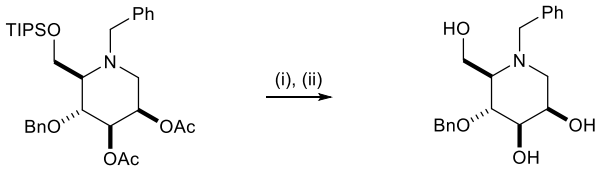


conditions	product ratio 205:203	yield of 205 [% (dr)]
(i)	70:30	-
(ii)	95:5	-
(iii)	100:0	52 (>99:1)

Scheme 58. *Reagents and conditions:* (i) 3.0 M aq HCl, 50 °C, 3 h, then K_2CO_3, MeOH, rt, 6 h; (ii) 6.0 M aq HCl, 50 °C, 3 h, then K_2CO_3, MeOH, rt, 6 h; (iii) 6.0 M aq HCl, 50 °C, 16 h, then K_2CO_3, MeOH, rt, 6 h.

In an attempt to improve the overall yield of these deprotections, an alternative *O*-desilylation procedure was next investigated. Thus, treatment of **252** with HF·pyridine in THF at 0 °C, followed by methanolysis of the crude reaction mixture led to the isolation of triol **205** in 70% yield and >99:1 dr (Scheme 59). The relative configuration within **205** was unambiguously

established by single crystal X-ray diffraction analysis;[17] furthermore, the determination of a Flack *x* parameter[18] of −0.09(12) for the structure of **205**·$CHCl_3$ allowed the assigned absolute (*R*,*R*,*R*,*R*)-configuration within **205** to be confirmed (Figure 23). This analysis also unambiguously established the absolute configurations within the synthetic precursors: diacetate **252**, diol **203**, and carbonate **246**.



252, >99:1 dr **205**, 70%, >99:1 dr

Scheme 59. *Reagents and conditions:* (i) HF·pyridine, THF, 0 °C to rt, 16 h; (ii) K_2CO_3, MeOH, rt, 6 h.

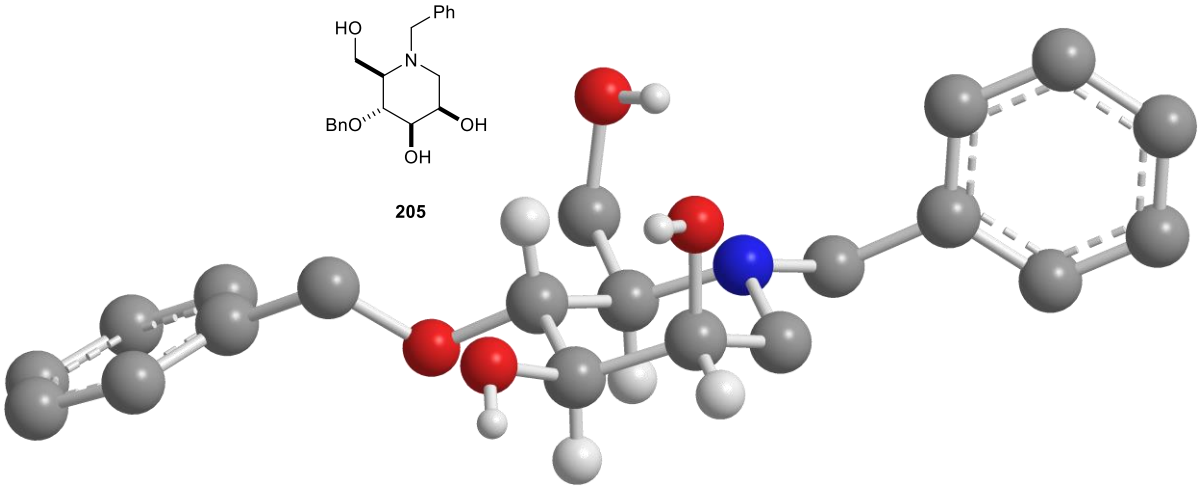
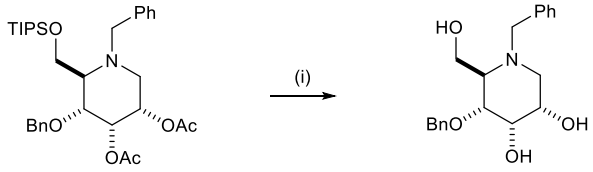


Figure 23. X-Ray crystal structure of (*R*,*R*,*R*,*R*)-**205**·$CHCl_3$ ($CHCl_3$ and selected H atoms have been omitted for clarity).

Similarly, *O*-silyl deprotection of diacetate **255** was first attempted under acidic conditions. Thus, treatment of **255** with 6.0 M aq HCl at 50 °C for 16 h and subsequent methanolysis afforded triol **260** in 86% yield and >99:1 dr, after chromatographic purification (Scheme 60). The relative configuration within **260** was unambiguously established by single crystal X-ray diffraction analysis;[17] furthermore, the determination of a Flack *x* parameter[18] of −0.05(16) for the structure of **260** allowed the assigned absolute (2*R*,3*R*,4*S*,5*S*)-configuration within **260** to be confirmed (Figure 24). This analysis also unambiguously established the absolute configurations within the synthetic precursors: diacetate **255**, diol **254**, and carbonate **253**.



255, >99:1 dr **260**, 86%, >99:1 dr

Scheme 60. *Reagents and conditions:* (i) 6.0 M aq HCl, 50 °C, 16 h, then K_2CO_3, MeOH, rt, 6 h.

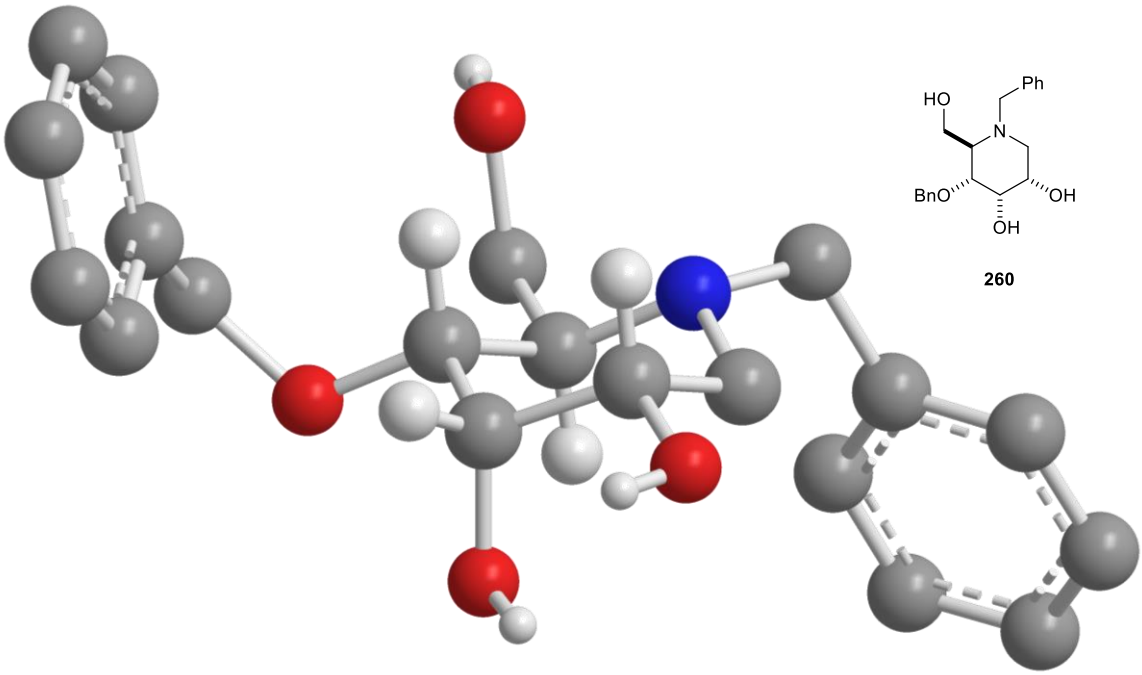
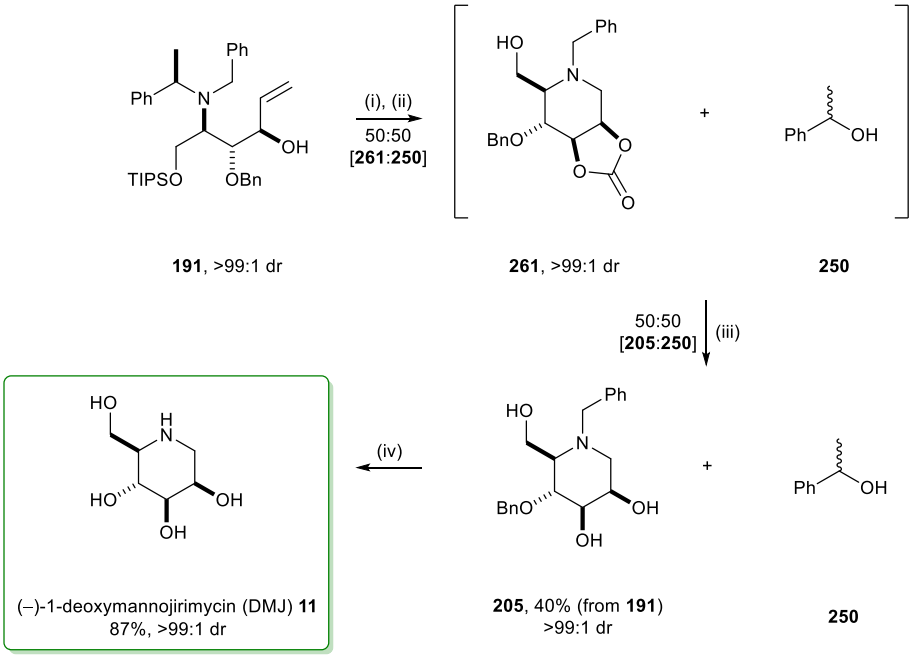


Figure 24. X-Ray crystal structure of (2*R*,3*R*,4*S*,5*S*)-**260** (selected H atoms have been omitted for clarity).

3.7. Optimised route to (–)-DMJ and (+)-DANJ

It was next anticipated that triol **205** could be synthesised efficiently by developing a telescoped process from bishomoallylic amine **191**, directly. Under the optimised conditions, iodoamination of **191** with I_2 and $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) followed by immediate *O*-desilylation of the crude reaction mixture, upon treatment with HF·pyridine, gave a 50:50 mixture of carbonate **261** (>99:1 dr) and α-methylbenzyl alcohol **250**. Subsequent methanolysis of the carbonate moiety within **261** furnished triol **205** which was isolated in 40% yield over three steps (from **191**) and >99:1 dr, after chromatographic purification. Hydrogenolytic *N*- and *O*-debenzylation of **205** upon treatment with Pearlman's catalyst [$Pd(OH)_2$/C] under an atmosphere of H_2 (5atm), followed by purification of this sample by ion exchange chromatography on Dowex 50WX8 (H^+ form) resin afforded (−)-1-deoxymannojirimycin (DMJ) **11** in 87% yield and >99:1 dr (Scheme 61).[19,20,21]



Scheme 61. *Reagents and conditions:* (i) I_2, $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (ii) HF·pyridine, THF, 0 °C to rt, 16 h; (iii) K_2CO_3, MeOH, rt, 6 h; (iv) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 48 h, then Dowex 50WX8 (H^+ form).

The melting point, specific rotation and ^1H and ^{13}C NMR spectra of this sample of (−)-1-deoxymannojirimycin **11** were in excellent agreement with those previously reported in the literature (Tables 6, 7 and 8).

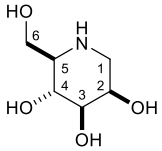
^{1}H NMR data for (−)-1-deoxymannojirimycin **11** in D_2O 						
H	Van Boom *et al.*[20a] δ_H (300 MHz)	Clapés *et al.*[20f] δ_H (400 MHz)	Jung *et al.*[20e] δ_H (400 MHz)	Cheng *et al.*[20h] δ_H (600 MHz)	Asano *et al.*[22] δ_H (400 MHz) (for *ent*-**11**)	This study δ_H (400 MHz)
C(1)H_A	2.95 dd *J* 14.0, 1.6	2.75 dd *J* 14.3, 1.2	2.77 d *J* 14.0	2.81 dd *J* 14.3, 1.4	2.77 dd *J* 14.2, 1.4	2.72 dd *J* 14.3, 1.4
C(1)H_B	3.12 dd *J* 14.0, 2.3	3.01 dd *J* 14.3, 2.7	3.01 d *J* 14.0	3.04 dd *J* 14.3, 2.8	3.01 dd *J* 14.2, 2.7	2.96 dd *J* 14.3, 2.7
C(2)*H*	4.09 dt *J* 3.2, 2.3	3.99 br dd *J* 4.4, 2.9	3.97 br s -	4.03 br -	4.01 ddd *J* 3.2, 2.7, 1.4	3.94-3.97 m -
C(3)*H*	3.61 dd *J* 9.7, 3.2	3.56 dd *J* 9.6, 3.1	3.51 dd *J* 10.0, 3.0	3.59 dd *J* 9.7, 3.2	3.58 dd *J* 9.6, 3.2	3.52 dd *J* 9.8, 2.9
C(4)*H*	3.71 t *J* 9.7	3.60 t *J* 9.3	3.58 t *J* 10.0	3.64 t *J* 9.7	3.62 t *J* 9.6	3.56 app t *J* 9.8
C(5)*H*	2.74 ddd *J* 5.3, 3.1	2.47 dt *J* 9.4, 3.8	2.52 br t *J* 4.5	2.54 dt *J* 9.7, 4.2	2.49 dt *J* 9.6, 4.1	2.44 dt *J* 9.8, 4.1
C(6)H_A	3.78 dd *J* 11.9, 5.3	3.76 d *J* 3.9	3.70-3.74 m -	3.80 d *J* 4.2	3.78 d -	3.73 d *J* 4.1
C(6)H_B	3.86 dd *J* 11.9, 3.1	3.76 d *J* 3.9	3.70-3.74 m -	3.80 d *J* 4.2	3.78 d -	3.73 d *J* 4.1

Table 6. Comparison of ^{1}H NMR data for the sample of (−)-1-deoxymannojirimycin **11** prepared in this study with representative examples from the literature [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

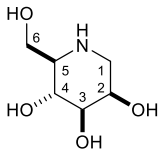
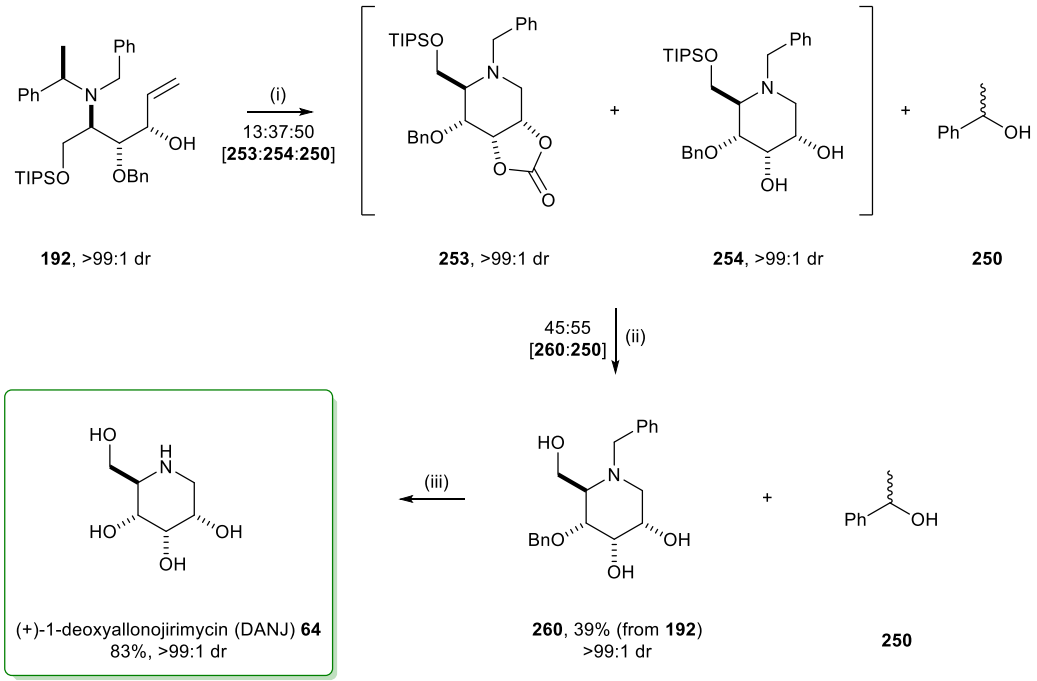
^{13}C NMR data for (−)-1-deoxymannojirimycin **11** in D_2O 							
C	Asano *et al.*[19b] δ_C (100 MHz) (isolation)	Van Boom *et al.*[20a] δ_C (50.1 MHz)	Clapés *et al.*[20f] δ_C (101 MHz)	Jung *et al.*[20e] δ_C (125 MHz)	Cheng *et al.*[20h] δ_C (150 MHz)	Asano *et al.*[22] δ_C (100 MHz) (for *ent*-**11**)	This study δ_C (100 MHz)
C(1)	51.5	50.5	50.8	48.30	48.1	51.0	48.1
C(2)	72.1	70.5	71.6	68.81	68.9	72.0	69.0
C(3)	77.5	76.3	77.0	74.39	74.3	77.4	74.4
C(4)	71.3	69.9	70.7	68.09	68.0	71.1	68.2
C(5)	63.4	63.0	63.1	60.48	60.4	63.2	60.4
C(6)	63.7	62.8	63.1	60.67	60.4	63.5	60.5

Table 7. Comparison of ^{13}C NMR data for the sample of (−)-1-deoxymannojirimycin **11** prepared in this study with representative examples from the literature [chemical shifts (δ_C) are reported in ppm].

Selected physical data for (−)-1-deoxymannojirimycin **11**		
	Specific rotation (H_2O)	Melting point (°C)
Asano *et al.*[19b] (isolation)	$[\alpha]_D$ −41.4 (*c* 0.74)	-
Van Boom *et al.*[20a]	$[\alpha]_D^{20}$ −40 (*c* 1.35)	185
Clapés *et al.*[20f]	$[\alpha]_D^{22}$ −36.1 (*c* 1.3)	-
Jung *et al.*[20e]	$[\alpha]_D^{25}$ −39.0 (*c* 0.1)	179-180
Xu *et al.*[20b]	-	185
Asano *et al.*[22] (for *ent*-**11**)	$[\alpha]_D$ +40.2 (*c* 0.65)	-
This study	$[\alpha]_D^{20}$ −38.6 (*c* 1.0)	180-182

Table 8. Comparison of the specific rotation and melting point of (−)-1-deoxymannojirimycin **11**.

Reaction of the epimeric bishomoallylic amine **192** with I_2 and $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) produced a 73:27 mixture of diol **254** and cyclic carbonate **253**, respectively (along with α-methylbenzyl alcohol **250**). Subsequent treatment of the crude reaction mixture with 6.0 M aq HCl, followed by immediate methanolysis furnished triol **260** in 39% yield over two steps (from **192**) as single diastereoisomer (>99:1 dr). Hydrogenolysis of **260** upon treatment with Pearlman's catalyst under an atmosphere of H_2 (5atm), followed by purification of this sample by ion exchange chromatography on Dowex 50WX8 (H^+ form) resin afforded (+)-1-deoxyallonojirimycin (DANJ) **64** in 83% yield and >99:1 dr (Scheme 62).[21,23,24]



Scheme 62. *Reagents and conditions:* (i) I_2, $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (ii) 6.0 M aq HCl, 50 °C, 16 h, then K_2CO_3, MeOH, rt, 6 h; (iii) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 48 h, then Dowex 50WX8 (H^+ form).

The melting point, specific rotation and ^1H and ^{13}C NMR spectra of this sample of (+)-1-deoxyallonojirimycin **64** were in excellent agreement with those previously reported in the literature (Tables 9, 10 and 11).

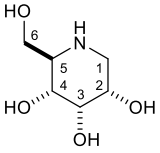
^{1}H NMR data for (+)-1-deoxyallonojirimycin **64** in D_2O 						
H	Asano *et al.*[19b] δ_H (400 MHz) (isolation)	Asano *et al.*[22] δ_H (400 MHz) (for *ent*-**64**)	Takahata *et al.*[24c] δ_H (300 MHz)	Ruiz *et al.*[24d] δ_H (400 MHz)	Ikota *et al.*[24a] δ_H (100 MHz)	Jung *et al.*[20e] δ_H (500 MHz)	This study δ_H (400 MHz)
C(1)H_A	2.78 dd *J* 13.2, 8.1	2.70 dd *J* 12.4, 11.4	2.55-2.67 m -	2.71 t *J* 11.7	2.39-2.87 m -	2.69 t *J* 12.0	2.65 app t *J* 11.8
C(1)H_B	2.99 dd *J* 13.2, 3.7	2.86 dd *J* 12.4, 5.0	2.76 dd *J* 12.0, 4.9	2.89 dd *J* 11.7, 5.2	2.39-2.87 m -	2.85 dd *J* 12.0, 5.0	2.81 dd *J* 11.8, 5.0
C(2)*H*	3.59-3.65 m -	3.71 ddd *J* 11.4, 5.0, 2.7	3.52-3.63 m -	3.72 ddd *J* 11.7, 5.2, 2.5	3.30-3.80 m -	3.65-3.69 m -	3.65 ddd *J* 11.8, 5.0, 2.8
C(3)*H*	3.59-3.65 m -	4.11 t *J* 2.7	4.00 br s -	4.13 br s -	3.90-4.05 m -	4.03 br s -	4.04 app t *J* 2.8
C(4)*H*	3.75 dd *J* 8.1, 4.4	3.49 dd *J* 10.1, 2.7	3.38 dd *J* 10.1, 2.5	3.50 dd *J* 11.0, 3.0	3.30-3.80 m -	3.46 dd *J* 10.0, 2.0	3.43 dd *J* 10.2, 2.8
C(5)*H*	3.19 ddd *J* 8.1, 6.2, 4.4	2.75 ddd *J* 10.1, 6.0, 3.2	2.55-2.67 m -	2.76 ddd *J* 11.6, 5.5, 3.0	2.39-2.87 m -	2.75-2.80 m -	2.70 ddd *J* 10.2, 5.8, 2.8
C(6)H_A	3.76-3.80 m -	3.66 dd *J* 11.4, 6.0	3.52-3.63 m -	3.66 dd *J* 11.0, 5.5	3.30-3.80 m -	3.61 dd *J* 12.0, 5.0	3.60 dd *J* 11.8, 5.8
C(6)H_B	3.76-3.80 m -	3.82 dd *J* 11.4, 3.2	3.71 dd *J* 11.5, 2.5	3.83 dd *J* 11.6, 3.0	3.30-3.80 m -	3.75 dd *J* 12.0, 3.0	3.75 dd *J* 11.8, 2.8

Table 9. Comparison of ^{1}H NMR data of (+)-1-deoxyallonojirimycin **64** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

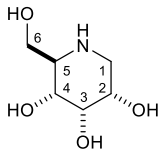
^{13}C NMR data for (+)-1-deoxyallonojirimycin **64** in D_2O 						
C	Asano *et al.*[19b] δ_C (100 MHz) (isolation)	Asano *et al.*[22] δ_C (100 MHz) (for *ent*-**64**)	Takahata *et al.*[24c] δ_C (75 MHz)	Ruiz *et al.*[24d] δ_C (100 MHz)	Ikota *et al.*[24a] δ_C (100 MHz)	Jung *et al.*[20e] δ_C (125 MHz)	This study δ_C (100 MHz)
C(1)	46.9	46.4	44.5	46.4	44.44	43.51	43.4
C(2)	72.7	71.0	69.0	71.0	68.91	67.80	67.8
C(3)	75.0	74.3	72.3	74.2	72.27	71.45	71.3
C(4)	73.3	71.5	69.5	71.5	69.39	68.36	68.3
C(5)	59.2	57.3	55.3	57.2	55.36	54.77	54.4
C(6)	60.7	64.2	62.2	64.2	62.03	60.96	60.9

Table 10. Comparison of ^{13}C NMR data of (+)-1-deoxyallonojirimycin **64** [chemical shifts (δ_C) are reported in ppm].

Physical data for (+)-1-deoxyallonojirimycin **64**		
	Specific rotation	Melting point (°C)
Asano *et al.*[19b] (isolation)	$[\alpha]_D^{20}$ +25.7 (*c* 0.65 in H_2O)	-
Ikota *et al.*[24a]	$[\alpha]_D$ +28.1 (*c* 0.8 in H_2O)	149-150
Hong *et al.*[20d]	$[\alpha]_D^{25}$ +30.5 (*c* 0.15 in H_2O)	149-150
Ruiz *et al.*[24d]	$[\alpha]_D^{25}$ +30.5 (*c* 1.0 in H_2O)	150-152
This study	$[\alpha]_D^{20}$ +28.3 (*c* 1.0 in H_2O)	162-164
Takahata *et al.*[24c]	$[\alpha]_D^{25}$ +36.2 (*c* 0.83 in MeOH)	165
Jung *et al.*[20e]	$[\alpha]_D^{25}$ +34.0 (*c* 0.1 in MeOH)	164-165
Sridhar *et al.*[24e]	$[\alpha]_D^{25}$ +35.1 (*c* 1.0 in MeOH)	163
Asano *et al.*[22] (for *ent*-**64**)	$[\alpha]_D$ −37.0 (*c* 1.04 in MeOH)	-
This study	$[\alpha]_D^{20}$ +30.2 (*c* 1.0 in MeOH)	162-164

Table 11. Comparison of the specific rotation and melting point of (+)-1-deoxyallonojirimycin **64**.

3.8. Summary

A protocol for the ring-expansion of iodomethyl pyrrolidine **174** was developed, proceeding via the intermediacy of aziridinium **201**, which was regioselectively ring-opened at the C(5)-position by a tethered nucleophile (following the formal trapping of CO_2 by the hydroxyl group within **201**) to give cyclic carbonate **246** as single diastereoisomer. One-pot ring-closing iodoamination/ring-expansion of bishomoallylic amine **191** proved efficacious to furnish **246**; subsequent deprotection afforded triol **205** in 40% yield and >99:1 dr. Similarly, treatment of epimeric bishomoallylic amine **192** with I_2 and $NaHCO_3$ gave a mixture of cyclic carbonate **253** and diol **254**, followed by immediate tandem *O*-desilylation/methanolysis afforded triol **260** in 39% yield and >99:1 dr. Finally, hydrogenolysis of **205** and **260** furnished (−)-DMJ **11** and (+)-DANJ **64** in 7.4% and 3.3% overall yield, respectively, from commercially available starting materials (Figure 25).

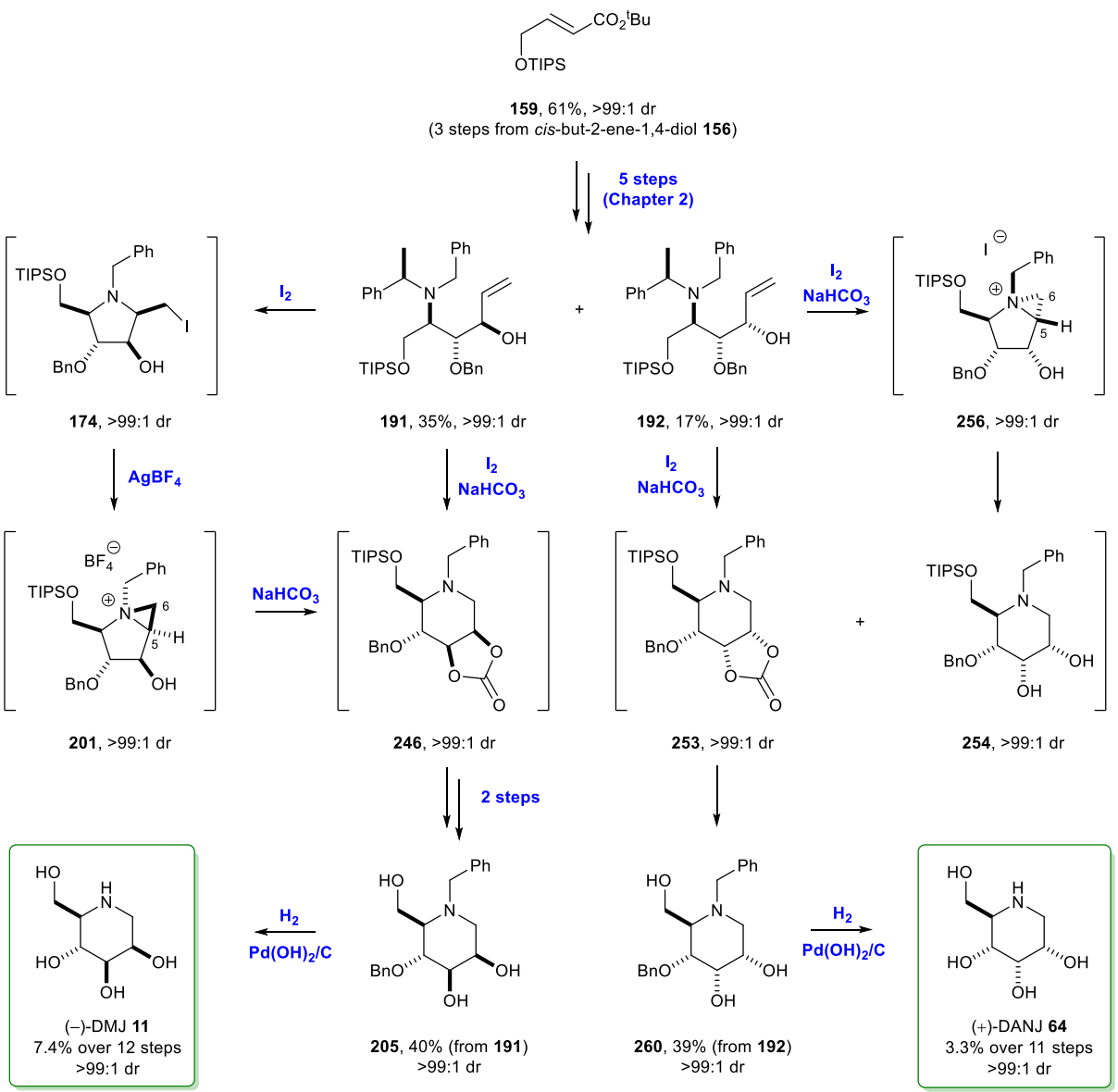


Figure 25. The total asymmetric syntheses of (−)-DMJ **11** and (+)-DANJ **64** via a ring-expansion approach.

3.9. References and notes

[1] Cresswell, A. J.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Tyte, M. J. *Org. Lett.* **2010**, *12*, 2936.

[2] The reaction outcome is consistent with the transfer of all three fluorine atoms from $BF_3{\cdot}OEt_2$. The necessity to use only 0.33 equiv of this reagent had been previously reported; see: Islas-González, G.; Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Riera, A.; Pericàs, M. A. *Tetrahedron Lett.* **2004**, *45*, 6337.

[3] Tomasini, C.; Vacchione, A. *Org. Lett.* **1999**, *1*, 2153.

[4] (a) Herlem, D.; Khuong-Huu, F. *Tetrahedron* **1997**, *53*, 673. (b) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

[5] Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209.

[6] Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626.

[7] Minakata, S.; Sasaki, I.; Ide, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1309.

[8] Venturello, C.; D'Aloisio, R. *Synthesis* **1985**, 33.

[9] Cao, L.; Ding, J.; Gao, M.; Wang, Z.; Li, J.; Wu, A. *Org. Lett.* **2009**, *11*, 3810.

[10] An authentic sample of **251** was synthesised in 85% yield and >99:1 dr from α-methylbenzyl alcohol **250** upon treatment with Ac_2O and pyridine.

[11] Axial-axial ^{1}H NMR ^3J coupling constants in a 6-membered ring system are typically reported to be >10 Hz; see: Clayden, J.; Greeves, N.; Warren, S. G. *Organic Chemistry*; Oxford University Press: Oxford, 2012.

[12] (a) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Russell, A. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758. (b) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett*. **1984**, *25*, 1063. (c) Palmer, A. M.; Jäger, V. *Synlett* **2000**, 1405.

[13] The ^{13}C NMR chemical shift for CH_2I carbons in pyrrolidines have been reported to be lower (typically δ_C = 1.5−12 ppm) than the carbon shift for *C*HI in piperidines (typically δ_C = 20−40 ppm) for similar substrates; see: Ref. 12a. See also compound **174** in Chapter 2 and compounds **288** and **289** in Chapter 4.

[14] The sp^2 character of *C*(6) within aziridinium **259** and presumably the $J_{C\text{-}H}$ coupling constants for C(6)H_A and C(6)H_B made the C(6)H_2 protons appear as if they were supported by different carbons in the HSQC spectrum. I would like to thank Prof. Tim Claridge for the discussion.

[15] Starting material **259** in Scheme 56 was contaminated with *N*-α-methylbenzyl acetamide **139**, as the crude reaction mixture of aziridinium **259** could not be purified due to the instability of **259** towards flash column chromatography.

[16] Diol **254** was obtained in 70% mass return; however this sample was not purified by column chromatography as the reaction was performed on a prohibitively small scale (~20 mg).

[17] X-Ray crystal structure determination was performed by Dr. J. E. Thomson and Dr. A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[18] (a) Flack, H. D. *Acta. Crystallogr., Sect. A* **1983**, *39*, 876. (b) Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908. (c) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.

[19] For selected references concerning the isolation of (−)-DMJ **11** from natural sources, see: (a) Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953. (b) Asano, N.; Oseki, K.; Kizu, H.; Matsui, K. *J. Med. Chem.* **1994**, *37*, 3701. (c) Kim, H. S.; Kim, Y. H.; Hong, Y. S.; Paek, N. S.; Lee, H. S.; Kim, T. H.; Kim, K. W.; Lee, J. J. *Planta Med.* **1999**, *65*, 437. (d) Kato, A.; Yamashita, Y.; Nakagawa, S.; Koike, Y.; Adachi, I.; Hollinshead, J.; Nash, R. J.; Ikeda, K.; Asano, N. *Bioorg. Med. Chem.* **2010**, *18*, 3790.

[20] For selected previous syntheses of (−)-DMJ **11**, see: (a) Broxterman, H. J. G.; Neefjes, J. J.; Van der Marel, G. A.; Ploegh, H. L.; Van Boom, J. H. *J. Carbohydr. Chem.* **1988**, *7*, 593. (b) Xu, X.-M.; Zhou, W.-S. *Tetrahedron Lett.* **1996**, *37*, 1461. (c) Berteau, O.; Sandstroem, C.; Bielicki, J.; Anson, D. S.; Kenne, L. *J. Am. Chem. Soc.* **2003**, *125*, 15296. (d) Hong, B.-C.; Chen, Z.-Y.; Nagarajan, A.; Kottani, R.; Chavan, V.; Chen, W.-H.; Jiang, Y.-F.; Zhang, S.-C.; Liao, J.-H; Sarshar, S. *Carbohydrate Res.* **2005**, *340*, 2457. (e) Kim, I. S.; Lee, H. Y.; Jung, Y. H. *Heterocycles* **2007**, *71*, 1787. (f) Concia, A. L.; Lozano, C.; Castillo, J. A.; Parella, T.; Joglar, J.; Clapés, P. *Chem. Eur. J.* **2009**, *15*, 3808. (g) Racine, E.; Bello, C.; Gerber-Lemaire, S.; Vogel, P.; Py,

S. *J. Org. Chem.* **2009**, *74*, 1766. (h) Chan, T. H.; Chang, Y. F.; Hsu, J. J. Cheng, W. C. *Eur. J. Org. Chem.* **2010**, 5555.

[21] Part of this work has been published, see: Davies, S. G.; Figuccia, A. L. A.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, *15*, 2042.

[22] Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036.

[23] For references concerning the isolation of (+)-DANJ **64** from natural sources, see: (a) Asano, N.; Yamauchi, T.; Kagamifuchi, K.; Shimizu, N.; Takahashi, S.; Takatsuka, H.; Ikeda, K.; Kizu, H.; Chuakul, W.; Kettawan, A.; Okamoto, T. *J. Nat. Prod.* **2005**, *68*, 1238. (b) Kato, A.; Kato, N.; Miyauchi, S.; Minoshima, Y.; Adachi, I.; Ikeda, K.; Asano, N.; Watson, A. A.; Nash, R. J. *Phytochemistry* **2008**, *69*, 1261. See also Ref. 19b and 22.

[24] For previous syntheses of (+)-DANJ **64**, see: (a) Ikota, N.; Hirano, J.-I.; Gamage, R.; Nakagawa, H.; Hama-Inaba, H. *Heterocycles* **1997**, *46*, 637. (b) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstorm, E. M. Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841. (c) Takahata, H.; Banba, Y.; Sasatani, M.; Nemoto, H.; Kato, A.; Adachi, I. *Tetrahedron* **2004**, *60*, 8199. (d) Ruiz, M.; Ruanova, T. M.; Blanco, O.; Nunez, F.; Pato, C.; Ojea, V. *J. Org. Chem.* **2008**, *73*, 2240. (e) Sridhar, R.; Srinivas, B.; Rao, K. *Tetrahedron* **2009**, *65*, 70701. See also Ref. 20d and 20e.

Chapter 4: Studies towards the Trapping of Alternative Electrophiles: Asymmetric Syntheses of (–)-ADMJ and (+)-ADANJ

This chapter describes investigations into the ring-expansion of iodomethyl pyrrolidines **214** via the trapping of "X=C=Y" electrophiles in the synthesis of bicyclic derivatives **262**. The application of this methodology in the asymmetric syntheses of (–)-ADMJ **112** and (+)-ADANJ **263**, the 2-deoxy-2-amino analogues of (–)-DMJ **11** and (+)-DANJ **64**, respectively, is also discussed (Figure 26).

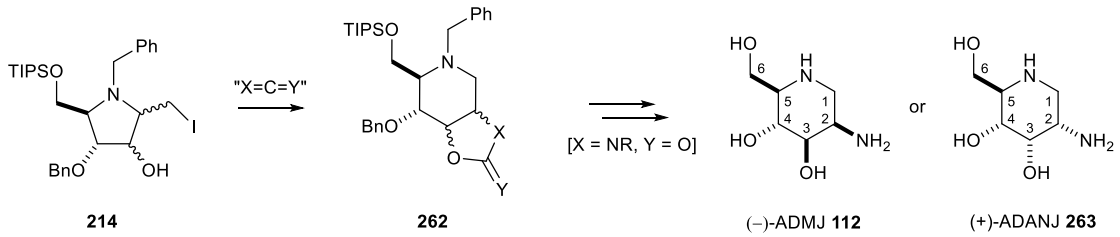


Figure 26. Strategy for the ring-expansion of iodomethyl pyrrolidines **214** via the trapping of "X=C=Y" electrophiles to piperidine iminosugar deoxy-amino analogues, (–)-ADMJ **112** and (+)-ADANJ **263**.

4.1. Chapter aims

Following the successful trapping of CO_2 in the ring-expansion of iodomethyl pyrrolidine **174** (*vide supra*, Chapter 3), it was envisaged that racemic bishomoallylic amine **264** could be utilised as a model substrate to investigate the trapping of alternative electrophiles and broaden the scope of the ring-expansion methodology. In the first instance, bishomoallylic amine **264** would be subjected to the ring-closing iodoamination/ring-expansion conditions via the trapping of CO_2, which should result in the regioselective ring-opening of aziridinium **265** at the C(5)-position by the tethered nucleophile, to give cyclic carbonate **266**. By analogy, it was anticipated that the trapping of alternative "X=C=Y" electrophiles (e.g., X, Y = O, NR, S) in the ring-expansion step would lead to the formation of the corresponding aziridiniums **267**, which could then undergo intramolecular cyclisation in a similar fashion, to give bicyclic derivatives **268** (Figure 27). The application of this methodology to enantiopure bishomoallylic amines **191** and **192** (which were synthesised in Chapter 2) and subsequent global deprotection of the piperidine scaffold would consequently allow access to analogues of (–)-DMJ **11** and (+)-DANJ **64**.

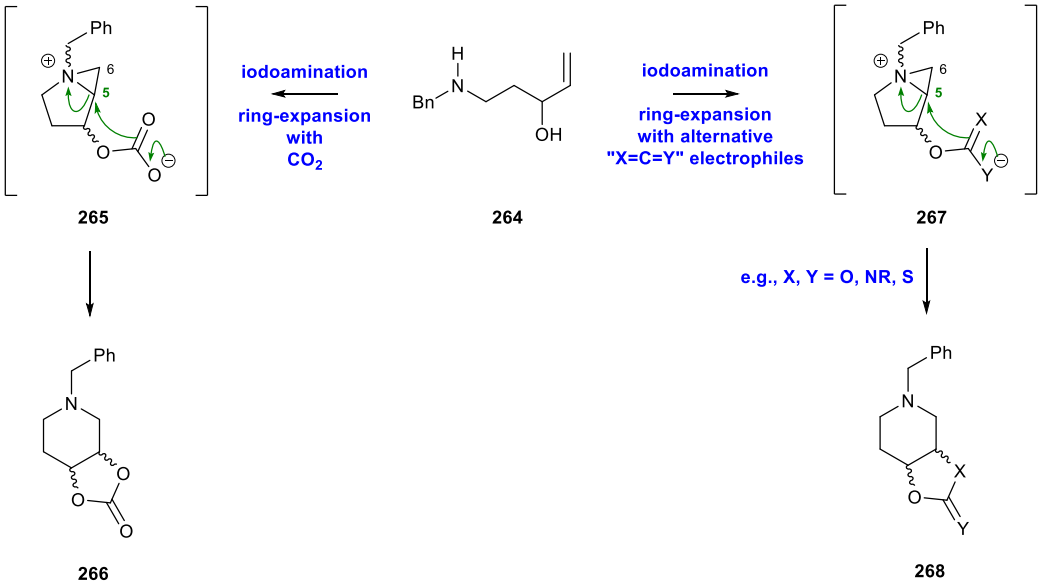
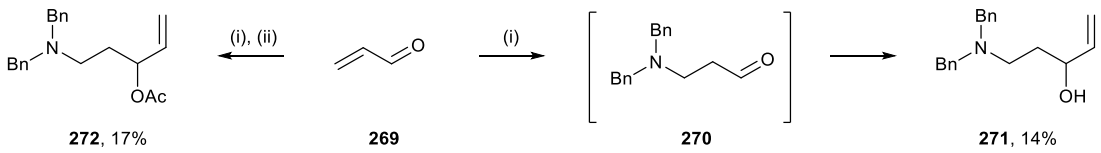


Figure 27. Methodology for the trapping of a range of "X=C=Y" electrophiles in the iodoamination/ ring-expansion of model substrate **264**.

4.2. Preparation of the requisite racemic bishomoallylic amine as a model substrate

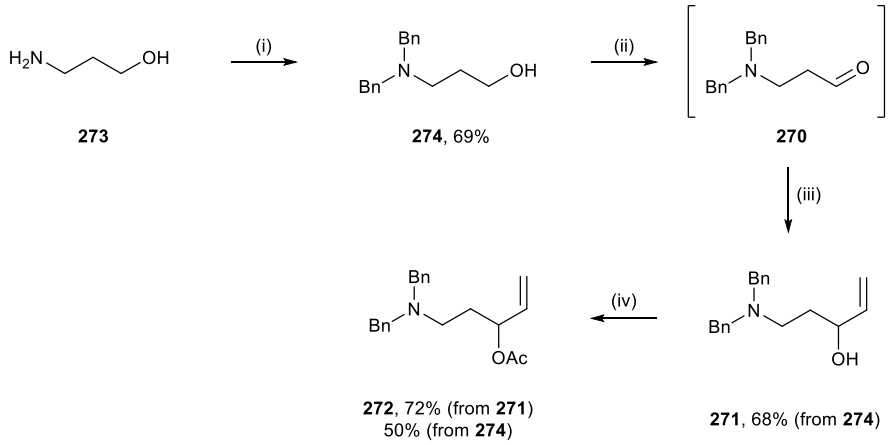
It was first envisaged that *N*,*N*-dibenzyl protected bishomoallylic amine **271** could be an easily accessible and useful precursor for the preparation of *N*-benzyl protected bishomoallylic amine **264**. Following a one-pot procedure developed by Marko *et al.* for the synthesis of related substrates,[1] treatment of acrolein **269** with $NHBn_2$ and DBU in THF at –15 °C followed by the addition of vinylmagnesium bromide resulted in the formation of *N*,*N*-dibenzyl protected bishomoallylic amine **271**.[2] Although **271** was observed as the major product of the reaction upon inspection of the ^{1}H NMR spectrum of the crude reaction mixture, **271** was isolated in only 14% yield after chromatographic purification. Repetition of the reaction and subsequent acetylation of the crude reaction mixture (in an effort to facilitate purification) proved unsuccessful at producing a higher overall yield for this process and acetate **272** was obtained in only 17% isolated yield (Scheme 63).



Scheme 63. *Reagents and conditions:* (i) $NHBn_2$, DBU, THF, –15 °C, 20 min, then CH_2=CHMgBr, –15 °C, 30 min; (ii) Ac_2O, pyridine, DMAP, 0 °C to rt, 16 h.

Attention next turned to the preparation of **271** from *N*,*N*-dibenzyl alcohol **274**, which was readily obtained in 69% isolated yield upon treatment of amino alcohol **273** with BnBr and K_2CO_3.[3] Oxidation of the hydroxyl moiety within **274** under Swern conditions gave the

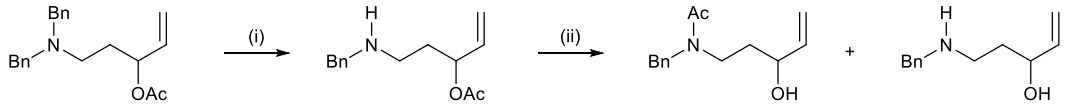
corresponding aldehyde **270**, which underwent reaction with vinylmagnesium bromide to furnish bishomoallylic amine **271** in 68% yield over two steps, after chromatographic purification. Previous investigations by Davies *et al.* have demonstrated that protection of any free hydroxyl group within a substrate was required in order to achieve monodebenzylation of an *N*,*N*-dibenzyl-amino moiety using CAN.[4,5] Thus, treatment of an analytically pure sample of **271** with Ac_2O and DMAP delivered acetate **272** in 72% yield. A telescoped process (i.e., omitting the purification of alcohol **271**) was consequently employed to obtain **272** in 50% yield over three steps (from **274**) on multigram scales (Scheme 64).



Scheme 64. *Reagents and conditions:* (i) BnBr, K_2CO_3, acetone, rt, 16 h; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 40 min, then Et_3N, −78 °C to rt, 1 h; (iii) CH_2=CHMgBr, THF, 0 °C to rt, 16 h; (iv) Ac_2O, pyridine, DMAP, 0 °C to rt, 16 h.

Under optimised conditions,[6] monodebenzylation of *N*,*N*-dibenzyl protected amine **272** upon treatment with CAN delivered *N*-benzyl substituted amine **275** in quantitative yield. Deprotection of the *O*-acetyl moiety within **275** was first investigated under acidic conditions. Treatment of **275** with 2.0 M HCl in MeOH at rt resulted in the formation of an 8:53:39 mixture of starting material **275**, acetamide **276** and amine **264**, respectively. Purification of the crude reaction mixture upon flash column chromatography afforded **276** in 39% yield and **264** in 15% yield. Full ^{1}H and ^{13}C NMR spectroscopic analyses of **276**, including a ^{1}H–^{13}C HMBC study, confirmed the structures of **275** and **276**. As the reaction proceeded with competing acyl transfer, **275** was next submitted to 6.0 M aq HCl at 50 °C in the hope of effecting both *N*-acetyl and *O*-acetyl deprotection. Unfortunately, these conditions led to degradation of the sample, presumably due to the formation of the corresponding allylic cation, thus attention next turned to the use of basic conditions. Methanolysis of **275** upon treatment with K_2CO_3 in MeOH gave an 80:20 mixture of **276** and **264**, respectively, whilst

subjection of **275** to 1.0 M aq KOH in MeOH/H_2O (1:1) at rt for 4 h[7] resulted in the sole formation of acetamide **276**. Performing this latter reaction at 50 °C for 16 h showed signs of *N*-acetyl deprotection; thus it was anticipated that an increase in the reaction temperature would help to drive the conversion to **264** further. Although repetition of the reaction at 100 °C for 2 h gave a 40:60 mixture of **276** and **264**, respectively, conducting the reaction at 100 °C for 16 h allowed the reaction to reach completion. Unfortunately, **264** was isolated in only 32% yield after purification via flash column chromatography (Scheme 65).

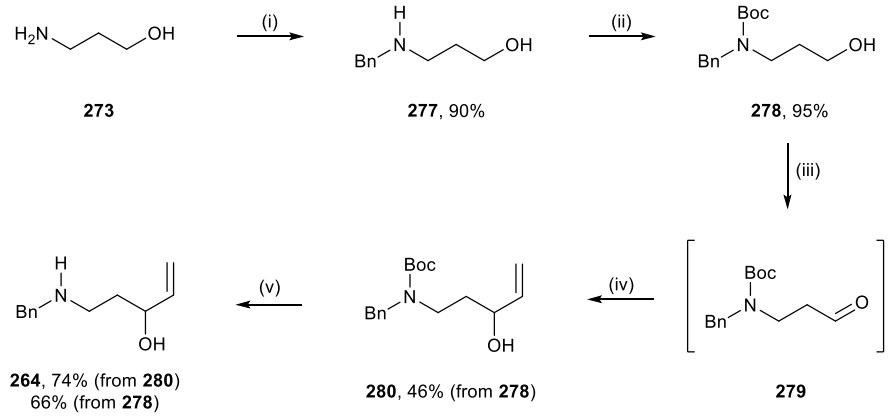


272 **275**, quant **276** **264**

acid/base	solvent	temperature/ time	crude ratio [275:276:264]	isolated yield of 276 (%)	isolated yield of 264 (%)
HCl (2.0 M)	MeOH	rt / 16 h	8:53:39	39	15
HCl (6.0 M)	H_2O	50 °C / 3 h	degradation	-	-
K_2CO_3	MeOH	rt / 16 h	0:80:20	68	-
KOH (1.0 M)	MeOH/H_2O (1:1)	rt / 4 h	0:100:0	-	-
KOH (1.0 M)	MeOH/H_2O (1:1)	50 °C / 16 h	0:70:30	-	-
KOH (1.0 M)	MeOH/H_2O (1:1)	100 °C / 2 h	0:40:60	-	-
KOH (1.0 M)	MeOH/H_2O (1:1)	100 °C / 16 h	0:0:100	-	32

Scheme 65. *Reagents and conditions:* (i) CAN, MeCN/H_2O (5:1), rt, 16 h; (ii) see table.

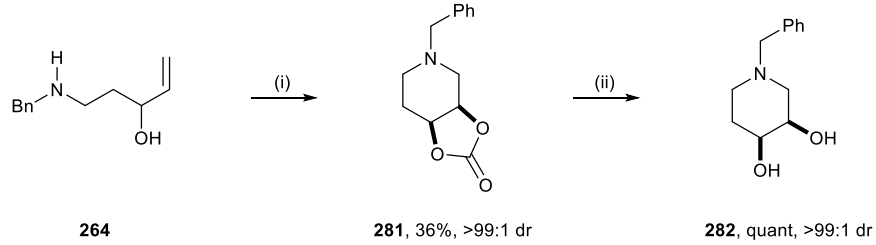
As the *O*-acetyl deprotection of **275** proved difficult and low yielding, it was next envisaged that the synthesis of *N*-Boc-*N*-benzyl protected bishomoallylic amine **280** would allow access to *N*-benzyl amine **264** without the requirement for protection of the free hydroxyl moiety within **280**. Thus, monobenzylation of amino alcohol **273** upon treatment with benzaldehyde and $CH(OMe)_3$ followed by $NaBH_4$ gave *N*-benzyl substituted amino alcohol **277** in 90% yield.[8] Subsequent reaction of **277** with $(Boc)_2O$ in a mixture of CH_2Cl_2 and 1.0 M aq NaOH (5:1) at 0 °C delivered *N*-Boc-*N*-benzyl protected amino alcohol **278** in 95% yield.[9] Oxidation of the primary alcohol moiety within **278** under Swern conditions, followed by direct treatment of the crude reaction mixture of aldehyde **279** with vinylmagnesium bromide afforded bishomoallylic amine **280** in 46% yield over two steps (from **278**). Subjection of **280** to 1.25 M HCl in MeOH at 40 °C effected *N*-Boc deprotection and *N*-benzyl substituted bishomoallylic amine **264** was isolated in 74% yield, after chromatographic purification. Repetition of this procedure while omitting the purification of **280** led to the production of **264** in 66% isolated yield over three steps (from **278**) on multigram scales (Scheme 66).



Scheme 66. *Reagents and conditions:* (i) PhCHO, $CH(OMe)_3$, rt, 5 h, then $NaBH_4$, 0 °C to rt, 15 min; (ii) $(Boc)_2O$, CH_2Cl_2/1.0 M aq NaOH (5:1), 0 °C to rt, 16 h; (iii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 40 min, then Et_3N, −78 °C to rt, 1 h; (iv) CH_2=CHMgBr, THF, 0 °C to rt, 16 h; (v) HCl (1.25 M in MeOH), 40 °C, 16 h.

4.3. Ring-closing iodoamination/ring-expansion of the model substrate bishomoallylic amine via the trapping of CO_2

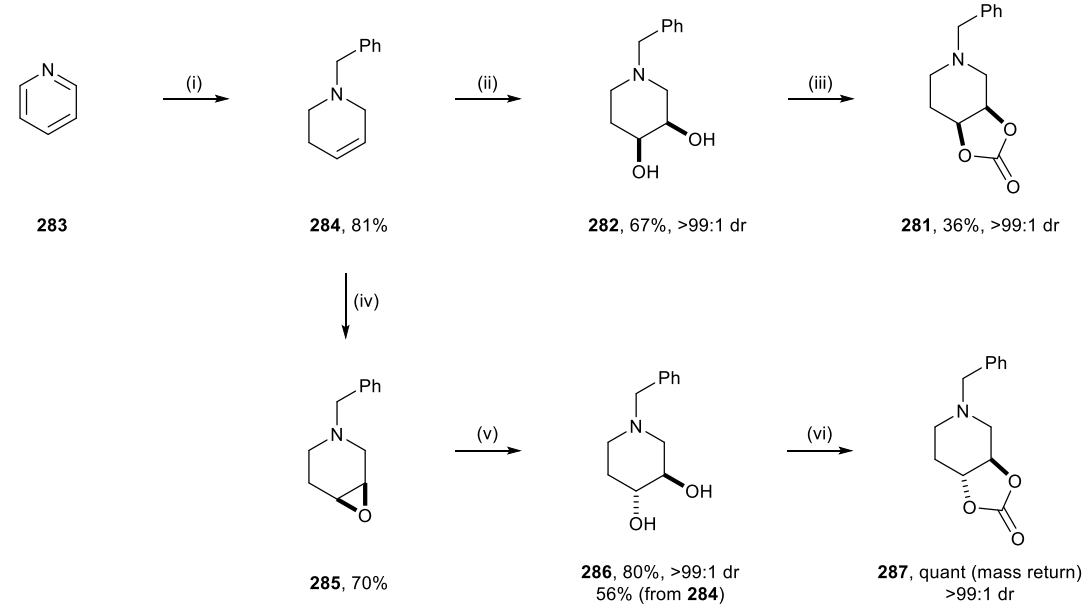
With bishomoallylic amine **264** in hand, it was now possible to commence investigations into the ring-closing iodoamination/ring-expansion of **264** using the previously optimised conditions developed for the trapping of CO_2 in the corresponding one-pot reaction of bishomoallylic amines **191** and **192** (*vide supra*, Chapter 3). Thus, treatment of **264** with 3.0 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) resulted in the formation of cyclic carbonate **281**. Although **281** was observed as the major compound in the ^{1}H NMR spectrum of the crude reaction mixture, **281** was isolated in only 36% yield after flash column chromatography. Full ^{1}H and ^{13}C NMR spectroscopic analyses of **281** supported the identity of the assigned bicyclic system; furthermore the IR spectrum of **281** displayed a diagnostic C=O absorbance at 1799 cm^{-1} that confirmed the presence of a carbonate moiety. Methanolysis of an analytical pure sample of **281** upon treatment with K_2CO_3 and MeOH afforded diol **282** in quantitative yield (Scheme 67). Analysis of the ^{1}H NMR ^3J coupling constants within **282** proved difficult due to the peaks in the ^{1}H NMR spectrum of **282** (recorded in $CDCl_3$) being broad;[10] thus the assigned relative configuration within diol **282**, and within the carbonate precursor **281**, were confirmed via chemical correlation upon preparation of authentic samples of **282** and **281**.



264 **281**, 36%, >99:1 dr **282**, quant, >99:1 dr

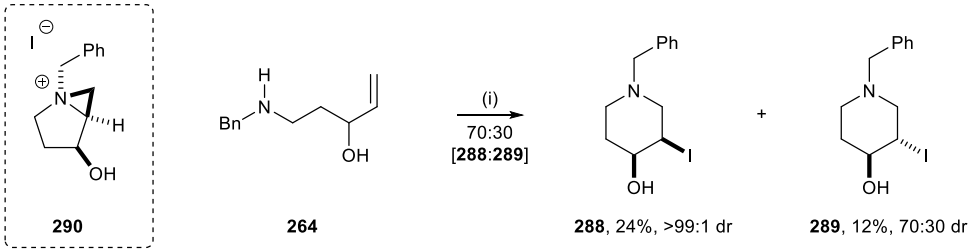
Scheme 67. *Reagents and conditions:* (i) I_2, $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h; (ii) K_2CO_3, MeOH, rt, 16 h.

It was anticipated that tetrahydropyridine **284** would be the ideal common precursor for the syntheses of authentic samples of both *cis*-diol **282**[11] and *trans*-diol **286**[12] (and the corresponding carbonates *cis*-**281** and *trans*-**287**). The preparation of **284** was achieved via the reduction of a pyridine scaffold following a literature procedure:[13] treatment of **283** with BnCl at 140 °C followed by reduction of the corresponding ammonium species with $NaBH_4$ delivered tetrahydropyridine **284**[13] in 81% yield. Stereospecific dihydroxylation[14] of **284** upon treatment with OsO_4 and NMO (i.e., under Upjohn conditions[15]) in a mixture of THF/H_2O (5:1) gave *cis*-diol **282**, which was isolated in 67% yield after purification via flash column chromatography. Alternatively, epoxidation of the corresponding ammonium salt of **284** (to prevent *N*-oxidation) using HBF_4 and *m*-CPBA in CH_2Cl_2 produced epoxide **285**,[14] which underwent reaction with H_2SO_4 in dioxane/H_2O (40:1) to furnish *trans*-diol **286** in 56% yield over two steps.[16] In addition, authentic samples of *cis*-carbonate **281** and *trans*-carbonate **287** were synthesised from *cis*-diol **282** and *trans*-diol **286**, respectively. Thus, treatment of *cis*-diol **282** with CDI and DMAP in THF led to the complete conversion into *cis*-carbonate **281**, which was observed as the sole product of the reaction in the ^{1}H NMR spectrum of the crude reaction mixture and was subsequently isolated in 36% yield, after column chromatography. The preparation of *trans*-carbonate **287** using similar conditions required 4 days to reach completion and **287** was characterised as the sole product of the reaction upon inspection of the ^{1}H NMR spectrum of the crude reaction mixture. Attempted purification of *trans*-**287** by flash column chromatography led to its degradation, therefore full ^{1}H and ^{13}C NMR spectroscopic analyses were recorded using the crude reaction mixture (Scheme 68). The comparison of the ^{1}H NMR spectra of these authentic samples of *cis*-carbonate **281** and *trans*-carbonate **287** with the ^{1}H NMR spectrum of the ring-closing iodoamination/ring-expansion product **281**, along with the analogous comparison of the authentic samples of *cis*-diol **282** and *trans*-diol **286** with the sample of **282**, which derived from carbonate **281**, confirmed the assigned relative configuration within both **281** and **282**.



Scheme 68. *Reagents and conditions:* (i) BnCl, 140 °C, 1 h, then $NaBH_4$, EtOH, 0 °C to rt, 16 h; (ii) OsO_4, NMO, THF/H_2O (5:2), rt, 16 h; (iii) CDI, DMAP, THF, rt, 24 h; (iv) 40% aq HBF_4, CH_2Cl_2, rt, 5 min, then *m*-CPBA, CH_2Cl_2, 0 °C to rt, 16 h; (v) H_2SO_4, dioxane/H_2O (40:1), rt, 16 h; (vi) CDI, DMAP, THF, rt, 4 days.

Having established that the conditions developed for the trapping of CO_2 could be applied in the one-pot ring-closing iodoamination/ring-expansion of the model substrate **264**, a study into the mechanism of reaction was next initiated. Iodoamination of **264**[17] upon treatment with 3.0 equiv of I_2 and 3.0 equiv of $NaHCO_3$ in MeCN resulted in the formation of a 70:30 mixture of iodopiperidines **288** and **289**, respectively. Although the crude reaction mixture was obtained in quantitative mass return, the purification of **288** and **289** upon flash column chromatography proved difficult and only **288** could be isolated as a pure sample in 24% yield. An enriched sample of **289**[18] (70:30 dr) was nonetheless collected in 12% yield, and was subsequently employed to confirm the structure and stereochemistry within **289** (Scheme 69). The formation of iodopiperidines **288** and **289** (i.e., a six-membered ring) in the iodoamination of **264** was in direct contrast with the formation of iodomethyl pyrrolidine **174** (i.e., a five-membered ring) when bishomoallylic amine **191** was subjected to the same iodoamination conditions (*vide supra*, Chapter 2). This reaction outcome could be rationalised by either 5-*exo* cyclisation of the corresponding iodonium species of **264** followed by rearrangement (presumably via the intermediacy of aziridinium **290**) or 6-*endo* type cyclisation.



Scheme 69. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h.

The relative configuration within **288** was unambiguously established by single crystal X-ray diffraction analysis[19] (Figure 28). Full ^{1}H and ^{13}C NMR spectroscopic analyses of **289**, including a ^{1}H–^{13}C HMBC study, supported the connectivity within **289**. It was interesting to note that the chemical shift of the carbon directly bonded to iodine in the ^{13}C NMR spectrum of **289** (δ_C = 38.4 ppm) was diagnostic of the iodine being supported by a *C*HI carbon (i.e., a piperidine scaffold) as opposed to a *C*H$_2$I carbon (i.e., a pyrrolidine scaffold).[20] The ^{1}H NMR ^3J coupling constant analysis of this sample of **289** allowed the relative configuration within **289** to be established. It was anticipated that **289** would preferentially adopt chair conformation **289A**, where the C(3)-iodo and the C(4)-hydroxy groups both occupy equatorial positions. The $^3J_{2ax,3}$ value of 11.5 Hz, the $^3J_{3,4}$ value of 9.8 Hz, and the $^3J_{4,5ax}$ value of 10.8 Hz were all diagnostic of **289** adopting chair conformation **289A** and were consistent with the C(3)*H* proton and the C(4)*H* proton occupying axial positions, thereby confirming the assigned *trans*-configuration within **289**. In contrast to the sharp peaks displayed by the ^{1}H NMR spectrum of **289** (in $CDCl_3$), the peaks observed in the ^{1}H NMR spectrum of **288** (in $CDCl_3$) were extremely broad[21] and only a limited number of correlations could be distinguished in the ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC NMR spectra. A study involving the recording of the ^{1}H and ^{13}C NMR spectra of **288** at high temperature was consequently initiated. Full ^{1}H and ^{13}C NMR spectroscopic analyses of **288** in PhMe-d_8 at 363 K allowed the peaks in these 1D NMR spectra to be resolved and correlations between these peaks were also observed in the corresponding 2D NMR spectra; these data were all consistent with the assigned structure of **288**. The chemical shift of *C*(3) in the ^{13}C NMR spectrum of **288** (δ_C = 39.7 ppm, PhMe-d_8) was also consistent with previous observations concerning this class of iodopiperidines.[20] Since the ^{1}H NMR spectrum of **288** had broad peaks at rt (in $CDCl_3$), it was next envisaged that recording the ^{1}H NMR spectrum of **288** at low temperature would allow observation of two distinct conformers. Although two compounds were clearly distinguished upon inspection of the ^{1}H NMR spectrum of **288**

recorded in PhMe-d_8 at 208 K, the relative configuration within the two conformers could not be determined by ^{1}H NMR ^3J coupling constant analyses due to insufficient dispersion of peaks. However, analyses of the ^3J coupling constants in the ^{1}H NMR spectrum of **288** recorded in PhMe-d_8 at 363 K were consistent with chair conformation **288A** being the predominant conformer at equilibrium. The $^3J_{2ax,3}$ value of 8.8 Hz, the $^3J_{3,4}$ value of 3.0 Hz, the $^3J_{4,5ax}$ value of < 3.0 Hz and the $^3J_{4,5eq}$ value of < 3.0 Hz all suggest that **288** adopts chair conformation **288A**, where the C(3)-iodo group occupies an equatorial position and the C(4)-hydroxy group occupies an axial position, thereby supporting the assigned *cis*-configuration within **288** (Figure 29).

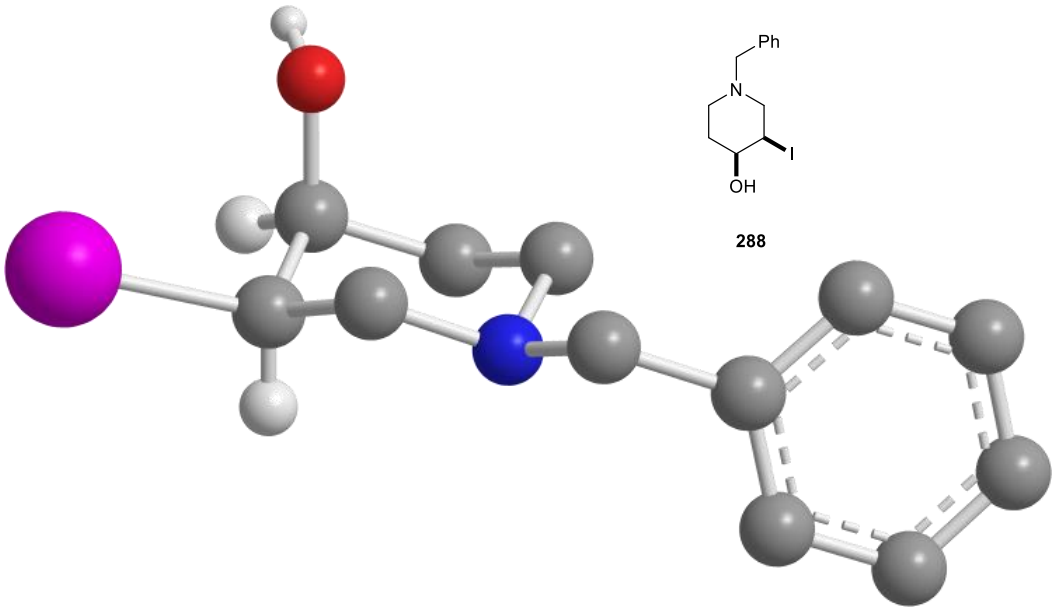


Figure 28. X-Ray crystal structure of (*RS*,*SR*)-**288** (selected H atoms have been omitted for clarity).

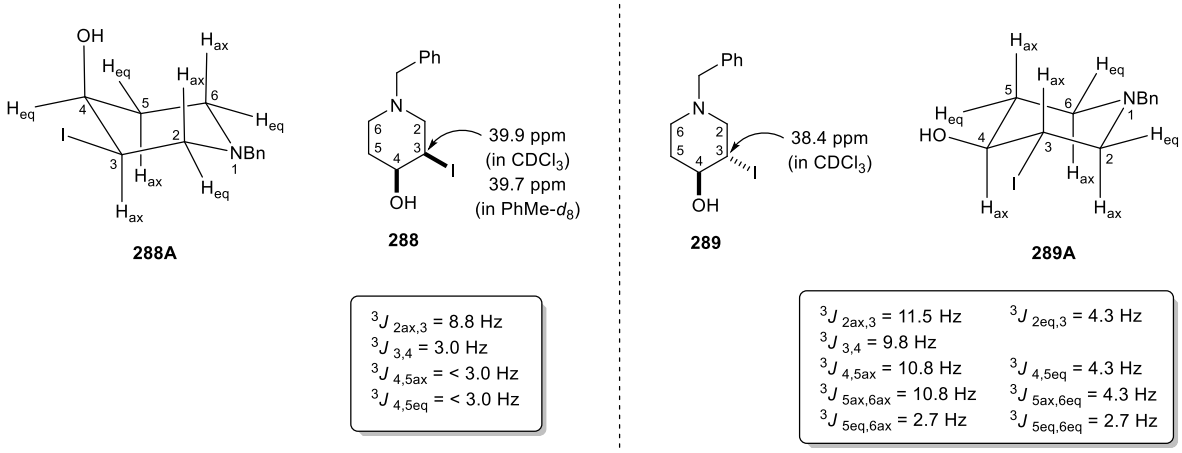
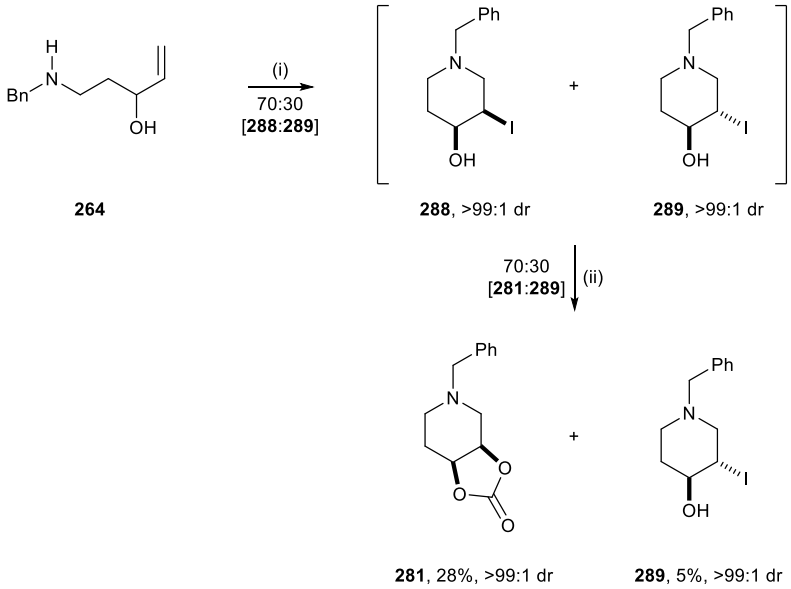


Figure 29. ^{1}H NMR ^3J coupling constant analyses of iodopiperidines **288** and **289**.

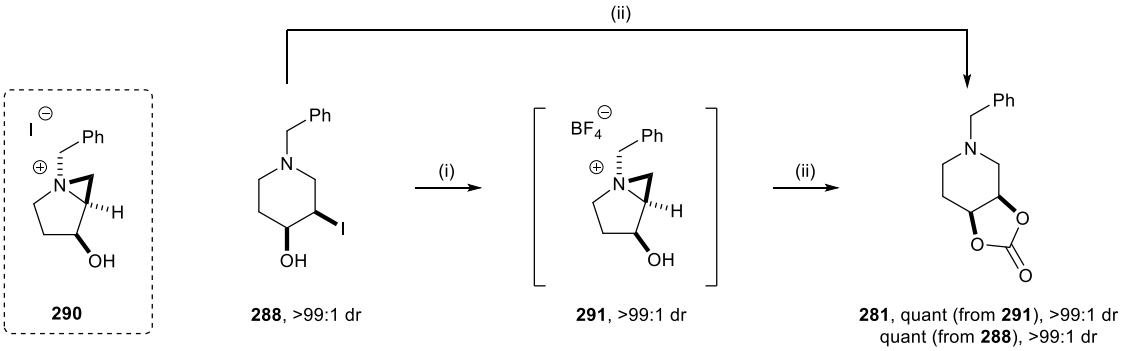
Repetition of the iodoamination of **264** followed by direct treatment of the 70:30 crude reaction mixture of **288** and **289** with $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) afforded a 70:30 mixture of carbonate **281** and iodopiperidine **289**. Subsequent purification by flash column chromatography led to the isolation of carbonate **281** in 28% yield and iodopiperidine **289** in 5% yield, as single diastereoisomers (>99:1 dr) in both cases (Scheme 70). The isolation of **289** following this stepwise process was in contrast with the sole isolation of carbonate **281** when performing the corresponding one-pot transformation (*vide supra*).[22] The isolation of **289** after this two-step process also provided some insight into the reaction mechanism: carbonate **281** seemed to derive from *cis*-**288**, while *trans*-**289** did not react under the reaction conditions. With analytically pure samples of **288** and **289** in hand, it was now possible to investigate the trapping of CO_2 from $NaHCO_3$ by each diastereoisomer separately (>99:1 dr).



Scheme 70. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h.

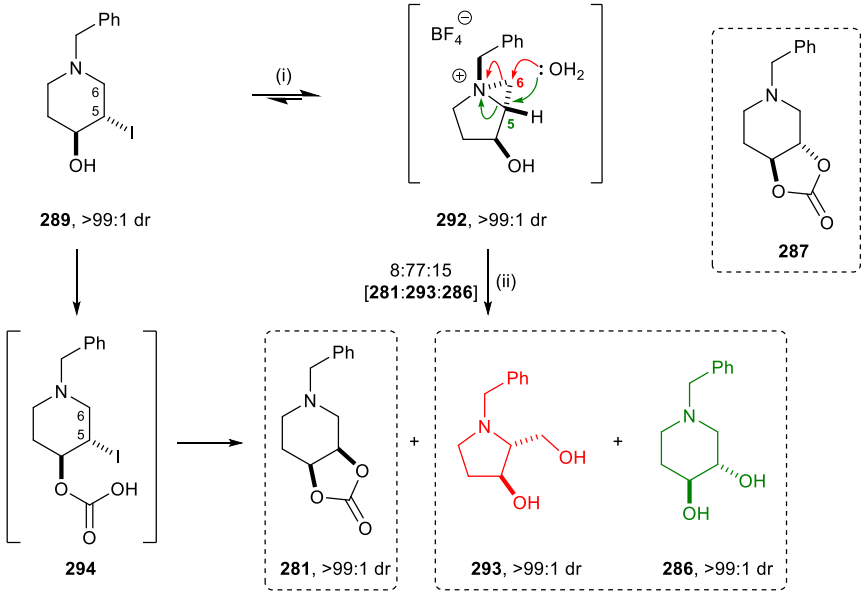
Treatment of *cis*-**288** with $AgBF_4$ in CH_2Cl_2 delivered the corresponding aziridinium **291**, which could not be isolated due to degradation. Therefore, full ^1H and ^{13}C NMR spectroscopic analyses[23] of **291** were performed upon treatment of **288** with $AgBF_4$ in CD_2Cl_2. Aziridinium **291** was subsequently subjected to the trapping conditions (i.e., $NaHCO_3$ in a 3:1 mixture of dioxane/H_2O was added to the NMR sample) to give carbonate **281** in quantitative yield as a single diastereoisomer (>99:1 dr). Direct treatment of *cis*-**288** with $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) promoted the formation of carbonate **281**,

which was also obtained in quantitative yield and >99:1 dr, thereby supporting the intermediacy of aziridinium **290** in the transformation of **288** to **281** (Scheme 71).



Scheme 71. *Reagents and conditions:* (i) $AgBF_4$, CD_2Cl_2, rt, 5 min; (ii) $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h.

In contrast, *trans*-iodopiperidine **289** was converted into the corresponding aziridinium **292** (which was also too unstable to isolate, thus ^1H and ^{13}C NMR spectroscopic analyses of **292** were performed upon treatment of **289** with $AgBF_4$ in CD_2Cl_2),[24] and subjected to the same trapping conditions to give an 8:77:15 mixture of carbonate **281**, pyrrolidine **293** and piperidine **286**, respectively. While aziridinium **292** did not undergo the expected ring-expansion via the trapping of CO_2 to produce *trans*-carbonate **287**, the intermolecular ring-opening of **292** by H_2O gave pyrrolidine **293** [i.e., ring-opening at C(6)] and piperidine **286** [i.e., ring-opening at C(5) with inversion of configuration] instead. The formation of carbonate **281** was rationalised by the trapping of CO_2 by *trans*-iodopiperidine **289** (which was presumably formed by the reversible ring-opening of aziridinium **292** with iodide) and subsequent S_N2-type substitution of the C(5)-iodide (Scheme 72). Direct treatment of *trans*-**289** with $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) resulted in the formation of a complex mixture of products.



Scheme 72. *Reagents and conditions:* (i) $AgBF_4$, CD_2Cl_2, rt, 5 min; (ii) $NaHCO_3$, dioxane/H_2O (3:1), rt, 16 h.

4.4. Incorporating sulphur: attempted trapping of sulphur-containing "X=C=Y" electrophiles

Having demonstrated that aziridinium **291** successfully underwent ring-expansion via the trapping of CO_2 to give carbonate **281**, attention next turned to examine the trapping of sulphur-containing "X=C=Y" electrophiles by **291**. It was envisaged that the trapping of isothiocyanates (RNCS) by aziridinium **291** would result in the subsequent intramolecular ring-opening of **295** at the C(5)-position by the sulphur atom (which was expected to be the superior nucleophile) to give bicyclic derivatives **296**. Subsequent hydrolysis of the oxathiolan-2-imine moiety within **296** would allow access to the corresponding oxathiolan-2-one **297** (Figure 30).

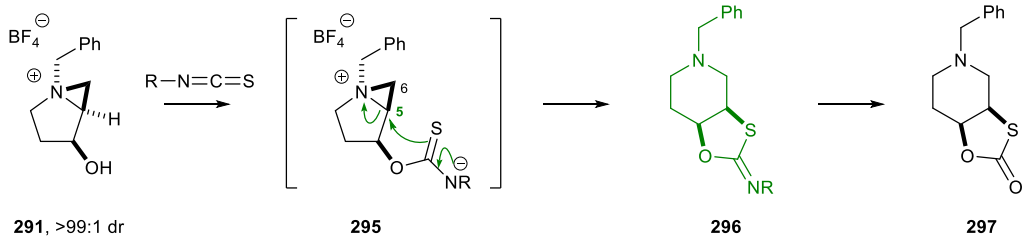
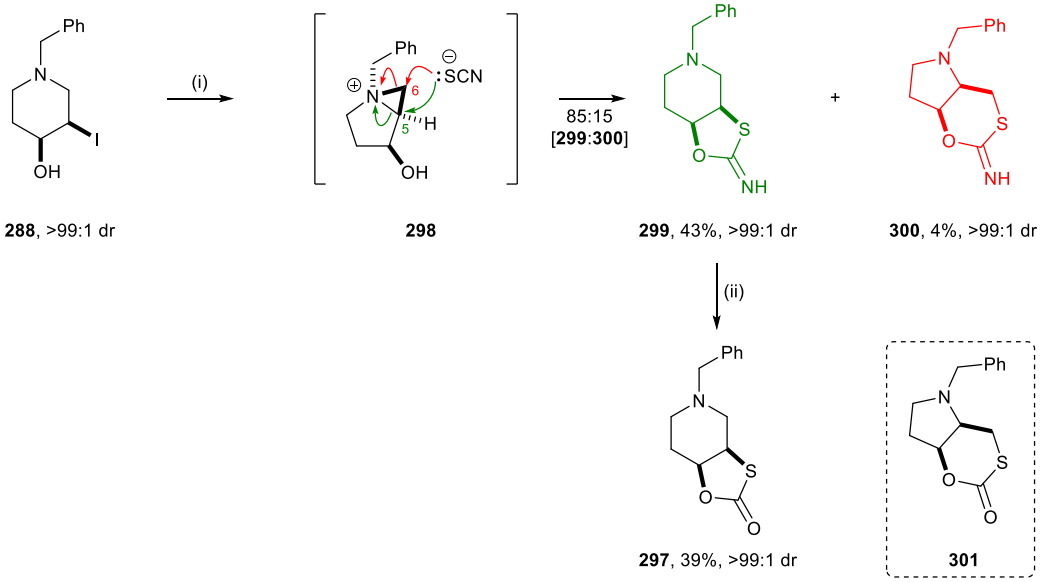


Figure 30. Strategy for the ring-expansion of aziridiniums **295** via the trapping of sulphur-containing electrophiles.

Prior to investigating the trapping of isothiocyanates, it was envisaged that the synthesis of authentic samples of oxathiolan-2-ones **297** and **301** could be achieved by the ring-opening of aziridinium **298** by the thiocyanate anion [$(SCN)^-$] followed by hydrolysis of the corresponding oxathiolan-2-imines **299** and **300**. Thus, treatment of **288** with AgSCN resulted

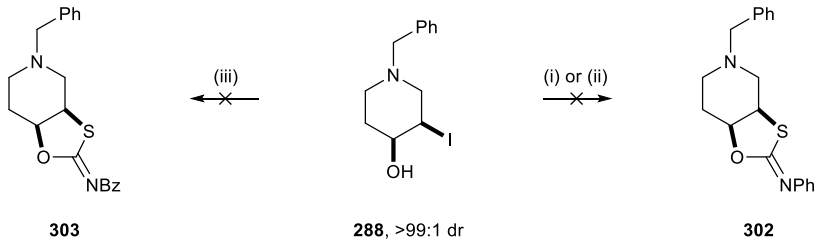
in the formation of an 85:15 mixture of bicyclic derivatives **299** and **300**, from which **299** was isolated in 43% yield and >99:1 dr, and **300** was isolated in 4% yield and >99:1 dr (Scheme 73). The ring-opening of aziridinium **298** by $(SCN)^-$ at the C(5)-position (with inversion of configuration) was responsible for the formation of the major regioisomer **299**, whilst ring-opening of **298** at the C(6)-position [with the configuration at C(5) being unchanged] was responsible for the formation of the minor regioisomer **300**. Full ^1H and ^{13}C NMR spectroscopic analyses of **299** and **300**, including ^1H–^{13}C HMBC studies, were consistent with the bicyclic systems. In addition, characteristic C=N absorbances at 1639 cm^{-1} in the IR spectra of both **299** and **300**, along with diagnostic chemical shifts for S*C*N (~δ_C = 169 ppm) in the ^{13}C NMR spectra of both **299** and **300**, confirmed the presence of an oxathiolan-2-imine moiety. Hydrolysis of **299** upon treatment with 1.0 M aq HCl delivered **297** in 39% yield and >99:1 dr. The IR spectrum of **297** displayed a diagnostic C=O absorbance at 1732 cm^{-1}; which, along with the diagnostic chemical shift at δ_C = 172.5 ppm for the S*C*O carbon observed in the ^{13}C NMR spectrum of **297**, fully supported the oxathiolan-2-one structure within **297**.



Scheme 73. *Reagents and conditions:* (i) AgSCN, CH_2Cl_2, rt, 16 h; (ii) 1.0 M aq HCl, rt, 16 h.

It was envisaged that CH_2Cl_2 would be a suitable solvent to conduct the trapping of isothiocyanates: the conversion of **288** to the corresponding aziridinium **291** was already performed in CH_2Cl_2, which should not promote the hydrolysis of isothiocyanates (as opposed to more polar solvents). Treatment of **288** with $AgBF_4$ in CH_2Cl_2 (to convert **288** to the corresponding aziridinium **291**) followed by addition of PhNCS gave a complex mixture

of products. Alternatively, reaction of **288** with PhNCS followed by $AgBF_4$ also resulted in the formation of a complex mixture of products. It was next envisaged that the use of a more reactive isothiocyanate electrophile could help the reaction to proceed. Unfortunately, treatment of **288** with BzNCS followed by addition of $AgBF_4$ failed to give bicyclic derivative **303** and the ^1H NMR spectrum of the crude reaction mixture was again complex (Scheme 74). In light of these results, the trapping of isothiocyanates was abandoned and attention next turned to the trapping of isocyanates in the hope of incorporating a nitrogen substituent in the piperidine scaffold.

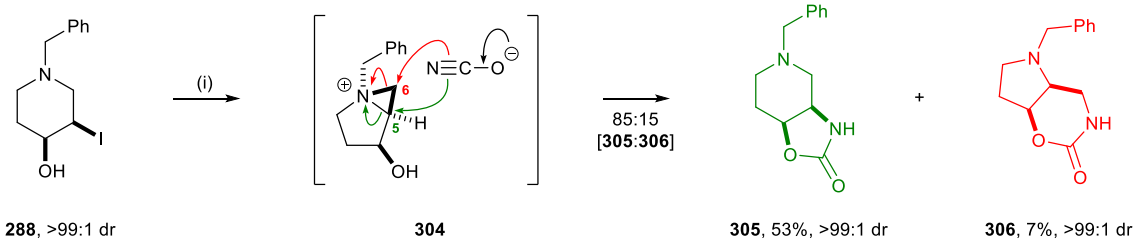


303 **288**, >99:1 dr **302**

Scheme 74. *Reagents and conditions:* (i) $AgBF_4$, CH_2Cl_2, rt, 5 min, then PhNCS, rt, 16 h; (ii) PhNCS, CH_2Cl_2, rt, 5 min, then $AgBF_4$, rt, 16 h; (iii) BzNCS, CH_2Cl_2, rt, 5 min, then $AgBF_4$, rt, 16 h.

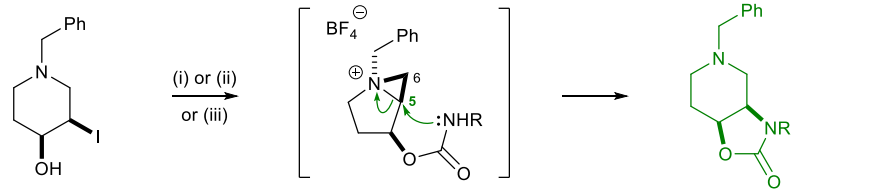
4.5. Incorporating nitrogen: studies towards the trapping of nitrogen-containing "X=C=Y" electrophiles

By analogy to the synthesis of the authentic sample of oxathiolan-2-one **297**, it was anticipated that treatment of **288** with AgOCN would result in the formation of aziridinium **304**, which could then undergo intermolecular ring-opening by the cyanate anion $[(OCN)^-]$ either at the C(5)-position (with inversion of configuration) to give carbamate **305** or at the C(6)-position [with the configuration at C(5) being unchanged] to give carbamate **306**. Indeed, reaction of **288** with AgOCN afforded an 85:15 mixture of **305** and **306**, from which **305** was isolated in 53% yield and >99:1 dr, and **306** was isolated in 7% yield and >99:1 dr (Scheme 75). Full ^1H and ^{13}C NMR spectroscopic analyses of **305** and **306** supported the assigned structures, including the $^1H–^{13}C$ HMBC study of **305** being consistent with the [5,6]-bicyclic system and the $^1H–^{13}C$ HMBC study of **306** being consistent with the alternative [5,6]-bicyclic system. In addition, the presence of diagnostic C=O absorbances at 1749 cm^{-1} in the IR spectrum of **305**, and at 1756 cm^{-1} in the IR spectrum of **306**, were entirely consistent with the nucleophilic attack of $(OCN)^-$ proceeding via the nitrogen atom.



Scheme 75. *Reagents and conditions:* (i) AgOCN, CH_2Cl_2, rt, 16 h.

While treatment of **288** with PhNCO followed by the addition of $AgBF_4$ did not provide **310**, submission of **288** to the same reaction conditions with BzNCO resulted in the formation of carbamate **311**, which was observed as the major product in the ^{1}H NMR spectrum of the crude reaction mixture. Purification of the crude reaction mixture by flash column chromatography afforded **311** in 23% yield and as single diastereoisomer;[25] and this analytically pure sample of **311** was utilised to confirm the connectivity and configuration within this bicyclic derivative. Full ^{1}H and ^{13}C NMR spectroscopic analyses of **311** were consistent with the [5,6]-bicyclic system and the IR spectrum of **311** displayed a diagnostic absorbance at 1786 cm^{-1} for the C=O of the carbamate moiety and a diagnostic absorbance at 1680 cm^{-1} for the C=O of the benzoyl functionality. The relative configuration within **311** was first assigned on the basis that the ring-opening of aziridinium **308** proceeds with inversion of configuration at the C(5)-position and was later confirmed via coupling constant correlations with analogous substrates (*vide infra*). Following this result, it was anticipated that the presence of a more effective electron-withdrawing group within the isocyanate reagent (i.e., making it a better electrophile) would facilitate its trapping by **288**. Thus, treatment of **288** with *p*-TsNCO followed by addition of $AgBF_4$ produced carbamate **312**, which was observed as the sole product of the reaction upon inspection of the ^{1}H NMR spectrum of the crude reaction mixture and obtained in 62% yield and >99:1 dr after purification by flash column chromatography (Scheme 31). The relative configuration within **312** was unambiguously established by single crystal X-ray diffraction analysis[19] (Figure 31). Furthermore, full ^{1}H and ^{13}C NMR spectroscopic analyses of **312**, along with the IR spectrum of **312** (which displayed a diagnostic absorbance at 1782 cm^{-1} for the C=O of the carbamate moiety) confirmed the connectivity within **312**.

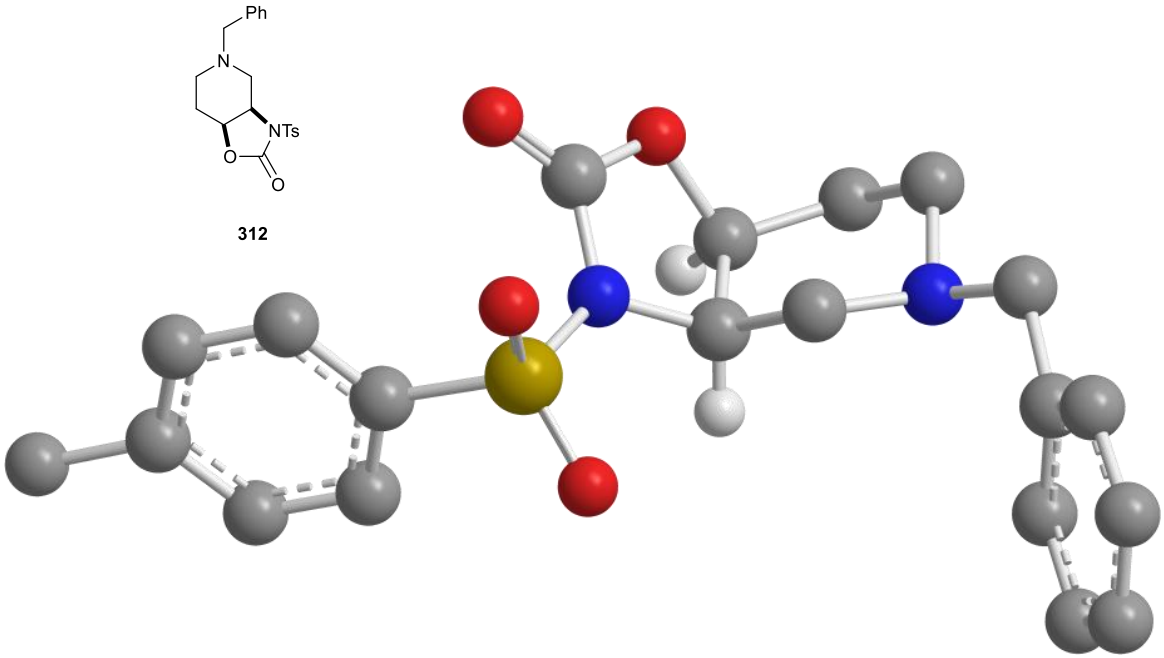


288, >99:1 dr

307, R = Ph
308, R = Bz
309, R = Ts

310, R = Ph
311, R = Bz, 23%, >99:1 dr
312, R = Ts, 62%, >99:1 dr

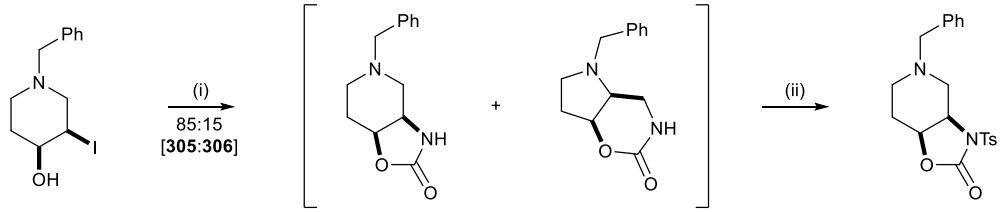
Scheme 76. *Reagents and conditions:* (i) PhNCO, CH_2Cl_2, rt, 5 min, then $AgBF_4$, rt, 16 h; (ii) BzNCO, CH_2Cl_2, rt, 5 min, then $AgBF_4$, rt, 16 h; (iii) *p*-TsNCO, CH_2Cl_2, rt, 5 min, then $AgBF_4$, rt, 16 h.



312

Figure 31. X-Ray crystal structure of (*RS*,*SR*)-**312** (selected H atoms have been omitted for clarity).

Treatment of **288** with AgOCN followed by reaction of the crude reaction mixture (an 85:15 mixture of **305** and **306**, respectively) with NaH and *p*-TsCl in a mixture of THF/DMF (1:1) afforded **312** as the major product (~85% purity) and in >99:1 dr (Scheme 77). Comparison of the ^{1}H NMR spectrum of the crude reaction mixture with the ^{1}H NMR spectrum of **312** synthesised via the trapping methodology also confirmed the connectivity and relative configuration within **312**.



288, >99:1 dr

305, >99:1 dr

306, >99:1 dr

312,[a] >99:1 dr

Scheme 77. *Reagents and conditions:* (i) AgOCN, CH_2Cl_2, rt, 16 h; (ii) NaH, *p*-TsCl, THF/DMF (1:1), 0 °C to rt, 16 h. [[a] ~85% purity]

Analysis of the ^{1}H NMR ^{3}J coupling constants of carbamates **305**, **311** and **312** was initiated next. Although most of the ^{1}H NMR ^{3}J coupling constants could not be resolved in the ^{1}H NMR spectra of **305**, **311** and **312**, a comparison of the three sets of $^{3}J_{2a,3}$, $^{3}J_{2b,3}$ and $^{3}J_{3,4}$ coupling constants showed diagnostic values that were entirely consistent with **305**, **311** and **312** adopting the same conformation; therefore confirming the assigned configuration within *N*-benzoyl carbamate **311** (Figure 32).

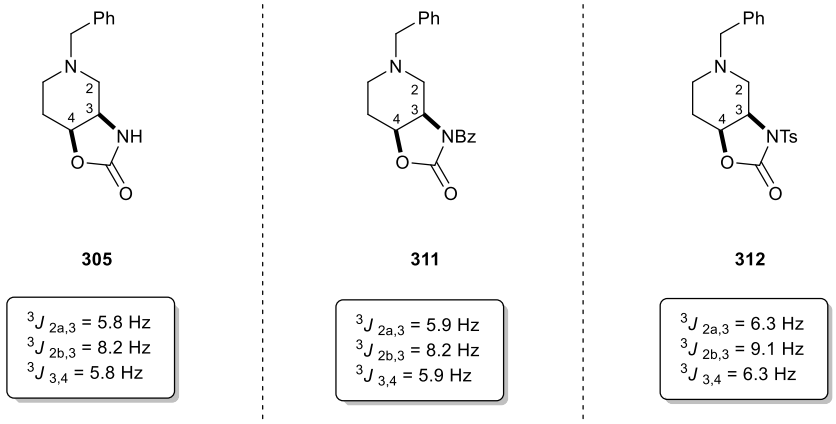
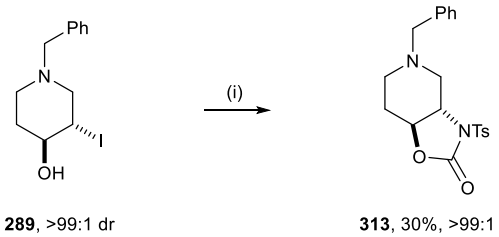


Figure 32. Comparison of the ^{1}H NMR ^{3}J coupling constants for carbamates **305**, **311** and **312**.

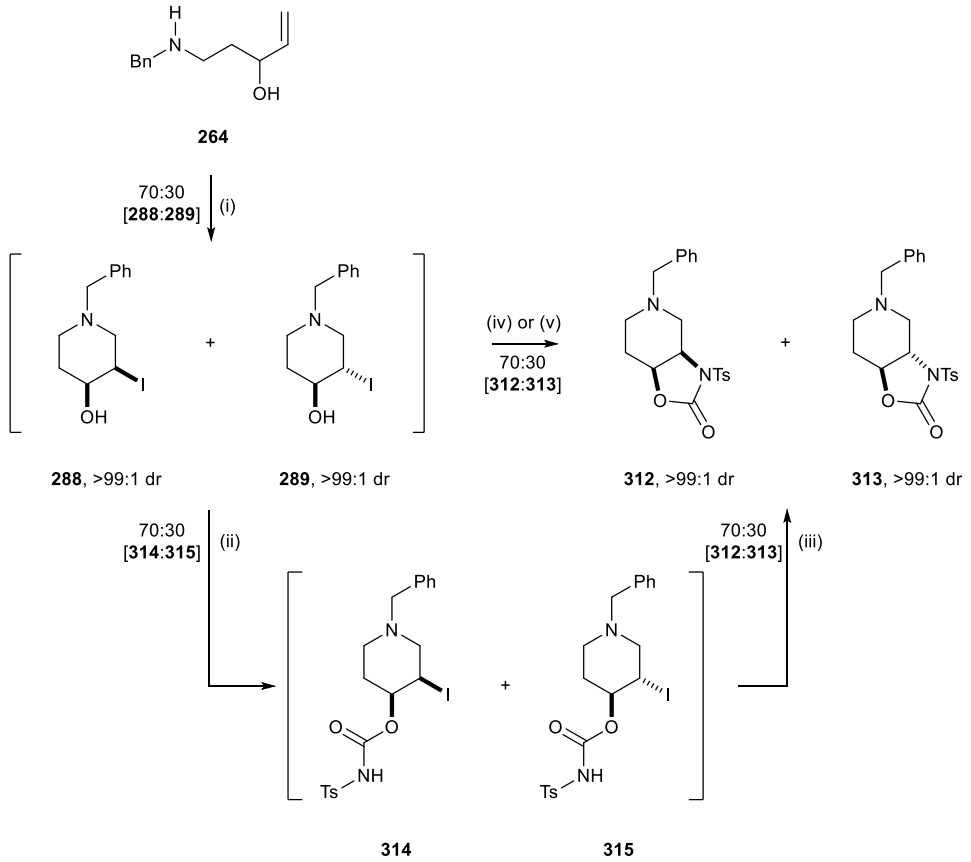
Subjecting *trans*-**289** to the isocyanate trapping methodology upon treatment with *p*-TsNCO in CH_2Cl_2 followed by addition of $AgBF_4$ led to the isolation of *trans*-carbamate **313** in 30% yield[26] and >99:1 dr (Scheme 78). Full ^{1}H and ^{13}C NMR spectroscopic analyses of **313** were entirely consistent with the bicyclic system within **313**, along with the IR spectrum of **313** displaying a diagnostic C=O absorbance at 1797 cm^{-1}.[27] It was interesting to note that the formation of *trans*-carbamate **313** from the formal trapping of *p*-TsNCO by *trans*-iodopiperidine **289** was in direct contrast with the unsuccessful formation of *trans*-carbonate **287** from **289**.



289, >99:1 dr **313**, 30%, >99:1 dr

Scheme 78. *Reagents and conditions:* (i) *p*-TsNCO, CH_2Cl_2, rt, 5 min, then $AgBF_4$, rt, 16 h.

In light of these results, a study into the reaction mechanism using a diastereoisomeric mixture of **288** and **289** was initiated next. Thus, iodoamination of **264** followed by direct treatment of the 70:30 crude reaction mixture of **288** and **289** with *p*-TsNCO in CH_2Cl_2 for 16 h led to the isolation of a 70:30 mixture of **314** and **315**. Although the ^{1}H NMR spectrum of the crude reaction mixture was found to be extremely broad in a variety of solvents ($CDCl_3$, CD_2Cl_2, PhMe-d_8, C_6D_6) at rt, recording the ^{1}H NMR spectrum in DMSO-d_6 at high temperature (363 K) allowed the peaks to be resolved. Full ^{1}H and ^{13}C NMR spectroscopic analyses of this crude reaction mixture (in DMSO-d_6 at 363 K) allowed the structure of the major diastereoisomer **314** to be assigned. Despite full characterisation of **315** being unamenable due to insufficient dispersion of peaks in the ^{1}H and ^{13}C NMR spectra, the IR spectrum (which displayed a diagnostic C=O absorbance of a secondary carbamate moiety at 1647 cm^{-1}) together with the HRMS of the mixture of **314** and **315** were entirely consistent with the assigned structures of **314** and **315**. Subsequent treatment of the mixture of **314** and **315** with $AgBF_4$ in CH_2Cl_2 afforded a 70:30 mixture of carbamates **312** and **313**. Indeed, when the 70:30 mixture of **288** and **289** was treated with *p*-TsNCO in CH_2Cl_2 followed by addition of $AgBF_4$ in one-pot, a 70:30 mixture of carbamates **312** and **313** was obtained after 16 h. However, when the 70:30 mixture of **288** and **289** was treated with *p*-TsNCO in CH_2Cl_2 (i.e., omitting $AgBF_4$), carbamates **312** and **313** were observed in a 70:30 ratio in the ^{1}H NMR spectrum of the corresponding crude reaction mixture after 72 h (Scheme 79).

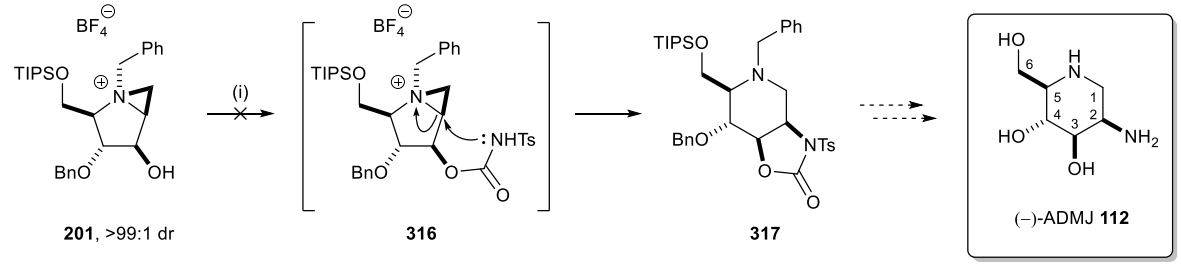


Scheme 79. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) *p*-TsNCO, CH_2Cl_2, rt, 16 h; (iii) $AgBF_4$, CH_2Cl_2, rt, 5 min; (iv) *p*-TsNCO, CH_2Cl_2, rt, 5 min, then $AgBF_4$, rt, 16 h; (v) *p*-TsNCO, CH_2Cl_2, rt, 72 h.

In summary, the model system was utilised to demonstrate that the trapping methodology of CO_2 could be applied to iodopiperidine **288** to deliver carbonate **281**. While the trapping of isothiocyanates by the hydroxyl group within **288** was unsuccessful, the trapping of *p*-TsNCO led to the isolation of carbamate **312** and it was envisaged that this methodology could be employed in the syntheses of deoxy-amino analogues of (–)-DMJ **11** and (+)-DANJ **64**.

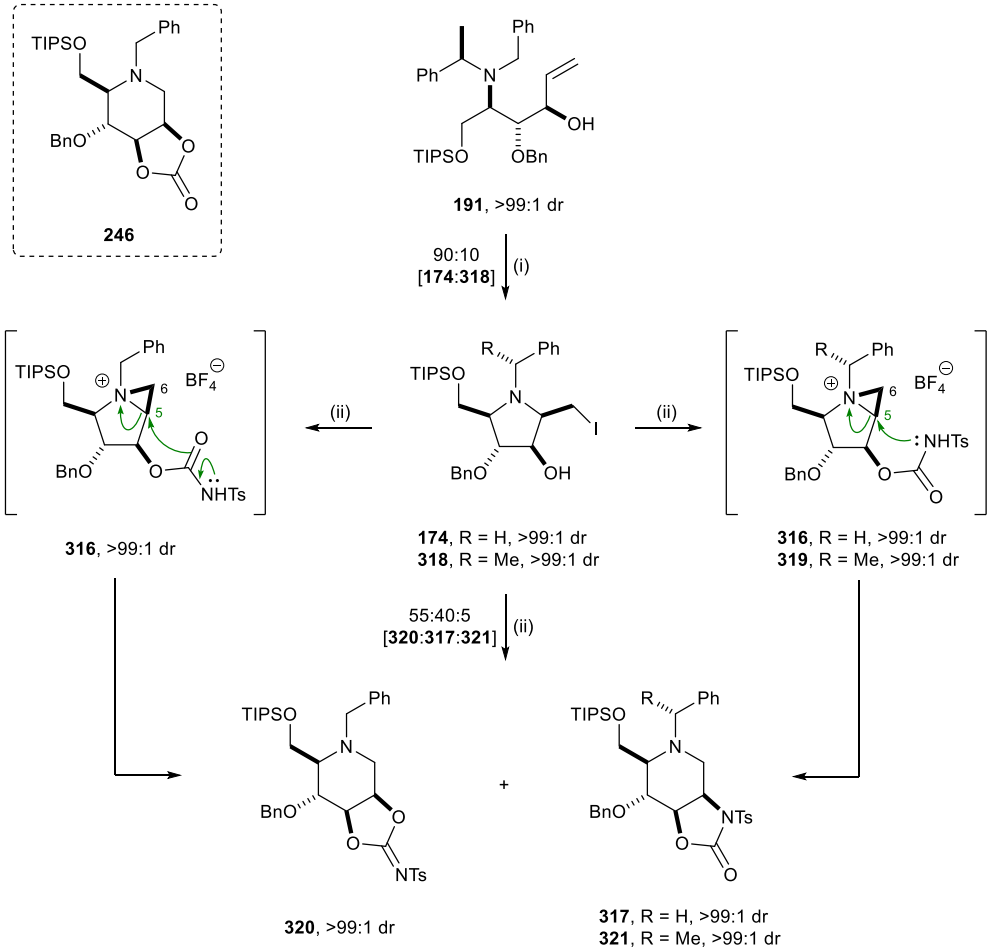
4.6. Ring-closing iodoamination/ring-expansion of enantiopure bishomoallylic amines via the trapping of *p*-tosyl isocyanate

By analogy to the trapping of CO_2 by aziridinium **201** to give carbonate **246** (*vide supra*, Chapter 3), it was envisaged that the trapping of *p*-TsNCO by **201** would produce the corresponding aziridinium **316**, which would undergo intramolecular ring-opening by the nucleophilic nitrogen atom within **316** to give carbamate **317**. Subsequent global deprotection of **317** would therefore allow access to (–)-ADMJ **112**, the 2-deoxy-2-amino analogue of (–)-DMJ **11**. Unfortunately, treatment of **201** with *p*-TsNCO in CH_2Cl_2 led to the degradation of **201** and a complex mixture of products was observed upon inspection of the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 80).



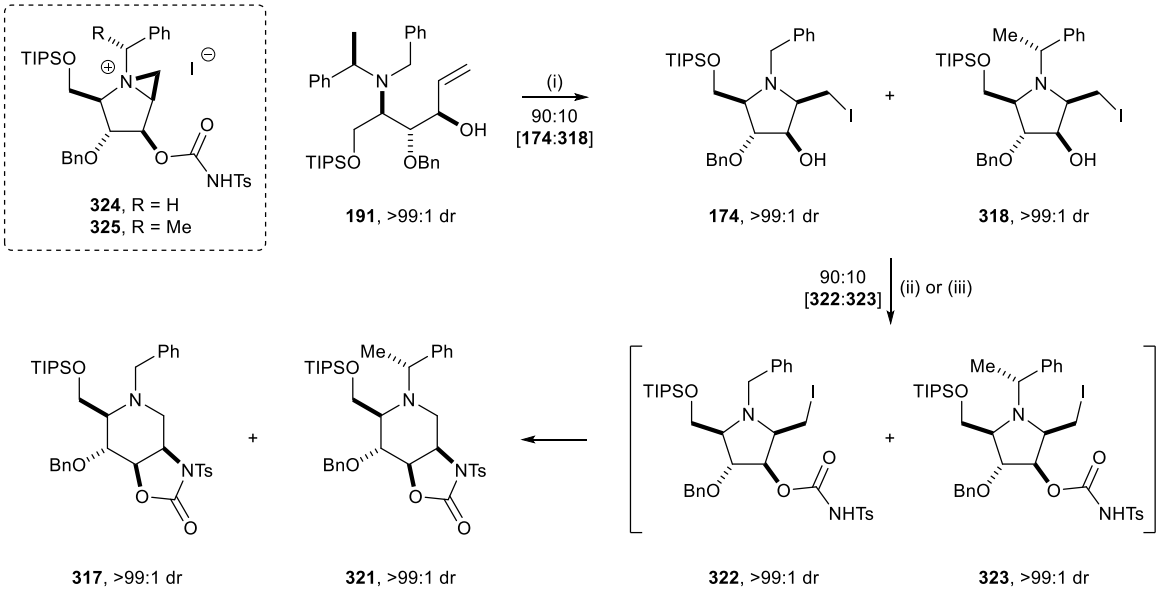
Scheme 80. *Reagents and conditions:* (i) *p*-TsNCO, CH_2Cl_2, rt, 16 h.

However, when iodomethylpyrrolidine **174** (which contained ~10% of **318**)[28] was treated with *p*-TsNCO in CH_2Cl_2 for 5 min followed by the addition of $AgBF_4$ (to facilitate conversion into the corresponding aziridiniums **316** and **319**), a 55:40:5 mixture of dioxolan-2-imine **320** and carbamates **317** and **321**, respectively, was obtained in quantitative mass return (Scheme 81). Even though this procedure provided access to bicyclic compounds, the ambident nature of the tethered nucleophile led to mixtures of regioisomers and intramolecular nucleophilic attack via the oxygen atom [with inversion of configuration at the C(5)-position] was responsible for the formation of regioisomer **320**. The regioselectivity of aziridiniums **316** and **319** ring-opening at C(5) only was, as expected, high due to the tethered strategy. The IR spectrum of the crude reaction mixture displayed a diagnostic C=N absorbance at 1640 cm^{-1}, which was consistent with the formation of **320**. Furthermore, the recovery of carbonate **246** (which derived from hydrolysis of **320**) after attempted purification of **320** by flash column chromatography, was also entirely consistent with the presence of regioisomer **320** in the crude reaction mixture. Although carbamates **317** and **321** were found to be inseparable by flash column chromatography, full ^{1}H and ^{13}C NMR spectroscopic analyses of a 90:10 mixture of **317** and **321**, along with a diagnostic C=O absorbance at 1788 cm^{-1} in the IR spectrum of this mixture were in support of the assigned bicyclic system. The presence of α-methylbenzyl iodomethylpyrrolidine **318** (~10%) in this sample of **174** was responsible for the formation of α-methylbenzyl carbamate **321**. The relative configurations within **317** and **321** were initially assigned by analogy to the stereochemical outcome of this transformation observed for the model substrate **264**, and was later confirmed via ^{1}H NMR ^{3}J coupling constant analyses of derivatives (*vide infra*).



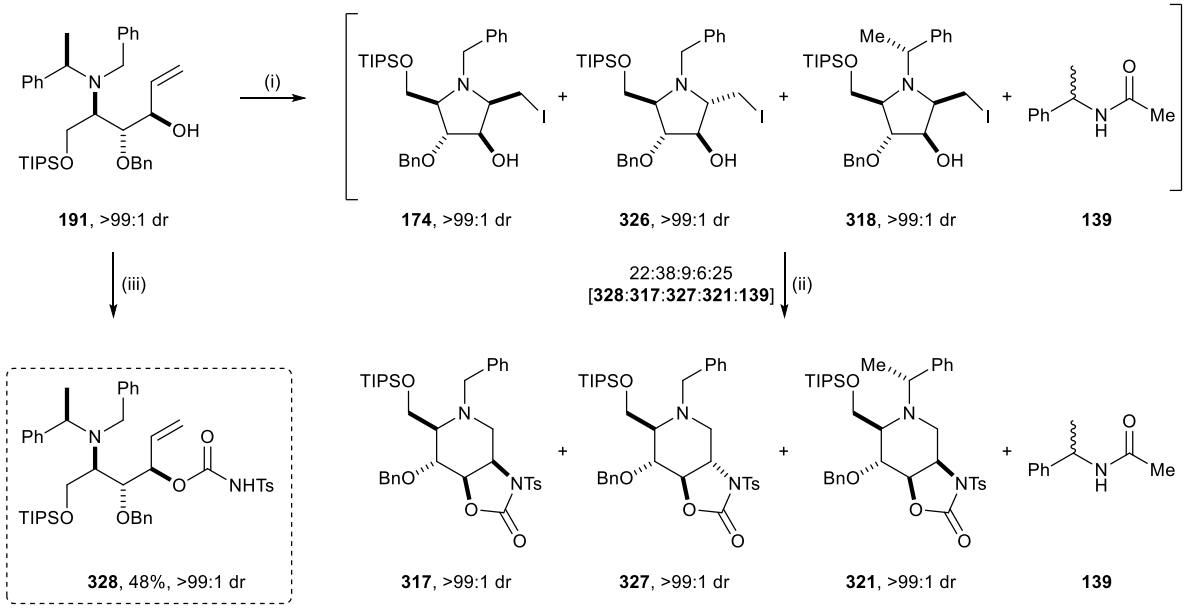
Scheme 81. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) *p*-TsNCO, CH_2Cl_2, rt, 5 min, then $AgBF_4$, rt, 16 h.

Following this result, it was next anticipated that the solvent in which the trapping is carried out could play a major role in the reaction outcome. Thus, iodoamination of bishomoallylic amine **191** followed by treatment of a 90:10 mixture of **174** and **318** with *p*-TsNCO in MeCN followed by addition of $AgBF_4$ resulted in the formation of a 90:10 mixture of carbamates **317** and **321** in quantitative mass return. Repetition of the trapping upon treatment of a 90:10 mixture of **174** and **318** with *p*-TsNCO in MeCN (i.e., omitting the addition of $AgBF_4$) produced iodomethyl pyrrolidines **322** and **323**, which were observed by LRMS after 5 min. Inspection of the ^{1}H NMR spectrum of the crude reaction mixture after 16 h led to the observation of a 90:10 mixture of carbamates **317** and **321**, thereby supporting the rationale of the formation of aziridiniums **324** and **325** *in situ* (Scheme 82).



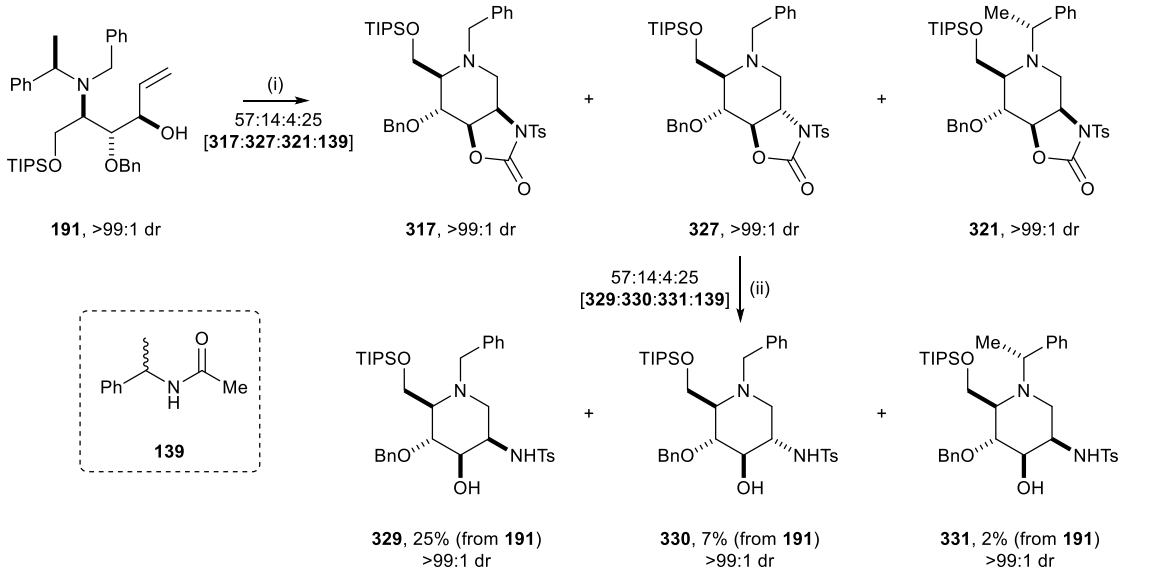
Scheme 82. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) *p*-TsNCO, MeCN, rt, 5 min, then $AgBF_4$, rt, 16 h; (iii) *p*-TsNCO, MeCN, rt, 16 h.

Treatment of **191** with I_2 and $NaHCO_3$ in MeCN, followed by direct reaction of the crude reaction mixture with *p*-TsNCO in MeCN gave a 22:38:9:6:25 mixture of **328**, **317**, **327**, **321** and **139**, respectively, in quantitative mass return. Attempts to isolate **317** by flash column chromatography proved unsuccessful, however a major fraction consisting of a 64:23:13 mixture of carbamates **317**, **327** and **321**, respectively, was isolated. In addition, full ^{1}H and ^{13}C NMR spectroscopic analyses of a 50:50 mixture of **317** and **327** (isolated as a minor fraction for characterisation purposes after flash column chromatography) allowed the diastereoisomer **327** to be identified and the assigned relative configuration within **327** was later confirmed via ^{1}H NMR ^3J coupling constant analysis of a derivative (*vide infra*). The formation of *trans*-carbamate **327** was ascribed to the result of ring-expansion of iodomethyl pyrrolidine **326** (which was observed in the crude reaction mixture of the iodoamination step).[29] The observation of bishomoallylic amine **328** in the crude reaction mixture of the trapping step was consistent with the previous observations made on the recovery of bishomoallylic amine **191** while performing the iodoamination step (after purification or a subsequent step, *vide supra*, Chapter 2). An authentic sample of **328** was also synthesised in 48% yield and >99:1 dr upon treatment of **191** with *p*-TsNCO in MeCN (Scheme 83).



Scheme 83. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) *p*-TsNCO, MeCN, rt, 16 h; (iii) *p*-TsNCO, MeCN, rt, 16 h.

Treatment of **191** with I_2 and $NaHCO_3$ in MeCN followed by the addition of 4.5 equiv[30] of *p*-TsNCO to the reaction mixture after 16 h led to the formation of a 57:14:4:25 mixture of **317**, **327**, **321** and **139**, respectively, bishomoallylic amine **328** was not evident upon inspection of the ^{1}H NMR spectrum of the crude reaction mixture. Purification of the crude reaction mixture by flash column chromatography resulted in the isolation of a 75:20:5 mixture of **317**, **327** and **321**, respectively. Repetition of the reaction followed by direct methanolysis of the crude reaction mixture upon treatment with K_2CO_3 and MeOH gave a 57:14:4:25 mixture of **329**, **330**, **331** and **139**, respectively. Purification of the crude reaction mixture by flash column chromatography gave **329** in 25% yield, **330** in 7% yield and **331** in 2% yield (from **191**), as single diastereoisomers (>99:1 dr) in each case (Scheme 84).



Scheme 84. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h, then *p*-TsNCO, rt, 16 h; (ii) K_2CO_3, MeOH, rt, 16 h.

A study of the relative configurations within piperidines **329**, **330** and **331** employing ^{1}H NMR ^3J coupling constant analyses was initiated next. Following from the known configurations of the C(2), C(3) and C(4) stereogenic centres within **329**, it was envisaged that **329** would preferentially adopt conformation **329A**, where the C(2)-silyloxymethyl, C(3)-benzyloxy and C(4)-hydroxyl groups all occupy equatorial positions. The $^3J_{2,3}$ and $^3J_{3,4}$ values of 8.0 Hz within **329** fully supported this hypothesis,[31] and the $^3J_{4,5}$ value of 3.9 Hz, $^3J_{5,6ax}$ value of 5.3 Hz and $^3J_{5,6eq}$ value of 2.4 Hz were entirely consistent with the C(5)*H* proton occupying an equatorial position, thereby confirming the *cis*-relationship between the C(4)*H* and the C(5)*H* protons. An analogous analysis of the ^{1}H NMR ^3J coupling constants of **331** confirmed the homochirality between **329** and **331**. Although most of the ^3J coupling constants of **330** could not be resolved in $CDCl_3$, recording the ^{1}H NMR spectrum in MeOH-d_4 effected resolution of the peaks. The $^3J_{2,3}$, the $^3J_{3,4}$ and the $^3J_{4,5}$ values of 9.8 Hz, along with the $^3J_{5,6ax}$ value of 11.2 Hz were all consistent with **330** adopting chair conformation **330A** and were diagnostic of the C(4)*H* and C(5)*H* protons displaying a *trans*-relationship (Figure 33). This study therefore confirmed the assigned relative configurations within **329**, **330** and **331**, and hence those within the synthetic precursors **317**, **327** and **321**; the absolute configurations of these compounds were assigned by reference to the known configurations of the C(2), C(3) and C(4) stereogenic centres.

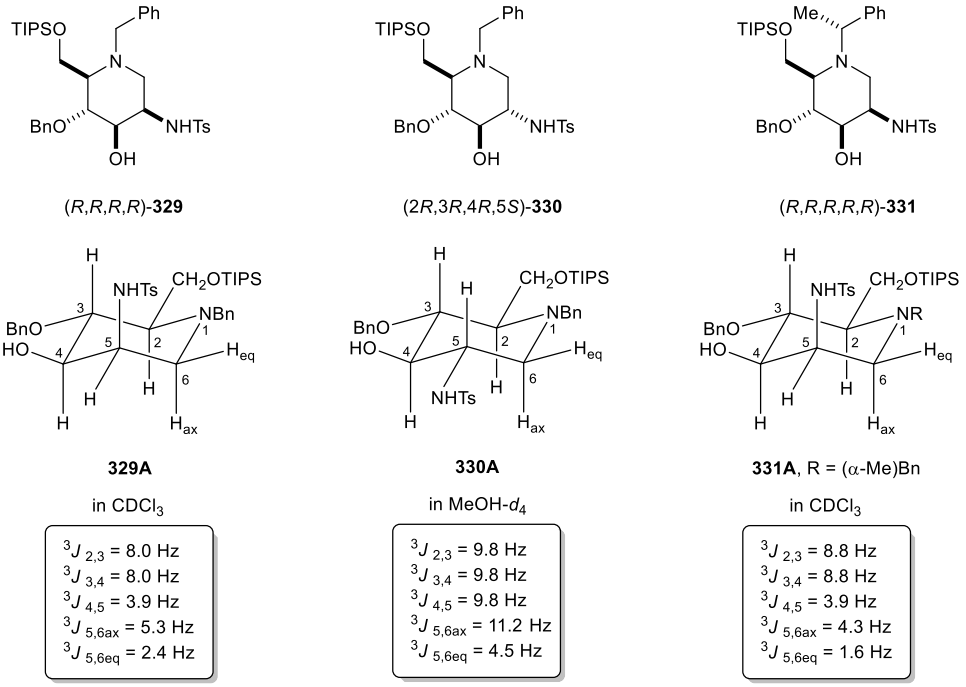
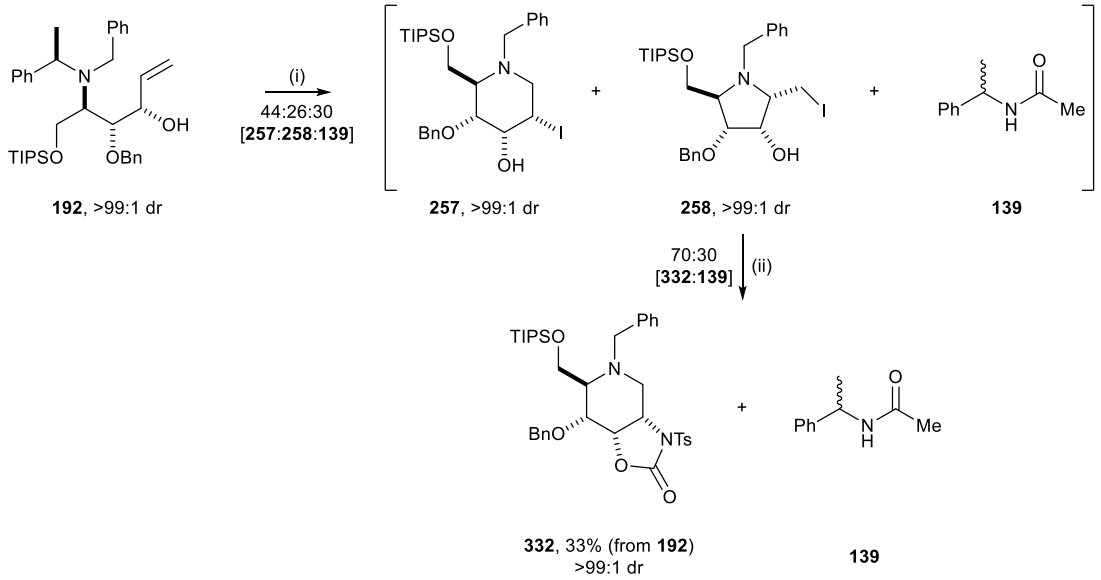


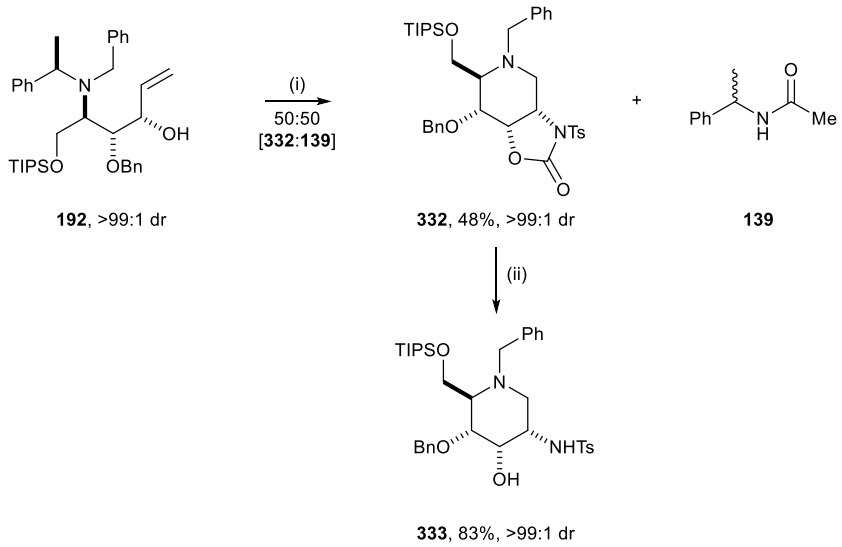
Figure 33. ^{1}H NMR ^{3}J coupling constant analyses of piperidines **329**, **330** and **331**.

It was next anticipated that the trapping of *p*-TsNCO developed in the ring-closing iodoamination/ring-expansion of **191** could be applied to the epimeric bishomoallylic amine **192**. Thus, iodoamination of **192** using I_2 and $NaHCO_3$ in MeCN resulted in the formation of a 44:26:30 mixture of piperidine **257**, pyrrolidine **258** and *N*-α-methylbenzyl acetamide **139**, respectively (*vide supra*, Chapter 3). Subjection of this crude reaction mixture to the isocyanate trapping conditions upon treatment with *p*-TsNCO in MeCN led to the formation of a 70:30 mixture of **332** and **139**, from which carbamate **332** was isolated in 33% yield and >99:1 dr (Scheme 85). Full ^{1}H and ^{13}C NMR spectroscopic analyses of **332**, along with a diagnostic C=O absorbance at 1785 cm^{-1} observed in the IR spectrum of **332**, were entirely consistent with the assigned bicyclic system. The relative configuration within **332** was initially assigned by analogy to the stereochemical outcome of the ring-expansion of iodomethyl pyrrolidine **174**, and was later confirmed by single crystal X-ray diffraction analysis of a derivative (*vide infra*).



Scheme 85. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h; (ii) *p*-TsNCO, MeCN, rt, 16 h.

One-pot ring-closing iodoamination/ring-expansion of **192** upon treatment with I_2 and $NaHCO_3$ followed by addition of *p*-TsNCO after 16 h resulted in the formation of a 50:50 mixture of carbamate **332** and by-product **139**. Purification of the crude reaction mixture upon flash column chromatography afforded **332** in 48% yield and >99:1 dr. Subsequent treatment of **332** with K_2CO_3 and MeOH led to the isolation of piperidine **333** in 83% yield and >99:1 dr (Scheme 86). The relative configuration within **333** was unambiguously established by single crystal X-ray diffraction analysis[19] (Figure 34). Furthermore, the determination of a Flack *x* parameter[32] of −0.004(9) for the crystal structure of **333** allowed the assigned absolute (2*R*,3*R*,4*S*,5*S*)-configuration of **333** to be confirmed. This analysis also unambiguously established the absolute configuration within the carbamate precursor **332**.



Scheme 86. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, rt, 16 h, then *p*-TsNCO, rt, 16 h; (ii) K_2CO_3, MeOH, rt, 16 h.

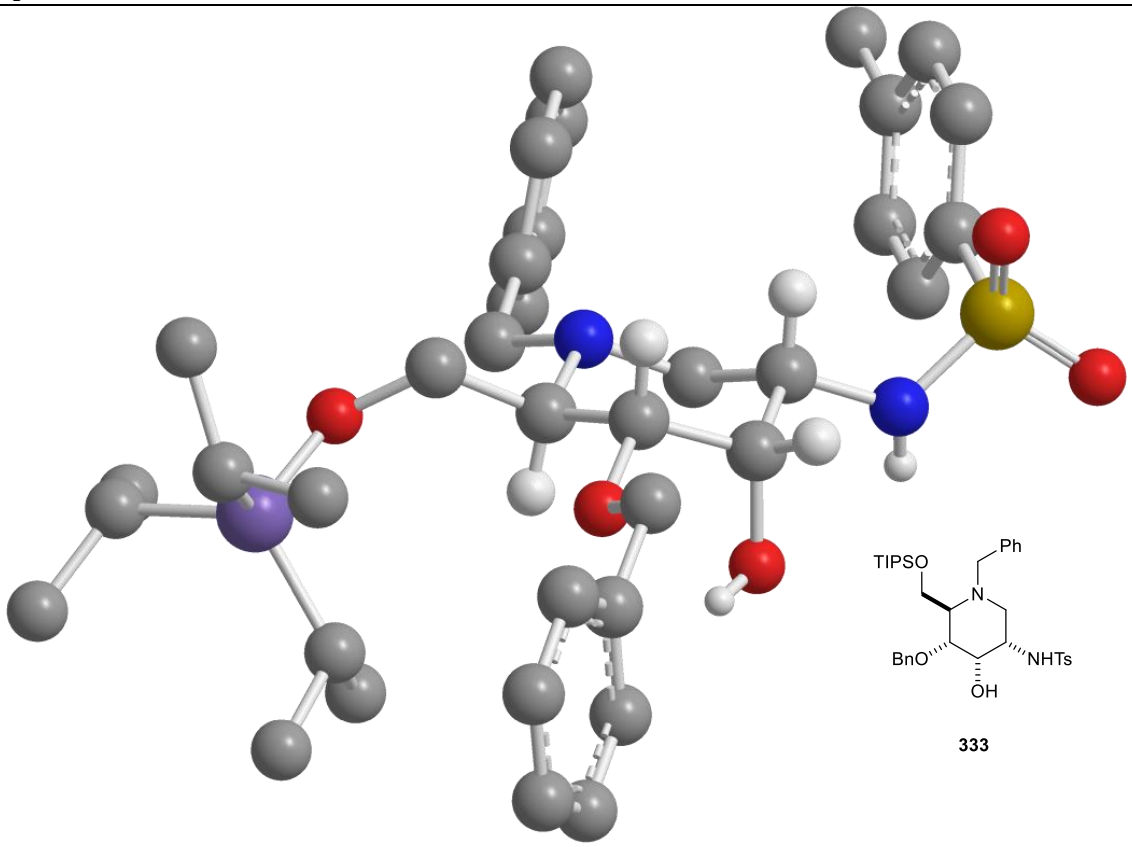
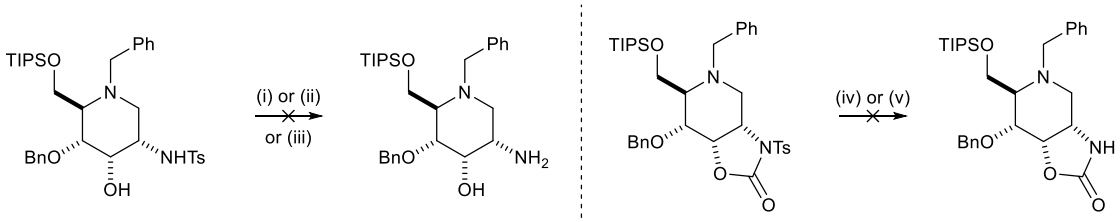


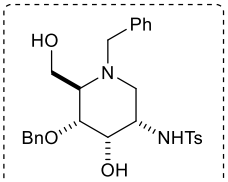
Figure 34. X-Ray crystal structure of (2*R*,3*R*,4*S*,5*S*)-**333** (selected H atoms have been omitted for clarity).

4.7. Deprotection towards (−)-ADMJ and (+)-ADANJ

With piperidines **329** and **333** in hand, it was now possible to commence investigations into the deprotection of the *N*-tosyl moiety. Treatment of **333** with 1.25 M HCl in MeOH[33] at 40 °C failed to effect *N*-tosyl deprotection but proceeded with the loss of the *O*-TIPS group to give diol **336** in quantitative mass return. Submission of **333** to stronger acidic conditions[34] upon treatment with conc H_2SO_4 resulted in the formation of a complex mixture of products and attention next turned to the use of Mg to promote *N*-tosyl deprotection. Following a literature procedure,[35] treatment of **333** with Mg in MeOH at reflux for 4 h returned starting material. This result was consistent with the observations reported in the literature[36] regarding the necessity for the *N*-tosyl moiety to be activated with an electron-withdrawing group (i.e., *N*-Boc- or oxazolidin-2-one protection) in order to effect the *N*-tosyl deprotection. However, subjection of **332** to the same reaction conditions led to the formation of **333** and no signs of *N*-tosyl deprotection could be gleaned. Repetition of the reaction at rt (performed under sonication to activate the Mg)[37] for 1 h also returned **333** (Scheme 87); therefore sodium naphthalide was employed in subsequent attempts at *N*-tosyl deprotection.



333, >99:1 dr **334** **332**, >99:1 dr **335**

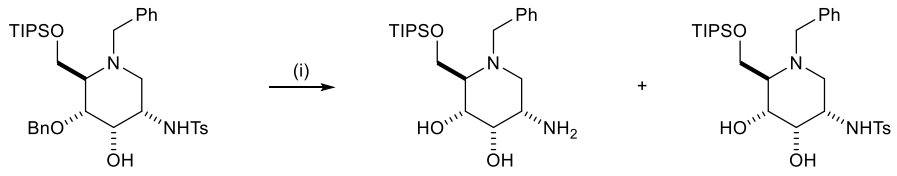


336

conditions	reagents	temperature/ time	product (yield)
(i)	HCl (1.25 M in MeOH)	40 °C / 16 h	**336** (44%)
(ii)	conc H_2SO_4	rt / 1 h	complex mixture of products
(iii)	Mg (turnings), MeOH	reflux / 4 h	returned starting material
(iv)	Mg (turnings), MeOH	reflux / 4 h	**333**
(v)	Mg (turnings), MeOH	rt (sonication) / 1 h	**333**

Scheme 87. *Reagents and conditions:* see table.

Following a literature procedure,[38] treatment of **333** with Na and naphthalene in THF at –78 °C (which was allowed to warm up to –10 °C) for 3 h proceeded with concomitant *O*-benzyl deprotection to give a 40:60 mixture of **337** and **338**, respectively. Purification of the crude reaction mixture upon flash column chromatography gave **337** in 40% yield and >99:1 dr, and **338** in 60% yield and >99:1 dr. While conducting the reaction in DME under the same reaction conditions had no effect on the reaction outcome, repetition of the reaction in DME at –78 °C, which was then allowed to reach rt for 8 h, led to the formation of a 70:30 mixture of **337** and **338**, respectively. Subsequently, treatment of **333** with Na and naphthalene in THF at –78 °C to rt for 16 h gave a 93:7 mixture of **337** and **338**, respectively. Purification of this mixture via flash column chromatography led to the isolation of **337** in 61% yield and >99:1 dr, and **338** in 6% yield and >99:1 dr (Scheme 88).

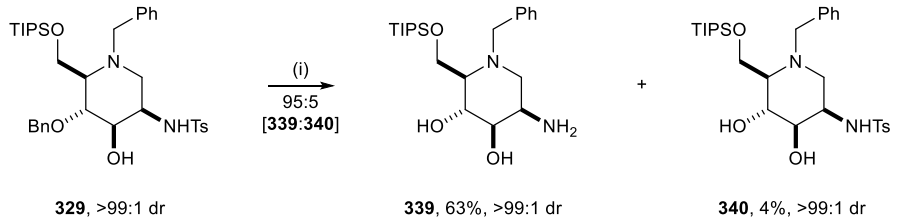


333, >99:1 dr **337**, >99:1 dr **338**, >99:1 dr

solvent	temperature	time	crude ratio [337:338]	isolated yield of 337 [% (dr)]	isolated yield of 338 [% (dr)]
THF	–78 °C to –10 °C	3 h	40:60	40 (>99:1)	60 (>99:1)
DME	–78 °C to –10 °C	3 h	40:60	-	-
DME	–78 °C to rt	8 h	70:30	-	-
DME	–78 °C to rt	16 h	93:7	61 (>99:1)	6 (>99:1)

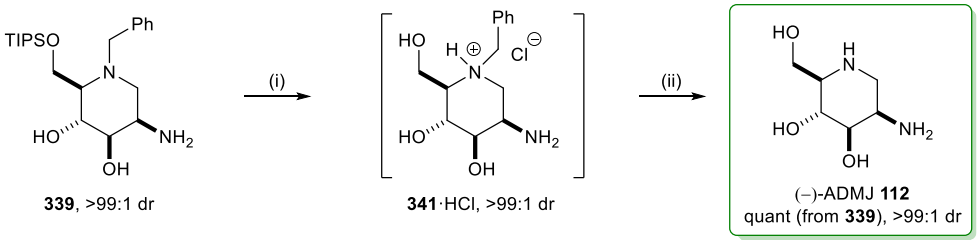
Scheme 88. *Reagents and conditions:* (i) Na, naphthalene, see table.

Similarly, submission of **329** to these optimised reaction conditions to effect *N*-tosyl and concomitant *O*-benzyl deprotection resulted in the formation of a 95:5 mixture of **339** and **340**, from which **339** was isolated in 63% yield and >99:1 dr, and **340** was isolated in 4% yield and 99:1 dr (Scheme 89).



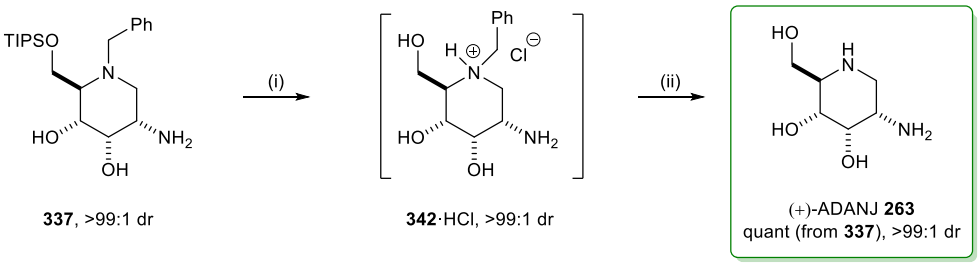
Scheme 89. *Reagents and conditions:* (i) Na, naphthalene, DME, −78 °C to rt, 16 h.

Treatment of amino alcohol **339** with 6.0 M aq HCl in MeOH at 40 °C effected *O*-TIPS deprotection to furnish the corresponding hydrochloride salt **341**·HCl. Hydrogenolysis of **341**·HCl upon treatment with Pearlman's catalyst under an atmosphere of H_2 (5 atm), followed by purification of this sample by ion exchange chromatography on Dowex 50WX8 (H^+ form) resin afforded (−)-ADMJ **112** in quantitative yield (from **339**) and >99:1 dr (Scheme 90).[39]



Scheme 90. *Reagents and conditions:* (i) 6.0 M aq HCl, MeOH, 40 °C, 16 h; (ii) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 48 h, then Dowex 50WX8 (H^+ form).

Similarly, subjecting **337** to 6.0 M aq HCl in MeOH at 40 °C resulted in the formation of hydrochloride salt **342**·HCl, which underwent treatment with Pearlman's catalyst [$Pd(OH)_2/C$] under an atmosphere of H_2 (5 atm) to furnish (+)-ADANJ **263** in quantitative yield (from **337**) and >99:1 dr (Scheme 91).



Scheme 91. *Reagents and conditions:* (i) 6.0 M aq HCl, MeOH, 40 °C, 16 h; (ii) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 48 h, then Dowex 50WX8 (H^+ form).

While there was no precedent in the literature for the synthesis or identification of (+)-ADANJ **263**, the specific rotation and ^{1}H and ^{13}C NMR spectra of this sample of (−)-ADMJ **112** {$[\alpha]_D^{20}$ –11.5 (*c* 0.3 in H_2O)} were in excellent agreement with data previously reported for a synthetic sample of (−)-ADMJ **112** by Le Merrer *et al.*[39] {$[\alpha]_D$ –14 (*c* 0.4 in H_2O)} (Tables 12 and 13).

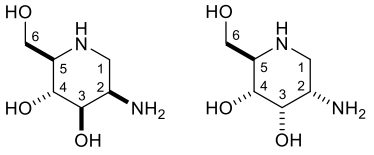
^{1}H NMR data for (−)-ADMJ **112** and (+)-ADANJ **263**  **112** **263**			
H	Le Merrer *et al.*[39] δ_H (250 MHz, D_2O)	This study: (−)-ADMJ **112** δ_H (400 MHz, D_2O)	This study: (+)-ADANJ **263** δ_H (400 MHz, D_2O)
C(1)H_A	2.89 br d *J* 14.0	2.84 dd *J* 14.0, 2.4	2.52 app t *J* 11.8
C(1)H_B	3.05 br d *J* 14.0	3.00 dd *J* 14.0, 2.4	2.76 dd *J* 12.3, 4.8
C(2)*H*	3.32 m -	3.29-3.33 m -	2.79-2.85 m -
C(3)*H*	3.70 dd *J* 9.5, 3.5	3.63-3.68 m -	3.93-3.95 m -
C(4)*H*	3.53 t *J* 9.5	3.44 t *J* 9.7	3.42 dd *J* 10.4, 2.8
C(5)*H*	2.58 m -	2.50 ddd *J* 9.7, 5.8, 3.0	2.69 ddd *J* 10.4, 5.8, 2.8
C(6)H_A	3.74 dd *J* 11.0, 5.5	3.63-3.68 m -	3.59 dd *J* 11.7, 5.8
C(6)H_B	3.86 br d *J* 11.0	3.77 dd *J* 11.7, 3.0	3.76 dd *J* 11.7, 2.8

Table 12. Comparison of ^{1}H NMR data of (−)-ADMJ **112** and (+)-ADANJ **263** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

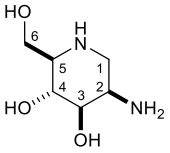
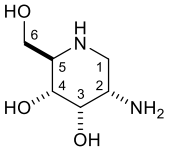
^{13}C NMR data for (−)-ADMJ **112** and (+)-ADANJ **263**  **112**  **263**			
C	Le Merrer *et al.*[39] δ_C (63 MHz, D_2O)	This study: (−)-ADMJ **112** δ_C (100 MHz, D_2O)	This study: (+)-ADANJ **263** δ_C (100 MHz, D_2O)
C(1)	49.9	46.4	44.6
C(2)	53.9	51.2	50.1
C(3)	76.6	73.1	71.4
C(4)	71.0	68.0	69.1
C(5)	63.8	60.9	54.5
C(6)	63.9	60.9	61.5

Table 13. Comparison of ^{13}C NMR data of (−)-ADMJ **112** and (+)-ADANJ **263** [chemical shifts (δ_C) are reported in ppm].

4.8. Summary

Iodoamination of racemic bishomoallylic amine **264** resulted in the formation of a 70:30 mixture of iodopiperidines *cis*-**288** and *trans*-**289**, from which *cis*-**288** was isolated in 24% yield and >99:1 dr. Trapping of CO_2 (from $NaHCO_3$) followed by intramolecular ring-opening of aziridinium **343** at the C(5)-position by the tethered nucleophile gave carbonate **281** in quantitative yield and >99:1 dr. The extension of this methodology to the use of alternative "X=C=Y" electrophiles led to the development of the trapping of *p*-TsNCO by **288**, which produced after intramolecular ring-opening of aziridinium **344** via the nitrogen atom, carbamate **312** in 62% yield and >99:1 dr. The application of the trapping of *p*-TsNCO to enantiopure iodomethyl pyrrolidine **174** afforded aziridinium **324**, which by analogy to the model system, gave carbamate **317**. Development of the one-pot ring-closing iodoamination/ring-expansion of bishomoallylic amine **191** provided access to **317** directly, and subsequent methanolysis of **317** furnished amino alcohol **329** in 25% yield and >99:1 dr (from **191**). Similarly, treatment of the epimeric bishomoallylic amine **192** with I_2 and *p*-TsNCO gave carbamate **332** in 48% yield, which underwent methanolysis to give **333** in

83% yield and >99:1 dr. Finally, global deprotection of **329** and **333** furnished (−)-ADMJ **112** and (+)-ADANJ **263** in 3.4% and 2.5% overall yield, respectively, in thirteen steps from commercially available starting materials (Figure 35).

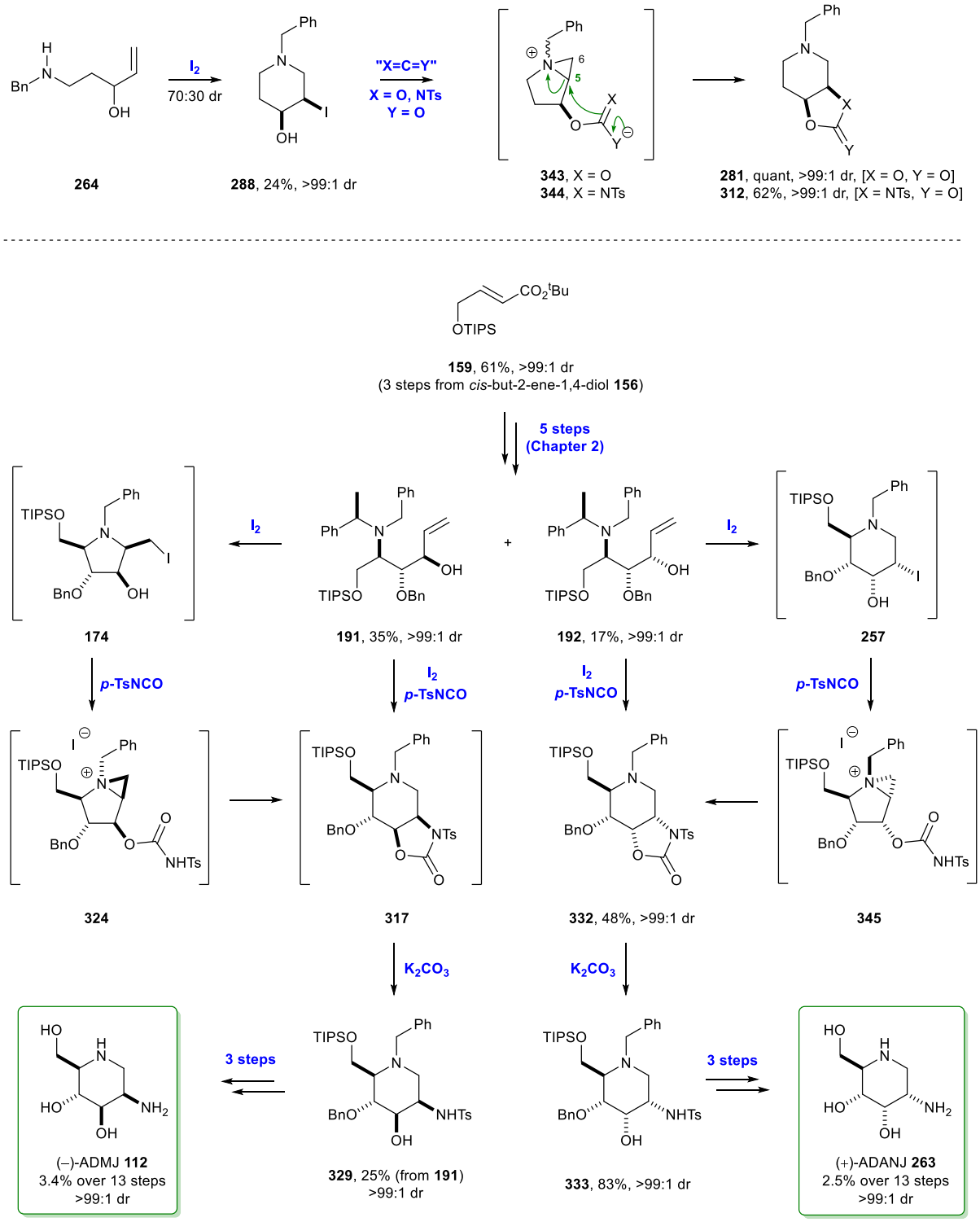


Figure 35. The trapping of "X=C=Y" electrophiles in the model system and the application to the total asymmetric syntheses of (−)-ADMJ **112** and (+)-ADANJ **263** via a ring-expansion approach.

4.9. Conclusions and future work

The syntheses of the pyrrolidine iminosugar (+)-DGDP **14** and its 1-deoxy-1-amino analogue (+)-ADGDP **104** were successfully achieved employing the ring-closing iodoamination of bishomoallylic amine **191** as the key step (Chapter 2). A ring-expansion methodology involving the trapping of CO_2 from $NaHCO_3$ was subsequently developed to access piperidine iminosugars (−)-1-deoxymannojirimycin (DMJ) **11** and (+)-1-deoxyallonojirimycin (DANJ) **64** (Chapter 3). Further studies on the trapping of alternative electrophiles (utilising a model system) culminated in the development of a ring-expansion protocol involving the trapping of *p*-TsNCO and the application of this methodology to the syntheses of 2-deoxy-2-amino analogues of (−)-DMJ **11** and (+)-DANJ **64**: (−)-ADMJ **112** and (+)-DANJ **263**, respectively (Chapter 4). Future work on this project will be concerned with the investigations on the trapping of "F containing electrophiles" by aziridinium **349** to give **350**, which could undergo ring-opening at the C(5)-position via fluoride transfer to deliver 2-deoxy-2-fluoro iminosugar analogue **347**. In addition, the trapping of "SO_3" electrophiles could proceed via aziridinium **351** to give bicyclic derivative **352**. The sulfonate moiety within **352** could subsequently act as a leaving group in intermolecular displacement reactions to allow access to 2,3-*anti*-configured analogues of (−)-DMJ **11** (Figure 36).

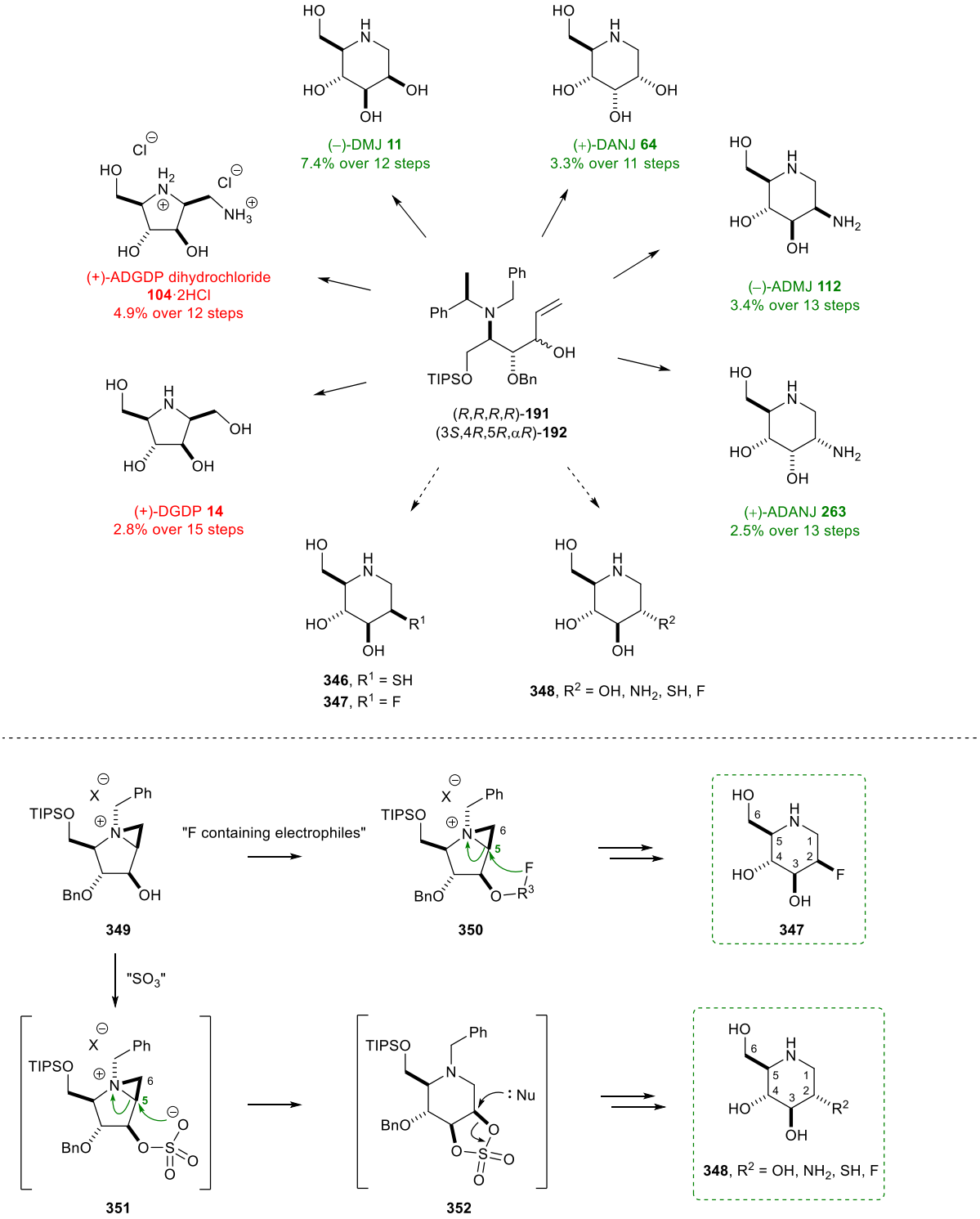


Figure 36. Iminosugar natural products and analogues synthesised/accessible by employing the ring-closing iodoamination and ring-expansion strategy.

4.10. References and notes

[1] Chesney, A.; Marko, I. E. *Synth. Commun.* **1990**, *20*, 3167.

[2] The procedure reported by Marko *et al.* was slightly modified by quenching the reaction with satd aq NH_4Cl instead of EtOAc, as the addition of EtOAc resulted in the formation of a mixture of alcohol **271** and the acetylated derivative **272**.

[3] Almiento, G. M.; Balducci, D.; Bottoni, A.; Calvaresi, M.; Porzi, G. *Tetrahedron: Asymmetry* **2007**, *18*, 2695.

[4] Davies, S. G.; Foster, E. M. personal communication.

[5] Attempts to monodebenzylate *N*,*N*-dibenzyl protected bishomoallylic amine **271** using CAN in MeCN/H_2O (5:1) at rt for 16 h led to only 23% conversion into *N*-benzyl substituted bishomoallylic amine **264**.

[6] Whilst treatment of *N*,*N*-dibenzyl amine **272** with 2.1 equiv of CAN for 16 h led to 84% conversion into *N*-benzyl amine **275**, repetition of the reaction using 3.0 equiv of CAN for 16 h allowed the reaction to reach completion.

[7] Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Waul, M. A. *Tetrahedron* **2014**, *70*, 7106.

[8] Cook, P. D. US Patent, 9810286, **1998**.

[9] Solé, D.; Garcia-Rubio, S.; Bosch, J.; Bonjoch, J. *Heterocycles* **1996**, *43*, 2415.

[10] The ^{1}H NMR spectrum of *cis*-diol **282** was also recorded in CH_2Cl_2 at low temperature (208 K); however even though two conformers of **282** were observed in the spectrum, the ^{1}H NMR ^3J coupling constants of these two conformers could not be resolved due to insufficient dispersion of peaks.

[11] An authentic sample of *cis*-diol **282** was synthesised as only one reference in the literature reported the ^{1}H NMR characterisation data for **282**; see: Ortiz, A.; Young, I. S.; Sawyer, J. R.; Hsiao, Y.; Singh, A.; Sugiyama, M.; Corbett, R. M.; Chau, M.; Shi, Z.; Conlon, D. A. *Org. Biomol. Chem.* **2012**, *10*, 5253.

[12] An authentic sample of *trans*-diol **286** was synthesised as only one reference in the literature reported the ^{1}H NMR characterisation data for **286**; see: Terentiev, P. B.; Zilberstein, T. M.; Borisenko, A. A.; Shmorgunov, V. A.; Piskunkova, N. F.; Grishina, G. V. *Chem. Heterocycl. Compd.* **2003**, *39*, 885.

[13] Pavlova, M.; Hoenke, C.; Christoffers, J. *Synthesis* **2009**, 1659.

[14] Csatayová, K.; Davies, S. G.; Ford, J. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 12397.

[15] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

[16] Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762.

[17] It was anticipated that the ring-closing iodoamination of the secondary bishomoallylic amine **264** (model substrate) would deliver ring-closed products; for example see: Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Biomol. Chem.* **2013**, *11*, 3187.

[18] Attempts to synthesise an authentic sample of **289** were unsuccessful.

[19] X-Ray crystal structure determination was performed by Dr. J. E. Thomson and Dr. A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[20] The ^{13}C NMR chemical shift for *C*H_2I carbons in pyrrolidines have been reported to be lower (typically δ_C = 1.5−12 ppm) than the carbon shift for *C*HI in piperidines (typically δ_C = 20−40 ppm) for similar substrates, see: Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Russell, A. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758. See also compound **174** in Chapter 2 and compounds **257** and **258** in Chapter 3.

[21] The C(4)*H* proton could not be observed in the ^{1}H NMR spectrum of **288** in $CDCl_3$ at rt.

[22] Only traces (i.e., <5%) of *trans*-iodopiperidine **289** were observed upon inspection of the ^{1}H NMR spectrum of the crude reaction mixture following the one-pot transformation.

[23] The sp^2 character of *C*(6) within aziridinium **291** and presumably the $J_{C\text{-}H}$ coupling constants for C(6)H_A and C(6)H_B made the C(6)H_2 protons appear as if they were supported by different carbons in the HSQC spectrum. I would like to thank Prof. Tim Claridge for the discussion.

[24] The sp^2 character of *C*(6) within aziridinium **292** and presumably the $J_{C\text{-}H}$ coupling constants for C(6)H_A and C(6)H_B made the C(6)H_2 protons appear as if they were supported by different carbons in the HSQC spectrum. I would like to thank Prof. Tim Claridge for the discussion.

[25] *N*-Benzoyl carbamate **311** was obtained in quantitative mass return and was observed as the major product upon inspection of the ^{1}H NMR spectrum of the crude reaction mixture.

[26] *trans*-Carbamate **313** was obtained in 30% mass return and **313** was observed as the sole product of the reaction upon inspection of the ^{1}H NMR spectrum of the crude reaction mixture.

[27] ^{1}H NMR ^3J coupling constant analyses of **313** showed that the $^3J_{2ax,3}$, $^3J_{3,4}$, $^3J_{4,5ax}$ and $^3J_{5ax,6ax}$ values of 11.5 Hz were all consistent with a chair conformation accommodating the bicyclic system, and the $^3J_{2ax,3}$ and $^3J_{3,4}$ values of 11.5 Hz were therefore diagnostic of the C(3)*H* and the C(4)*H* protons adopting a *trans*-configuration.

[28] Evidence for the presence of the α-methylbenzyl moiety within **318** [δ = 1.5 ppm (3H, d, C(α)*Me*) and δ = 4.12 ppm (1H, q, C(α)*H*)] were observed in the ^{1}H NMR spectrum of this purified sample of **174**. Full characterisation of **318** was unsuccessful due to insufficient dispersion of peaks.

[29] Evidence for the presence of diastereoisomeric iodomethyl pyrrolidine **326** was observed in the ^{13}C NMR spectrum of the crude reaction mixture (diagnostic δ_C = 1.5−12 ppm for *C*H_2I).

[30] The use of 4.5 equiv of *p*-TsNCO was found to be optimal for conversion of iodomethyl pyrrolidines **174**, **326** and **318** into the corresponding carbamates **317**, **327** and **321**.

[31] The axial-axial ^{1}H NMR ^3J coupling constant values were consistent with the values observed in similar substrates (see Chapter 2 and 3).

[32] (a) Flack, H. D. *Acta. Crystallogr., Sect. A* **1983**, *39*, 876. (b) Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908. (c) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.

[33] Goddard, E. C. *D.Phil. Thesis*, University of Oxford, **2008**.

[34] Katagiri, T.; Katayama, Y.; Taeda, M.; Ohshima, T.; Iguchi, N.; Uneyama, K. *J. Org. Chem.* **2011**, *76*, 9305.

[35] Zhu, H.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014**, *136*, 1766.

[36] Lee, G. H.; Youn, I. K.; Choi, E. B.; Lee, H. K.; Yon, G. H.; Yang, H. C. Pak, C. S. *Curr. Org. Chem.* **2004**, *8*, 1263.

[37] Matthews, J. L.; M^{c}Arthur, D. R.; Muir, K. W. *Tetrahedron Lett.* **2002**, *43*, 5401.

[38] Llaveria, J.; Beltrán, A.; Sameera, W. M. C.; Locati, A.; Mar Díaz-Requejo, M.; Matheu, M. I.; Castillón, S.; Maseras, F.; Pérez, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 5342.

[39] For the only previous synthesis of (−)-ADMJ **112**, see: Le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg. Med. Chem.* **1997**, *5*, 519.

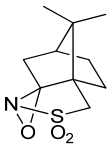
Chapter 5: Experimental

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. 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 a thin film on a diamond ATR module (ATR). Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated and at rt unless otherwise specified. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. When the diastereotopic methyl groups of isopropyl functionality could not be unambiguously assigned, the descriptors *Me*CMe and *Me*CHMe were employed, respectively. In the ^1H 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.

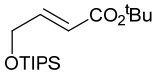
5.2. Experimental for Chapter 2

(−)-Camphorsulfonyloxaziridine [(−)-CSO] 147



$SOCl_2$ (252 mL, 3.44 mol) was added dropwise to a stirred solution of (−)-camphorsulfonic acid (200 g, 864 mmol) in $CHCl_3$ (1 L) and the resultant mixture was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (1 L) and the resultant solution was added dropwise to a stirred solution of 35% aq NH_3 (2 L) at 0 °C. The resultant mixture was stirred at rt for 4 h, then the aqueous layer was extracted with CH_2Cl_2 (2 × 1 L) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in PhMe (1 L) 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 and then allowed to cool to rt. The reaction 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, then $MeCO_3H$ (36% in AcOH, 276 mL, 1.31 mol) was then added dropwise, whilst still maintaining the reaction temperature below 5 °C, and the resultant mixture was allowed to warm to rt over 8 h. Satd aq Na_2SO_3 (80 mL) and 1.0 M aq NaOH (800 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 800 mL). The combined organic extracts were washed with H_2O (200 mL) and satd aq $NaHCO_3$ (800 mL), then dried and concentrated *in vacuo*. Purification via recrystallisation (CH_2Cl_2/40-60 °C petrol) gave **147** as a white solid (138 g, 80%);[2] mp 168-172 °C; {lit.[2] mp 165-167 °C}; $[\alpha]_D^{20}$ −40.7 (*c* 1.0 in $CHCl_3$); {lit.[2] $[\alpha]_D^{25}$ –43.6 (*c* 2.2, $CHCl_3$)}; 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*$_A$), 1.89-2.15 (4H, m, 2 × CH_2), 2.63-2.65 (1H, m, C*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$_2$).

tert-Butyl (*E*)-4-(triisopropylsilyloxy)but-2-enoate 159

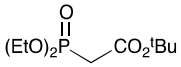


Step 1: TIPSCl (48.6 mL, 227 mmol) was added to a stirred solution of **156** (10.0 g, 114 mmol), imidazole (23.2 g, 341 mmol) and DMAP (277 mg, cat.) in CH_2Cl_2 (300 mL) at rt. The resultant mixture was stirred at rt for 16 h then concentrated *in vacuo*. The residue was dissolved in Et_2O (300 mL) and the resultant solution was washed with 1.0 M aq HCl (300 mL), then dried and concentrated *in vacuo* to give **157** as a colourless oil (43.2 g, 95%);[3] δ_H (400 MHz, $CDCl_3$) 1.02-1.12 (42H, m, Si(C*H*(*Me*)$_2$)$_3$), 4.29-4.33 (4H, m, C(1)H_2, C(4)H_2), 5.55-5.59 (2H, C(2)*H*, C(3)*H*).

Step 2: O_3 was bubbled through a stirred solution of the residue of **157** (43.2 g, 108 mmol) in CH_2Cl_2 (300 mL) at –78 ºC until a blue colouration was apparent. The reaction mixture was then purged with O_2 until it became colourless. DMS (5 mL) was then added dropwise and the resultant mixture was stirred at rt for 16 h. The reaction mixture was concentrated *in vacuo*, the residue was dissolved in Et_2O (300 mL) and the resultant solution was washed with H_2O (300 mL), then dried and concentrated *in vacuo* to give **158** as a colourless oil (42.0 g, 90%);[3] δ_H (400 MHz, $CDCl_3$) 1.02-1.10 (21H, m, Si(C*H*(*Me*)$_2$)$_3$), 4.25 (2H, d, *J* 1.0, C(2)H_2), 9.73 (1H, t, *J* 1.0, C*H*O).

Step 3: **160** (45.5 g, 180 mmol), LiCl (38.2 g, 902 mmol) and $^{i}Pr_2NEt$ (28.9 mL, 165 mmol) were added to a stirred solution of the residue of **158** (32.5 g, 150 mmol) in MeCN (500 mL). The reaction mixture was stirred at rt for 72 h and then H_2O (50 mL) was added. The aqueous layer was extracted with EtOAc (2 × 300 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **159** as a colourless oil (21.9 g, 61% from **156**, >99:1 dr);[3] δ_H (400 MHz, $CDCl_3$) 1.03-1.16 (21H, m, Si(C*H*(*Me*)$_2$)$_3$), 1.49 (9H, s, C*Me*$_3$), 4.38-4.42 (2H, m, C(4)H_2) 6.02-6.08 (1H, m, C(3)*H*), 6.85-6.92 (1H, m, C(2)*H*).

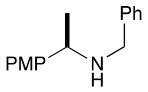
tert-Butyl (diethylphosphono)acetate 160



A stirred mixture of *tert*-butyl bromoacetate (50.0 g, 256 mmol) and $P(OEt)_3$ (44.0 mL, 256 mmol) was heated at 50 °C for 16 h. The reaction mixture was then quenched with 2.0 M aq KOH (10 mL) and partitioned between EtOAc (250 mL) and water (250 mL). The organic

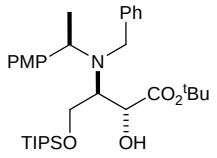
layer was washed with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), dried and concentrated *in vacuo* to give **160** as a colourless oil (59.8 g, 92%);[3] δ_H (400 MHz, $CDCl_3$) 1.35 (6H, t, *J* 6.9, $P(OCH_2CH_3)_2$), 1.48 (9H, s, CMe_3), 2.89 (2H, d, *J* 21.5, PCH_2), 4.08-4.23 (4H, m, $P(OCH_2CH_3)_2$).

(*R*)-*N*-Benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amine 161

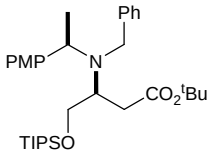


Benzaldehyde (17.7 mL, 174 mmol) was added dropwise to a stirred solution of (*R*)-α-methyl-*p*-methoxybenzylamine (24.4 mL, 165 mmol, 99% ee) in EtOH (100 mL) at rt and the resultant mixture was heated at reflux for 2 h. The reaction mixture was then allowed to cool to rt, cooled further to 0 °C and $NaBH_4$ (6.25 g, 165 mmol) was then added portionwise. The resultant suspension was allowed to warm to rt and was stirred at rt for 48 h. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (200 mL) and CH_2Cl_2 (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 9:1) gave **161** as a colourless oil (38.4 g, 96%, >99:1 ee);[4] $[\alpha]_D^{20}$ +59.3 (*c* 1.0 in $CHCl_3$); {lit.[4] $[\alpha]_D^{22}$ +46.9 (*c* 1.3 in $CHCl_3$}; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.7, C(α)*Me*), 1.61 (1H, s, N*H*), 3.63 (1H, d, *J* 13.3, NCH_AH_BPh), 3.71 (1H, d, *J* 13.3, NCH_AH_BPh), 3.82 (1H, q, *J* 6.7, C(α)*H*), 3.83 (3H, s, O*Me*), 6.88-6.92 (2H, m, C(3)*H*, C(5)*H*), 7.23-7.34 (7H, m, C(2)*H*, C(6)*H, Ph*).

***tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-4-(triisopropylsilyloxy)butanoate 163 and *tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-4-(triisopropylsilyloxy)butanoate 164**



163

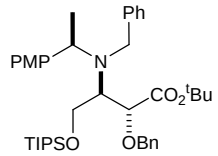


164

BuLi (2.0 M in hexanes, 31.8 mL, 63.6 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**161** (15.3 g, 63.6 mmol) in THF (250 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min before a solution of **159** (10.0 g, 31.8 mmol, >99:1 dr) in THF (250 mL) at −78 °C was added dropwise via cannula. The resultant mixture was stirred

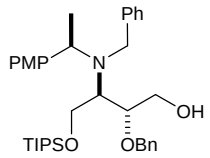
at −78 °C for 2 h, then (−)-CSO **147** (18.3 g, 79.5 mmol) was added and the reaction mixture was allowed to warm to rt over 16 h. Satd aq NH_4Cl (10 mL) was then added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between 10% aq citric acid (500 mL) and CH_2Cl_2 (500 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 250 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (500 mL) and brine (500 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **163** as a colourless oil (11.7 g, 66%, >99:1 dr); $[\alpha]_D^{20}$ −31.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3500 (O−H), 2942, 2866 (C−H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.04-1.09 (21H, m, Si(C*HMe*$_2$)$_3$), 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 3.03 (1H, d, *J* 6.8, O*H*), 3.47-3.53 (1H, m, C(3)*H*), 3.78 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.80 (3H, s, O*Me*), 3.86 (2H, d, *J* 7.2, C(4)*H*$_2$), 3.93-4.00 (2H, m, C(α)*H*, C(2)*H*), 4.15 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 6.81-6.87 (2H, m, C(3′)*H*, C(5′)*H*), 7.20-7.35 (5H, m, *Ph*), 7.42-7.44 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 18.5 (C(α)*Me*), 28.1 (C*Me*$_3$), 51.1 (N*C*H$_2$Ph), 55.2 (O*Me*), 57.1 (*C*(α)), 60.2 (*C*(3)), 62.0 (*C*(4)), 71.8 (*C*(2)), 82.1 (*C*Me$_3$), 113.4 (*C*(3′), *C*(5′)), 126.5 (*p-Ph*), 128.1, 128.3, 128.9 (*C*(2′), *C*(6′), *o,m-Ph*), 135.8, 142.0 (*C*(1′), *i-Ph*), 158.4 (*C*(4′)), 173.6 (*C*(1)); *m/z* (ESI$^+$) 572 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{54}NO_5Si^+$ ([M+H]$^+$) requires 572.3766; found 572.3748. Further elution gave **164** as a colourless oil (706 mg, 4%, >99:1 dr); $[\alpha]_D^{20}$ −1.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2942, 2866 (C−H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99-1.08 (21H, m, Si(C*HMe*$_2$)$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 2.05 (1H, dd, *J* 15.3, 4.9, C(2)*H*$_A$), 2.29 (1H, dd, *J* 15.3, 8.0, C(2)*H*$_B$), 3.50-3.57 (1H, m, C(3)*H*), 3.60-3.69 (2H, m, C(4)*H*$_A$, NC*H*$_A$H$_B$Ph), 3.72-3.82 (4H, m, C(4)*H*$_B$, O*Me*), 3.83-3.93 (2H, m, NCH$_A$*H*$_B$Ph, C(α)*H*), 6.79-6.87 (2H, m, C(3′)*H*, C(5′)*H*), 7.14-7.33 (5H, m, *Ph*), 7.40-7.42 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$, 19.6 (C(α)*Me*), 28.1 (C*Me*$_3$), 35.3 (*C*(2)), 50.7 (N*C*H$_2$Ph), 55.2 (O*Me*), 55.6 (*C*(3)), 57.7 (*C*(α)), 65.3 (*C*(4)), 79.9 (*C*Me$_3$), 113.3 (*C*(3′), *C*(5′)), 126.4 (*p-Ph*), 128.0, 128.2, 128.9 (*C*(2′), *C*(6′), *o,m-Ph*), 142.1 (*C*(1′), *i-Ph*), 158.4 (*C*(4′)), 172.0 (*C*(1)); *m/z* (ESI$^+$) 556 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{54}NO_4Si^+$ ([M+H]$^+$) requires 556.3817; found 556.3801.

tert-Butyl (*R*,*R*,*R*)-2-benzyloxy-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-4-(triisopropylsilyloxy)butanoate 165

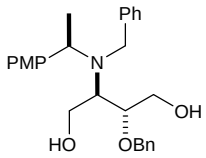


A solution of **163** (1.00 g, 1.75 mmol, >99:1 dr) in THF (10 mL) was added via syringe to a stirred slurry of NaH (60% dispersion in mineral oil, 140 mg, 3.50 mmol) in THF (10 mL) at 0 °C. The resultant mixture was allowed to warm to rt over 1 h. BnBr (0.42 mL, 3.50 mmol) and 15-crown-5 (0.69 mL, 3.50 mmol) were then added sequentially and the reaction mixture was stirred for 16 h. Satd aq NH_4Cl (2 mL) was then added and the organic layer was washed with brine (10 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, 25:1) gave **165** as a colourless oil (933 mg, 81%, >99:1 dr); $[\alpha]_D^{20}$ +36.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2942, 2866 (C−H), 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 1.03-1.14 (21H, m, Si(C*H*Me$_2$)$_3$), 1.33 (3H, d, *J* 6.9, C(α)*Me*), 1.44 (9H, s, C*Me*$_3$), 3.45-3.56 (1H, m, C(3)*H*), 3.64 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ph), 3.75 (1H, d, *J* 2.7, C(2)*H*), 3.77-3.89 (4H, m, C(4)*H*$_A$, O*Me*), 3.90-4.06 (2H, m, C(4)*H*$_B$, C(α)*H*), 4.12-4.33 (2H, m, NCH$_A$*H*$_B$Ph, OC*H*$_A$H$_B$Ph), 4.55 (1H, d, *J* 11.2, OCH$_A$*H*$_B$Ph), 6.74-6.90 (2H, m, C(3′)*H*, C(5′)*H*), 7.12-7.36 (10H, m, *Ph*), 7.38-7.48 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.2 (Si(CH*Me*$_2$)$_3$), 19.4 (C(α)*Me*), 28.1 (C*Me*$_3$), 51.0 (NCH_2Ph), 55.2 (O*Me*), 57.7 (*C*(α)), 60.6 (*C*(3)), 61.1 (*C*(4)), 72.4 (OCH_2Ph), 80.2 (*C*(2)), 81.2 (*C*Me$_3$), 113.3 (*C*(3′), *C*(5′)), 126.2, 127.6, 128.0, 128.2, 128.3, 128.4, 129.0 (*C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 136.2, 137.6, 142.7 (*C*(1′), *i*-*Ph*), 158.2 (*C*(4′)), 171.0 (*C*(1)); *m/z* (ESI$^+$) 662 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{40}H_{60}NO_5Si^+$ ([M+H]$^+$) requires 662.4235; found 662.4231.

(*R*,*R*,*R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-4-(triisopropylsilyloxy)butan-1-ol 166 and (*R*,*R*,*R*)-2-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-3-benzyloxybutane-1,4-diol 167



166



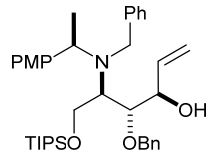
167

Method A: DIBAL-H (1.0 M in CH_2Cl_2, 6.04 mL, 6.04 mmol) was added dropwise to a stirred solution of **165** (1.00 g, 1.51 mmol, >99:1 dr) in CH_2Cl_2 (50 mL) at −78 °C. The reaction mixture was allowed to warm to rt over 2 h and then satd aq NH_4Cl (1 mL) was added. The resultant mixture was filtered through Celite® (eluent CH_2Cl_2), then the filtrate was dried and concentrated *in vacuo* to give **166** as a colourless oil (882 mg, 98%, >99:1 dr); $[\alpha]_D^{20}$ +24.2 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3389 (O−H), 2942, 2866 (C−H); δ_H (400 MHz, $CDCl_3$) 1.05-1.13 (21H, m, Si(C*H*Me$_2$)$_3$), 1.40 (3H, d, *J* 6.8, C(α)*Me*), 3.14-3.17 (1H, m, C(3)*H*), 3.25-3.34 (1H, m, O*H*), 3.36-3.54 (3H, m, C(1)H_2, C(2)*H*), 3.80 (3H, s, O*Me*), 3.93-4.06 (4H, m, C(α)*H*, C(4)H_A, NCH_2Ph), 4.10-4.19 (1H, m, C(4)H_B), 4.37 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.55 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 6.80-6.87 (2H, m, C(3′)*H*, C(5′)*H*), 7.16-7.20 (2H, m, C(2′)*H*, C(6′)*H*), 7.22-7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.1 (Si(*C*HMe$_2$)$_3$), 17.1 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 52.1 (N*C*H$_2$Ph), 55.2 (O*Me*), 57.2 (*C*(α)), 60.1 (*C*(3)), 62.4 (*C*(1)), 62.7 (*C*(4)), 71.4 (O*C*H$_2$Ph), 77.8 (*C*(2)), 113.6 (*C*(3′), *C*(5′)), 126.9, 127.5, 127.8, 128.2, 128.3, 128.8, 128.9 (*C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 136.1, 138.4, 141.0 (*C*(1′), *i*-*Ph*), 158.5 (*C*(4′)); *m/z* (ESI$^+$) 592 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{54}NO_4Si^+$ ([M+H]$^+$) requires 592.3817; found 592.3803.

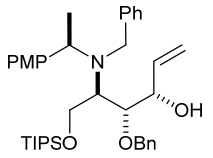
Method B: $LiAlH_4$ (1.0 M in THF, 2.80 mL, 2.80 mmol) was added dropwise to a stirred solution of **165** (930 mg, 1.40 mmol, >99:1 dr) in THF (6 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was cooled to 0 °C and ice (5 mg) was then carefully added. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between Rochelle's salt (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a 46:54 mixture of **166** and **167**, respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 9:1) gave **166** as a colourless oil (237 mg, 29%, >99:1 dr). Further elution (eluent 30-40 °C petrol/EtOAc, 1:1) gave **167** as a colourless oil (220 mg, 36%, >99:1 dr); $[\alpha]_D^{20}$ +80.5 (*c* 1.0 in

$CHCl_3$); ν_{max} (film) 3410 (O−H), 2933 (C−H); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 7.0, C(α)*Me*), 2.75 (1H, br s, O*H*), 3.07 (1H, td, *J* 7.1, 4.3, C(3)*H*), 3.33 (1H, dd, *J* 11.5, 4.9, C(1)H_A), 3.42-3.48 (1H, m, C(2)*H*), 3.49-3.54 (1H, m, C(1)H_B), 3.75-3.93 (8H, m, C(α)*H*, C(4)H_2, NCH_2Ph, O*Me*), 4.40 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.61 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 6.86 (2H, d, *J* 8.5, C(3′)*H*, C(5′)*H*), 7.16 (2H, d, *J* 8.5, C(2′)*H*, C(6′)*H*), 7.25-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 50.8 (N*C*H$_2$Ph), 55.2 (O*Me*), 56.2 (*C*(α)), 58.5 (*C*(3)), 61.9 (*C*(1)), 62.6 (*C*(4)), 71.9 (O*C*H$_2$Ph), 80.2 (*C*(2)), 113.6 (*C*(3′), *C*(5′)), 127.6, 127.2, 128.0, 128.1, 128.5, 128.6, 128.9 (*C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 134.8, 137.5, 140.0 (*C*(1′), *i*-*Ph*), 158.7 (*C*(4′)); *m/z* (ESI$^+$) 436 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{34}NO_4Si^+$ ([M+H]$^+$) requires 436.2483; found 436.2469.

(*R*,*R*,*R*,*R*)- and (3*S*,4*R*,5*R*,α*R*)-4-Benzyloxy-5-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-6-(triisopropylsilyloxy)hex-1-en-3-ol 169 and 170



169



170

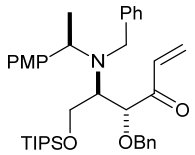
Step 1: DMSO (2.16 mL, 30.5 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.10 mL, 12.5 mmol) in CH_2Cl_2 (100 mL) at −78 °C. After 20 min, a solution of **166** (4.10 g, 6.93 mmol, >99:1 dr) in CH_2Cl_2 (100 mL) at −78 °C was added dropwise via cannula. After a further 20 min, Et_3N (5.80 mL, 41.6 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min before being allowed to warm to rt over a period of 30 min. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (250 mL) and Et_2O (250 mL). The aqueous layer was extracted with Et_2O (2 × 75 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **168** as a yellow oil (1.62 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.02-1.12 (21H, m, Si(C*HMe*$_2$)$_3$), 1.35 (3H, d, *J* 7.0, C(α)*Me*), 3.45-3.51 (1H, m, C(3)*H*), 3.57 (1H, m, C(2)*H*), 3.76 (1H, d, *J* 14.7, NCH_AH$_B$Ph), 3.80-3.87 (5H, m, C(4)H_A, C(α)*H*, O*Me*), 4.05 (1H, m, C(4)H_B), 4.10 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 4.35 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.48 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 6.86 (2H, m, C(3′)*H*, C(5′)*H*), 7.15-7.39 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*), 9.18 (1H, m, C(1)*H*).

Step 2: Vinylmagnesium bromide (1.0 M in THF, 8.24 mL, 8.24 mmol) was added dropwise to a stirred solution of the residue of **168** (1.62 g, 2.74 mmol, >99:1 dr) in THF (50 mL) at

0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and H_2O (1 mL) was added dropwise. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL) and the combined organic extracts were washed with brine (50 mL), then dried and concentrated *in vacuo* to give a 70:30 mixture of **169** and **170**. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 25:1) gave **169** as a colourless oil (937 mg, 55% from **166**, >99:1 dr); $[\alpha]_D^{20}$ +39.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3370 (O−H), 2942, 2866 (C−H), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.08-1.14 (21H, m, Si(C*H*M*e*$_2$)$_3$), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 3.27 (1H, dd, *J* 7.7, 2.4, C(4)*H*), 3.36-3.47 (2H, m, C(5)*H,* O*H*), 3.80 (3H, s, O*Me*), 3.95 (2H, app s, NCH_2Ph), 3.97-4.04 (1H, m, C(6)H_A), 4.05-4.12 (2H, m, C(α)*H*, C(6)H_B), 4.31 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.42-4.50 (1H, m, C(3)*H*), 4.52 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 5.04 (1H, dt, *J* 10.5, 1.7, C(1)H_A), 5.23 (1H, dt, *J* 17.2, 1.7, C(1)H_B), 5.59 (1H, ddd, *J* 17.2, 10.5, 4.8, C(2)*H*), 6.83-6.89 (2H, m, C(3′)*H*, C(5′)*H*), 7.16-7.34 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.1 (Si(*C*HMe$_2$)$_3$), 18.2 (Si(CH*Me*$_2$)$_3$), 19.3 (C(α)*Me*), 51.8 (N*C*H$_2$Ph), 55.3 (O*Me*), 59.2 (*C*(5)), 59.6 (*C*(α)), 62.7 (*C*(6)), 72.0 (*C*(3)), 73.8 (O*C*H$_2$Ph), 80.5 (*C*(4)), 113.6 (*C*(3′), *C*(5′)), 114.7 (*C*(1)), 126.7, 127.6, 127.8, 128.2, 128.9 (*C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 137.5, 138.2 (*i*-*Ph*), 139.5 (*C*(2)), 141.4 (*C*(1′)), 158.5 (*C*(4′)); *m/z* (ESI$^+$) 618 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{56}NO_4Si^+$ ([M+H]$^+$) requires 618.3973; found 618.3965. Further elution gave **170** as a colourless oil (180 mg, 5% from **166**, >99:1 dr); $[\alpha]_D^{20}$ +4.2 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 3370 (O−H), 2942, 2866 (C−H), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.03-1.16 (21H, m, Si(C*H*M*e*$_2$)$_3$), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 3.23 (1H, app q, *J* 5.7, C(5)*H*), 3.50 (1H, app t, *J* 4.8, C(4)*H*), 3.80 (3H, s, O*Me*), 3.88-3.99 (3H, m, C(6)H_A, NCH_2Ph), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.14-4.22 (2H, m, C(6)H_B, C(3)*H*), 4.38 (1H, d, *J* 11.3, OCH_AH$_B$Ph), 4.66 (1H, d, *J* 11.3, OCH$_A$$H_B$Ph), 4.98 (1H, d, *J* 10.6, C(1)H_A), 5.17-5.22 (2H, m, C(1)H_B, O*H*), 5.49-5.57 (1H, m, C(2)*H*), 6.83 (2H, d, *J* 8.5, C(3′)*H*, C(5′)*H*), 7.20-7.32 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 18.4 (C(α)*Me*), 51.6 (N*C*H$_2$Ph), 55.3 (O*Me*), 58.3 (*C*(α)), 59.3 (*C*(5)), 61.8 (*C*(6)), 71.8 (O*C*H$_2$Ph), 72.7 (*C*(3)), 82.0 (*C*(4)), 113.5 (*C*(3′), *C*(5′)), 115.6 (*C*(1)), 126.7, 127.5, 127.8, 128.2, 128.7, 128.9 (*C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 136.8 (*i*-*Ph*), 138.2 (*C*(2)), 138.3 (*i*-*Ph*), 141.2 (*C*(1′)), 158.4 (*C*(4′)); *m/z*

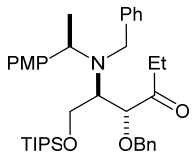
(ESI$^+$) 618 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{56}NO_4Si^+$ ([M+H]$^+$) requires 618.3973; found 618.3965.

(*R*,*R*,*R*)-4-Benzyloxy-5-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-6-(triisopropylsilyloxy)hex-1-en-3-one 172



IBX (272 mg, 0.97 mmol) was added to a solution of **169** and **170** (15:85, 200 mg, 0.32 mmol, >99:1 dr) in DMSO (15 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (75 mL), washed with H_2O (3 × 75 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 50:1) gave **172** as a yellow oil (118 mg, 60%, >99:1 dr); $[\alpha]_D^{20}$ +8.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2943, 2866 (C−H), 1700 (C=O), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.01-1.12 (21H, m, Si(C*H*Me$_2$)$_3$), 1.34 (3H, d, *J* 6.8, C(α)*Me*), 3.41 (1H, q, *J* 5.3, C(5)*H*), 3.80 (3H, s, O*Me*), 3.84-4.05 (5H, m, NCH_AH$_B$Ph, C(α)*H*, C(4)*H*, C(6)H_2), 4.08 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 4.27 (1H, d, *J* 11.3, OCH_AH$_B$Ph), 4.43 (1H, d, *J* 11.3, OCH$_A$$H_B$Ph), 5.39 (1H, dd, *J* 12.5, 2.1, C(1)H_A), 6.08 (1H, dd, *J* 15.4, 2.1, C(1)H_B), 6.22-6.27 (1H, m, C(2)*H*), 6.81-6.83 (2H, m, C(3′)*H*, C(5′)*H*), 7.17-7.40 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 16.7 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 51.9 (N*C*H$_2$Ph), 55.2 (O*Me*), 56.5 (*C*(α)), 60.0 (*C*(5)), 62.2 (*C*(6)), 72.4 (O*C*H$_2$Ph), 85.0 (*C*(4)), 113.3 (*C*(3′), *C*(5′)), 126.6, 127.7, 128.7, 129.4 (*C*(1), *C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 131.6 (*C*(2)), 135.6, 137.5 (*i*-*Ph*), 141.6 (*C*(1′)), 158.4 (*C*(4′)), 200.1 (*C*(3)); *m/z* (ESI$^+$) 616 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{54}NO_4Si^+$ ([M+H]$^+$) requires 616.3817; found 616.3808.

(*R*,*R*,*R*)-4-Benzyloxy-5-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-6-(triisopropylsilyloxy)hexan-3-one 173

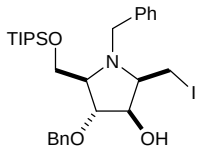


Step 1:[5] A solution of $ZnCl_2$ (4.00 g, 29.3 mmol) in THF (50 mL) was added via cannula to a stirred suspension of $NaBH_4$ (2.55 g, 67.5 mmol, >99:1 dr) in THF (150 mL) at rt and the

resultant mixture was stirred at rt for 72 h. The reaction mixture was then allowed to stand for 2 h to give a solution of $Zn(BH_4)_2$ (1.4 M in THF) which was decanted.

Step 2:[6] $Zn(BH_4)_2$ (1.4 M in THF, 0.24 mL, 0.24 mmol) was added dropwise to a stirred solution of **172** (50 mg, 0.08 mmol, >99:1 dr) in THF (5 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 16 h and then satd aq NH_4Cl (1 mL) was added. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 20:1) gave **173** as a yellow oil (20 mg, 40%, >99:1 dr); $[\alpha]_D^{20}$ +12.2 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 2942, 2866 (C−H), 1716 (C=O); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.2, C(1)*H*$_3$), 1.02-1.10 (21H, m, Si(C*H*M*e*$_2$)$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 1.71 (1H, dq, *J* 18.8, 7.3, C(2)*H*$_A$), 2.20 (1H, dq, *J* 18.8, 7.2, C(2)*H*$_B$), 3.36 (1H, app q, *J* 5.2, C(5)*H*), 3.80 (3H, s, O*Me*), 3.88-4.10 (6H, m, C(4)*H*, C(6)*H*$_2$, C(α)*H*, NC*H*$_2$Ph), 4.32 (1H, d, *J* 11.3, OC*H*$_A$H$_B$Ph), 4.42 (1H, d, *J* 11.3, OCH$_A$*H*$_B$Ph), 6.84 (2H, d, *J* 8.5, C(3′)*H*, C(5′)*H*), 7.20-7.40 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 8.2 (*C*(1)), 12.3 (Si(*C*HMe$_2$)$_3$), 16.4 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 30.2 (*C*(2)), 51.9 (NCH$_2$Ph), 55.2 (O*Me*), 56.3 (*C*(α)), 59.5 (*C*(5)), 62.4 (*C*(6)), 72.7 (O*C*H$_2$Ph), 85.5 (*C*(4)), 113.3 (*C*(3′), *C*(5′)), 126.6, 127.9, 128.0, 128.4, 128.5, 129.3 (*C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 135.7, 137.6 (*i*-*Ph*), 141.6 (*C*(1′)), 158.4 (*C*(4′)); *m/z* (ESI^+) 618 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{38}H_{56}NO_4Si^+$ ($[M+H]^+$) requires 618.3973; found 618.3957.

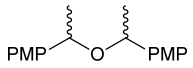
(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(iodomethyl)pyrrolidine 174



I_2 (518 mg, 2.04 mmol) and $NaHCO_3$ (171 mg, 2.04 mmol) were added to a stirred solution of **169** (400 mg, 0.68 mmol, >99:1 dr) in MeCN (20 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (50 mL), washed with satd aq $Na_2S_2O_3$ (50 mL) and the organic layer was dried and concentrated *in vacuo* to give a 75:25 mixture of **174** and **139**. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 50:1) gave **174** as a yellow oil (83 mg, 20%, >99:1 dr); $[\alpha]_D^{20}$ +50.7

(*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3384 (O−H), 2942, 2866 (C−H); δ_H (400 MHz, $CDCl_3$) 0.95–1.04 (21H, m, Si(C*H*Me$_2$)$_3$), 3.11 (1H, dd, *J* 8.9, 3.1, C*H*$_A$H$_B$I), 3.19 (1H, m, C(2)*H*), 3.22–3.28 (1H, m, C(2)C*H*$_A$H$_B$), 3.30 (1H, d, *J* 8.9, CH$_A$*H*$_B$I), 3.40 (1H, app dt, *J* 11.1, 3.1, C(5)*H*), 3.48 (1H, d, *J* 10.4, C(2)CH$_A$*H*$_B$), 3.68 (1H, d, *J* 14.0, NC*H*$_A$H$_B$Ph), 3.86 (1H, app s, C(3)*H*), 3.95–4.02 (2H, m, NCH$_A$*H*$_B$Ph, O*H*), 4.23 (1H, dd, *J* 11.1, 3.2, C(4)*H*), 4.53 (1H, d, *J* 12.0, OC*H*$_A$H$_B$Ph), 4.66 (1H, d, *J* 12.0, OCH$_A$*H*$_B$Ph), 7.22–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 3.4 (*C*H$_2$I), 11.8 (Si(*C*HMe$_2$)$_3$), 17.8 (Si(CH*Me*$_2$)$_3$), 58.8 (N*C*H$_2$Ph), 64.5 (C(2)*C*H$_2$), 70.0 (*C*(5)), 71.2 (O*C*H$_2$Ph), 74.0 (*C*(4)), 74.3 (*C*(2)), 84.7 (*C*(3)), 127.2, 127.6, 127.7, 128.3, 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 138.0, 139.7 (*i*-*Ph*); *m/z* (ESI$^+$) 610 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{45}INO_3Si^+$ ([M+H]$^+$) requires 610.2208; found 610.2198. Data for **139**: δ_H (400MHz, $CDCl_3$) 1.48 (3H, d, *J* 7.1, C(α)*Me*), 1.97 (3H, s, CO*Me*), 5.08-5.16 (1H, m, C(α)*H*), 5.98 (1H, br s, N*H*), 7.24-7.36 (5H, m, Ph).

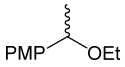
(*RS*,*RS*)- and (*RS*,*SR*)-Bis-α-methyl-*p*-methoxybenzyl ether 176 and 177



176:177

TsCl (63.0 mg, 0.33 mmol) and Et_3N (0.18 mL, 1.31 mmol) were added to a solution of **175** (100 mg, 0.65 mmol) in CH_2Cl_2 (5 mL) at rt. The resultant solution was stirred at rt for 16 h. The reaction mixture was then washed with satd aq $NaHCO_3$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was washed with brine (5 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 20:1) gave a 50:50 mixture of **176** and **177** as a colourless oil (60 mg, 32%).[7] Data for **176**: δ_H (400 MHz, $CDCl_3$) 1.36 (6H, d, *J* 6.5, C(α)*Me*), 3.80 (6H, s, O*Me*), 4.19 (2H, q, *J* 6.5, C(α)*H*), 6.81-6.87 (4H, m, C(3′)*H*, C(5′)*H*), 7.20-7.22 (4H, m, C(2′)*H*, C(6′)*H*). Data for **177**: δ_H (400 MHz, $CDCl_3$) 1.44 (6H, d, *J* 6.5, C(α)*Me*), 3.83 (6H, s, O*Me*), 4.48 (2H, q, *J* 6.5, C(α)*H*), 6.88-6.94 (4H, m, C(3′)*H*, C(5′)*H*), 7.20-7.22 (4H, m, C(2′)*H*, C(6′)*H*).

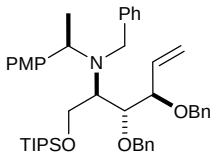
(*RS*)-Ethyl α-methyl-*p*-methoxybenzyl ether 181



I_2 (10.0 mg, 0.04 mmol) was added to a solution of **175** (100 mg, 0.65 mmol) and EtOH (0.05 mL, 0.78 mmol) in MeCN (2 mL) at 0 °C. The resultant solution was stirred at rt for 16

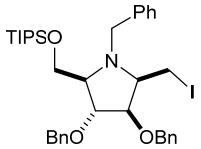
h, then washed with satd aq $Na_2S_2O_3$ (25 mL) and extracted with EtOAc (25 mL). The organic layer was washed with brine (25 mL), then dried and concentrated *in vacuo* to give **181** as a yellow oil (101 mg, 86%);[8] δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.0, OCH_2CH_3), 1.43 (3H, d, *J* 6.5, C(α)*Me*), 3.33 (2H, q, *J* 7.0, OCH_2CH_3), 3.81 (3H, s, O*Me*), 4.37 (1H, q, *J* 6.5, C(α)*H*), 6.86-6.92 (2H, m, C(3′)*H*, C(5′)*H*), 7.22-7.26 (2H, m, C(2′)*H*, C(6′)*H*).

(*R*,*R*,*R*,*R*)-3,4-Dibenzyloxy-5-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-6-(triisopropylsilyloxy)hex-1-ene 184



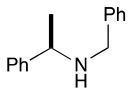
A solution of **169** (500 mg, 0.80 mmol, >99:1 dr) in THF (5 mL) was added via syringe to a stirred slurry of NaH (60% dispersion in mineral oil, 64 mg, 1.64 mmol) in THF (5 mL) at 0 °C. The resultant mixture was allowed to warm to rt over 1 h. BnBr (0.20 mL, 1.64 mmol) and 15-crown-5 (0.32 mL, 1.64 mmol) were then added and the resultant mixture was stirred at rt for 16 h. Satd aq NH_4Cl (1 mL) was then added and the organic layer was washed with brine (5 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, 50:1) gave **184** as a colourless oil (340 mg, 60%, >99:1 dr); $[\alpha]_D^{20}$ +28.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2942, 2865 (C−H), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.02-1.12 (21H, m, Si(C*H*Me$_2$)$_3$), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 3.14-3.20 (1H, m, C(5)*H*), 3.53 (1H, dd, *J* 7.2, 2.2, C(4)*H*), 3.80 (3H, s, O*Me*), 3.83 (1H, d, *J* 14.7, NCH_AH$_B$Ph), 3.89-4.13 (5H, m, NCH$_A$$H_B$Ph, C(6)$H_2$, C(α)*H*, C(3)*H*), 4.19 (1H, d, *J* 11.6, OCH_AH$_B$Ph), 4.46 (1H, d, *J* 11.6, OCH$_A$$H_B$Ph), 4.54 (1H, d, *J* 11.4, OCH_CH$_D$Ph), 4.96 (1H, d, *J* 11.4, OCH$_C$$H_D$Ph), 4.98-5.11 (2H, m, C(1)H_2), 5.36 (1H, ddd, *J* 17.5, 10.1, 7.9, C(2)*H*), 6.79-6.83 (2H, m, C(3′)*H*, C(5′)*H*), 7.16-7.28 (15H, m, *Ph*), 7.36-7.39 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.2 (Si(CH*Me*$_2$)$_3$), 18.4 (C(α)*Me*), 51.2 (N*C*H$_2$Ph), 55.3 (O*Me*), 57.4 (*C*(α)), 58.5 (*C*(5)), 62.1 (*C*(6)), 70.5, 74.4 (O*C*H$_2$Ph), 83.5 (*C*(3)), 84.9 (*C*(4)), 113.3 (*C*(3′), *C*(5′)), 118.5 (*C*(1)), 126.3, 128.0, 128.4 (*C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 135.8 (*C*(2)), 137.4, 138.7, 139.3 (*i*-*Ph*), 142.6 (*C*(1′)), 158.2 (*C*(4′)); *m/z* (ESI$^+$) 708 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{45}H_{62}NO_4Si^+$ ([M+H]$^+$) requires 708.4443; found 708.4421.

(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3,4-dibenzyloxy-5-(iodomethyl)pyrrolidine 185



I_2 (366 mg, 1.44 mmol) and $NaHCO_3$ (121 mg, 1.44 mmol) were added to a stirred solution of **184** (340 mg, 0.48 mmol, >99:1 dr) in MeCN (15 mL) at rt and the resultant mixture was allowed to stir at rt for 16 h. The reaction mixture was then diluted with Et_2O (40 mL), washed with satd aq $Na_2S_2O_3$ (40 mL) and the organic layer was dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/ Et_2O, 33:1) gave **185** as a yellow oil (20 mg, 6%, >99:1 dr); $[\alpha]_D^{20}$ +26.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2941, 2866 (C−H); δ_H (400 MHz, $CDCl_3$) 0.89-0.95 (21H, m, Si(C*H*Me$_2$)$_3$), 3.11-3.22 (3H, m, C(2)*H*, C*H*$_A$H$_B$I, C*H*$_A$H$_B$C(2)H), 3.35 (1H, dd, *J* 11.1, 8.8, CH$_A$*H*$_B$I), 3.40-3.56 (2H, m, C(5)*H*, CH$_A$*H*$_B$C(2)), 3.68 (1H, d, *J* 13.1, NC*H*$_A$H$_B$Ph), 3.95 (1H, d, *J* 13.1, NCH$_A$*H*$_B$Ph), 4.04 (1H, m, C(3)*H*), 4.12 (1H, d, *J* 4.5, C(4)*H*), 4.45-4.62 (4H, m, 2 × OC*H*$_2$Ph), 7.19-7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 3.7 (*C*H$_2$I), 11.8 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 60.1 (N*C*H$_2$Ph), 64.6 (*C*H$_2$C(2)), 69.7 (*C*(5)), 70.7, 72.9 (O*C*H$_2$Ph), 73.6 (*C*(2)), 81.4 (*C*(3)), 83.4 (*C*(4)), 127.2, 127.5, 127.6, 127.7, 128.2, 128.3, 128.4, 129.0 (*o,m,p-Ph*), 137.9, 138.4, 139.6 (*i-Ph*); *m/z* (ESI$^+$) 722 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{51}INO_3Si^+$ ([M+H]$^+$) requires 700.2677; found 700.2662.

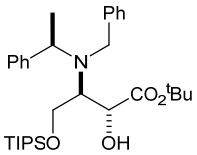
(*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine 186



Benzaldehyde (42.8 mL, 418 mmol) was added to a solution of (*R*)-α-methylbenzylamine (53.2 mL, 410 mmol, 99% ee) in EtOH (250 mL) at rt and the resultant mixture was heated at reflux for 2 h. The reaction mixture was then allowed to cool to rt, cooled further to 0 °C and $NaBH_4$ (15.6 g, 418 mmol) was then added portionwise. The resultant suspension was allowed to warm to rt and was stirred at rt for 48 h. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (250 mL) and CH_2Cl_2 (400 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (75

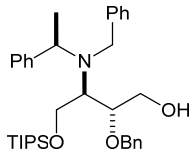
mL) and the resultant solution was added dropwise to a flask containing 10 M aq HCl (50 mL) and Et_2O (500 mL) at 0 °C. The resultant precipitate was collected by filtration, washed with Et_2O (150 mL) and dissolved in CH_2Cl_2 (500 mL). The resultant solution was then dried and concentrated *in vacuo* to give **186**·HCl as a white solid (160 g, 78%, >99:1 ee[9]). The free amine was regenerated quantitatively by treatment of **186**·HCl with 2 M aq NaOH (200 mL), followed by extraction with CH_2Cl_2 (2 × 400 mL). The combined organic layers were dried and concentrated *in vacuo* to give (*R*)-**186** as a colourless oil;[10] $[\alpha]_D^{20}$ +52.8 (*c* 1.0 in $CHCl_3$); {lit.[10] $[\alpha]_D^{25}$ +54.4 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.5, C(α)*Me*), 1.62 (1H, s, N*H*), 3.65 (1H, d, *J* 13.0, NCH_APh), 3.73 (1H, d, *J* 13.0, NCH_BPh), 3.82 (1H, q, *J* 6.5, C(α)*H*), 7.21-7.41 (10H, m, *Ph*).

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4 -(triisopropylsilyloxy)butanoate 187



BuLi (2.0 M in hexanes, 29.6 mL, 59.1 mmol) was added dropwise via syringe to a stirred solution of (*R*)-**186** (12.5 g, 59.1 mmol) in THF (300 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min before a solution of **159** (11.6 g, 36.9 mmol, >99:1 dr) in THF (300 mL) at −78 °C was added dropwise via cannula. The resultant mixture was stirred at −78 °C for 2 h, then (−)-CSO **147** (16.9 g, 73.8 mmol) was added and the reaction mixture was allowed to warm to rt over 16 h. Satd aq NH_4Cl (15 mL) was then added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between 10% aq citric acid (500 mL) and CH_2Cl_2 (500 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (500 mL) and brine (500 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **187** as a colourless oil (16.0 g, 80%, >99:1 dr);[11] $[\alpha]_D^{20}$ −43.4 (*c* 1.0 in $CHCl_3$); {lit.[11] for enantiomer $[\alpha]_D^{20}$ +37.4 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.02-1.09 (21H, m, Si(C*HMe*$_2$)$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 3.03 (1H, d, *J* 6.5, O*H*), 3.45-3.54 (1H, m, C(3)*H*), 3.80 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.86 (2H, d, *J* 6.8, C(4)H_2), 3.95-4.06 (2H, m, C(α)*H*, C(2)*H*), 4.20 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 7.18-7.50 (10H, m, *Ph*).

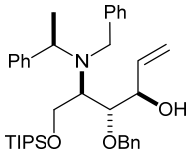
(*R*,*R*,*R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triisopropylsilyloxy)butan-1-ol 189



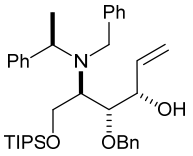
Step 1: A solution of **187** (16.0 g, 29.6 mmol, >99:1 dr) in THF (250 mL) was added via syringe to a stirred slurry of NaH (60% dispersion in mineral oil, 2.37 g, 59.2 mmol) in THF (250 mL) at 0 °C. The resultant mixture was allowed to warm to rt over 1 h. BnBr (7.03 mL, 59.2 mmol) and 15-crown-5 (11.7 mL, 59.2 mmol) were then successively added and the reaction mixture was stirred for 16 h. Satd aq NH_4Cl (30 mL) was then added and the organic layer was washed with brine (300 mL). The aqueous layer was extracted with Et_2O (3 × 200 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 100:1) gave **188** as a colourless oil (18.7 g, >99:1 dr);[11] $[\alpha]_D^{20}$ +24.9 (*c* 1.0 in $CHCl_3$); {lit.[11] for enantiomer $[\alpha]_D^{20}$ −33.1 (*c* 0.7 in $CHCl_3$}; δ_H (400 MHz, $CDCl_3$) 1.05-1.14 (21H, m, Si(C*H*Me$_2$)$_3$), 1.34 (3H, d, *J* 6.8, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 3.47-3.52 (1H, m, C(3)*H*), 3.65 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.75 (1H, d, *J* 2.6, C(2)*H*), 3.82 (1H, dd, *J* 10.9, 3.8, C(4)H_A), 3.98 (1H, dd, *J* 10.9, 8.6, C(4)H_B), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.17 (1H, d, *J* 11.1, OCH_AH$_B$Ph), 4.26 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.54 (1H, d, *J* 11.1, OCH$_A$$H_B$Ph), 7.16-7.46 (15H, m, *Ph*).

Step 2: DIBAL-H (1.0 M in CH_2Cl_2, 118.4 mL, 118.4 mmol) was added dropwise to a stirred solution of the residue of **188** (18.7 g, 29.6 mmol, >99:1 dr) in CH_2Cl_2 (500 mL) at −78 °C. The reaction mixture was allowed to warm to rt over 2 h and then satd aq NH_4Cl (20 mL) was added. The resultant mixture was filtered through Celite® (eluent CH_2Cl_2) and the filtrate was dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 33:1) gave **189** as a colourless oil (13.3 g, 80% from **187**, >99:1 dr);[11] $[\alpha]_D^{20}$ +8.9 (*c* 1.1 in $CHCl_3$); {lit.[11] for enantiomer $[\alpha]_D^{20}$ −30.2 (*c* 0.7 in $CHCl_3$}; δ_H (400 MHz, $CDCl_3$) 1.05-1.18 (21H, m, Si(C*H*Me$_2$)$_3$), 1.43 (3H, d, *J* 6.8, C(α)*Me*), 3.08 (1H, t, *J* 5.2, O*H*), 3.18 (1H, app q, *J* 6.2, C(3)*H*), 3.37-3.54 (3H, m, C(1)H_2, C(2)*H*), 3.90-4.08 (4H, m, C(α)*H*, C(4)H_A, NCH_2Ph), 4.16 (1H, dd, *J* 10.2, 5.1, C(4)H_B), 4.36 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 4.55 (1H, d, *J* 11.5, OCH$_A$$H_B$Ph), 7.22-7.35 (15H, m, *Ph*).

(*R*,*R*,*R*,*R*)- and (3*S*,4*R*,5*R*,α*R*)-4-Benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisopropylsilyloxy)hex-1-en-3-ol 191 and 192



191



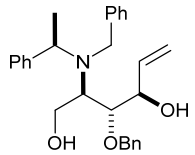
192

Step 1: DMSO (6.73 mL, 94.8 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (3.70 mL, 42.7 mmol) in CH_2Cl_2 (250 mL) at −78 °C. After 20 min, a solution of **189** (13.3 g, 23.7 mmol, >99:1 dr) in CH_2Cl_2 (250 mL) at −78 °C was added dropwise via cannula. After a further 20 min, Et_3N (19.8 mL, 142.2 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min before being allowed to warm to rt over a period of 30 min. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (250 mL) and Et_2O (250 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **190** as a yellow oil (13.7 g, >99:1 dr);[11] δ_H (400 MHz, $CDCl_3$) 1.01–1.12 (21H, m, Si(C*H*Me$_2$)$_3$), 1.38 (3H, d, *J* 7.1, C(α)*Me*), 3.45–3.51 (1H, m, C(3)*H*), 3.56 (1H, dd, *J* 4.0, 2.7, C(2)*H*), 3.78 (1H, d, *J* 14.8, NCH_AH$_B$Ph), 3.81–3.92 (2H, m, C(4)H_A, C(α)*H*), 4.06 (1H, dd, *J* 9.6, 7.6, C(4)H_B), 4.12 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 4.34 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.48 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 7.16–7.40 (15H, m, *Ph*), 9.19 (1H, d, *J* 2.7, C(1)*H*).

Step 2: Vinylmagnesium bromide (1.0 M in THF, 23.7 mL, 23.7 mmol) was added dropwise to a stirred solution of the residue of **190** (13.7 g, >99:1 dr) in THF (300 mL) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and H_2O (10 mL) was added dropwise. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (300 mL) and EtOAc (300 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic extracts were washed with brine (300 mL), then dried and concentrated *in vacuo* to give a 65:35 mixture of **191** and **192**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 25:1) gave **191** as a colourless oil (7.66 g, 55% from **189**, >99:1 dr); $[\alpha]_D^{20}$ +36.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3370 (O−H), 2942, 2866 (C−H); δ_H (400 MHz, $CDCl_3$) 1.05–1.14 (21H, m, Si(C*H*Me$_2$)$_3$), 1.45 (3H, d, *J* 6.8, C(α)*Me*), 3.18 (1H, d, *J* 7.0, O*H*), 3.23 (1H, dd, *J* 7.8, 2.3, C(4)*H*), 3.38–3.49 (1H, m, C(5)*H*), 3.96 (2H, app s, NCH_2Ph), 3.97–4.04 (1H, m, C(6)H_A), 4.05–4.19 (2H, m, C(6)H_B, C(α)*H*), 4.29 (1H, d,

J 11.3, OCH_AH_BPh), 4.46 (1H, br s, C(3)*H*), 4.51 (1H, d, *J* 11.3, OCH_AH_BPh), 5.04 (1H, dd, *J* 10.5, 1.6, C(1)H_A), 5.24 (1H, dd, *J* 17.2, 1.6, C(1)H_B), 5.58 (1H, ddd, *J* 17.2, 10.6, 4.6, C(2)*H*), 7.14–7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.1 (Si(*C*HMe_2)$_3$), 18.2 (Si(CH*Me*$_2$)$_3$), 19.5 (C(α)*Me*), 52.0 (N*C*H_2Ph), 59.2 (*C*(5)), 60.5 (*C*(α)), 62.7 (*C*(6)), 71.9 (*C*(3)), 74.0 (O*C*H_2Ph), 80.7 (*C*(4)), 114.6 (*C*(1)), 126.8, 126.9, 127.6, 127.8, 127.9, 128.2, 128.3, 128.9 (*o*,*m*,*p*-*Ph*), 138.2 (*i*-*Ph*), 139.6 (*C*(2)), 141.4, 145.6 (*i*-*Ph*); *m/z* (ESI^+) 588 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{37}H_{54}NO_3Si^+$ ($[M+H]^+$) requires 588.3867; found 588.3857. Further elution gave **192** as a colourless oil (3.62 g, 26% from **189**, >99:1 dr); $[\alpha]_D^{20}$ +2.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3376 (O−H), 2942, 2866 (C−H); δ_H (400 MHz, $CDCl_3$) 1.03–1.18 (21H, m, Si(C*HMe*$_2$)$_3$), 1.34 (3H, d, *J* 6.7, C(α)*Me*), 3.20–3.26 (1H, m, C(5)*H*), 3.52 (1H, app t, *J* 4.4, C(4)*H*), 3.88–4.01 (3H, m, NCH_2Ph, C(6)H_A), 4.06 (1H, q, *J* 6.7, C(α)*H*), 4.12–4.20 (1H, m, C(6)H_B), 4.24 (1H, br s, C(3)*H*), 4.38 (1H, d, *J* 11.1, OCH_AH_BPh), 4.67 (1H, d, *J* 11.1, OCH_AH_BPh), 4.95 (1H, app d, *J* 10.4, C(1)H_A), 5.02 (1H, br s, O*H*), 5.18 (1H, app d, *J* 17.1, C(1)H_B), 5.43–5.54 (1H, m, C(2)*H*), 7.15–7.36 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe_2)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 18.7 (C(α)*Me*), 51.7 (N*C*H_2Ph), 59.1 (*C*(α)), 59.3 (*C*(5)), 61.8 (*C*(6)), 71.7 (O*C*H_2Ph), 72.4 (*C*(3)), 82.1 (*C*(4)), 115.6 (*C*(1)), 126.7, 126.8, 127.5, 127.8, 128.2, 128.7 (*o*,*m*,*p*-*Ph*), 138.1 (*C*(2)), 138.3, 141.3, 144.8 (*i*-*Ph*); *m/z* (ESI^+) 588 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{37}H_{54}NO_3Si^+$ ($[M+H]^+$) requires 588.3867; found 588.3847.

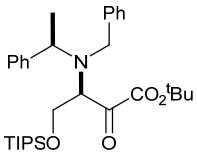
(*R*,*R*,*R*,*R*)-4-Benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-1-en-3,6-diol 193



TBAF (1.0 M in THF, 2.49 mL, 2.49 mmol) was added dropwise to a stirred solution of **191** (978 mg, 1.66 mmol, >99:1 dr) in THF (80 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 6:1) gave **193** as a white solid (555 mg, 77%, >99:1 dr); mp 74–76 °C; $[\alpha]_D^{20}$ +105.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3409 (O−H), 2931 (C−H); δ_H (400

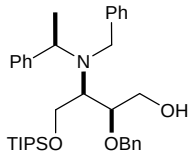
MHz, $CDCl_3$) 1.46 (3H, d, *J* 6.8, C(α)*Me*), 2.61 (1H, br s, O*H*), 2.91 (1H, br s, O*H*), 3.20–3.27 (1H, m, C(5)*H*), 3.45–3.50 (1H, m, C(4)*H*), 3.72–3.85 (3H, m, C(6)H_2, NC$H_A$$H_B$Ph), 3.89 (1H, d, *J* 14.1, NCH$_A$$H_B$Ph), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.26 (1H, br s, C(3)*H*), 4.39 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.60 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 5.06 (1H, app dt, *J* 10.6, 1.5, C(1)H_A), 5.20 (1H, app d, *J* 17.1, C(1)H_B), 5.52 (1H, ddd, *J* 17.1, 10.6, 4.7, C(2)*H*), 7.20–7.37 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 50.6 (N*C*H$_2$Ph), 58.3 (*C*(α)), 59.3 (*C*(5)), 61.9 (*C*(6)), 71.9 (*C*(3)), 74.0 (O*C*H$_2$Ph), 81.5 (*C*(4)), 115.2 (*C*(1)), 127.3, 127.5, 128.1, 128.2, 128.2, 128.2, 128.5, 128.6, 129.0 (*o*,*m*,*p*-*Ph*), 137.3, 140.1, 142.8 (*i*-*Ph*), 138.6 (*C*(2)); *m/z* (ESI$^+$) 432 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{34}NO_3^+$ ([M+H]$^+$) requires 432.2533; found 432.2522.

tert-Butyl (*R*,*R*)-2-oxo-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triisopropylsilyloxy)butanoate 194



DMSO (1.15 mL, 16.2 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.57 mL, 6.66 mmol) in CH_2Cl_2 (70 mL) at −78 °C. After 20 min, a solution of **187** (2.00 g, 3.69 mmol, >99:1 dr) in CH_2Cl_2 (70 mL) at −78 °C was added dropwise via cannula. After a further 20 min, Et_3N (3.10 mL, 22.2 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min before being allowed to warm to rt over a period of 30 min. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (200 mL) and Et_2O (200 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **194** as a yellow oil (1.66 g, 83%, >99:1 dr); $[\alpha]_D^{20}$ +34.7 (*c* 1.4 in $CHCl_3$); ν_{max} (film) 2942, 2866 (C−H), 1723, 1636 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01-1.09 (21H, m, Si(C*H*Me$_2$)$_3$), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 3.96 (2H, app d, *J* 6.5, NCH_2Ph), 4.03-4.14 (3H, m, C(4)H_2, C(α)*H*), 4.41 (1H, app t, *J* 6.2 , C(3)*H*), 7.19-7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 17.7 (C(α)*Me*), 18.0 (Si(CH*Me*$_2$)$_3$), 27.8 (C*Me*$_3$), 51.4 (N*C*H$_2$Ph), 58.8 (*C*(α)), 61.3 (*C*(4)), 62.6 (*C*(3)), 83.4 (*C*Me$_3$), 126.8, 127.0, 127.8, 128.1, 128.2, 128.7 (*o*,*m*,*p*-*Ph*), 140.6, 143.9 (*i*-*Ph*), 161.9 (*C*(1)), 193.9 (*C*(2)); *m/z* (ESI$^+$) 572 ([M+MeOH+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{54}NO_5Si^+$ ([M+MeOH+H]$^+$) requires 572.3766; found 572.3766.

(2*S*,3*R*,α*R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triisopropylsilyloxy)butan-1-ol 197



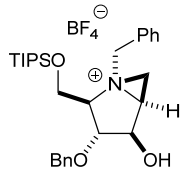
Step 1:[12] $NaBH_4$ (117 mg, 3.08 mmol) was added to a stirred solution of **194** (1.66 g, 3.08 mmol, >99:1 dr) in MeOH (100 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. The reaction mixture was then concentrated *in vacuo* to give **195** as a colourless oil (1.70 g, 95:5 dr); $[\alpha]_D^{20}$ −30.1 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3500 (O−H), 2942, 2866 (C−H); 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.05-1.16 (21H, m, Si(C*H*Me$_2$)$_3$), 1.41 (9H, s, C*Me*$_3$), 1.46 (3H, d, *J* 6.8, C(α)*Me*), 3.25-3.34 (1H, m, C(3)*H*), 3.86-4.00 (4H, m, C(2)*H*, C(4)*H*$_2$, NC*H*$_A$H$_B$Ph), 4.05 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 4.15-4.23 (1H, m, C(α)*H*), 7.18-7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 17.4 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 27.9 (C*Me*$_3$), 51.0 (N*C*H$_2$Ph), 58.8 (*C*(α)), 61.5 (*C*(3)), 61.7 (*C*(4)), 70.0 (*C*(2)), 81.6 (*C*Me$_3$), 126.9, 127.0, 127.9, 128.3, 128.7 (*o,m,p-Ph*), 140.7, 143.7 (*i-Ph*), 173.0 (*C*(1)); *m/z* (ESI^+) 564 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{32}H_{51}NNaO_4Si^+$ ($[M+Na]^+$) requires 564.3480; found 564.3490.

Step 2: A solution of the residue of **195** (1.70 g, 95:5 dr) in THF (25 mL) was added via syringe to a stirred slurry of NaH (60% dispersion in mineral oil, 246 mg, 6.16 mmol) in THF (25 mL) at 0 °C. The resultant mixture was allowed to warm to rt over 1 h. BnBr (0.73 mL, 6.16 mmol) and 15-crown-5 (1.22 mL, 6.16 mmol) were then added and the reaction mixture was stirred at rt for 16 h. Satd aq NH_4Cl (5 mL) was then added and the organic layer was washed with brine (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 **196** as a yellow oil (2.08 g, 95:5 dr); $[\alpha]_D^{20}$ −8.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2942, 2866 (C−H); 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02-1.09 (21H, m, Si(C*H*Me$_2$)$_3$), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 3.40-3.47 (1H, m, C(3)*H*), 3.81-3.87 (2H, m, C(4)*H*$_A$, NC*H*$_A$H$_B$Ph), 3.97 (1H, d, *J* 8.8, C(4)*H*$_B$), 4.04 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 4.15 (1H, d, *J* 4.0, C(2)*H*), 4.27 (1H, d, *J* 11.1, OC*H*$_A$H$_B$Ph), 4.35 (1H, q, *J* 6.8, C(α)*H*), 4.68 (1H, d, *J* 11.1, OCH$_A$*H*$_B$Ph), 7.16-7.34 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 18.2 (Si(CH*Me*$_2$)$_3$), 18.6 (C(α)*Me*), 51.1 (N*C*H$_2$Ph), 59.3 (*C*(α)), 60.5 (*C*(4)), 62.2 (*C*(3)), 73.1 (O*C*H$_2$Ph), 80.7 (*C*(2)), 126.2, 126.4, 127.3 (*p-Ph*), 127.6, 127.7, 127.8, 128.1, 128.2, 128.8 (*o,m-Ph*), 138.4, 142.3, 144.9 (*i-Ph*),

171.5 (*C*(1)); *m/z* (ESI$^+$) 632 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{58}NO_4Si^+$ ([M+H]$^+$) requires 632.4130; found 632.4129.

Step 3: DIBAL-H (1.0 M in CH_2Cl_2, 9.24 mL, 9.24 mmol) was added dropwise to a stirred solution of the residue of **196** (2.08 g, 95:5 dr) in CH_2Cl_2 (50 mL) at −78 °C. The resultant mixture was allowed to warm to rt over 2 h and then quenched with satd aq NH_4Cl (5 mL). The reaction mixture was then filtered through Celite® (eluent CH_2Cl_2) and the filtrate was dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 25:1) gave **197** as a colourless oil (450 mg, 26% from **194**, >99:1 dr); $[\alpha]_D^{20}$ −5.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2942, 2866 (C−H); δ_H (400 MHz, $CDCl_3$) 1.05-1.15 (21H, m, Si(C*HMe*$_2$)$_3$), 1.45 (3H, d, *J* 6.8, C(α)*Me*), 2.97-3.03 (1H, m, C(3)*H*), 3.23-3.29 (1H, m, C(1)H_A), 3.58-3.65 (2H, m, C(1)H_B, C(2)*H*), 3.74 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 4.05-4.08 (1H, m, C(4)H_A), 4.11-4.15 (1H, m, C(4)H_B), 4.17-4.25 (1H, m, C(α)*H*), 4.36 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 4.44 (1H, d, *J* 11.7, OCH_AH$_B$Ph), 4.62 (1H, d, *J* 11.7, OCH$_A$$H_B$Ph), 7.22-7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 13.7 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 52.1 (N*C*H$_2$Ph), 56.4 (*C*(α)), 59.3 (*C*(3)), 61.2 (*C*(4)), 61.9 (*C*(1)), 72.3 (O*C*H$_2$Ph), 79.5 (*C*(2)), 127.0, 127.3, 127.4, 127.8, 128.1, 128.2, 128.3, 128.4, 129.3 (*o*,*m*,*p*-*Ph*), 139.0, 139.1, 140.9, (*i*-*Ph*); *m/z* (ESI$^+$) 562 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{52}NO_3Si^+$ ([M+H]$^+$) requires 562.3711; found 562.3706.

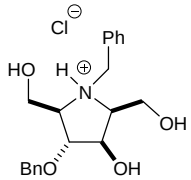
(1*S*,2*R*,3*R*,4*R*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-1-azabicyclo[3.1.0]hexanium tetrafluoroborate 201



$AgBF_4$ (23 mg, 0.118 mmol) was added to a stirred solution of **174** (60 mg, 0.10 mmol, >99:1 dr) in CH_2Cl_2 at rt and the resultant mixture was allowed to stir at rt for 1 h. The reaction mixture was then filtrated through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo* to give **201** as an orange oil (65 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ +0.6 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 3510 (O−H), 2945, 2867 (C−H); δ_H (400 MHz, CD_2Cl_2) 0.94–1.24 (21H, m, Si(C*HMe*$_2$)$_3$), 3.09 (1H, dd, *J* 8.0, 4.5, C(6)H_A), 3.56 (1H, dd, *J* 6.3, 4.5, C(6)H_B), 3.76–3.86 (2H, m, C(2)*H*, C(3)*H*), 3.98–4.04 (2H, m, C(2)CH_AH$_B$, O*H*), 4.07–4.20 (2H, m, C(2)CH$_A$$H_B$, C(5)*H*), 4.42 (1H, d, *J* 13.1, NCH_AH$_B$Ph), 4.54 (1H, d, *J* 11.6, OCH_AH$_B$Ph), 4.77 (1H, d, *J* 13.1,

NCH_AH_BPh), 4.82 (1H, d, *J* 11.6, OCH_AH_BPh), 4.83–4.88 (1H, m, C(4)*H*), 7.28–7.58 (10H, m, *Ph*); δ_C (100 MHz, CD_2Cl_2) 11.7 ($Si(CHMe_2)_3$), 17.8 ($Si(CHMe_2)_3$), 37.4 (*C*(6)), 49.2 (*C*(5)), 59.5 (C(2)CH_2), 61.3 (NCH_2Ph), 68.3 (*C*(2)), 72.6 (*C*(4)), 72.7 (OCH_2Ph), 79.0 (*C*(3)), 128.1, 128.3, 128.5, 129.9, 131.0, 131.2 (*o*,*m*,*p*-*Ph*), 136.9 (2 × *i*-*Ph*); *m/z* (ESI^+) 514 ($[M+MeOH]^+$, 40%), 482 ($[M]^+$, 100%); HRMS (ESI^+) $C_{30}H_{48}NO_4Si^+$ ($[M+MeOH]^+$) requires 514.3347; found 514.3345.

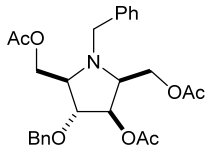
(2*R*,3*R*,4*R*,5*S*)-*N*(1)-Benzyl-2,5-bis(hydroxymethyl)-3-benzyloxy-4-hydroxypyrrolidine hydrochloride 204·HCl



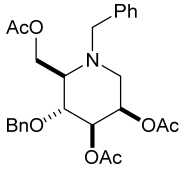
Step 1: K_2CO_3 (54 mg, 0.39 mmol) was added to a stirred solution of **206** (61 mg, 0.13 mmol, >99:1 dr) in MeOH (4 mL) at rt and the resultant mixture was allowed to stir at rt for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (15 mL) and $CHCl_3$/^{i}PrOH (3:1, 15 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 5 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **204** as a yellow oil (55 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ +11.9 (*c* 1.0 in $CHCl_3$).

Step 2: HCl (2.0 M in Et_2O, 1 mL) was added to a stirred solution of the residue of **204** (55 mg, >99:1 dr) in Et_2O (4 mL) and the resultant mixture was stirred at rt for 10 min. The reaction mixture was then concentrated *in vacuo* to give **204**·HCl as a yellow solid (49 mg, quant from **206**, >99:1 dr); mp 64–66 °C; $[\alpha]_D^{20}$ +18.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3307 (O−H), 2929 (C−H); δ_H (400 MHz, $CDCl_3$) 3.74–3.87 (4H, m, C(2)*H*, C(3)*H*, C(5)*H*, C(5)CH_AH_B), 4.09–4.17 (2H, m, C(5)CH_AH_B, NCH_AH_BPh), 4.32 (1H, d, *J* 13.1, NCH_AH_BPh), 4.43–4.49 (3H, m, C(4)*H*, C(2)CH_AH_B, OCH_AH_BPh), 4.54 (1H, d, *J* 12.0, OCH_AH_BPh), 4.72 (1H, d, *J* 13.1, C(2)CH_AH_B), 4.74 (1H, br s, O*H*), 5.16 (1H, br s, O*H*), 5.46 (1H, d, *J* 4.7, O*H*), 7.12–7.16 (2H, m, *Ph*), 7.31–7.38 (3H, m, *Ph*), 7.44–7.49 (3H, m, *Ph*), 7.60–7.64 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 57.7 (NCH_2Ph), 60.1 (C(5)CH_2), 61.1 (C(2)CH_2), 70.7 (*C*(2)), 71.9 (OCH_2Ph), 73.9 (*C*(4)), 74.1 (*C*(5)), 83.4 (*C*(3)), 127.5, 128.3, 128.6, 129.4, 130.5, 132.1 (*o*,*m*,*p*-*Ph*), 136.4 (2 × *i*-*Ph*); *m/z* (ESI^+) 344 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}NO_4^+$ ($[M+H]^+$) requires 344.1856; found 344.1851.

(2*R*,3*R*,4*R*,5*S*)-*N*(1)-Benzyl-2,5-bis(acetoxymethyl)-3-benzyloxy-4-acetoxypyrrolidine 206 and (*R*,*R*,*R*,*R*)-*N*(1)-benzyl-2-(acetoxymethyl)-3-benzyloxy-4,5-diacetoxypiperidine 207



206



207

Step 1: A solution of **201** (138 mg, 0.25 mmol, >99:1 dr) in dioxane/H_2O (3:1, 4 mL) was allowed to stir at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with 2.0 M aq KOH (15 mL), then dried and concentrated *in vacuo* to give a 90:10 mixture of **202** and **203** (124 mg), respectively. Data for mixture: ν_{max} (ATR) 3406 (O−H), 2942, 2866 (C−H); *m/z* (ESI^+) 500 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{46}NO_4Si^+$ ($[M+H]^+$) requires 500.3191; found 500.3166. Data for **202**: δ_H (400 MHz, $CDCl_3$) 0.90–1.08 (21H, m, Si(C*H*Me$_2$)$_3$), 3.00 (1H, app q, *J* 3.4, C(2)*H*), 3.11–3.16 (1H, m, C(5)*H*), 3.51 (1H, app t, *J* 4.4, C(2)CH_2), 3.57 (2H, dd, *J* 11.6, 4.8, C(5)CH_AH$_B$), 3.70 (1H, dd, *J* 11.6, 1.6, C(5)CH$_A$$H_B$), 3.77 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.82–3.87 (2H, m, C(3)*H*, NCH$_A$$H_B$Ph), 4.18–4.25 (1H, m, C(4)*H*), 4.52 (1H, d, *J* 11.7, OCH_AH$_B$Ph), 4.64 (1H, d, *J* 11.7, OCH$_A$$H_B$Ph), 7.18–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 58.2 (N*C*H$_2$Ph), 60.0 (C(5)*C*H$_2$), 63.8 (C(2)*C*H$_2$), 66.7 (*C*(5)), 70.4 (*C*(2)), 71.5 (O*C*H$_2$Ph), 76.8 (*C*(4)), 85.4 (*C*(3)), 127.6, 127.6, 128.4, 128.5, 128.5, 129.0 (*o*,*m*,*p*-*Ph*), 138.2 (2 × *i*-*Ph*). Data for **203**: δ_H (400 MHz, $CDCl_3$) 1.02–1.14 (21H, m, Si(C*H*Me$_2$)$_3$), 2.24 (1H, d, *J* 12.4, C(6)H_A), 2.38–2.47 (1H, m, C(2)*H*), 2.92 (1H, dd, *J* 12.4, 4.6, C(6)H_B), 3.36 (1H, d, *J* 13.3, NCH_AH$_B$Ph), 3.57 (1H, app t, *J* 8.1, C(3)*H*), 3.65 (1H, dd, *J* 8.1, 3.3, C(4)*H*), 3.72–3.80 (1H, m, C(5)*H*), 4.03 (1H, dd, *J* 11.1, 4.0, C(2)CH_AH$_B$), 4.22 (1H, dd, *J* 11.1, 1.8, C(2)CH$_A$$H_B$), 4.43 (1H, d, *J* 13.3, NCH$_A$$H_B$Ph), 4.65 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 5.03 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 7.26–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 54.1 (*C*(6)), 57.2 (N*C*H$_2$Ph), 61.9 (C(2)*C*H$_2$), 66.6 (*C*(2)), 67.9 (*C*(5)), 74.3 (O*C*H$_2$Ph), 75.8 (*C*(4)), 78.6 (*C*(3)), 127.2, 127.6, 127.9, 128.4, 128.5, 129.0 (*o*,*m*,*p*-*Ph*), 138.5 (2 × *i*-*Ph*).

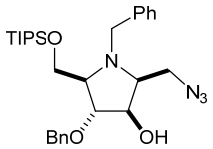
Step 2: HF·pyridine (70% in pyridine, 0.19 mL, 7.50 mmol) was added dropwise to a stirred solution of the residue of **202** and **203** (90:10, 124 mg), respectively, in THF (4 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and satd aq $NaHCO_3$ (0.5 mL) was added carefully. The

resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (10 mL) and $CHCl_3$/^{i}PrOH (3:1, 10 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 5 mL) and the combined organic extracts were then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (10 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give a 90:10 mixture of **204** and **205** (85 mg), respectively. Data for mixture: ν_{max} (ATR) 3368 (O−H), 2926 (C−H); *m/z* (ESI^+) 344 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}NO_4^+$ ($[M+H]^+$) requires 344.1856; found 344.1846. Data for **204**: δ_H (400 MHz, $CDCl_3$) 3.02−3.06 (1H, m, C(2)*H*), 3.15–3.19 (1H, m, C(5)*H*), 3.39 (1H, dd, *J* 11.3, 3.5, C(2)CH_AH_B), 3.54 (1H, dd, *J* 11.3, 1.6, C(2)CH_AH_B), 3.70 (1H, dd, *J* 11.8, 4.6, C(5)CH_AH_B), 3.77−3.84 (3H, m, C(3)*H*, C(5)CH_AH_B, NCH_AH_BPh), 3.88 (1H, d, *J* 13.4, NCH_AH_BPh), 4.29 (1H, dd, *J* 5.4, 2.5, C(4)*H*), 4.59 (1H, d, *J* 12.0, OCH_AH_BPh), 4.69 (1H, d, *J* 12.0, OCH_AH_BPh), 7.25–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 57.8 (N*C*H_2Ph), 60.7 (C(5)*C*H_2), 61.5 (C(2)*C*H_2), 66.6 (*C*(5)), 69.6 (*C*(2)), 71.8 (O*C*H_2Ph), 76.6 (*C*(4)), 86.2 (*C*(3)), 127.6, 127.6, 127.8, 128.5, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 138.0, 138.7 (*i*-*Ph*). Data for **205**: δ_H (400 MHz, $CDCl_3$) 2.29–2.34 (2H, m, C(2)*H*, C(6)H_A), 3.04 (1H, dd, *J* 12.6, 3.8, C(6)H_B), 3.39 (1H, d, *J* 13.2, NCH_AH_BPh), 3.60 (1H, dd, *J* 8.7, 3.3, C(4)*H*), 3.77 (1H, app t, *J* 8.7, C(3)*H*), 3.85 (1H, br s, C(5)*H*), 3.93 (1H, dd, *J* 12.0, 1.6, C(2)CH_AH_B), 4.03 (1H, dd, *J* 12.0, 2.7, C(2)CH_AH_B), 4.14 (1H, d, *J* 13.2, NCH_AH_BPh), 4.78 (1H, d, *J* 11.3, OCH_AH_BPh), 4.93 (1H, d, *J* 11.3, OCH_AH_BPh), 7.26–7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 54.8 (*C*(6)), 57.0 (N*C*H_2Ph), 58.3 (C(2)*C*H_2), 65.7 (*C*(2)), 67.8 (*C*(5)), 75.0 (O*C*H_2Ph), 75.2 (*C*(4)), 77.2 (*C*(3)), 127.5, 128.0, 128.1, 128.6, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 137.7, 138.3 (*i*-*Ph*).

Step 3: Ac_2O (0.24 mL, 2.50 mmol) and DMAP (6 mg, 0.05 mmol) were added to a stirred solution of the residue of **204** and **205** (90:10, 85 mg), respectively, in pyridine (4 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (15 mL) and EtOAc (15 mL), and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo* to give a 90:10 mixture of **206** and **207**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 9:1) gave **206** as a yellow oil (76 mg, 65% from **201**, >99:1 dr); $[\alpha]_D^{20}$ +50.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1741 (C=O); δ_H (400 MHz, $CDCl_3$) 1.87 (3H, s, CO*Me*), 1.99 (3H, s, CO*Me*),

2.08 (3H, s, CO*Me*), 3.16 (1H, ddd, *J* 8.2, 5.6, 2.1, C(2)*H*), 3.51 (1H, app dt, *J* 7.6, 5.2, C(5)*H*), 3.67−3.73 (2H, m, C(3)*H*, C(2)CH_AH_B), 3.86 (1H, d, *J* 13.9, NCH_AH_BPh), 3.93–4.01 (2H, m, C(2)CH_AH_B, NCH_AH_BPh), 4.03–4.14 (2H, m, C(5)CH_2), 4.58 (1H, d, *J* 12.1, OCH_AH_BPh), 4.68 (1H, d, *J* 12.1, OCH_AH_BPh), 5.30 (1H, dd, *J* 5.2, 1.6, C(4)*H*), 7.25–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.7, 20.8, 21.0 (CO*Me*), 59.1 (N*C*H_2Ph), 62.4 (C(5)*C*H_2), 63.4 (*C*(5)), 64.5 (C(2)*C*H_2), 68.0 (*C*(2)), 71.4 (O*C*H_2Ph), 76.1 (*C*(4)), 86.3 (*C*(3)), 127.4, 127.7, 127.8, 128.4, 128.4, 128.8 (*o,m,p-Ph*), 137.7, 138.6 (*i-Ph*), 170.2, 170.6, 170.6 (*C*OMe); *m/z* (ESI$^+$) 492 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{31}NNaO_7^+$ ([M+Na]$^+$) requires 492.1993; found 492.1983. Further elution gave **207** as a yellow oil (5 mg, 4% from **201**, >99:1 dr); $[\alpha]_D^{20}$ +1.5 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 2.03 (3H, s, CO*Me*), 2.05 (3H, s, CO*Me*), 2.09 (3H, s, CO*Me*), 2.50 (1H, dd, *J* 13.1, 2.7, C(6)H_A), 2.81−2.85 (1H, m, C(2)*H*), 3.00 (1H, dd, *J* 13.1, 6.0, C(6)H_B), 3.58 (1H, d, *J* 13.9, NCH_AH_BPh), 3.85 (1H, app t, *J* 7.0, C(3)*H*), 4.08 (1H, d, *J* 13.9, NCH_AH_BPh), 4.37 (1H, dd, *J* 12.3, 4.7, C(2)CH_AH_B), 4.51 (1H, dd, *J* 12.3, 3.8, C(2)CH_AH_B), 4.62 (1H, d, *J* 11.3, OCH_AH_BPh), 4.73 (1H, d, *J* 11.3, OCH_AH_BPh), 5.13 (1H, dd, *J* 7.0, 3.5, C(4)*H*), 5.28 (1H, ddd, *J* 6.0, 3.5, 2.7, C(5)*H*), 7.24–4.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.9, 21.0 (3 × CO*Me*), 49.9 (*C*(6)), 57.2 (N*C*H_2Ph), 60.9 (C(2)*C*H_2), 61.8 (*C*(2)), 66.9 (*C*(5)), 73.2 (*C*(4)), 74.0 (O*C*H_2Ph), 74.8 (*C*(3)), 127.2, 127.7, 127.8, 128.3, 128.5, 128.5 (*o,m,p-Ph*), 137.8, 138.4 (*i-Ph*), 170.0, 170.2, 170.7 (*C*OMe); *m/z* (ESI$^+$) 470 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{31}NNaO_7^+$ ([M+Na]$^+$) requires 492.1993; found 492.1981.

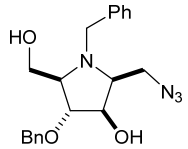
(2*R*,3*R*,4*R*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(azidomethyl)pyrrolidine 210



Step 1: I_2 (453 mg, 1.79 mmol) and $NaHCO_3$ (150 mg, 1.79 mmol) were added to a stirred solution of **191** (350 mg, 0.60 mmol, >99:1 dr) in MeCN (20 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 satd aq $Na_2S_2O_3$ (50 mL), then dried and concentrated *in vacuo* to give a 75:25 mixture of **174** and **139** (397 mg).

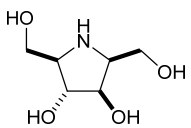
Step 2: NaN_3 (193 mg, 2.98 mmol) was added to a stirred solution of the residue of **174** and **139** (75:25, 397 mg) in DMF (15 mL). The resultant mixture was heated at 80 °C for 16 h before being allowed to cool to rt. The reaction mixture was then diluted with H_2O (50 mL) and EtOAc (50 mL), and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine/H_2O (1:1, 5 × 50 mL), then dried and concentrated *in vacuo* to give a 37:8:30:25 mixture of **210**, **211**, **191** and **139**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 50:1) gave **210** as a pale yellow oil (72 mg, 23% from **191**, >99:1 dr); $[\alpha]_D^{20}$ +46.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3406 (O−H), 2942, 2866 (C−H), 2100 (N_3); δ_H (400 MHz, $CDCl_3$) 0.97–1.04 (21H, m, Si(C*H*Me$_2$)$_3$), 3.05 (1H, br s, C(2)*H*), 3.16–3.22 (1H, m, C(5)*H*), 3.25–3.30 (2H, m, C(5)CH_AH$_B$, C(2)CH_AH$_B$), 3.50 (1H, dd, *J* 10.1, 2.5, C(2)CH$_A$*H*$_B$), 3.63 (1H, dd, *J* 11.8, 8.7, C(5)CH$_A$*H*$_B$), 3.71 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.85 (1H, app s, C(3)*H*), 3.96–4.02 (2H, m, NCH$_A$*H*$_B$Ph, O*H*), 4.11 (1H, dd, *J* 11.0, 3.8, C(4)*H*), 4.53 (1H, d, *J* 12.0, OC*H*$_A$H$_B$Ph), 4.64 (1H, d, *J* 12.0, OCH$_A$*H*$_B$Ph), 7.23–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 50.3 (C(5)*C*H$_2$), 59.0 (N*C*H$_2$Ph), 64.6 (C(2)*C*H$_2$), 67.3 (*C*(5)), 71.3 (O*C*H$_2$Ph), 72.7 (*C*(2)), 73.5 (*C*(4)), 85.4 (*C*(3)), 127.2, 127.6, 127.7, 128.3, 128.4, 128.8 (*o,m,p-Ph*), 138.0, 139.6 (*i-Ph*); *m/z* (ESI$^+$) 525 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{45}N_4O_3Si^+$ ([M+H]$^+$) requires 525.3255; found 525.3248. Further elution gave **191** as a yellow oil (59.9 mg, 17%, >99:1 dr). Data for **211**: δ_H (400 MHz, $CDCl_3$) 0.89–1.12 (21H, m, Si(C*H*Me$_2$)$_3$), 2.47 (1H, dd, *J* 12.6, 3.5, C(6)*H*$_A$), 2.68–2.74 (1H, m, C(2)*H*), 3.11 (1H, dd, *J* 12.6, 7.4, C(6)*H*$_B$), 3.60 (1H, d, *J* 13.9, NC*H*$_A$H$_B$Ph), 3.68 (1H, t, *J* 5.7, C(3)*H*), 3.78 (1H, app dt, *J* 7.4, 3.5, C(5)*H*), 3.88 (1H, dd, *J* 10.7, 4.7, C(2)CH_AH$_B$), 3.92–3.98 (1H, m, C(4)*H*), 4.15 (1H, dd, *J* 10.7, 3.5, C(2)CH$_A$*H*$_B$), 4.28 (1H, d, *J* 13.9, NCH$_A$*H*$_B$Ph), 4.64 (1H, d, *J* 11.4, OC*H*$_A$H$_B$Ph), 4.72 (1H, d, *J* 11.4, OCH$_A$*H*$_B$Ph), 7.21–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 49.2 (*C*(6)), 58.0 (*C*(5)), 58.5 (N*C*H$_2$Ph), 63.0 (C(2)*C*H$_2$), 63.7 (*C*(2)), 72.2 (*C*(4)), 73.4 (O*C*H$_2$Ph), 78.7 (*C*(3)), 127.0, 127.6, 128.3, 128.5, 128.6, 128.8, 129.0 (*o,m,p-Ph*), 138.2, 139.1 (*i-Ph*).

(2*R*,3*R*,4*R*,5*S*)-*N*(1)-Benzyl-2-(hydroxymethyl)-3-benzyloxy-4-hydroxy-5-(azidomethyl)pyrrolidine 213



HF·pyridine (70% in pyridine, 0.06 mL, 2.40 mmol) was added dropwise to a stirred solution of **210** (42 mg, 0.08 mmol, >99:1 dr) in THF (2 mL) at 0 °C, and the resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was cooled to 0 °C and satd aq $NaHCO_3$ (0.5 mL) was then carefully added. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (5 mL) and $CHCl_3/^iPrOH$ (3:1, 5 mL). The aqueous layer was extracted with $CHCl_3/^iPrOH$ (3:1, 2 × 5 mL) and the combined organic extracts were then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (10 mL), and the resultant solution was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 50:1) gave **213** as a yellow oil (29 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ +41.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3381 (O−H), 2927 (C−H), 2100 (N_3); δ_H (400 MHz, $CDCl_3$) 3.02–3.04 (1H, m, C(2)*H*), 3.17 (1H, dd, *J* 11.3, 3.5, C(2)CH_AH_B), 3.26 (1H, dt, *J* 7.6, 4.7, C(5)CH_AH_B), 3.34 (1H, app dd, *J* 12.3, 4.7, C(5)*H*), 3.45 (1H, app d, *J* 11.3, C(2)CH_AH_B), 3.51 (1H, dd, *J* 12.3, 7.6, C(5)CH_AH_B), 3.74 (1H, d, *J* 13.6, NCH_AH_BPh), 3.83 (1H, app t, *J* 2.5, C(3)*H*), 3.92 (1H, d, *J* 13.6, NCH_AH_BPh), 4.17 (1H, br s, C(4)*H*), 4.58 (1H, d, *J* 12.0, OCH_AH_BPh), 4.68 (1H, d, *J* 12.0, OCH_AH_BPh), 7.27–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 50.4 (C(5)CH_2), 58.5 (NCH_2Ph), 61.5 (C(2)CH_2), 66.4 (*C*(5)), 70.6 (*C*(2)), 71.8 (OCH_2Ph), 74.2 (*C*(4)), 86.5 (*C*(3)), 127.6, 127.7, 127.9, 128.5, 128.7, 128.7 (*o*,*m*,*p*-*Ph*), 137.9, 138.8 (*i*-*Ph*); *m/z* (ESI^+) 369 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{25}N_4O_3^+$ ($[M+H]^+$) requires 369.1921; found 369.1924.

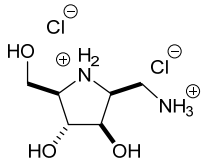
2,5-Dideoxy-2,5-imino-D-glucitol [(+)-DGDP] 14



$Pd(OH)_2$/C (22 mg, 20% w/w) was added to a stirred solution of **204**·HCl (44 mg, 0.13 mmol, >99:1 dr) in degassed MeOH (4 mL) and the resultant suspension was stirred at rt for 48 h under an atmosphere of H_2 (5 atm). HCl (2.0 M in Et_2O, 1 mL) was then added and the

resultant suspension was stirred for 5 min before being filtered through Celite® (eluent MeOH), and concentrated *in vacuo* to give **14**·HCl. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **14** as a white solid (21 mg, quant, >99:1 dr); mp 124–127 °C; {lit.[13] for sample isolated from the natural source mp 127–130 °C; lit.[14] mp 139–141 °C; lit.[15] mp 136–138 °C}; $[\alpha]_D^{20}$ +22.2 (*c* 0.5 in H_2O); $[\alpha]_D^{20}$ +14.4 (*c* 0.5 in MeOH); {lit.[13] for sample isolated from the natural source $[\alpha]_D$ +26.1 (*c* 0.84 in H_2O); lit.[16] $[\alpha]_D^{28}$ +22.7 (*c* 0.14 in H_2O); lit.[17] $[\alpha]_D^{22}$ +24.1 (*c* 1.0 in H_2O)}; ν_{max} (ATR) 3300 (O−H), 2926 (C−H); δ_H (400 MHz, D_2O) 2.99 (1H, app q, *J* 5.2, C(5)*H*), 3.30 (1H, app q, *J* 5.5, C(2)*H*), 3.60−3.67 (2H, m, C(1)H_A, C(6)H_A), 3.70−3.78 (2H, m, C(1)H_B, C(6)H_B), 3.84 (1H, dd, *J* 5.2, 2.8, C(4)*H*), 4.08 (1H, dd, *J* 5.5, 2.8, C(3)*H*); δ_C (100 MHz, D_2O) 59.9 (*C*(1)), 60.8 (*C*(2)), 62.1 (*C*(6)), 64.8 (*C*(5)), 77.2 (*C*(3)), 78.9 (*C*(4)); *m/z* (ESI^+) 164 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{14}NO_4^+$ ($[M+H]^+$) requires 164.0917; found 164.0913.

1,2,5-Trideoxy-1-amino-2,5-imino-D-glucitol dihydrochloride [(+)-ADGDP·2HCl] 104·2HCl

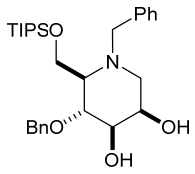


$Pd(OH)_2/C$ (14 mg) and HCl (2.0 M in Et_2O, 0.5 mL) were added to a stirred solution of **213** (27 mg, 0.07 mmol, >99:1 dr) in degassed MeOH (2 mL), and the resultant suspension was stirred at rt for 48 h under an atmosphere of H_2 (5 atm). The resultant suspension was filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave (+)-ADGDP **104** as a colourless oil. HCl (2.0 M in Et_2O, 1 mL) was added to a stirred solution of (+)-ADGDP **104** in Et_2O (2 mL) and the resultant mixture was stirred at rt for 10 min then concentrated *in vacuo* to give **104**·2HCl as pale yellow glassy solid (16 mg, quant, >99:1 dr); mp >170 °C; {lit.[18] mp >150 °C}; $[\alpha]_D^{20}$ +33.2 (*c* 0.6 in H_2O); {lit.[18] $[\alpha]_D^{25}$ +43 (*c* 1.43 in H_2O)}; ν_{max} (ATR) 3300 (O−H), 3300 (N−H); δ_H (400 MHz, D_2O) 3.46 (1H, dd, *J* 13.9, 6.0, C(1)H_A), 3.58 (1H, dd, *J* 13.9, 7.0, C(1)H_B), 3.64–3.68 (1H, m, C(5)*H*), 3.81 (1H, dd, *J* 12.1, 9.0, C(6)H_A), 3.94 (1H, dd, *J* 12.1, 4.7, C(6)H_B), 4.05 (1H, app td, *J* 6.5, 3.6, C(2)*H*), 4.08–4.11 (1H, m, C(4)*H*), 4.29–4.32 (1H, m, C(3)*H*); δ_C (100 MHz,

D_2O) 35.4 (*C*(1)), 58.7 (*C*(2)), 59.3 (*C*(6)), 68.3 (*C*(5)), 74.5 (*C*(3)), 75.6 (*C*(4)); *m/z* (ESI^+) 163 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{15}N_2O_3^+$ ($[M+H]^+$) requires 163.1077; found 163.1073.

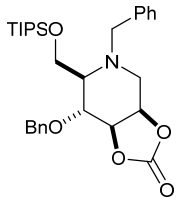
5.3. Experimental for Chapter 3

(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4,5-dihydroxypiperidine 203



K_2CO_3 (95 mg, 0.68 mmol) was added to a stirred solution of **252** (40 mg, 0.07 mmol, >99:1 dr) in MeOH (2 mL) at rt and the resulting mixture was allowed to stir at rt for 6 h. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (15 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **203** as a yellow oil (35 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ −19.8 (*c* 1.0 in $CHCl_3$).[19]

(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4,5-dihydroxy-4,5-*O*-carbonylpiperidine 246



*Method A (from **201**)*: $NaHCO_3$ (29 mg, 0.34 mmol) was added to a stirred solution of **201** (65 mg, 0.11 mmol, >99:1 dr) in dioxane/H_2O (3:1, 4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL), then dried and concentrated *in vacuo* to give **246** as a yellow oil (58 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ −32.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2943, 2866 (C−H), 1810 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02–1.15 (21H, m, Si(C*HMe*$_2$)$_3$), 2.83 (1H, dd, *J* 13.7, 1.0, C(6)H_A), 2.90 (1H, dd, *J* 13.7, 2.0, C(6)H_B), 2.98 (1H, app dd, *J* 9.2, 4.5, C(2)*H*), 3.43 (1H, d, *J* 14.2, NCH_AH$_B$Ph), 3.71 (1H, app t, *J* 9.2, C(2)CH_AH$_B$), 3.91 (1H, dd, *J* 10.1, 4.5, C(2)CH$_A$$H_B$), 4.06 (1H, d, *J* 14.2, NCH$_A$$H_B$Ph), 4.30 (1H, app d, *J* 3.6, C(3)*H*), 4.52 (1H, d, *J* 11.6, OCH_AH$_B$Ph), 4.70–4.78 (2H, m, C(5)*H*, OCH$_A$$H_B$Ph), 4.79–4.84 (1H, dd, *J* 8.3, 3.6, C(4)*H*), 7.23–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 49.1 (*C*(6)), 59.6 (N*C*H$_2$Ph), 62.8 (C(2)*C*H$_2$), 65.0 (*C*(2)), 71.8 (O*C*H$_2$Ph), 72.4 (*C*(3)), 73.4 (*C*(4)), 74.4 (*C*(5)), 127.3, 127.6, 128.0, 128.3, 128.5, 128.5 (*o*,*m*,*p*-*Ph*), 137.5,

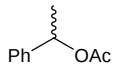
137.9 (*i-Ph*), 154.6 (*C*O); *m/z* (ESI$^+$) 526 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{44}NO_5Si^+$ ([M+H]$^+$) requires 526.2983; found 526.2968.

*Method B (from **174**)*: $NaHCO_3$ (21 mg, 0.25 mmol) was added to a stirred solution of **174** (50 mg, 0.08 mmol, >99:1 dr) in dioxane/H_2O (3:1, 4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL), then dried and concentrated *in vacuo* to give **246** as a yellow oil (43 mg, quant, >99:1 dr).

*Method C (from **191**) – Step 1*: I_2 (129 mg, 0.51 mmol) and $NaHCO_3$ (43 mg, 0.51 mmol) were added to a stirred solution of **191** (100 mg, 0.17 mmol, >99:1 dr) in dioxane/H_2O (3:1, 4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL), then dried and concentrated *in vacuo* to give a 50:50 mixture of **246** and **250** (100 mg). Data for **250**:[20] δ_H (400 MHz, $CDCl_3$) 1.50 (3H, d, *J* 6.8, C(α)*Me*), 1.77 (1H, s, O*H*), 4.91 (1H, q, *J* 6.8, C(α)*H*), 7.27-7.40 (5H, m, *Ph*).

*Method C (from **191**) – Step 2*: Ac_2O (0.18 mL, 1.9 mmol) and DMAP (4 mg, 0.04 mmol) were added to a stirred solution of the residue of **246** and **250** (50:50, 100 mg) in pyridine (8 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (20 mL) and EtOAc (20 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, then dried and concentrated *in vacuo* to give a 50:50 mixture of **246** and **251**. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 12:1) gave **246** as a colourless oil (23 mg, 26% from **191**, >99:1 dr).

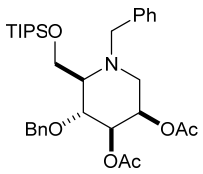
(*RS*)-α-Methylbenzyl acetate 251



Ac_2O (0.90 mL, 8.19 mmol) and DMAP (20 mg, 0.16 mmol) were added to a stirred solution of **250** (100 mg, 0.82 mmol, >99:1 dr) in pyridine (8 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (25 mL) and EtOAc (25 mL) and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2) gave **251** as a

colourless oil (115 mg, 85%, >99:1 dr);[21] δ_H (400 MHz, $CDCl_3$) 1.52 (3H, d, *J* 6.8, C(α)*Me*), 2.06 (3H, s, CO*Me*), 5.86 (1H, q, *J* 6.8, C(α)*H*), 7.24-7.40 (5H, m, *Ph*).

(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4,5-diacetoxypiperidine 252



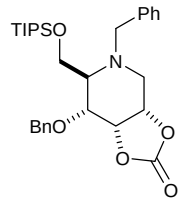
Step 1: I_2 (97 mg, 0.38 mmol) and $NaHCO_3$ (32 mg, 0.38 mmol) were added to a stirred solution of **191** (75 mg, 0.13 mmol, >99:1 dr) in H_2O/dioxane (1:3, 4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL), washed with satd aq $Na_2S_2O_3$ (15 mL), dried and concentrated *in vacuo* to give a 50:50 mixture of **246** and **250** (75 mg).

Step 2: K_2CO_3 (59 mg, 0.43 mmol) was added to a stirred solution of the residue of **246** and **250** (50:50, 75 mg) in MeOH (5 mL) at rt and the resulting mixture was allowed to stir at rt for 6 h. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (15 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 50:50 mixture of **203** and **250** (60 mg).

Step 3: Ac_2O (0.11 mL, 1.20 mmol) and DMAP (3 mg, 0.02 mmol) were added to a stirred solution of the residue of **203** and **250** (50:50, 60 mg) in pyridine (4 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (15 mL) and EtOAc (15 mL) and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to give a 50:50 mixture of **252** and **251**. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 9:1) gave **252** as a yellow oil (24 mg, 32% from **191**, >99:1 dr); $[\alpha]_D^{20}$ −14.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2942, 2866 (C−H), 1748 (C=O); δ_H (400 MHz, $CDCl_3$) 0.90–1.07 (21H, m, Si(C*H*Me_2)$_3$), 2.00 (3H, s, CO*Me*), 2.07 (3H, s, CO*Me*), 2.41 (1H, dd, *J* 13.2, 2.6, C(6)H_A), 2.66–2.72 (1H, m, C(2)*H*), 2.94 (1H, dd, *J* 13.2, 6.2, C(6)H_B), 3.53 (1H, d, *J* 14.0, NCH_AH$_B$Ph), 3.88 (1H, app t, *J* 7.3, C(3)*H*), 3.98 (1H, dd, *J* 10.6, 5.3, C(2)CH_AH$_B$), 4.12 (1H, dd, *J* 10.6, 3.5, C(2)CH$_A$$H_B$), 4.33 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 4.62 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.74 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 5.15 (1H,

dd, *J* 7.3, 3.2, C(4)*H*), 5.26 (1H, app dt, *J* 6.2, 3.2, C(5)*H*), 7.20–7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.0 (2 × CO*Me*), 49.9 (*C*(6)), 57.7 (N*C*H$_2$Ph), 60.4 (C(2)*C*H$_2$), 61.3 (*C*(2)), 65.2 (*C*(5)), 67.1 (*C*(4)), 73.8 (O*C*H$_2$Ph), 75.0 (*C*(3)), 126.9, 127.4, 127.6, 128.1, 128.3, 128.5 (*o*,*m*,*p*-*Ph*), 138.3, 139.3 (*i*-*Ph*), 170.1, 170.3 (*C*OMe); *m/z* (ESI$^+$) 584 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{50}NO_6Si^+$ ([M+H]$^+$) requires 584.3402; found 584.3401.

(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4,5-dihydroxy-4,5-*O*-carbonylpiperidine 253

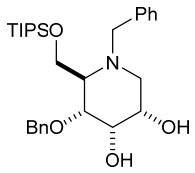


Step 1: I_2 (259 mg, 1.02 mmol) and $NaHCO_3$ (86 mg, 1.02 mmol) were added to a stirred solution of **192** (200 mg, 0.34 mmol, >99:1 dr) in H_2O/dioxane (1:3, 4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL), washed with satd aq $Na_2S_2O_3$ (15 mL), dried and concentrated *in vacuo* to give a 15:30:55 mixture of **253**, **254** and **250**, respectively (200 mg).

Step 2: Ac_2O (0.38 mL, 4.00 mmol) and DMAP (10 mg, 0.08 mmol) were added to a stirred solution of the residue of **253**, **254** and **250** (15:30:55, 200 mg) in pyridine (8 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (20 mL) and EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried and concentrated *in vacuo* to give a 15:30:55 mixture of **253**, **255** and **251**, respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 25:1) gave **255** as a colourless oil (45 mg, 23% from **192**, >99:1 dr); $[\alpha]_D^{20}$ −1.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2944, 2866 (C−H), 1747 (C=O); δ_H (400 MHz, $CDCl_3$) 0.95–1.12 (21H, m, Si(C*HMe*$_2$)$_3$), 1.95 (3H, s, CO*Me*), 2.12 (3H, s, CO*Me*), 2.41 (1H, t, *J* 10.9, C(6)H_A), 2.64 (1H, dd, *J* 10.9, 4.7, C(6)H_B), 2.69 (1H, app dd, *J* 9.6, 3.2, C(2)*H*), 3.31 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.58 (1H, dd, *J* 9.6, 2.2, C(3)*H*), 3.96 (1H, dd, *J* 11.1, 3.2, C(2)CH_AH$_B$), 4.22 (1H, app d, *J* 11.1, C(2)CH$_A$$H_B$), 4.36 (1H, d, *J* 10.8, OCH_AH$_B$Ph), 4.50 (1H, d, *J* 13.7, NCH$_A$$H_B$Ph), 4.69 (1H, d, *J* 10.8, OCH$_A$$H_B$Ph), 4.83–4.89 (1H, m, C(5)*H*), 5.83 (1H, br s, C(4)*H*), 7.22–7.36 (10H,

m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 20.8, 20.9 (CO*Me*), 48.8 (*C*(6)), 57.1 (N*C*H$_2$Ph), 61.9 (C(2)*C*H$_2$), 62.8 (*C*(2)), 66.6 (*C*(4)), 68.0 (*C*(5)), 71.1 (O*C*H$_2$Ph), 74.2 (*C*(3)), 126.9, 127.7, 128.2, 128.2, 128.3, 128.7 (*o,m,p-Ph*), 137.6, 139.4 (*i-Ph*), 170.0, 170.5 (*C*OMe); *m/z* (ESI$^+$) 584 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{50}NO_6Si^+$ ([M+H]$^+$) requires 584.3402; found 584.3402. Further elution (eluent 30-40 °C petrol/EtOAc, 12:1) gave **253** as a yellow oil (21 mg, 12% from **192**, >99:1 dr); $[\alpha]_D^{20}$ −2.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2943, 2866 (C−H), 1804 (C=O); δ_H (400 MHz, $CDCl_3$) 1.00-1.16 (21H, m, Si(C*HMe*$_2$)$_3$), 2.95 (1H, dd, *J* 12.3, 6.1, C(6)*H*$_A$), 3.01-3.06 (1H, m, C(2)*H*), 3.21 (1H, dd, *J* 12.3, 5.6, C(6)*H*$_B$), 3.67 (1H, d, *J* 13.7, NC*H*$_A$H$_B$Ph), 3.72-3.80 (2H, m, C(2)C*H*$_2$), 3.89 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ph), 4.13 (1H, dd, *J* 5.8, 3.2, C(3)*H*), 4.60 (1H, d, *J* 11.4, OC*H*$_A$H$_B$Ph), 4.68-4.76 (2H, m, C(5)*H*, OCH$_A$*H*$_B$Ph), 4.96 (1H, dd, *J* 8.4, 3.2, C(4)*H*), 7.24-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 48.7 (*C*(6)), 58.6 (N*C*H$_2$Ph), 61.7 (*C*(2)), 62.0 (C(2)*C*H$_2$), 72.6 (O*C*H$_2$Ph), 73.6 (*C*(4)), 73.8, 73.9 (*C*(3), *C*(5)), 127.7, 127.8, 128.2, 128.4, 128.6 (*o,m,p-Ph*), 137.5, 138.0 (*i-Ph*), 155.2 (*C*O); δ_H (400 MHz, CD_3CN) 1.06-1.20 (21H, m, Si(C*HMe*$_2$)$_3$), 2.79 (1H, dd, *J* 13.1, 4.3, C(6)*H*$_A$), 2.95-3.00 (1H, m, C(2)*H*), 3.26 (1H, dd, *J* 13.1, 4.3, C(6)*H*$_B$), 3.84 (1H, dd, *J* 10.9, 3.0, C(2)C*H*$_A$H$_B$), 3.89 (2H, app s, NC*H*$_2$Ph), 3.92 (1H, dd, *J* 10.9, 4.3, C(2)CH$_A$*H*$_B$), 4.13 (1H, dd, *J* 5.7, 2.9, C(3)*H*), 4.56 (1H, d, *J* 11.6, OC*H*$_A$H$_B$Ph), 4.69 (1H, d, *J* 11.6, OCH$_A$*H*$_B$Ph), 4.80 (1H, dt, *J* 8.3, 4.2, C(5)*H*), 5.16 (1H, dd, *J* 8.3, 2.9, C(4)*H*), 7.25-7.40 (10H, m, *Ph*); δ_C (100 MHz, CD_3CN) 12.1 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 49.0 (*C*(6)), 57.6 (N*C*H$_2$Ph), 60.6 (*C*(2)), 62.0 (C(2)*C*H$_2$), 71.9 (O*C*H$_2$Ph), 73.7 (*C*(4)), 73.8 (*C*(3)), 74.8 (*C*(5)), 127.5, 128.1, 128.4, 128.6, 128.7, 129.0 (*o,m,p-Ph*), 138.5, 139.2 (*i-Ph*), 155.8 (*C*O); *m/z* (ESI$^+$) 526 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{44}NO_5Si^+$ ([M+H]$^+$) requires 526.2983; found 526.2970.

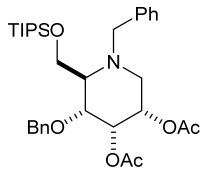
2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4,5-dihydroxypiperidine 254



K_2CO_3 (32 mg, 0.23 mmol) was added to a stirred solution of **255** (45 mg, 0.08 mmol, >99:1 dr) in MeOH (4 mL) at rt and the resultant mixture was allowed to stir at rt for 6 h. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O

(10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **254** as a yellow oil (40 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ −1.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3425 (O−H), 2942, 2866 (C−H); δ_H (400 MHz, $CDCl_3$) 1.01–1.12 (21H, m, Si(C*H*Me$_2$)$_3$), 2.80 (1H, dd, *J* 12.4, 4.0, C(6)H_A), 2.94 (1H, dd, *J* 12.4, 2.0, C(6)H_B), 3.10–3.18 (1H, m, C(2)*H*), 3.70–3.75 (1H, m, C(5)*H*), 3.80–3.98 (6H, m, C(3)*H*, C(4)*H*, C(2)CH_2, NCH_2Ph), 4.44 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 4.52 (1H, d, *J* 11.5, OCH$_A$$H_B$Ph), 7.25–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 52.6 (*C*(6)), 58.1, 58.3 (C(2)*C*H$_2$, NCH$_2$Ph), 59.9 (*C*(2)), 67.4 (*C*(4)), 69.7 (*C*(5)), 72.1 (O*C*H$_2$Ph), 78.6 (*C*(3)), 127.2, 127.8, 127.9, 128.3, 128.5, 128.6 (*o,m,p-Ph*), 137.8 (*i-Ph*); *m/z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{46}NO_4Si^+$ ([M+H]$^+$) requires 500.3191; found 500.3185.

(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4,5-diacetoxypiperidine 255



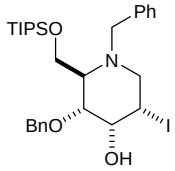
Step 1: I_2 (1.35 g, 5.31 mmol) and $NaHCO_3$ (446 mg, 5.31 mmol) were added to a stirred solution of **192** (1.04 g, 1.77 mmol, >99:1 dr) in dioxane/H_2O (3:1, 40 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (50 mL) and washed with satd aq $Na_2S_2O_3$ (50 mL), then dried and concentrated *in vacuo* to give a 35:15:50 mixture of **253**, **254** and **250**, respectively (1.10 g).

Step 2: K_2CO_3 (734 mg, 5.31 mmol) was added to a stirred solution of the residue of **253**, **254** and **250** (35:15:50, 1.10 g) in MeOH (50 mL) at rt and the resultant mixture was allowed to stir at rt for 6 h. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 × 25 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a 70:30 mixture of **254** and **250**, respectively (760 mg).

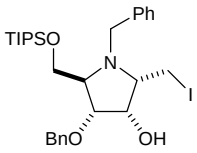
Step 3: Ac_2O (1.67 mL, 17.7 mmol) and DMAP (43 mg, 0.35 mmol) were added to a stirred solution of the residue of **254** and **250** (70:30, 760 mg) in pyridine (40 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (50 mL) and EtOAc (50 mL), and the aqueous layer was

extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with brine (25 mL), then dried and concentrated *in vacuo* to give a 70:30 mixture of **255** and **251**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 12:1) gave **255** as a colourless oil (465 mg, 45% from **192**, >99:1 dr).

(2*R*,3*R*,4*R*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-iodopiperidine 257 and (2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(iodomethyl)pyrrolidine 258



257

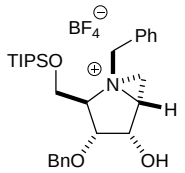


258

I_2 (129 mg, 0.51 mmol) and $NaHCO_3$ (43 mg, 0.51 mmol) were added to a stirred solution of **192** (100 mg, 0.17 mmol, >99:1 dr) in MeCN (5 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL), washed with satd aq $Na_2S_2O_3$ (20 mL) and the organic layer was dried and concentrated *in vacuo* to give a 44:26:30 mixture of **257**, **258** and **139**, respectively, as a brown oil (105 mg). Data for mixture: ν_{max} (ATR) 3384 (O−H), 2942, 2865 (C−H), 1650 (C=O); *m/z* (ESI^+) 610 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{44}INO_3Si^+$ ($[M+H]^+$) requires 610.2208; found 610.2210. Data for **257**: δ_H (400 MHz, MeCN-d_3) 0.84–1.01 (21H, m, Si(C*H*Me$_2$)$_3$), 2.54 (1H, dd, *J* 11.3, 4.5, C(6)H_A), 2.64 (1H, app t, *J* 11.3, C(6)H_B), 2.64–2.68 (1H, m, C(2)*H*), 3.28 (1H, d, *J* 13.8, NCH_AH$_B$Ph), 3.44 (1H, dd, *J* 9.8, 2.7, C(3)*H*), 3.82 (1H, dd, *J* 11.1, 5.3, C(2)CH_AH$_B$), 4.12 (1H, dd, *J* 11.1, 1.5, C(2)CH$_A$$H_B$), 4.15–4.18 (1H, m, C(5)*H*), 4.20–4.23 (1H, m, C(4)*H*), 4.26 (1H, d, *J* 13.8, NCH$_A$$H_B$Ph), 4.33 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.61 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 7.10–7.32 (10H, m, *Ph*); δ_H (400 MHz, $CDCl_3$) 0.88–1.13 (21H, m, Si(C*H*Me$_2$)$_3$), 2.69–2.85 (3H, m, C(2)*H*, C(6)H_2), 3.35 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.62 (1H, dd, *J* 9.5, 2.7, C(3)*H*), 3.95–3.99 (1H, m, C(2)CH_AH$_B$), 4.17–4.22 (2H, m, C(2)CH$_A$$H_B$, C(5)*H*), 4.32–4.35 (1H, m, C(4)*H*), 4.37 (1H, d, *J* 13.7, NCH$_A$$H_B$Ph), 4.51 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.67 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 7.15–7.41 (10H, m, *Ph*); δ_C (100 MHz, MeCN-d_3) 12.9 (Si(*C*HMe$_2$)$_3$), 18.6 (Si(CH*Me*$_2$)$_3$), 29.7 (*C*(5)), 55.3 (*C*(6)), 56.8 (NCH$_2$Ph), 62.7 (*C*(2)), 64.2 (C(2)*C*H$_2$), 69.3 (*C*(4)), 71.7 (O*C*H$_2$Ph), 77.4 (*C*(3)), 128.2, 128.3 (*p-Ph*), 129.0, 129.4, 129.6, 129.8 (*o*,*m-Ph*), 139.8, 141.2 (*i-Ph*); δ_C (100 MHz, $CDCl_3$) 12.0

(Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 27.5 (*C*(5)), 54.1 (*C*(6)), 56.3 (N*C*H$_2$Ph), 61.8 (*C*(2)), 62.3 (C(2)*C*H$_2$), 68.6 (*C*(4)), 71.4 (O*C*H$_2$Ph), 76.4 (*C*(3)), 126.2, 126.9 (*p-Ph*), 128.0, 128.3, 128.5, 128.7 (*o,m-Ph*), 137.2, 139.2 (*i-Ph*). Data for **258**: δ_H (400 MHz, $CDCl_3$) 0.88–1.13 (21H, m, Si(C*H*Me$_2$)$_3$), 3.24–3.27 (1H, m, C*H*$_A$H$_B$I), 3.28–3.33 (1H, m, C(2)*H*), 3.39–3.42 (1H, m, CH$_A$*H*$_B$I), 3.53–3.56 (1H, m, C(2)C*H*$_A$H$_B$), 3.66–3.71 (1H, m, C(2)CH$_A$*H*$_B$), 3.92–3.94 (1H, m, NC*H*$_A$H$_B$Ph), 4.00–4.02 (1H, m, NCH$_A$*H*$_B$Ph), 4.15–4.17 (1H, m, C(3)*H*), 4.18–4.21 (1H, m, C(5)*H*), 4.48 (1H, d, *J* 11.4, OC*H*$_A$H$_B$Ph), 4.60 (1H, app d, *J* 4.7, C(4)*H*), 4.67 (1H, d, *J* 11.4, OCH$_A$*H*$_B$Ph), 7.15–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 3.4 (*C*H$_2$I), 12.0 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 51.3 (N*C*H$_2$Ph), 62.5 (C(2)*C*H$_2$), 70.9 (*C*(5)), 71.4 (O*C*H$_2$Ph), 72.2 (*C*(4)), 74.0 (*C*(2)), 80.3 (*C*(3)), 127.4, 127.6 (*p-Ph*), 128.1, 128.3, 128.4, 128.5 (*o,m-Ph*), 136.1, 137.3 (*i-Ph*).

(1*R*,2*R*,3*R*,4*S*,5*R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-1-azabicyclo[3.1.0]hexanium tetrafluoroborate 259

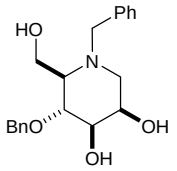


Step 1: I_2 (129 mg, 0.51 mmol) and $NaHCO_3$ (43 mg, 0.51 mmol) were added to a stirred solution of **192** (100 mg, 0.17 mmol, >99:1 dr) in MeCN (5 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL), washed with satd aq $Na_2S_2O_3$ (20 mL) and the organic layer was dried and concentrated *in vacuo* to give a 44:26:30 mixture of **257**, **258** and **139**, respectively, as a brown oil (105 mg).

Step 2: $AgBF_4$ (40 mg, 0.20 mmol) was added to a stirred solution of the residue of **257**, **258** and **139** (44:26:30, 105 mg) in CH_2Cl_2 at rt and the resultant mixture was allowed to stir at rt for 1 h. The reaction mixture was then filtrated through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo* to give a 70:30 mixture of **259** and **139**, respectively, as a brown oil (100 mg). Data for mixture: ν_{max} (ATR) 3384 (O−H), 2942, 2865 (C−H), 1650 (C=O). Data for **259**: δ_H (400 MHz, CD_2Cl_2) 0.95–1.26 (21H, m, Si(C*H*Me$_2$)$_3$), 3.02 (1H, dd, *J* 7.3, 4.7, C(6)*H*$_A$), 3.65–3.70 (1H, m, C(6)*H*$_B$), 3.76–3.82 (1H, m, C(5)*H*), 4.06 (1H, app d, *J* 11.0, C(2)C*H*$_A$H$_B$), 4.37 (1H, dd, *J* 11.0, 2.5, C(2)CH$_A$*H*$_B$), 4.39–4.43 (2H, m, C(3)*H*, OC*H*$_A$H$_B$Ph), 4.48–4.52 (2H, m, C(2)*H*, NC*H*$_A$H$_B$Ph), 4.69 (1H, app d, *J* 6.6, O*H*), 4.83 (1H, d, *J* 10.1, OCH$_A$*H*$_B$Ph), 4.86 (1H, d, *J* 13.9, NCH$_A$*H*$_B$Ph), 5.18–5.22 (1H, m, C(4)*H*), 7.38–7.60 (10H,

m, *Ph*); δ_C (100 MHz, CD_2Cl_2) 12.3 (Si(*C*HMe$_2$)$_3$), 18.4 (Si(CH*Me*$_2$)$_3$), 39.2 (*C*(6)), 50.7 (*C*(5)), 57.3 (N*C*H$_2$Ph), 61.2 (C(2)*C*H$_2$), 69.1 (*C*(4)), 73.6 (*C*(2)), 73.9 (O*C*H$_2$Ph), 80.7 (*C*(3)), 127.5, 128.9, 129.1, 129.5, 129.7, 131.7 (*o,m,p-Ph*), 138.7 (*i-Ph*); *m/z* (ESI$^+$) 514 ([M+MeOH]$^+$, 40%), 482 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{48}NO_4Si^+$ ([M+MeOH]$^+$) requires 514.3347; found 514.3346.

(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-(hydroxymethyl)-3-benzyloxy-4,5-dihydroxypiperidine 205



*Method A (from **252**) – Step 1*: HF·pyridine (70%, 0.15 mL, 5.70 mmol) was added dropwise to a stirred solution of **252** (111 mg, 0.19 mmol, >99:1 dr) in THF (5 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was cooled to 0 °C and satd aq $NaHCO_3$ (0.5 mL) was then carefully added. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were then dried and concentrated *in vacuo* (89 mg).

*Method A (from **252**) – Step 2*: K_2CO_3 (73 mg, 0.57 mmol) was added to a stirred solution of the residue (89 mg) in MeOH (5 mL) at rt and the resultant mixture was allowed to stir at rt for 6 h before being concentrated *in vacuo*. The residue was dissolved in H_2O (10 mL) and extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 5 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 50:1) gave **205** as a white solid (46 mg, 70% from **252**, >99:1 dr); mp 70–72 °C; $[\alpha]_D^{20}$ −36.0 (*c* 1.0 in $CHCl_3$).[22]

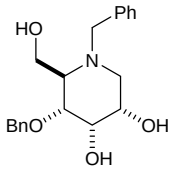
*Method B (from **191**) – Step 1*: I_2 (411 mg, 1.62 mmol) and $NaHCO_3$ (136 mg, 1.62 mmol) were added to a stirred solution of **191** (319 mg, 0.54 mmol, >99:1 dr) in dioxane/H_2O (3:1, 20 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (20 mL) and washed with satd aq $Na_2S_2O_3$ (20 mL), then dried and concentrated *in vacuo* to give a 50:50 mixture of **246** and **250** (319 mg).

*Method B (from **191**) – Step 2*: HF·pyridine (70%, 0.46 mL, 17.7 mmol) was added dropwise to a solution of the residue of **246** and **250** (50:50, 319 mg) in THF (5 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction

mixture was then cooled to 0 °C and satd aq $NaHCO_3$ (1 mL) was carefully added. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a 50:50 mixture of **261** and **250** (230 mg).

*Method B (from **191**) – Step 3*: K_2CO_3 (245 mg, 1.77 mmol) was added to a stirred solution of the residue of **261** and **250** (50:50, 230 mg) in MeOH (5 mL) at rt and the resultant mixture was allowed to stir at rt for 6 h before being concentrated *in vacuo*. The residue was then dissolved in H_2O (10 mL) and extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 5 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 50:50 mixture of **205** and **250**. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 50:1) gave **205** as a white solid (75 mg, 40% from **191**, >99:1 dr).

(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-(hydroxymethyl)-3-benzyloxy-4,5-dihydroxypiperidine 260



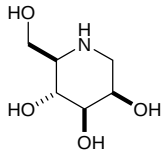
*Method A (from **255**)*: 6.0 M aq HCl (2 mL) was added to a stirred solution of **255** (110 mg, 0.19 mmol, >99:1 dr) in MeOH (5 mL) and the resultant mixture was heated at 50 °C for 16 h before being allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in MeOH (5 mL) and K_2CO_3 (520 mg, 3.76 mmol) was added to the resultant solution. The reaction mixture was then stirred at rt for 6 h, then concentrated *in vacuo*. The residue was then dissolved in H_2O (10 mL) and the resultant solution was extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 5 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 50:1) gave **260** as a white solid (56 mg, 86%, >99:1 dr); mp 70–72 °C; $[\alpha]_D^{20}$ −5.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3500 (O−H); δ_H (400 MHz, $CDCl_3$) 2.53 (1H, dd, *J* 11.1, 9.3, C(6)H_A), 2.57 (1H, br s, O*H*), 2.68–2.74 (1H, m, C(2)*H*), 2.80 (1H, dd, *J* 11.1, 4.2, C(6)H_B), 3.45 (1H, d, *J* 13.6, NCH_AH$_B$Ph), 3.61–3.69 (1H, m, C(5)*H*), 3.71 (1H, dd, *J* 7.8, 3.0, C(3)*H*), 3.88 (1H, dd, *J* 11.6, 2.0, C(2)CH_AH$_B$), 3.95 (1H, dd, *J* 11.6, 3.8, C(2)CH$_A$$H_B$), 4.06 (1H, d, *J* 13.6, NCH$_A$$H_B$Ph), 4.10–4.14 (1H, m, C(4)*H*), 4.62 (2H, app s, OCH_2Ph), 7.25–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 51.8 (*C*(6)), 57.5 (NCH_2Ph), 57.8 (C(2)*C*H$_2$), 59.9 (*C*(2)), 67.6 (*C*(4)),

68.0 (*C*(5)), 72.2 (O*C*H_2Ph), 76.5 (*C*(3)), 127.4, 128.0, 128.2, 128.5, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 137.5, 138.2 (*i*-*Ph*); *m/z* (ESI$^+$) 344 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{25}NNaO_4^+$ ([M+Na]$^+$) requires 366.1676; found 366.1682.

*Method B (from **192**) – Step 1*: I_2 (207 mg, 0.82 mmol) and $NaHCO_3$ (69.0 mg, 0.82 mmol) were added to a stirred solution of **192** (160 mg, 0.27 mmol, >99:1 dr) in dioxane/H_2O (3:1, 4 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 satd aq $Na_2S_2O_3$ (10 mL), then dried and concentrated *in vacuo* to give a 13:37:50 mixture of **253**, **254** and **250**, respectively (127 mg).

*Method B (from **192**) – Step 2*: 6.0 M aq HCl (3 mL) was added to a stirred solution of the residue of **253**, **254** and **250** (13:37:50, 127 mg) in MeOH (5 mL) and the resultant mixture was heated at 50 °C for 16 h before being concentrated *in vacuo*. The residue was dissolved in MeOH (5 mL) and K_2CO_3 (752 mg, 5.44 mmol) was added to the resultant solution. The reaction mixture was then stirred at rt for 6 h, then concentrated *in vacuo*. The residue was then dissolved in H_2O (10 mL) and the resultant solution was extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 5 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 45:55 mixture of **260** and **250**, respectively. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 50:1) gave **260** as a white solid (37 mg, 39% from **192**, >99:1 dr).

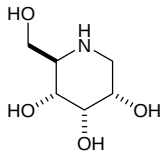
(*R*,*R*,*R*,*R*)-1,5-Dideoxy-1,5-imino-D-mannose [(–)-1-deoxymannojirimycin (DMJ)] 11



$Pd(OH)_2$/C (35 mg) was added to a stirred solution of **205** (70 mg, 0.20 mmol, >99:1 dr) in degassed MeOH (4 mL) and the resultant suspension was stirred at rt for 48 h under an atmosphere of H_2 (5 atm). HCl (1.0 M in Et_2O, 1 mL) was then added and the resultant suspension was stirred for a further 5 min before being filtered through Celite® (eluent MeOH). The filtrate was concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **11** as a white solid (29 mg, 87%, >99:1 dr); mp 180–182 °C; {lit.[23] mp 185 °C}; $[\alpha]_D^{20}$ −38.6 (*c* 1.0 in H_2O); {lit.[24] for sample isolated from a natural source $[\alpha]_D$ –41.4 (*c* 0.74 in H_2O); lit.[25] $[\alpha]_D^{20}$ –40 (*c* 1.35 in H_2O); lit.[26] $[\alpha]_D^{22}$ –36.1 (*c* 0.33 in H_2O); lit.[27] $[\alpha]_D$

–39.0 (*c* 0.1 in H_2O); lit.[28] for enantiomer $[\alpha]_D$ +40.2 (*c* 0.65 in H_2O); lit.[29] for enantiomer $[\alpha]_D$ +40.42 (*c* 0.728 in H_2O)}; ν_{max} (ATR) 3300 (O−H), 2921 (C−H); δ_H (400 MHz, D_2O) 2.44 (1H, dt, *J* 9.8, 4.1, C(5)*H*), 2.72 (1H, dd, *J* 14.3, 1.4, C(1)H_A), 2.96 (1H, dd, *J* 14.3, 2.7, C(1)H_B), 3.52 (1H, dd, *J* 9.8, 2.9, C(3)*H*), 3.56 (1H, app t, *J* 9.8, C(4)*H*), 3.73 (2H, d, *J* 4.1, C(6)H_2), 3.94–3.97 (1H, m, C(2)*H*); δ_C (100 MHz, D_2O) 48.1 (*C*(1)), 60.4 (*C*(5)), 60.5 (*C*(6)), 68.2 (*C*(4)), 69.0 (*C*(2)), 74.4 (*C*(3)); *m/z* (FI^+) 163 ($[M]^+$, 100%); HRMS (FI^+) $C_6H_{13}NO_4^+$ ($[M]^+$) requires 163.0839; found 163.0851.

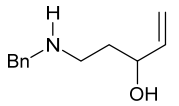
(2*S*,3*S*,4*R*,5*R*)-1,5-Dideoxy-1,5-imino-D-allose [(+)-1-deoxyallonojirimycin (DANJ)] 64



$Pd(OH)_2$/C (32 mg) was added to a stirred solution of **260** (64 mg, 0.19 mmol, >99:1 dr) in degassed MeOH (4 mL) and the resultant suspension was stirred at rt for 48 h under an atmosphere of H_2 (5 atm). HCl (1.0 M in Et_2O, 1 mL) was then added and the resultant suspension was stirred for a further 5 min before being filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **64** as a white solid (25 mg, 83%, >99:1dr); mp 162–164 °C; {lit.[30] mp 163 °C}; $[\alpha]_D^{20}$ +28.3 (*c* 1.0 in H_2O); $[\alpha]_D^{20}$ +30.2 (*c* 1.0 in MeOH); {lit.[24] for sample isolated from a natural source $[\alpha]_D$ +25.7 (*c* 0.65 in H_2O); lit.[31] $[\alpha]_D^{25}$ +30.5 (*c* 0.15 in H_2O); lit.[32] $[\alpha]_D^{20}$ +28.1 (*c* 0.8 in H_2O); lit.[28] for enantiomer $[\alpha]_D$ −37.0 (*c* 1.04 in MeOH); lit.[30] $[\alpha]_D^{25}$ +35.1 (*c* 0.1 in MeOH); lit.[27] $[\alpha]_D$ +34.0 (*c* 0.1 in MeOH)}; ν_{max} (ATR) 3275 (O−H), 2873 (C−H); δ_H (400 MHz, D_2O) 2.65 (1H, app t, *J* 11.8, C(1)H_A), 2.70 (1H, ddd, *J* 10.2, 5.8, 2.8, C(5)*H*), 2.81 (1H, dd, *J* 11.8, 5.0, C(1)H_B), 3.43 (1H, dd, *J* 10.2, 2.8, C(4)*H*), 3.60 (1H, dd, *J* 11.8, 5.8, C(6)CH_A), 3.65 (1H, ddd, *J* 11.8, 5.0, 2.8, C(2)*H*), 3.75 (1H, dd, *J* 11.8, 2.8, C(6)H_B), 4.04 (1H, app t, *J* 2.8, C(3)*H*); δ_C (100 MHz, D_2O) 43.4 (*C*(1)), 54.4 (*C*(5)), 60.9 (*C*(6)), 67.8 (*C*(2)), 68.3 (*C*(4)), 71.3 (*C*(3)); *m/z* (FI^+) 163 ($[M]^+$, 100%); HRMS (FI^+) $C_6H_{13}NO_4^+$ ($[M]^+$) requires 163.0839; found 163.0852.

5.4. Experimental for Chapter 4

5-(*N*-Benzylamino)pent-1-en-3-ol 264



*Method A (from **280**)*: **280** (50 mg, 0.17 mmol) was dissolved in HCl (1.25 M in MeOH, 2 mL) and the resultant mixture was heated at 40 °C for 16 h before being allowed to cool to rt and concentrated *in vacuo*. The residue was then partitioned between 2.0 M aq KOH (10 mL) and $CHCl_3$/^{i}PrOH (3:1, 10 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 5 mL) and the combined organic extracts were then dried over Na_2SO_4 and concentrated *in vacuo* to give **264** as a yellow oil (24 mg, 74%); ν_{max} (ATR) 3298 (N−H, O−H), 2924, 2850 (C−H), 1495, 1454 (C=C); δ_H (400 MHz, $CDCl_3$) 1.60–1.70 (1H, m, C(4)H_A), 1.76–1.84 (1H, m, C(4)H_B), 2.86 (1H, ddd, *J* 12.3, 9.1, 3.5, C(5)H_A), 3.01 (1H, ddd, *J* 12.3, 6.4, 3.5, C(5)H_B), 3.65 (1H, br s, O*H*), 3.80 (1H, d, *J* 13.0, NCH_AH$_B$Ph), 3.84 (1H, d, *J* 13.0, NCH$_A$$H_B$Ph), 4.32–4.39 (1H, m, C(3)*H*), 5.08 (1H, app dt, *J* 10.5, 1.5, C(1)H_A), 5.27 (1H, app dt, *J* 17.0, 1.5, C(1)H_B), 5.85 (1H, ddd, *J* 17.0, 10.5, 5.2, C(2)*H*), 7.25–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 34.4 (*C*(4)), 47.1 (*C*(5)), 53.4 (NCH_2Ph), 73.5 (*C*(3)), 113.9 (*C*(1)), 127.5 (*p-Ph*), 128.4, 128.6 (*o*,*m-Ph*), 138.2 (*i-Ph*), 140.7 (*C*(2)); *m/z* (ESI$^+$) 192 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{18}NO^+$ ([M+H]$^+$) requires 192.1383; found 192.1387.

*Method B (from **278**) – Step 1*: DMSO (5.90 mL, 83.0 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (2.92 mL, 34.0 mmol) in CH_2Cl_2 (400 mL) at −78 °C. After 20 min, a solution of **278** (5.00 g, 18.9 mmol) in CH_2Cl_2 (400 mL) at −78 °C was added dropwise via cannula. After a further 20 min, Et_3N (15.8 mL, 114 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min before being allowed to warm to rt over 30 min. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (500 mL) and Et_2O (500 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **279** as a yellow oil (5.26 g); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 2.60–2.72 (2H, m, C(2)H_2), 3.39–3.56 (2H, m, C(3)H_2), 4.40–4.47 (2H, m, NCH_2Ph), 7.25–7.37 (5H, m, *Ph*), 9.75 (1H, s, C(1)*H*).

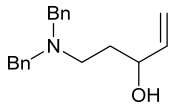
*Method B (from **278**) – Step 2*: Vinylmagnesium bromide (1.0 M in THF, 56.7 mL, 56.7 mmol) was added dropwise to a stirred solution of the residue of **279** (5.26 g) in THF (400

mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and H_2O (20 mL) was added dropwise. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (400 mL) and EtOAc (400 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were washed with brine (400 mL), then dried and concentrated *in vacuo* to give **280** as a yellow oil (5.59 g); ν_{max} (ATR) 3428 (O–H), 2976, 2932 (C–H), 1692, 1670 (C=O), 1477, 1454, 1417 (C=C); δ_H (400 MHz, $CDCl_3$) 1.44–1.60 (10H, m, C*Me*$_3$, C(4)*H*$_A$), 1.68–1.76 (1H, m, C(4)*H*$_B$), 3.06–3.10 (1H, m, C(5)*H*$_A$), 3.72–3.76 (1H, m, C(5)*H*$_B$), 4.01 (1H, br s, O*H*), 4.06–4.10 (1H, m, C(3)*H*), 4.26–4.31 (1H, m, NC*H*$_A$H$_B$Ph), 4.53 (1H, d, *J* 15.6, NCH$_A$*H*$_B$Ph), 5.08 (1H, d, *J* 10.4, C(1)*H*$_A$), 5.23 (1H, d, *J* 17.2, C(1)*H*$_B$), 5.85 (1H, ddd, *J* 17.2, 10.4, 5.2, C(2)*H*), 7.21–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.4 (C*Me*$_3$), 35.2 (*C*(4)), 42.7 (*C*(5)), 50.6 (N*C*H$_2$Ph), 68.7 (*C*(3)), 80.5 (*C*Me$_3$), 113.8 (*C*(1)), 127.3 (*p-Ph*), 128.5, 128.6 (*o*,*m-Ph*), 138.1 (*i-Ph*), 140.4 (*C*(2)), 156.8 (N*C*O); *m/z* (ESI$^+$) 292 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{26}NO_3^+$ ([M+H]$^+$) requires 292.1907; found 292.1908.

*Method B (from **278**) – Step 3*: The residue of **280** (5.59 g) was dissolved in HCl (1.25 M in MeOH, 50 mL) and the resultant mixture was heated at 40 °C for 16 h before being allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between 2.0 M aq KOH (50 mL) and $CHCl_3$/^{i}PrOH (3:1, 50 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 20 mL) and the combined organic extracts were then dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 48:1) gave **264** as a yellow oil (2.40 g, 66% from **278**).

*Method C (from **275**)*: 1.0 M aq KOH (20 mL) was added to a stirred solution of **275** (1.27 g, 5.45 mmol) in MeOH/H_2O (1:1, 30 mL) and the resultant mixture was heated at 100 °C for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (30 mL) and $CHCl_3$/^{i}PrOH (3:1, 30 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 4 × 20 mL) and the combined organic extracts were then dried over Na_2SO_4 and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 48:1) gave **264** as a yellow oil (308 mg, 32%).

5-(*N*,*N*-Dibenzylamino)pent-1-en-3-ol 271

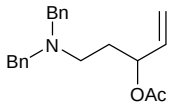


*Method A (from **274**) – Step 1*: DMSO (4.90 mL, 68.9 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (2.40 mL, 28.3 mmol) in CH_2Cl_2 (200 mL) at −78 °C. After 20 min, a solution of **274** (4.00 g, 15.7 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added dropwise via cannula. After a further 20 min, Et_3N (13.1 mL, 94.2 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min before being allowed to warm to rt over 30 min. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (400 mL) and Et_2O (400 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **270** as a yellow oil (4.10 g);[33] δ_H (400 MHz, $CDCl_3$) 2.55 (2H, td, *J* 6.6, 2.4, C(2)H_2), 2.85 (2H, t, *J* 6.6, C(3)H_2), 3.57 (4H, s, N(CH_2Ph)$_2$), 7.22–7.36 (10H, m, *Ph*), 9.57 (1H, t, *J* 2.4, C(1)*H*).

*Method A (from **274**) – Step 2*: Vinylmagnesium bromide (1.0 M in THF, 47.1 mL, 47.1 mmol) was added dropwise to a stirred solution of the residue of **270** (4.10 g) in THF (200 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and H_2O (10 mL) was added dropwise. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (200 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic extracts were washed with brine (200 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 9:1) gave **271** as a yellow oil (3.00 g, 68% from **274**); ν_{max} (ATR) 3300 (O−H), 2807, 2942 (C−H), 1494, 1452 (C=C); δ_H (400 MHz, $CDCl_3$) 1.62–1.73 (2H, m, C(4)H_2), 2.55–2.62 (1H, m, C(5)H_A), 2.64–2.69 (1H, m, C(5)H_B), 3.32 (2H, d, *J* 13.2, N(C$H_A$$H_B$Ph)$_2$), 3.71 (2H, d, *J* 13.2, N(C$H_A$$H_B$Ph)$_2$), 4.05–4.12 (1H, m, C(3)*H*), 4.92 (1H, app dt, *J* 10.5, 1.6, C(1)H_A), 5.09 (1H, app dt, *J* 17.3, 1.6, C(1)H_B), 5.68 (1H, ddd, *J* 17.3, 10.5, 5.1, C(2)*H*), 7.16–7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 32.1 (*C*(4)), 51.9 (*C*(5)), 58.4 (N(*C*H_2Ph)$_2$), 73.6 (*C*(3)), 113.7 (*C*(1)), 127.3 (*p-Ph*), 128.4, 129.3 (*o,m-Ph*), 137.8 (*i-Ph*), 140.5 (*C*(2)); *m/z* (ESI$^+$) 282 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{24}NO^+$ ([M+H]$^+$) requires 282.1852; found 282.1856.

*Method B (from **269**)*:[34] *N*,*N*-Dibenzylamine (1.92 mL, 10.0 mmol) and DBU (1.0 μL, 10 μmol) were dissolved in THF (10 mL) and the resultant mixture was cooled to –15 °C. Acrolein **269** (0.67 mL, 10.0 mmol) was added dropwise over a period of 5 min and the reaction mixture was stirred for 20 min at –15 °C. Vinylmagnesium bromide (1.0 M in THF, 12.0 mL, 12.0 mmol) was then added dropwise at –15 °C and the reaction mixture was stirred at –15 °C for 30 min, before being allowed to warm to rt. EtOAc (50 mL) was added and the resultant organic layer was washed with 0.1 M aq NaOH (50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 9:1) gave an 80:20 mixture of **272** and **271**, respectively, as a yellow oil (204 mg). Data for mixture: ν_{max} (ATR) 2797 (C−H), 1737 (C=O), 1494, 1452 (C=C). Data for **272**: δ_H (400 MHz, $CDCl_3$) 1.73–1.81 (2H, m, C(4)H_2), 1.84 (3H, s, CO*Me*), 2.34–2.40 (1H, m, C(5)H_A), 2.46–2.54 (1H, m, C(5)H_B), 3.44 (2H, d, *J* 13.5, N(C$H_A$$H_B$Ph)$_2$), 3.56 (2H, d, *J* 13.5, N(C$H_A$$H_B$Ph)$_2$), 5.00–5.09 (2H, m, C(1)H_2), 5.24–5.31 (1H, m, C(3)*H*), 5.64 (1H, ddd, *J* 17.1, 10.6, 6.2, C(2)*H*), 7.17–7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.1 (CO*Me*), 31.7 (*C*(4)), 48.9 (*C*(5)), 58.4 (N(*C*H_2Ph)$_2$), 72.7 (*C*(3)), 116.3 (*C*(1)), 126.8 (*p*-*Ph*), 128.2, 128.8 (*o*,*m*-*Ph*), 136.4 (*C*(2)), 139.5 (*i*-*Ph*), 170.2 (*C*OMe); *m/z* (ESI^+) 324 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{26}NO_2^+$ ($[M+H]^+$) requires 324.1958; found 324.1956. Further elution gave **271** as a yellow oil (400 mg, 14%).

5-(*N*,*N*-Dibenzylamino)pent-1-en-3-yl acetate 272



*Method A (from **271**)*: Ac_2O (6.72 mL, 71.1 mmol) and DMAP (173 mg, 1.42 mmol) were added to a stirred solution of **271** (2.00 g, 7.11 mmol) in pyridine (30 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (30 mL) and EtOAc (30 mL), and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 16:1) gave **272** as a colourless oil (1.65 g, 72%).

*Method B (from **274**) – Step 1*: DMSO (2.50 mL, 34.5 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.20 mL, 14.1 mmol) in CH_2Cl_2 (100 mL) at −78 °C. After 20 min, a solution of **274** (2.00 g, 7.83 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added dropwise via

cannula. After a further 20 min, Et_3N (6.60 mL, 47.0 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min before being allowed to warm to rt over 30 min. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (200 mL) and Et_2O (200 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **270** as a yellow oil (2.07 g).

*Method B (from **274**) – Step 2*: Vinylmagnesium bromide (1.0 M in THF, 23.5 mL, 23.5 mmol) was added dropwise to a stirred solution of the residue of **270** (2.07 g) in THF (100 mL) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and H_2O (5 mL) was added dropwise. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo* to give **271** as a yellow oil (2.50 g).

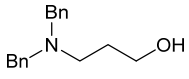
*Method B (from **274**) – Step 3*: Ac_2O (7.40 mL, 78.3 mmol) and DMAP (191 mg, 1.57 mmol) were added to a stirred solution of the residue of **271** (2.50 g) in pyridine (20 mL) at 0 °C. The resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (20 mL) and EtOAc (20 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 16:1) gave **272** as a colourless oil (1.27 g, 50% from **274**).

*Method C (from **269**) – Step 1*: *N*,*N*-Dibenzylamine (1.92 mL, 10.0 mmol) and DBU (1.0 μL, 10 μmol) were dissolved in THF (10 mL) and the resultant mixture was cooled to –15 °C. Acrolein (0.67 mL, 10.0 mmol) was added dropwise over a period of 5 min and the reaction mixture was stirred for 20 min at –15 °C. Vinylmagnesium bromide (1.0 M in THF, 12.0 mL, 12.0 mmol) was then added dropwise at –15 °C and the reaction mixture was stirred at –15 °C for 30 min, before being allowed to warm to rt. NH_4Cl (50 mL) was added and the resultant organic layer was washed with 0.1 M aq NaOH (50 mL) and brine (50 mL), then dried and concentrated *in vacuo* to give **271** as a yellow oil (2.86 g).

*Method C (from **269**) – Step 2*: Ac_2O (9.60 mL, 102 mmol) and DMAP (249 mg, 2.04 mmol) were added to a stirred solution of the residue of **271** (2.86 g) in pyridine (30 mL) at 0 °C. The

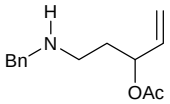
resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (30 mL) and EtOAc (30 mL), and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 50:1) gave **272** as a colourless oil (555 mg, 17% from **269**).

3-(*N*,*N*-Dibenzylamino)propan-1-ol 274



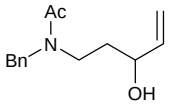
A mixture of 3-aminopropanol **273** (8.00 g, 107 mmol), BnBr (26.6 mL, 224 mmol) and K_2CO_3 (29.4 g, 213 mmol) in acetone (250 mL) was stirred at rt for 16 h. The reaction mixture was then filtrated and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **274** as a colourless oil (15.9 g, 69%);[35] δ_H (400 MHz, $CDCl_3$) 1.77 (2H, app dt, *J* 10.9, 5.6, C(2)H_2), 2.62–2.69 (2H, m, C(3)H_2), 3.58 (4H, s, N(CH_2Ph)$_2$), 3.66 (2H, t, *J* 5.6, C(1)H_2), 4.71 (1H, br s, O*H*), 7.27–7.36 (10H, m, *Ph*).

5-(*N*-Benzylamino)pent-1-en-3-yl acetate 275



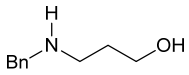
CAN (5.07 g, 9.25 mmol) was added to a stirred solution of **272** (1.00 g, 3.08 mmol) in MeCN/H_2O (5:1, 30 mL) and the resultant mixture was stirred at rt for 16 h. $NaHCO_3$ (5 mL) was then added, and the organic layer was decanted off and washed with brine (20 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with $NaHCO_3$ (2 × 20 mL), then dried over Na_2SO_4 and concentrated *in vacuo* to give **275** as a brown oil (719 mg, quant); ν_{max} (ATR) 3300 (N−H), 2925 (C−H), 1734 (C=O), 1454 (C=C); δ_H (400 MHz, $CDCl_3$) 1.80–1.89 (2H, m, C(4)H_2), 2.05 (3H, s, CO*Me*), 2.68 (2H, t, *J* 7.1, C(5)H_2), 3.79 (2H, s, NCH_2Ph), 5.16 (1H, d, *J* 10.6, C(1)H_A), 5.25 (1H, d, *J* 17.1, C(1)H_B), 5.36 (1H, q, *J* 6.5, C(3)*H*), 5.79 (1H, ddd, *J* 17.1, 10.6, 6.5, C(2)*H*), 7.25–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.1 (CO*Me*), 34.3 (*C*(4)), 44.9 (*C*(5)), 53.8 (N*C*H_2Ph), 72.9 (*C*(3)), 116.6 (*C*(1)), 127.0 (*p-Ph*), 128.1, 128.4 (*o*,*m-Ph*), 136.2 (*C*(2)), 139.8 (*i-Ph*), 170.3 (*C*OMe); *m/z* (ESI$^+$) 234 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{20}NO_2^+$ ([M+H]$^+$) requires 234.1489; found 234.1495.

5-(*N*-Acetyl-*N*-benzylamino)pent-1-en-3-ol 276



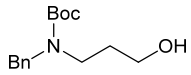
K_2CO_3 (445 mg, 3.22 mmol) was added to a stirred solution of **275** (250 mg, 1.07 mmol) in MeOH (4 mL) at rt and the resultant mixture was allowed to stir at rt for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give an 80:20 mixture of **276** and **264**, respectively. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 25:1) gave **276** as a yellow oil (170 mg, 68%); ν_{max} (ATR) 3379 (O−H), 1623 (C=O), 1423 (C=C); δ_H (400 MHz, $CDCl_3$) 1.52–1.60 (1H, m, C(4)H_A), 1.65–1.81 (1H, m, C(4)H_B), 2.16 (3H, s, CO*Me*), 3.12 (1H, dt, *J* 14.3, 4.8, C(5)H_A), 3.97 (1H, ddd, *J* 14.3, 10.2, 4.8, C(5)H_B), 4.02–4.11 (1H, m, C(3)*H*), 4.46 (1H, d, *J* 17.0, NC$H_A$$H_B$Ph), 4.60 (1H, d, *J* 17.0, NCH$_A$$H_B$Ph), 5.08 (1H, d, *J* 10.7, C(1)H_A), 5.26 (1H, d, *J* 17.0, C(1)H_B), 5.85 (1H, ddd, *J* 17.0, 10.7, 5.2, C(2)*H*), 7.17–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.6 (CO*Me*), 34.9 (*C*(4)), 42.3 (*C*(5)), 52.0 (NCH_2Ph), 68.7 (*C*(3)), 114.0 (*C*(1)), 127.8 (*p-Ph*), 126.2, 129.0 (*o*,*m-Ph*), 136.1 (*i-Ph*), 140.2 (*C*(2)), 172.5 (*C*OMe); *m/z* (ESI^+) 234 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{19}NNaO_2^+$ ($[M+Na]^+$) requires 256.1308; found 256.1315.

3-(*N*-Benzylamino)propan-1-ol 277



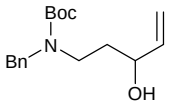
3-Aminopropan-1-ol **273** (5.00 g, 66.6 mmol) was added to a stirred solution of PhCHO (6.77 mL, 66.6 mmol) and $CH(OMe)_3$ (10.9 mL, 99.8 mmol) and the resultant mixture was stirred at rt for 5 h. The reaction mixture was then cooled to 0 °C and $NaBH_4$ (2.52 g, 66.6 mmol) was added portionwise. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (200 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **277** as a colourless oil (9.95 g, 90%);[36] δ_H (400 MHz, $CDCl_3$) 1.76 (2H, app quintet, *J* 5.5, C(2)H_2), 2.93 (2H, t, *J* 5.5, C(3)H_2), 3.16 (2H, br s, O*H*, N*H*), 3.82 (2H, s, NCH_2Ph), 3.84 (2H, t, *J* 5.5, C(1)H_2), 7.26–7.38 (5H, m, *Ph*).

3-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]propan-1-ol 278[37]



$(Boc)_2O$ (6.60 g, 30.3 mmol) was added to a stirred solution of **277** (5.00 g, 30.3 mmol) in CH_2Cl_2/1.0 M aq NaOH (5:1, 90 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was washed with H_2O (100 mL), then dried and concentrated *in vacuo* to give **278** as a colourless oil (7.66 g, 95%);[38] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.65 (2H, app br s, C(2)*H*$_2$), 2.75 (1H, br s, O*H*), 3.40 (2H, app br s, C(3)*H*$_2$), 3.57–3.61 (2H, m, C(1)*H*$_2$), 4.41 (2H, br s, NC*H*$_2$Ph), 7.23–7.38 (5H, m, *Ph*).

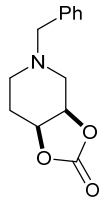
5-[*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)amino]pent-1-en-3-ol 280



Step 1: DMSO (0.24 mL, 3.3 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.12 mL, 1.4 mmol) in CH_2Cl_2 (15 mL) at −78 °C. After 20 min, a solution of **278** (200 mg, 0.75 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise via cannula. After a further 20 min, Et_3N (0.63 mL, 4.5 mmol) was added and the resultant mixture was stirred at −78 °C for 30 min before being allowed to warm to rt over 30 min. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (30 mL) and Et_2O (30 mL). The aqueous layer was extracted with Et_2O (2 × 15 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **279** as a yellow oil (204 mg).

Step 2: Vinylmagnesium bromide (1.0 M in THF, 2.25 mL, 2.25 mmol) was added dropwise to a stirred solution of the residue of **279** (204 mg) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and H_2O (1 mL) was added dropwise. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **280** as a yellow oil (100 mg, 46% from **278**).

(*RS*,*SR*)-*N*(1)-Benzyl-3,4-dihydroxy-3,4-*O*-carbonylpiperidine 281



*Method A (from **288**)*: $NaHCO_3$ (8 mg, 95 μmol) was added to a stirred solution of **288** (10 mg, 32 μmol) in dioxane/H_2O (3:1, 4 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 the organic layer was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give **281** as a yellow oil (8 mg, quant, >99:1 dr); ν_{max} (ATR) 2925 (C−H), 1799 (C=O); δ_H (400 MHz, $CDCl_3$) 1.98–2.07 (1H, m, C(5)H_A), 2.17 (1H, app dq, *J* 15.1, 4.2, C(5)H_B), 2.42–2.56 (3H, m, C(2)H_A, C(6)H_2), 2.94 (1H, ddd, *J* 12.5, 5.4, 1.4, C(2)H_B), 3.56 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.58 (1H, d, *J* 13.1, NCH$_A$$H_B$Ph), 4.69 (1H, app q, *J* 6.4, C(3)*H*), 4.73–4.78 (1H, m, C(4)*H*), 7.25–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.4 (*C*(5)), 47.3 (*C*(6)), 53.3 (*C*(2)), 62.2 (N*C*H_2Ph), 73.7 (*C*(3)), 74.1 (*C*(4)), 127.4 (*p-Ph*), 128.4, 128.8 (*o,m-Ph*), 137.2 (*i-Ph*), 155.0 (*C*O); *m/z* (ESI^+) 234 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{15}NNaO_3^+$ ($[M+Na]^+$) requires 256.0944; found 256.0950.

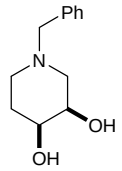
*Method B (from **288**)*: $AgBF_4$ (18 mg, 95 μmol) was added to **288** (25 mg, 78 μmol, >99:1 dr) in CD_2Cl_2 and the reaction mixture was shaken at rt for 5 min. The reaction mixture was then poured into a stirred solution of $NaHCO_3$ (20 mg, 0.23 mmol) in dioxane/H_2O (3:1, 4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (10 mL) and the organic layer was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give **281** as a yellow oil (20 mg, quant, >99:1 dr).

*Method C (from **264**)*: I_2 (1.20 g, 4.71 mmol) and $NaHCO_3$ (396 mg, 4.71 mmol) were added to a stirred solution of **264** (300 mg, 1.57 mmol) in dioxane/H_2O (3:1, 4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **281** as a yellow oil (130 mg, 36%, >99:1 dr).

*Method D (from **282**)*: CDI (59 mg, 0.36 mmol) and DMAP (6 mg, 0.05 mmol) were added to a stirred solution of **282** (50 mg, 0.24 mmol, >99:1 dr) in THF (2 mL) and the resultant mixture was allowed to stir at rt for 24 h. Satd aq NH_4Cl (0.5 mL) was added and the reaction

mixture was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **281** as a yellow oil (20 mg, 36%, >99:1 dr).

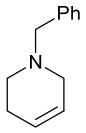
(*RS*,*SR*)-*N*(1)-Benzyl-3,4-dihydroxypiperidine 282



*Method A (from **281**)*: K_2CO_3 (116 mg, 0.84 mmol) was added to a stirred solution of **281** (65 mg, 0.28 mmol, >99:1 dr) in MeOH (4 mL) at rt and the resultant mixture was allowed to stir at rt for 16 h before being concentrated *in vacuo*. The residue was then partitioned between H_2O (5 mL) and $CHCl_3$/^{i}PrOH (3:1, 5 mL) and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 5 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **282** as a yellow oil (60 mg, quant, >99:1 dr);[39] ν_{max} (ATR) 3377 (O–H), 2812, 2926 (C–H); δ_H (400 MHz, CD_2Cl_2) 1.63–1.72 (1H, m, C(5)H_A), 1.73–1.78 (1H, m, C(5)H_B), 2.04–2.11 (1H, m, C(6)H_A), 2.26 (1H, app d, *J* 10.6, C(2)H_A), 2.65–2.72 (1H, m, C(6)H_B), 2.80 (1H, app br s, C(2)H_B), 3.50 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 3.53 (1H, m, NCH$_A$$H_B$Ph, C(4)*H*), 3.69–3.71 (1H, m, C(3)*H*), 7.23–7.33 (5H, m, *Ph*); δ_C (100 MHz, CD_2Cl_2) 30.5 (*C*(5)), 50.9 (*C*(6)), 57.5 (*C*(2)), 62.6 (N*C*H$_2$Ph), 69.3 (*C*(3)), 69.8 (*C*(4)), 127.7 (*p-Ph*), 128.8, 129.5 (*o,m-Ph*), 138.8 (*i-Ph*); *m/z* (ESI$^+$) 208 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{18}NO_2^+$ ([M+H]$^+$) requires 208.1332; found 208.1331.

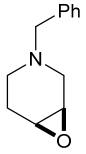
*Method B (from **284**)*:[40] OsO_4 (37 mg, 0.14 mmol) was added to a stirred solution of **284** (500 mg, 2.89 mmol) in THF (20 mL) and H_2O (5 mL), followed by a solution of NMO (1.22 g, 10.4 mmol) in H_2O (2.5 mL). The reaction mixture was stirred at rt for 16 h. Satd aq Na_2SO_3 (1 mL) was then added and the resultant mixture was allowed to stir at rt for 1 h. The reaction mixture was then extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (CH_2Cl_2/MeOH, 24:1) gave **282** as a yellow oil (399 mg, 67%, >99:1 dr).

_N_(1)-Benzyl-1,2,3,6-tetrahydropyridine 284[41]



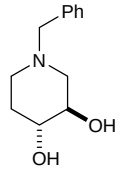
A mixture of pyridine **283** (10.2 mL, 126 mmol) and BnCl (17.5 mL, 152 mmol) was stirred at 140 °C for 1 h, before being allowed to cool to rt. The red resin was dissolved in EtOH (350 mL). Since the resin was barely soluble in EtOH, this dissolution was best performed by repeated addition of portions (~50 mL) of EtOH to the resin, equilibrating the mixture with ultrasonication and decanting the liquid phase. $NaBH_4$ (10.5 g, 277 mmol) was then added portionwise to the ethanolic solution at 0 °C and the resultant mixture was allowed to stir at rt for 16 h. H_2O (150 mL) was added and the organic layer was decanted off from the resultant colourless solid. The solid residue (2 × 50 mL) and the aqueous layer (3 × 10 mL) were both extracted with Et_2O and the combined organic extracts were then dried and concentrated *in vacuo* to give **284** as a yellow oil (17.6 g, 81%); δ_H (400 MHz, $CDCl_3$) 2.18–2.24 (2H, m, C(3)H_2), 2.60 (2H, t, *J* 5.7, C(2)H_2), 3.01 (2H, m, C(6)H_2), 3.62 (2H, s, NCH_2Ph), 5.66–5.74 (1H, m, C(4)*H*), 5.76–5.82 (1H, m, C(5)*H*), 7.26–7.43 (5H, m, *Ph*).

(*RS*,*SR*)-*N*(1)-Benzyl-3,4-epoxypiperidine 285[40]



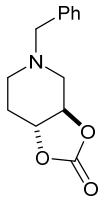
HBF_4 (40% aq, 4.53 mL, 28.9 mmol) was added to a stirred solution of **284** (1.00 g, 5.78 mmol) in CH_2Cl_2 (30 mL) and the resultant mixture was allowed to stir at rt for 5 min. *m*-CPBA (62%, 2.41 g, 8.67 mmol) was then added and the reaction mixture was stirred at rt for 16 h. Satd aq Na_2SO_3 (1 mL) was then added until starch-iodide paper indicated that no oxidant remained. The organic layer was washed with $NaHCO_3$ (3 × 10 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (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, 3:2) gave **285** as a yellow oil (77 mg, 70%);[42] δ_H (400 MHz, $CDCl_3$) 1.95–2.09 (2H, m, C(5)H_2), 2.21 (1H, ddd, *J* 11.5, 9.2, 4.3, C(6)H_A), 2.32–2.38 (1H, m, C(6)H_B), 2.69 (1H, d, *J* 13.4, C(2)H_A), 3.04 (1H, ddd, *J* 13.4, 4.3, 1.1, C(2)H_B), 3.22–3.27 (2H, m, C(3)*H*, C(4)*H*), 3.46 (1H, d, *J* 13.6, NCH_AH$_B$Ph), 3.48 (1H, d, *J* 13.6, NCH$_A$$H_B$Ph), 7.24–7.36 (5H, m, *Ph*).

(*RS*,*RS*)-*N*(1)-Benzyl-3,4-dihydroxypiperidine 286[43]



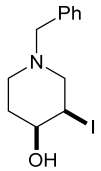
Conc. H_2SO_4 (1.4 mL) and a few drops of H_2O were added to a stirred solution of **285** (1.00 g, 5.28 mmol) in 1,4-dioxane (20 mL) and the resultant mixture was stirred at rt for 16 h, then concentrated *in vacuo*. $NaHCO_3$ (5 mL) was added to the residue and the reaction mixture was extracted with $CHCl_3$/^{i}PrOH (3:1, 3 × 10 mL). The combined organic extracts were washed with 2.0 M aq KOH (15 mL), then dried and concentrated *in vacuo* to give **286** as a yellow oil (874 mg, 80%, >99:1 dr);[44] δ_H (400 MHz, $CDCl_3$) 1.57–1.67 (1H, m, C(5)H_A), 1.91–2.00 (1H, m, C(5)H_B), 2.05 (1H, app t, *J* 9.8, C(2)H_A), 2.15 (1H, app td, *J* 11.0, 2.7, C(6)H_A), 2.25 (2H, br s, O*H*), 2.72–2.80 (1H, m, C(6)H_B), 2.95 (1H, dd, *J* 11.0, 2.7, C(2)H_B), 3.44–3.51 (1H, m, C(4)*H*), 3.52–3.60 (3H, m, C(3)*H*, NCH_2Ph), 7.25–7.35 (5H, m, *Ph*).

(*RS*,*RS*)-*N*(1)-Benzyl-3,4-dihydroxy-3,4-*O*-carbonylpiperidine 287



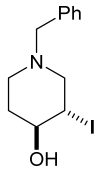
CDI (156 mg, 0.96 mmol) and DMAP (12 mg, 98 μmol) were added to a stirred solution of **286** (100 mg, 0.48 mmol, >99:1 dr) in THF (4 mL) and the resultant mixture was allowed to stir at rt for 4 days. NH_4Cl (1 mL) was added and the reaction mixture was extracted with EtOAc (2 × 10 mL). The combined organic extracts were then washed with brine (10 mL), dried and concentrated *in vacuo* to give **287** as a yellow oil (129 mg, >99:1 dr);[45] ν_{max} (ATR) 2925 (C−H), 1815 (C=O); δ_H (400 MHz, $CDCl_3$) 1.91–2.02 (1H, m, C(5)H_A), 2.25–2.40 (3H, m, C(2)H_A, C(5)H_B, C(6)H_A), 2.92–2.97 (1H, m, C(6)H_B), 3.27 (1H, dd, *J* 12.5, 4.7, C(2)H_B), 3.63 (2H, s, NCH_2Ph), 5.08–5.15 (1H, m, C(4)*H*), 5.30 (1H, td, *J* 9.3, 4.7, C(3)*H*), 7.27–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 29.1 (*C*(5)), 50.1 (*C*(6)), 54.4 (*C*(2)), 61.8 (N*C*H_2Ph), 74.5 (*C*(3)), 76.5 (*C*(4)), 128.5, 128.8, 130.9 (*o*,*m*,*p*-*Ph*), 137.1 (*i*-*Ph*), 147.9 (*C*O); *m/z* (ESI^+) 208 ($[(M–CO)+3H]^+$, 100%); HRMS (TOF MS EI^+) $C_{13}H_{15}NO_3^+$ (M^+) requires 233.1052; found 233.1052.

(*RS*,*SR*)-*N*(1)-Benzyl-3-iodopiperidin-4-ol 288



I_2 (398 mg, 1.57 mmol) and $NaHCO_3$ (132 mg, 1.57 mmol) were added to a stirred solution of **264** (100 mg, 0.52 mmol) in MeCN (4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL), then the organic layer was dried and concentrated *in vacuo* to give a 70:30 mixture of **288** and **289**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **288** as a brown solid (40 mg, 24%, >99:1 dr);[46] mp 103–105 °C; ν_{max} (ATR) 3350 (O−H), 2945 (C−H); δ_H (400 MHz, $CDCl_3$) 1.93–2.00 (1H, m, C(5)H_A), 2.08 (1H, app br s, C(5)H_B), 2.51 (1H, app br s, C(6)H_A), 2.60–2.78 (2H, m, C(2)H_A, C(6)H_B), 2.92 (1H, app t, *J* 10.0, C(2)H_B), 3.53 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 3.61 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 4.57 (1H, dt, *J* 8.5, 3.2, C(3)*H*), 7.24–7.36 (5H, m, *Ph*);[47] δ_H (400 MHz, PhMe-d_8, 363 K) 1.50–1.59 (1H, m, C(5)H_A), 1.66–1.73 (1H, m, C(5)H_B), 2.14–2.21 (1H, m, C(6)H_A), 2.41–2.48 (2H, m, C(2)H_A, C(6)H_B), 2.78 (1H, dd, *J* 11.7, 8.8, C(2)H_B), 3.07 (1H, app br s, C(4)*H*), 3.22 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 3.31 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 4.20 (1H, dt, *J* 8.8, 3.0, C(3)*H*), 7.00–7.24 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 31.9 (*C*(5)), 39.9 (*C*(3)), 48.3 (*C*(6)), 57.4 (*C*(2)), 62.1 (N*C*H$_2$Ph), 68.7 (*C*(4)), 127.3, 128.4, 129.0 (*o*,*m*,*p*-*Ph*), 137.7 (*i*-*Ph*);[48] δ_C (100 MHz, PhMe-d_8, 363 K) 32.0 (*C*(5)), 39.7 (*C*(3)), 48.0 (*C*(6)), 57.7 (*C*(2)), 61.8 (N*C*H$_2$Ph), 68.4 (*C*(4)), 124.4, 124.6, 124.8 (*o*,*m*,*p*-*Ph*), 137.1 (*i*-*Ph*); *m/z* (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{17}INO^+$ ([M+H]$^+$) requires 318.0349; found 318.0349. Further elution gave a 30:70 mixture of **288** and **289**, respectively, as a yellow oil (19 mg, 12%). Data for mixture: ν_{max} (ATR) 3350 (O−H), 2945 (C−H); *m/z* (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{17}INO^+$ ([M+H]$^+$) requires 318.0349; found 318.0347. Data for **289**: δ_H (400 MHz, $CDCl_3$) 1.71 (1H, dtd, *J* 12.6, 10.8, 4.3, C(5)H_A), 2.05 (1H, ddt, *J* 12.6, 4.3, 2.7, C(5)H_B), 2.21 (1H, app td, *J* 12.6, 2.7, C(6)H_A), 2.56 (1H, t, *J* 11.5, C(2)H_A), 2.93–2.99 (1H, m, C(6)H_B), 3.28 (1H, app dq, *J* 11.5, 2.2, C(2)H_B), 3.56 (2H, app d, *J* 1.7, NCH_2Ph), 3.64 (1H, app td, *J* 10.8, 4.3, C(4)*H*), 4.11 (1H, ddd, *J* 11.5, 9.8, 4.3, C(3)*H*), 7.25–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 33.3 (*C*(5)), 38.4 (*C*(3)), 51.5 (*C*(6)), 61.4 (*C*(2)), 61.4 (N*C*H$_2$Ph), 75.2 (*C*(4)), 127.3 (*p*-*Ph*), 128.4, 128.9 (*o*,*m*-*Ph*), 137.8 (*i*-*Ph*).

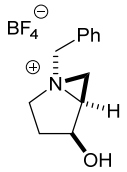
(*RS*,*RS*)-*N*(1)-Benzyl-3-iodopiperidin-4-ol 289



Step 1: I_2 (752 mg, 2.31 mmol) and $NaHCO_3$ (586 mg, 2.31 mmol) were added to a stirred solution of **264** (147 mg, 0.77 mmol) in MeCN (4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL), then the organic layer was dried and concentrated *in vacuo* to give a 70:30 mixture of **288** and **289**, respectively, as a yellow oil (205 mg).

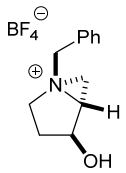
Step 2: $NaHCO_3$ (586 mg, 2.31 mmol) was added to a stirred solution of the residue of **288** and **289** (70:30, 205 mg) in dioxane/H_2O (3:1, 4 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and the organic layer was washed with satd aq $NaHCO_3$ (15 mL), then dried and concentrated *in vacuo* to give a 70:30 mixture of **281** and **289**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 5:1) gave **289** as a yellow oil (13 mg, 5%, >99:1 dr). Further elution gave **281** as a yellow oil (51 mg, 28%).

(1*RS*,4*SR*,5*SR*)-*N*(1)-Benzyl-4-hydroxy-1-azabicyclo[3.1.0]hexanium tetrafluoroborate 291[49]



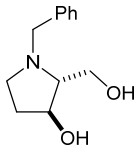
$AgBF_4$ (18 mg, 95 μmol) was added to a solution of **288** (25 mg, 78 μmol, >99:1 dr) in CD_2Cl_2 and the reaction mixture was shaken at rt for 5 min to give **291** (>99:1 dr); δ_H (400 MHz, CD_2Cl_2) 1.66–1.77 (1H, m, C(3)H_A), 2.42–2.47 (1H, m, C(3)H_B), 3.15 (1H, dd, *J* 7.7, 4.1, C(6)H_A), 3.18–3.22 (1H, m, C(6)H_B), 3.58 (1H, app d, *J* 12.6, C(2)H_A), 3.63 (1H, app d, *J* 12.6, C(2)H_B), 3.96 (1H, app dt, *J* 7.7, 5.5, C(5)*H*), 4.35 (1H, d, *J* 13.4, NCH_AH$_B$Ph), 4.58 (1H, d, *J* 13.4, NCH$_A$$H_B$Ph), 5.12 (1H, app td, *J* 8.2, 5.0, C(4)*H*), 7.19–7.52 (5H, m, *Ph*); δ_C (100 MHz, CD_2Cl_2) 28.6 (*C*(3)), 36.4 (*C*(6)), 52.0 (*C*(5)), 54.8 (*C*(2)), 62.6 (NCH_2Ph), 68.7 (*C*(4)), 130.3 (*p-Ph*), 128.9, 131.2 (*o,m-Ph*), 134.0 (*i-Ph*).

(1*RS*,4*RS*,5*SR*)-*N*(1)-Benzyl-4-hydroxy-1-azabicyclo[3.1.0]hexanium tetrafluoroborate 292[49]



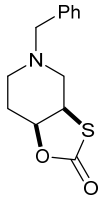
$AgBF_4$ (18 mg, 95 μmol) was added to a solution of **289** (25 mg, 78 μmol, >99:1 dr) in CD_2Cl_2 and the reaction mixture was shaken at rt for 5 min to give **292** (>99:1 dr); δ_H (400 MHz, CD_2Cl_2) 1.99–2.08 (1H, m, C(3)H_A), 2.17 (1H, app dd, *J* 15.3, 7.9, C(3)H_B), 2.83 (1H, dd, *J* 6.1, 4.9, C(6)H_A), 3.23 (1H, dd, *J* 8.1, 4.9, C(6)H_B), 3.49–3.57 (1H, m, C(2)H_A), 3.62–3.70 (1H, m, C(2)H_B), 3.92 (1H, app t, *J* 7.1, C(5)*H*), 4.48 (1H, d, *J* 13.4, NCH_AH$_B$Ph), 4.61 (1H, d, *J* 13.4, NCH$_A$$H_B$Ph), 4.70 (1H, app d, *J* 4.9, C(4)*H*), 7.25–7.51 (5H, m, *Ph*); δ_C (100 MHz, CD_2Cl_2) 30.8 (*C*(3)), 38.1 (*C*(6)), 53.7 (*C*(2)), 57.8 (*C*(5)), 62.4 (N*C*H$_2$Ph), 70.4 (*C*(4)), 128.9, 129.5, 130.2 (*o*,*m*,*p*-*Ph*), 131.2 (*i*-*Ph*).

(*RS*,*SR*)-*N*(1)-Benzyl-2-hydroxymethyl-3-hydroxypyrrolidine 293



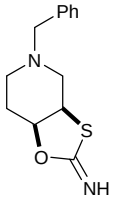
$AgBF_4$ (18 mg, 95 μmol) was added to a solution of **289** (25 mg, 78 μmol, >99:1 dr) in CD_2Cl_2 and the reaction mixture was shacken at rt for 5 min. The reaction mixture was then poured into a stirred solution of $NaHCO_3$ (20 mg, 0.23 mmol) in dioxane/H_2O (3:1, 4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (10 mL) and the organic layer was washed with satd aq $NaHCO_3$ (10 mL), then dried and concentrated *in vacuo* to give a 77:15:8 mixture of **293**, **286** and **281**, respectively (6 mg). Data for **293**:[50] δ_H (400 MHz, $CDCl_3$) 1.71 (1H, ddt, *J* 13.4, 6.8, 1.9, C(4)H_A), 1.93–2.01 (1H, m, C(4)H_B), 2.61–2.66 (2H, m, C(2)*H*, C(5)H_A), 2.96–3.01 (1H, m, C(5)H_B), 3.53 (1H, d, *J* 12.9, NCH_AH$_B$Ph), 3.62–3.65 (2H, m, C(2)CH_2), 3.96 (1H, d, *J* 12.9, NCH$_A$$H_B$Ph), 4.34 (1H, app dt, *J* 6.8, 2.8, C(3)*H*), 7.25–7.40 (5H, m, *Ph*).

(*RS*,*SR*)-*N*(1)-Benzyl-3-mercapto-4-hydroxy-3,4-*S*,*O*-carbonylpiperidine 297

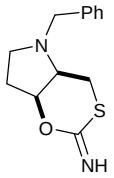


A solution of **299** (33 mg, 0.13 mmol) in 1.0 M aq HCl (4 mL) was stirred at rt for 16 h before being concentrated *in vacuo*. The reaction mixture was then partitioned between H_2O (10 mL) and $CHCl_3$/^{i}PrOH (3:1, 10 mL). The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 4 × 5 mL) and the combined organic extracts were washed with 2.0 M aq KOH, then dried and concentrated *in vacuo* to give **297** as a yellow oil (13 mg, 39%, >99:1 dr);[51] ν_{max} (ATR) 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.96–2.06 (1H, m, C(5)H_A), 2.27–2.35 (3H, m, C(2)H_A, C(5)H_B, C(6)H_A), 2.68–2.73 (1H, m, C(6)H_B), 3.05 (1H, ddd, *J* 12.0, 5.7, 1.8, C(2)H_B), 3.51 (1H, d, *J* 13.1, NCH_AH$_B$Ph), 3.58 (1H, d, *J* 13.1, NCH$_A$$H_B$Ph), 3.78 (1H, ddd, *J* 10.6, 5.7, 4.4, C(3)*H*), 4.69–4.73 (1H, m, C(4)*H*), 7.27–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7 (*C*(5)), 46.5 (*C*(3)), 47.5 (*C*(6)), 56.7 (*C*(2)), 62.5 (NCH_2Ph), 78.6 (*C*(4)), 127.4 (*p-Ph*), 128.4, 128.9 (*o*,*m-Ph*), 137.5 (*i-Ph*), 172.5 (S*C*O); *m/z* (ESI$^+$) 250 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{16}NO_2S^+$ ([M+H]$^+$) requires 250.0896; found 250.0894.

(*RS*,*SR*)-*N*(1)-Benzyl-3-mercapto-4-hydroxy-3,4-*S*,*O*-iminopiperidine 299 and (*RS*,*SR*)-(5-*N*-benzyl)hexahydro-[1,3]oxathiino[5,6-b]pyrrol-2-imine 300



299

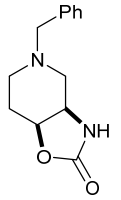


300

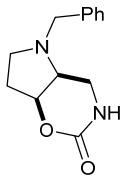
AgSCN (44 mg, 0.26 mmol) was added to a stirred solution of **288** (70 mg, 0.22 mmol, >99:1 dr) in CH_2Cl_2 (4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was filtrated through Celite® (eluent CH_2Cl_2) and the resultant solution was then washed with 2.0 M aq KOH (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a 85:15 mixture of **299** and **300**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:4) gave **300** as a yellow oil (4 mg, 4%, >99:1 dr); ν_{max} (ATR) 3437 (N–H), 1639 (C=N); δ_H (400 MHz, $CDCl_3$) 1.70–1.78 (1H, m, C(7)H_A), 2.19–2.31 (2H, m, C(6)H_A, C(7)H_B), 2.91 (1H, q, *J* 6.0, C(4a)*H*), 3.02–3.07 (1H, m,

C(6)H_B), 3.24–3.27 (2H, m, C(4)H_2), 3.42 (1H, d, *J* 13.1, NCH_AH$_B$Ph), 3.97 (1H, d, *J* 13.1, NCH$_A$$H_B$Ph), 4.42–4.46 (1H, m, C(7a)*H*), 7.28–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 33.4 (*C*(7)), 33.7 (*C*(4)), 51.3 (*C*(6)), 58.7 (N*C*H$_2$Ph), 66.2 (*C*(4a)), 72.4 (*C*(7a)), 113.6 (*C*(2)), 127.4, 128.5, 128.8 (*o*,*m*,*p*-*Ph*), 137.9 (*i*-*Ph*), 169.3 (S*C*N); *m/z* (ESI$^+$) 249 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{17}N_2OS^+$ ([M+H]$^+$) requires 249.1056; found 249.1054. Further elution gave **299** as a yellow oil (40 mg, 43%, >99:1 dr); ν_{max} (ATR) 3300 (N–H), 1639 (C=N); δ_H (400 MHz, $CDCl_3$) 1.94–2.02 (1H, m, C(5)H_A), 2.18–2.33 (3H, m, C(2)H_A, C(5)H_B, C(6)H_A), 2.67–2.73 (1H, m, C(6)H_B), 3.00 (1H, ddd, *J* 11.9, 5.8, 1.7, C(2)H_B), 3.50 (1H, d, *J* 13.1, NCH_AH$_B$Ph), 3.57 (1H, d, *J* 13.1, NCH$_A$$H_B$Ph), 3.67 (1H, ddd, *J* 10.8, 5.8, 4.1, C(3)*H*), 4.64–4.67 (1H, m, C(4)*H*), 7.26–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 (*C*(5)), 47.1 (*C*(3)), 47.5 (*C*(6)), 56.4 (*C*(2)), 62.5 (N*C*H$_2$Ph), 80.3 (*C*(4)), 127.3, 128.3, 129.0 (*o*,*m*,*p*-*Ph*), 137.6 (*i*-*Ph*), 169.1 (S*C*N); *m/z* (ESI$^+$) 249 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{17}N_2OS^+$ ([M+H]$^+$) requires 249.1056; found 249.1054.

(*RS*,*SR*)-*N*(1)-Benzyl-3-amino-4-hydroxy-3,4-*N*,*O*-carbonylpiperidine 305 and (*RS*,*RS*)-(5-*N*-benzyl)hexahydropyrrolo[2,3-*e*][1,3]oxazin-2(3*H*)-one 306



305

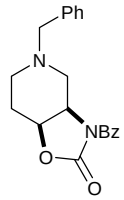


306

AgOCN (50 mg, 0.33 mmol) was added to a stirred solution of **288** (88 mg, 0.28 mmol, >99:1 dr) in CH_2Cl_2 (4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was filtrated through Celite® (eluent CH_2Cl_2) and the resultant solution was washed with 2.0 M aq KOH (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give an 85:15 mixture of **305** and **306**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 80:19:1) gave **305** as a yellow oil (34 mg, 53%, >99:1 dr); ν_{max} (ATR) 1749 (C=O); δ_H (400 MHz, $CDCl_3$) 2.00 (1H, ddd, *J* 15.5, 10.5, 5.2, C(5)H_A), 2.12–2.20 (2H, m, C(2)H_A, C(5)H_B), 2.37 (1H, td, *J* 10.5, 3.5, C(6)H_A), 2.58–2.64 (1H, m, C(6)H_B), 2.88 (1H, ddd, *J* 11.3, 5.8, 1.6, C(2)H_B), 3.50 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 3.56 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 3.77 (1H, dt, *J* 8.2, 5.8, C(3)*H*), 4.64 (1H, ddd, *J* 5.8, 4.7, 3.5, C(4)*H*), 5.41 (1H, br s, N*H*), 7.26–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.9 (*C*(5)), 48.1 (*C*(6)), 51.1 (*C*(3)), 55.7 (*C*(2)), 62.4 (N*C*H$_2$Ph), 74.3 (*C*(4)), 127.3 (*p*-*Ph*), 128.4, 128.9

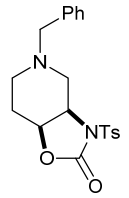
(*o*,*m*-*Ph*), 137.7 (*i*-*Ph*), 159.9 (N*C*O); *m/z* (ESI$^+$) 233 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{17}N_2O_2^+$ ([M+H]$^+$) requires 233.1285; found 233.1282. Further elution gave **306** as a yellow oil (5 mg, 7%, >99:1 dr); ν_{max} (ATR) 1756 (C=O); δ_H (400 MHz, $CDCl_3$) 2.00–2.09 (1H, m, C(7)H_A), 2.15–2.24 (1H, m, C(7)H_B), 2.30–2.37 (1H, m, C(6)H_A), 2.83–2.87 (1H, m, C(4a)*H*), 3.17 (1H, dd, *J* 8.5, 3.8, C(6)H_B), 3.25 (1H, ddd, *J* 12.7, 3.8, 3.2, C(4)H_A), 3.35 (1H, ddd, *J* 12.7, 5.3, 1.4, C(4)H_B), 3.52 (1H, d, *J* 13.4, NCH_AH$_B$Ph), 3.88 (1H, d, *J* 13.4, NCH$_A$$H_B$Ph), 4.82–4.88 (1H, m, C(7a)*H*), 5.44 (1H, br s, N*H*), 7.25–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 31.4 (*C*(7)), 40.4 (*C*(4)), 51.5 (*C*(6)), 57.9 (N*C*H$_2$Ph), 59.9 (*C*(4a)), 80.7 (*C*(7a)), 127.3, 128.4, 128.4 (*o*,*m*,*p*-*Ph*), 138.4 (*i*-*Ph*), 154.4 (*C*(2)); *m/z* (ESI$^+$) 233 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{17}N_2O_2^+$ ([M+H]$^+$) requires 233.1285; found 233.1282.

(*RS*,*SR*)-*N*(1)-Benzyl-3-(*N*-benzoylamino)-4-hydroxy-3,4-*N*,*O*-carbonylpiperidine 311



BzNCO (10 μL, 78 μmol) was added dropwise to a stirred solution of **288** (25 mg, 78 μmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt and the resultant mixture was stirred at rt for 5 min. $AgBF_4$ (18 mg, 94 μmol) was then added in one portion and the reaction mixture was stirred at rt for 16 h before being filtrated through Celite® (eluent CH_2Cl_2). The resultant solution was washed with 2.0 M aq KOH (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **311** as a yellow oil (6 mg, 23%, >99:1 dr); ν_{max} (ATR) 1786, 1680 (C=O); δ_H (400 MHz, $CDCl_3$) 2.04–2.11 (1H, m, C(5)H_A), 2.21 (1H, dq, *J* 15.1, 3.3, C(5)H_B), 2.33–2.41 (2H, m, C(2)H_A, C(6)H_A), 2.64 (1H, m, C(6)H_B), 3.50 (1H, d, *J* 13.1, NCH_AH$_B$Ph), 3.51–3.53 (1H, m, C(2)H_B), 3.66 (1H, d, *J* 13.1, NCH$_A$$H_B$Ph), 4.59 (1H, dt, *J* 8.2, 5.9, C(3)*H*), 4.73–4.77 (1H, m, C(4)*H*), 7.26–7.34 (5H, m, *Ph*), 7.42–7.45 (2H, m, *Ph*), 7.54–7.57 (1H, m, *Ph*), 7.63–7.65 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.8 (*C*(5)), 47.2 (*C*(6)), 53.7 (*C*(2)), 54.7 (*C*(3)), 62.4 (N*C*H$_2$Ph), 72.8 (*C*(4)), 127.3 (*p*-*Ph*), 127.9, 128.4, 128.9, 129.0 (*o*,*m*-*Ph*), 132.4 (*p*-*Ph*), 132.9, 137.6 (*i*-*Ph*), 153.3 (N*C*O), 169.6 (N*C*OPh); *m/z* (ESI$^+$) 337 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{21}N_2O_3^+$ ([M+H]$^+$) requires 337.1547; found 337.1537.

(*RS*,*SR*)-*N*(1)-Benzyl-3-(*N*-tosylamino)-4-hydroxy-3,4-*N*,*O*-carbonylpiperidine 312



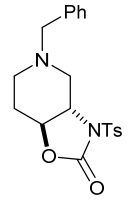
*Method A (from **288**)*: *p*-TsNCO (22 μL, 145 μmol) was added dropwise to a stirred solution of **288** (46 mg, 145 μmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt and the resultant mixture was stirred at rt for 5 min. $AgBF_4$ (37 mg, 188 μmol) was then added in one portion and the reaction mixture was stirred at rt for 16 h, then filtrated through Celite® (eluent CH_2Cl_2). The resultant solution was washed with 2.0 M aq KOH (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **312** as a yellow solid (35 mg, 62%, >99:1 dr); mp 111–113 °C; ν_{max} (ATR) 1782 (C=O); *m/z* (ESI^+) 387 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{23}N_2O_4S^+$ ($[M+H]^+$) requires 387.1373; found 387.1373; δ_H (400 MHz, $CDCl_3$) 1.90–2.00 (1H, m, C(5)H_A), 2.05–2.18 (3H, m, C(2)H_A, C(5)H_B C(6)H_A), 2.47 (3H, s, Ar*Me*), 2.56–2.65 (1H, m, C(6)H_B), 3.31 (1H, ddd, *J* 11.6, 6.3, 1.8, C(2)H_B), 3.47 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.50 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 4.51 (1H, dt, *J* 9.1, 6.3, C(3)*H*), 4.60–4.64 (1H, m, C(4)*H*), 7.21–7.38 (7H, m, *Ar*, *Ph*), 7.92 (2H, d, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.7 (Ar*Me*), 26.5 (*C*(5)), 46.8 (*C*(6)), 54.5 (*C*(2)), 56.3 (*C*(3)), 62.4 (N*C*H_2Ph), 73.3 (*C*(4)), 127.5 (*p-Ph*), 128.4, 128.5, 128.9, 129.7 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 135.4 (*C*(1′)), 137.1 (*i-Ph*), 145.5 (*C*(4′)), 151.9 (N*C*O).

*Method B (from **288**) – Step 1*: AgOCN (28 mg, 0.19 mmol) was added to a stirred solution of **288** (50 mg, 0.16 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was filtrated through Celite® (eluent CH_2Cl_2) and the resultant solution was washed with 2.0 M aq KOH (15 mL) and brine (15 mL), then dried and concentrated *in vacuo* to give an 85:15 mixture of **305** and **306**, respectively, as a yellow oil (33 mg).

*Method B (from **288**) – Step 2*: A solution of the residue of **305** and **306** (85:15, 33 mg) in THF (1 mL) and *p*-TsCl (39 mg, 0.20 mmol) were added to a stirred slurry of NaH (60% dispersion in mineral oil, 13 mg, 0.31 mmol) in THF/DMF (1:1, 2 mL) at 0 °C. The resultant mixture was allowed to warm to rt over 16 h. Satd aq NH_4Cl (1 mL) was then added at –78 °C and the reaction mixture was allowed to warm to rt. The resultant mixture was partitioned between H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 ×

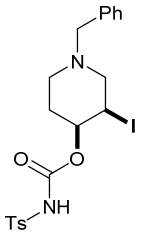
5 mL) and the combined organic extracts were then washed with satd aq $NaHCO_3$ (5 mL), then dried and concentrated *in vacuo* to give **312** as a yellow oil (40 mg, >99:1 dr).

(*RS*,*RS*)-*N*(1)-Benzyl-3-(*N*-tosylamino)-4-hydroxy-3,4-*N*,*O*-carbonylpiperidine 313



p-TsNCO (22 μL, 148 μmol) was added dropwise to a stirred solution of **289** (47 mg, 148 μmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt and the resultant mixture was stirred at rt for 5 min. $AgBF_4$ (37 mg, 188 μmol) was then added in one portion and the reaction mixture was stirred at rt for 16 h, then filtrated through Celite® (eluent CH_2Cl_2). The resultant solution was washed with 2.0 M aq KOH (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **313** as a yellow oil (17 mg, 30%, >99:1 dr); ν_{max} (ATR) 1797 (C=O); δ_H (400 MHz, $CDCl_3$) 1.72 (1H, qd, *J* 11.5, 4.5, C(5)H_A), 1.96–2.02 (1H, m, C(5)H_B), 2.15 (1H, td, *J* 11.5, 2.6, C(6)H_A), 2.40 (3H, s, Ar*Me*), 2.47 (1H, t, *J* 11.5, C(2)H_A), 2.90–2.92 (1H, m, C(6)H_B), 3.48–3.57 (2H, m, C(3)*H*, NC$H_A$$H_B$Ph), 3.68–3.75 (2H, m, C(2)H_B, NC$H_A$$H_B$Ph), 3.82 (1H, td, *J* 11.5, 4.5, C(4)*H*), 7.10–7.32 (7H, m, *Ar*, *Ph*), 7.81 (2H, d, *J* 8.2, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.7 (Ar*Me*), 27.9 (*C*(5)), 49.7 (*C*(6)), 55.4 (*C*(2)), 61.7 (N*C*H_2Ph), 62.4 (*C*(3)), 80.8 (*C*(4)), 126.2 (*p-Ph*), 127.5 (*C*(1′)), 128.4, 128.6, 129.9, 132.9 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 137.3 (*i-Ph*), 145.8 *C*(4′), 153.1 (N*C*O); *m/z* (ESI^+) 387 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{23}N_2O_4S^+$ ($[M+H]^+$) requires 387.1373; found 387.1374.

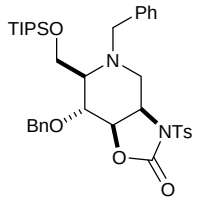
(*RS*,*SR*)-*N*(1)-Benzyl-3-iodo-4-(*N*-tosylcarbamoyloxy)piperidine 314



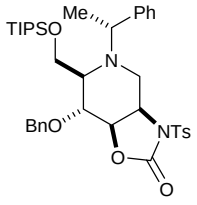
Step 1: I_2 (200 mg, 0.79 mmol) and $NaHCO_3$ (66 mg, 0.79 mmol) were added to a stirred solution of **264** (50 mg, 0.26 mmol) in MeCN (2 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (10 mL) and washed with satd aq $Na_2S_2O_3$ (10 mL), then the organic layer was dried and concentrated *in vacuo* to give a 70:30 mixture of **288** and **289**, respectively (50 mg).

Step 2: *p*-TsNCO (31 μL, 157 μmol) was added dropwise to a stirred solution of the residue of **288** and **289** (70:30, 50 mg, 157 μmol) in CH_2Cl_2 (2 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and washed with 2.0 M aq KOH (10 mL) and brine (10 mL), then the organic layer was dried and concentrated *in vacuo* to give a 70:30 mixture of **314** and **315**, respectively, as a yellow oil (46 mg).[52] Data for mixture: ν_{max} (ATR) 2918 (N–H), 1655 (C=O). Data for **314**: δ_H (400 MHz, DMSO-d_6, 363 K) 1.95–2.00 (2H, m, C(5)H_2), 2.20–2.27 (2H, m, C(2)H_A, C(6)H_A), 2.43 (3H, s, Ar*Me*), 2.50–2.57 (1H, m, C(6)H_B), 3.09 (1H, br s, N*H*), 3.14 (1H, dd, *J* 12.1, 5.2, C(2)H_B), 3.49 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.56 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 4.55 (1H, app q, *J* 6.3, C(3)*H*), 4.79 (1H, app dt, *J* 6.3, 3.4, C(4)*H*), 7.15–7.90 (9H, m, *Ar*, *Ph*); δ_C (100 MHz, DMSO-d_6, 363 K) 20.6 (Ar*Me*), 24.9 (*C*(5)), 45.9 (*C*(6)), 52.8 (*C*(2)), 55.6 (*C*(3)), 60.8 (N*C*H_2Ph), 72.6 (*C*(4)), 125.2 (*p-Ph*), 126.5 *C*(1′), 127.4, 127.6, 128.2, 129.3 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 137.0 (*C*(4′)), 144.8 (*i-Ph*), 151.0 (N*C*O); *m/z* (ESI^+) 515 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{23}IN_2NaO_4S^+$ ($[M+Na]^+$) requires 537.0315; found 537.0320.

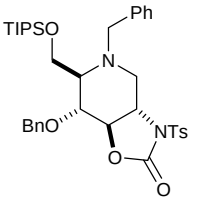
(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)-4,5-*O*,*N*-carbonylpiperidine 317, (*R*,*R*,*R*,*R*,*R*)-*N*(1)-(α-Methylbenzyl)-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)-4,5-*O*,*N*-carbonylpiperidine 321 and (2*R*,3*R*,4*R*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)-4,5-*O*,*N*-carbonylpiperidine 327



317



321



327

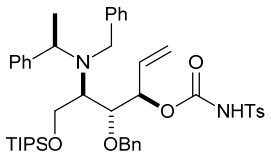
*Method A (from **191**) – Step 1*: I_2 (259 mg, 1.02 mmol) and $NaHCO_3$ (86 mg, 1.02 mmol) were added to a stirred solution of **191** (200 mg, 0.34 mmol, >99:1 dr) in MeCN (2 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL), then dried and concentrated *in vacuo* (210 mg).

*Method A (from **191**) – Step 2*: *p*-TsNCO (57 μL, 0.37 mmol) was added dropwise to a stirred solution of the residue (210 mg) in MeCN (4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (15 mL) and washed with satd aq

$NaHCO_3$ (15 mL), then dried and concentrated *in vacuo* to give a 38:9:6:25:22 mixture of **317**, **327**, **321**, **139** and **328**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave a 64:23:13 mixture of **317**, **327** and **321**, respectively, as a yellow oil (57 mg). Data for mixture: ν_{max} (ATR) 2942, 2865 (C−H), 1788, 1739 (C=O), 1173, 1090 (S=O). Data for **317**: δ_H (400 MHz, $CDCl_3$) 1.00–1.11 (21H, m, Si(C*H*Me$_2$)$_3$), 2.38 (3H, s, Ar*Me*), 2.94 (1H, app dd, *J* 9.5, 4.4, C(2)*H*), 3.06 (1H, dd, *J* 13.2, 2.2, C(6)H_A), 3.12 (1H, dd, *J* 13.2, 3.2, C(6)H_B), 3.50 (1H, app t, *J* 9.8, C(2)CH_AH$_B$), 3.57 (1H, d, *J* 14.3, NCH_AH$_B$Ph), 3.69 (1H, dd, *J* 10.1, 4.4, C(2)CH$_A$$H_B$), 3.75 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 4.19 (1H, dd, *J* 3.9, 1.2, C(3)*H*), 4.46 (1H, d, *J* 11.7, OCH_AH$_B$Ph), 4.59 (1H, dt, *J* 8.8, 3.2, C(5)*H*), 4.65–4.70 (2H, m, C(5)*H*, OCH$_A$$H_B$Ph), 7.12 (2H, dd, *J* 7.5, 1.8, *Ar*), 7.23–7.36 (10H, m, *Ph*), 7.87 (2H, d, *J* 7.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 50.4 (*C*(6)), 55.9 (*C*(5)), 60.6 (NCH$_2$Ph), 62.7 (C(2)*C*H$_2$), 64.8 (*C*(2)), 71.8 (OCH$_2$Ph), 72.5 (*C*(3)), 72.9 (*C*(4)), 127.1, 127.9 (*p-Ph*), 127.6, 128.2, 128.3, 128.4, 128.5, 129.7 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 135.3 (*C*(1′)), 137.6, 137.9 (*i-Ph*), 145.3 (*C*(4′)), 151.8 (N*C*O); *m/z* (ESI$^+$) 679 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{51}N_2O_6SSi^+$ ([M+H]$^+$) requires 679.3232; found 679.3218. Data for **321**: δ_H (400 MHz, $CDCl_3$) 0.99–1.09 (21H, m, Si(C*H*Me$_2$)$_3$), 1.40 (3H, d, *J* 6.8, C(α)*Me*), 2.43 (3H, s, Ar*Me*), 2.89 (1H, dd, *J* 13.4, 4.1, C(6)H_A), 3.15–3.19 (1H, m, C(2)*H*), 3.21 (1H, dd, *J* 13.4, 3.8, C(6)H_B), 3.64–3.67 (1H, m, C(2)CH_AH$_B$), 3.83 (1H, dd, *J* 10.1, 4.1, C(2)CH$_A$$H_B$), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.17–4.19 (1H, m, C(3)*H*), 4.45–4.49 (1H, m, C(5)*H*), 4.56–4.58 (1H, m, OCH_AH$_B$Ph), 4.58–4.60 (1H, m, C(4)*H*), 4.69–4.71 (1H, m, OCH$_A$$H_B$Ph), 7.11–7.13 (2H, m, *Ar*), 7.23–7.36 (10H, m, *Ph*), 7.86–7.88 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.5 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 44.1 (*C*(6)), 55.3 (*C*(5)), 58.6 (C(α)), 60.8 (*C*(2)), 62.9 (C(2)*C*H$_2$), 72.2 (OCH$_2$Ph), 73.1 (*C*(3)), 73.7 (*C*(4)), 127.0, 127.3 (*p-Ph*), 127.6, 128.1, 128.3, 128.4, 128.5, 129.8 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 135.1 (*C*(1′)), 137.6, 143.1 (*i-Ph*), 145.3 (*C*(4′)), 151.9 (*C*O); *m/z* (ESI$^+$) 693 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{53}N_2O_6SSi^+$ ([M+H]$^+$) requires 693.3388; found 693.3375. Further elution gave a 50:50 mixture of **317** and **327** (5 mg). Data for **327**: δ_H (400 MHz, $CDCl_3$) 1.00–1.11 (21H, m, Si(C*H*Me$_2$)$_3$), 2.48 (3H, s, Ar*Me*), 2.58 (1H, app t, *J* 10.5, C(6)H_A), 2.66–2.71 (1H, m, C(2)*H*), 3.45–3.52 (1H, m, C(5)*H*), 3.53–3.60 (1H, m, C(6)H_B), 3.61–3.65 (1H, m, C(3)*H*), 3.66–3.70 (1H, m, NCH_AH$_B$Ph), 3.95 (1H, dd, *J* 11.2, 4.3, C(2)CH_AH$_B$), 4.11–4.17 (2H, m, C(4)*H*, C(2)CH$_A$$H_B$), 4.30 (1H, d, *J* 14.2, NCH$_A$$H_B$Ph),

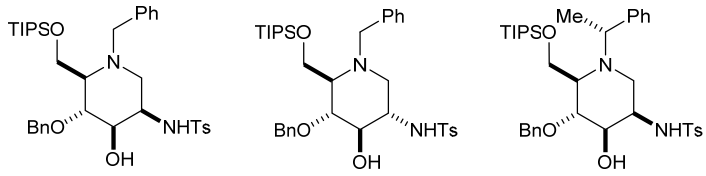
4.48 (1H, d, *J* 11.2, OC*H*$_A$H$_B$Ph), 4.83 (1H, d, *J* 11.2, OCH$_A$*H*$_B$Ph), 7.12 (2H, dd, *J* 7.5, 1.8, *Ar*), 7.23–7.36 (10H, m, *Ph*), 7.74 (2H, d, *J* 7.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.8 (Ar*Me*), 52.1 (*C*(6)), 56.4 (N*C*H$_2$Ph), 58.7 (*C*(5)), 61.6 (C(2)*C*H$_2$), 66.7 (*C*(2)), 73.0 (O*C*H$_2$Ph), 74.8 (*C*(3)), 84.6 (*C*(4)), 127.3, 127.6 (*p-Ph*), 128.0, 128.2, 128.4, 128.5, 128.6, 129.9 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 132.8 (*C*(1′)), 137.3, 138.3 (*i-Ph*), 145.9 (*C*(4′)), 152.8 (N*C*O); *m/z* (ESI$^+$) 679 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{51}N_2O_6SSi^+$ ([M+H]$^+$) requires 679.3232; found 679.3213.

(*R*,*R*,*R*,*R*)-[4-Benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisopropylsilyloxy)hex-1-en-3-yl]-*N*′-tosylcarbamate 328



p-TsNCO (14 μL, 94 μmol) was added dropwise to a stirred solution of **191** (50 mg, 85 μmol, >99:1 dr) in MeCN (4 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with EtOAc (15 mL) and washed with satd aq $NaHCO_3$ (15 mL), then the organic layer was dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 6:1) gave **328** as a yellow oil (32 mg, 48%, >99:1 dr); $[\alpha]_D^{20}$ –1.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2942, 2865 (C−H), 1752 (C=O), 1599 (C=C), 1163, 1090 (S=O); δ_H (400 MHz, $CDCl_3$) 1.05–1.16 (24H, m, Si(C*H*Me$_2$)$_3$, C(α)*Me*), 2.26 (3H, s, Ar*Me*), 3.05 (1H, dd, *J* 7.4, 3.3, C(4)*H*), 3.35–3.41 (1H, m, C(5)*H*), 3.80 (1H, d, *J* 14.5, NC*H*$_A$H$_B$Ph), 3.87 (1H, d, *J* 14.5, NCH$_A$*H*$_B$Ph), 4.02–4.06 (2H, m, C(6)*H*$_2$), 4.10 (1H, q, *J* 6.8, C(α)*H*), 4.20 (1H, d, *J* 11.2, OC*H*$_A$H$_B$Ph), 4.35 (1H, d, *J* 11.2, OCH$_A$*H*$_B$Ph), 4.94–5.01 (2H, m, C(1)*H*$_2$), 5.29 (1H, ddd, *J* 16.9, 10.7, 5.8, C(2)*H*), 5.62–5.66 (1H, m, C(3)*H*), 7.09 (2H, d, *J* 8.0, *Ar*), 7.12–7.30 (15H, m, *Ph*), 7.87 (2H, d, *J* 8.0, *Ar*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.2 (Si(CH*Me*$_2$)$_3$), 20.5 (C(α)*Me*), 21.5 (Ar*Me*), 51.5 (N*C*H$_2$Ph), 57.9 (*C*(5)), 62.0 (C(α)), 62.1 (*C*(6)), 74.9 (O*C*H$_2$Ph), 76.9 (*C*(3)), 81.3 (*C*(4)), 117.7 (*C*(1)), 126.6, 126.8, 127.8 (*p-Ph*), 127.5, 128.1, 128.3, 128.3, 128.3, 128.4, 128.9, 129.4 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 133.1 (*C*(2)), 135.3 (*C*(1′)), 137.7, 141.7 (*i-Ph*), 144.7 (*C*(4′)), 146.6 (*i-Ph*), 149.5 (N*C*O); *m/z* (ESI$^+$) 785 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{45}H_{61}N_2O_6SSi^+$ ([M+H]$^+$) requires 785.4014; found 785.3984.

(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)piperidine 329, (2*R*,3*R*,4*R*,5*S*)-*N*(1)-benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)piperidine 330 and (*R*,*R*,*R*,*R*,*R*)-*N*(1)-(α-methylbenzyl)-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)piperidine 331



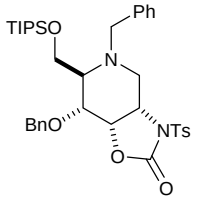
Step 1: I_2 (363 mg, 1.43 mmol) and $NaHCO_3$ (120 mg, 1.43 mmol) were added to a stirred solution of **191** (280 mg, 0.48 mmol, >99:1 dr) in MeCN (4 mL) at rt and the resultant mixture was stirred at rt for 16 h. *p*-TsNCO (0.33 mL, 2.16 mmol) was added dropwise and the reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was diluted with Et_2O (20 mL) and washed with satd aq $Na_2S_2O_3$ (20 mL), then dried and concentrated *in vacuo* to give a 57:14:4:25 mixture of **317**, **327**, **321** and **139**, respectively (300 mg).

Step 2: K_2CO_3 (267 mg, 1.93 mmol) was added to a stirred solution of the residue of **317**, **327**, **321** and **139** (57:14:4:25, 300 mg) in MeOH (5 mL) at rt and the resultant mixture was allowed to stir at rt for 16 h. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give a 57:14:4:25 mixture of **329**, **330**, **331** and **139**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 9:1) gave **331** as a colourless oil (6 mg, 2% from **191**, >99:1 dr); $[\alpha]_D^{20}$ +5.0 (*c* 0.06 in $CHCl_3$); ν_{max} (ATR) 3532, 3276 (O–H, N–H), 2942, 2865 (C−H), 1160, 1092 (S=O); δ_H (400 MHz, $CDCl_3$) 1.03–1.12 (21H, m, Si(C*H*Me$_2$)$_3$), 1.22 (3H, d, *J* 6.8, C(α)*Me*), 1.96 (1H, dd, *J* 12.3, 4.3, C(6)H_A), 2.16 (1H, dd, *J* 12.3, 1.6, C(6)H_B), 2.37 (3H, s, Ar*Me*), 2.59 (1H, ddd, *J* 8.8, 4.5, 1.3, C(2)*H*), 2.97 (1H, d, *J* 8.8, O*H*), 3.03–3.07 (1H, m, C(5)*H*), 3.31 (1H, app t, *J* 8.8, C(3)*H*), 3.54 (1H, app td, *J* 8.8, 3.9, C(4)*H*), 3.99 (1H, dd, *J* 11.0, 4.5, C(2)CH_AH$_B$), 4.16 (1H, dd, *J* 11.0, 1.3, C(2)CH$_A$$H_B$), 4.60 (1H, d, *J* 11.0, OCH_AH$_B$Ph), 4.65 (1H, q, *J* 6.8, C(α)*H*), 5.07–5.13 (2H, m, OCH$_A$$H_B$Ph, N*H*), 6.97–6.99 (2H, m, *Ar*), 7.02–7.05 (2H, m, *Ar*), 7.27–7.43 (8H, m, *Ph*), 7.48–7.51 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 9.6 (C(α)*Me*), 11.9 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.5 (Ar*Me*), 46.1 (*C*(6)), 52.4 (*C*(5)), 54.8 (*C*(α)), 63.3 (C(2)*C*H$_2$), 64.6

(*C*(2)), 74.7 (O*C*H$_2$Ph), 75.1 (*C*(4)), 78.9 (*C*(3)), 127.6, 127.6 (*p-Ph*), 127.1, 127.9, 128.1, 128.3, 128.7, 129.6 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 135.7 (*C*(1′)), 138.6 (*i-Ph*), 143.2 (*C*(4′)), 144.2 (*i-Ph*); *m/z* (ESI$^+$) 667 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{55}N_2O_5SSi^+$ ([M+H]$^+$) requires 667.3595; found 667.3571. Further elution gave **329** as a colourless oil (78 mg, 25% from **191**, >99:1 dr); $[\alpha]_D^{20}$ –16.2 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3532, 3276 (O–H, N–H), 2942, 2891 (C−H), 1160, 1091 (S=O); δ_H (400 MHz, $CDCl_3$) 1.02–1.13 (21H, m, Si(C*HMe*$_2$)$_3$), 2.08 (1H, dd, *J* 12.3, 2.4, C(6)*H*$_A$), 2.32 (1H, dd, *J* 12.3, 5.3, C(6)*H*$_B$), 2.36 (3H, s, Ar*Me*), 2.37–2.41 (1H, m, C(2)*H*), 3.12–3.16 (2H, m, O*H*, NC*H*$_A$H$_B$Ph), 3.27–3.32 (1H, m, C(5)*H*), 3.39 (1H, app t, *J* 8.0, C(3)*H*), 3.57 (1H, app td, *J* 8.0, 3.9, C(4)*H*), 3.88 (1H, dd, *J* 11.0, 4.4, C(2)C*H*$_A$H$_B$), 4.15 (1H, dd, *J* 11.0, 1.9, C(2)CH$_A$*H*$_B$), 4.39 (1H, d, *J* 13.2, NCH$_A$*H*$_B$Ph), 4.57 (1H, d, *J* 11.2, OC*H*$_A$H$_B$Ph), 4.97 (1H, d, *J* 11.2, OCH$_A$*H*$_B$Ph), 5.22 (1H, d, *J* 8.4, N*H*), 7.05 (2H, d, *J* 8.0, *Ar*), 7.26–7.42 (12H, m, *Ar*, *Ph*); δ_H (400 MHz, MeOH-d_4) 0.96–1.02 (21H, m, Si(C*HMe*$_2$)$_3$), 2.16 (1H, dd, *J* 12.5, 4.3, C(6)*H*$_A$), 2.35 (3H, s, Ar*Me*), 2.67 (1H, dd, *J* 12.5, 9.5, C(6)*H*$_B$), 2.75–2.78 (1H, m, C(2)*H*), 3.44–3.49 (1H, m, C(5)*H*), 3.60 (1H, d, *J* 13.7, NC*H*$_A$H$_B$Ph), 3.64 (1H, app t, *J* 4.0, C(3)*H*), 3.75 (1H, app t, *J* 4.0, C(4)*H*), 3.92 (1H, dd, *J* 10.1, 6.0, C(2)C*H*$_A$H$_B$), 3.99 (1H, dd, *J* 10.1, 5.8, C(2)CH$_A$*H*$_B$), 4.02 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ph), 4.47 (1H, d, *J* 12.0, OC*H*$_A$H$_B$Ph), 4.58 (1H, d, *J* 12.0, OCH$_A$*H*$_B$Ph), 7.12 (2H, d, *J* 8.0, *Ar*), 7.18–7.32 (10H, m, *Ph*), 7.62 (2H, d, *J* 8.0, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.5 (Ar*Me*), 51.8 (*C*(6)), 52.0 (*C*(5)), 57.2 (N*C*H$_2$Ph), 63.0 (C(2)*C*H$_2$), 65.9 (*C*(2)), 73.6 (*C*(4)), 74.2 (O*C*H$_2$Ph), 78.7 (*C*(3)), 127.3, 127.6 (*p-Ph*), 127.0, 127.9, 128.3, 128.6, 129.1, 129.6 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 136.3 (*C*(1′)), 138.4, 139.3 (*i-Ph*), 143.2 (*C*(4′)); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(*C*HMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 51.3 (*C*(6)), 51.8 (*C*(5)), 60.6 (N*C*H$_2$Ph), 63.3 (C(2)*C*H$_2$), 64.1 (*C*(2)), 73.0 (*C*(4)), 73.3 (O*C*H$_2$Ph), 79.0 (*C*(3)), 127.8, 128.6 (*p-Ph*), 128.0, 128.9, 129.2, 129.4, 130.1, 130.1 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 140.4, 141.4 (*i-Ph*), 141.7 (*C*(4′)), 144.3 (*C*(1′)); *m/z* (ESI$^+$) 653 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{53}N_2O_5SSi^+$ ([M+H]$^+$) requires 653.3439; found 653.3411. Further elution gave **330** as a colourless oil (22 mg, 7% from **191**, >99:1 dr); $[\alpha]_D^{20}$ –5.6 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3532, 3276 (O–H, N–H), 2926, 2865 (C−H), 1094, 1158 (S=O); δ_H (400 MHz, $CDCl_3$) 1.01–1.08 (21H, m, Si(C*HMe*$_2$)$_3$), 2.12 (1H, dd, *J* 12.1, 6.6, C(6)*H*$_A$), 2.39 (3H, s, Ar*Me*), 2.70 (1H, app q, *J* 4.0, C(2)*H*), 3.04 (1H, dd, *J* 12.1, 3.5, C(6)*H*$_B$), 3.25–3.30 (1H, m, C(5)*H*), 3.43–3.56 (4H, m, C(3)*H*, C(4)*H*,

NC*H*$_A$H$_B$Ph, O*H*), 3.76 (1H, dd, *J* 11.0, 4.0, C(2)C*H*$_A$H$_B$), 4.01 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ph), 4.16 (1H, dd, *J* 11.0, 3.2, C(2)CH$_A$*H*$_B$), 4.56 (1H, d, *J* 11.5, OC*H*$_A$H$_B$Ph), 4.66 (1H, d, *J* 11.5, OCH$_A$*H*$_B$Ph), 5.35 (1H, d, *J* 8.2, N*H*), 7.13–7.15 (2H, m, *Ar*), 7.25–7.38 (10H, m, *Ph*), 7.54–7.58 (2H, m, *Ar*); δ_H (400 MHz, MeOH-d_4) 0.95–1.02 (21H, m, Si(C*H*Me$_2$)$_3$), 1.71 (1H, app t, *J* 11.2, C(6)*H*$_A$), 2.30 (1H, app dd, *J* 9.8, 5.2, C(2)*H*), 2.45 (1H, dd, *J* 11.2, 4.5, C(6)*H*$_B$), 2.81 (1H, app dd, *J* 9.8, 4.5, C(5)*H*), 3.07 (1H, d, *J* 13.6, NC*H*$_A$H$_B$Ph), 3.20 (1H, app t, *J* 9.8, C(3)*H*), 3.39 (1H, app t, *J* 9.8, C(4)*H*), 3.85 (1H, dd, *J* 11.2, 5.2, C(2)C*H*$_A$H$_B$), 4.17 (1H, app d, *J* 9.8, C(2)CH$_A$*H*$_B$), 4.38 (1H, d, *J* 13.6, NCH$_A$*H*$_B$Ph), 4.58 (1H, d, *J* 12.0, OC*H*$_A$H$_B$Ph), 5.08 (1H, d, *J* 12.0, OCH$_A$*H*$_B$Ph), 7.00 (2H, d, *J* 8.0, *Ar*), 7.18–7.37 (10H, m, *Ph*), 7.50 (2H, d, *J* 8.0, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.5 (Ar*Me*), 50.9 (*C*(6)), 53.9 (*C*(5)), 57.5 (N*C*H$_2$Ph), 61.9 (C(2)*C*H$_2$), 63.0 (*C*(2)), 71.7 (*C*(4)), 73.1 (O*C*H$_2$Ph), 79.5 (*C*(3)), 127.0, 127.8 (*p-Ph*), 126.9, 127.7, 128.3, 128.5, 128.5, 129.6 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 137.7 (*C*(1′)), 138.0, 138.7 (*i-Ph*), 143.1 (*C*(4′)); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(*C*HMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 57.0 (*C*(5)), 57.9 (*C*(6)), 59.0 (N*C*H$_2$Ph), 65.2 (C(2)*C*H$_2$), 69.8 (*C*(2)), 75.7 (O*C*H$_2$Ph), 81.4 (*C*(3)), 81.8 (*C*(4)), 127.8, 128.6 (*p-Ph*), 128.0, 128.9, 129.2, 129.4, 130.1, 130.1 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 140.4, 141.4 (*i-Ph*), 141.7 (*C*(4′)), 144.3 (*C*(1′)); *m/z* (ESI$^+$) 653 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{53}N_2O_5SSi^+$ ([M+H]$^+$) requires 653.3439; found 653.3413.

(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)-4,5-*O*,*N*-carbonylpiperidine 332



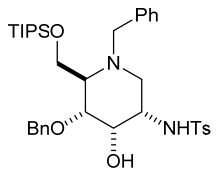
Method A: I_2 (129 mg, 0.51 mmol) and $NaHCO_3$ (43 mg, 0.51 mmol) were added to a stirred solution of **192** (100 mg, 0.17 mmol, >99:1 dr) in MeCN (2 mL) at rt and the resultant mixture was stirred at rt for 16 h. *p*-TsNCO (0.12 mL, 0.77 mmol) was added dropwise and the reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL), then dried and concentrated *in vacuo* to give a 50:50 mixture of **332** and **139**. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 9:1) gave **332** as a yellow oil (56 mg, 48%, >99:1 dr); $[\alpha]_D^{20}$

+14.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2942, 2865 (C−H), 1785 (C=O), 1173, 1100 (S=O); δ_H (400 MHz, $CDCl_3$) 1.02–1.11 (21H, m, Si(C*HMe*$_2$)$_3$), 2.36 (3H, s, Ar*Me*), 2.94 (1H, app quintet, *J* 3.2, C(2)*H*), 3.10 (1H, dd, *J* 12.0, 7.1, C(6)H_A), 3.43 (1H, dd, *J* 12.0, 6.0, C(6)H_B), 3.60–3.66 (2H, m, NCH_AH$_B$Ph, C(2)CH_AH$_B$), 3.70–3.73 (2H, m, NCH$_A$$H_B$Ph, C(2)CH$_A$$H_B$), 4.12 (1H, app t, *J* 3.2, C(3)*H*), 4.51 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.54–4.58 (2H, m, C(5)*H*, OCH$_A$$H_B$Ph), 4.84 (1H, dd, *J* 9.1, 3.2, C(4)*H*), 7.16–7.20 (6H, m, *Ar*, *Ph*), 7.25–7.33 (6H, m, *Ph*), 7.87 (2H, dd, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 50.6 (*C*(6)), 55.6 (*C*(5)), 58.8 (N*C*H$_2$Ph), 61.4 (*C*(2)), 61.8 (C(2)*C*H$_2$), 72.0 (*C*(4)), 72.5 (O*C*H$_2$Ph), 74.5 (*C*(3)), 127.3, 127.6 (*p-Ph*), 127.6, 128.1, 128.3, 128.3, 128.4, 129.6 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o*,*m-Ph*), 135.2 (*C*(1′)), 137.5, 137.9 (*i-Ph*), 145.1 (*C*(4′)), 152.5 (N*C*O); *m/z* (ESI$^+$) 679 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{51}N_2O_6SSi^+$ ([M+H]$^+$) requires 679.3232; found 679.3219.

Method B – Step 1: I_2 (259 mg, 1.02 mmol) and $NaHCO_3$ (86 mg, 1.02 mmol) were added to a stirred solution of **192** (200 mg, 0.34 mmol, >99:1 dr) in MeCN (2 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (15 mL) and washed with satd aq $Na_2S_2O_3$ (15 mL), then the organic layer was dried and concentrated *in vacuo* to give a 44:26:30 mixture of **257**, **258** and **139**, respectively (253 mg).

Method B – Step 2: *p*-TsNCO (62 μL, 0.41 mmol) was added dropwise to a stirred solution of the residue of **257**, **258** and **139** (44:26:30, 253 mg) in MeCN (2 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (15 mL) and washed with satd aq $NaHCO_3$ (15 mL), then dried and concentrated *in vacuo* to give a 70:30 mixture of **332** and **139**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/ Et_2O, 4:1) gave **332** as a yellow oil (75 mg, 33% from **192**, >99:1 dr).

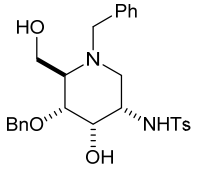
(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)piperidine 333



K_2CO_3 (175 mg, 1.26 mmol) was added to a stirred solution of **332** (85 mg, 0.12 mmol, >99:1 dr) in MeOH (4 mL) at rt and the resultant mixture was allowed to stir at rt for 16 h.

The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (15 mL) and EtOAc (15 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **333** as a white solid (68 mg, 83%, >99:1 dr); mp 88−90 °C; $[\alpha]_D^{20}$ +6.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3532, 3276 (O–H, N–H), 2942, 2865 (C−H), 1169, 1160, 1091 (S=O); δ_H (400 MHz, $CDCl_3$) 0.99–1.09 (21H, m, Si(C*H*Me$_2$)$_3$), 2.27 (1H, dd, *J* 12.0, 5.8, C(6)H_A), 2.36 (3H, s, Ar*Me*), 2.60 (1H, d, *J* 7.6, O*H*), 2.62 (1H, dd, *J* 12.0, 2.8, C(6)H_B), 2.89–2.92 (1H, m, C(2)*H*), 3.51–3.57 (2H, m, C(5)*H*, NCH_AH$_B$Ph), 3.67 (1H, app t, *J* 4.0, C(3)*H*), 3.80–3.86 (2H, m, NCH$_A$$H_B$Ph, C(2)C$H_AH_B$), 3.87–3.91 (2H, m, C(2)CH$_A$$H_B$, C(4)*H*), 4.46 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 4.51 (1H, d, *J* 11.5, OCH$_A$$H_B$Ph), 5.63 (1H, d, *J* 9.9, N*H*), 7.10 (2H, d, *J* 8.0, *Ar*), 7.24–7.39 (10H, m, *Ph*), 7.53 (2H, d, *J* 8.0, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.8 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 21.5 (Ar*Me*), 50.2 (*C*(6)), 53.0 (*C*(5)), 57.6 (N*C*H$_2$Ph), 59.5 (C(2)*C*H$_2$), 60.4 (*C*(2)), 66.2 (*C*(4)), 72.0 (O*C*H$_2$Ph), 77.6 (*C*(3)), 127.1, 128.0 (*p-Ph*), 126.6, 127.7, 128.3, 128.5, 128.6, 129.5 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o*,*m-Ph*), 137.6 (*i-Ph*), 138.5 (*C*(1′)), 139.0 (*i-Ph*), 142.8 (*C*(4′)); *m/z* (ESI$^+$) 653 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{53}N_2O_5SSi^+$ ([M+H]$^+$) requires 653.3439; found 653.3436.

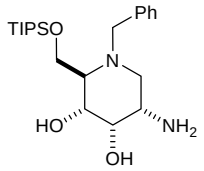
(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-hydroxymethyl-3-benzyloxy-4-hydroxy-5-(*N*-tosylamino)piperidine 336



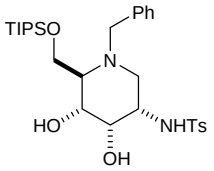
333 (30 mg, 0.05 mmol, >99:1 dr) was dissolved in HCl (1.25 M in MeOH, 2 mL) at rt and the resultant mixture was stirred at 40 °C for 16 h before being concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and washed with 1.0 M aq NaOH (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent EtOAc) gave **336** as a white solid (10 mg, 44%, >99:1 dr); mp 88–90 °C; $[\alpha]_D^{20}$ –8.6 (*c* 0.6 in $CHCl_3$); ν_{max} (ATR) 3501, 3282 (O−H, N−H), 2898 (C−H), 1158, 1090, 1065 (S=O); δ_H (400 MHz, $CDCl_3$) 1.97 (1H, br s, O*H*), 2.29 (1H, app t, *J* 11.0, C(6)H_A), 2.36–2.41 (4H, m, Ar*Me*, O*H*), 2.48–2.52 (2H, m, C(6)H_B, C(2)*H*), 3.27 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.45 (1H, m, C(5)*H*), 3.61 (1H, dd, *J* 9.0, 3.0, C(3)*H*), 3.78–3.82 (1H, m, C(2)CH_AH$_B$), 3.92–3.97 (3H, m, C(2)CH$_A$$H_B$, NCH$_A$$H_B$Ph, C(4)*H*), 4.53 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 4.56 (1H, d, *J* 11.5,

OCH_AH_BPh), 5.21 (1H, d, *J* 9.8, N*H*), 7.14–7.18 (4H, m, *Ar*, *Ph*), 7.27–7.40 (8H, m, *Ph*), 7.60–7.64 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.5 (Ar*Me*), 50.1 (*C*(6)), 51.4 (*C*(5)), 56.7 (NCH_2Ph), 57.9 (C(2)CH_2), 59.7 (*C*(2)), 66.5 (*C*(4)), 72.1 (OCH_2Ph), 75.7 (*C*(3)), 127.3, 128.3 (*p-Ph*), 126.7, 128.0, 128.5, 128.5, 128.7, 129.6 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o*,*m-Ph*), 137.2, 137.6 (*i-Ph*), 138.3 (*C*(1′)), 143.1 (*C*(4′)); *m/z* (ESI^+) 497 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{33}N_2O_5S^+$ ($[M+H]^+$) requires 497.2105; found 497.2090.

(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3,4-dihydroxy-5-aminopiperidine 337 and (2*R*,3*R*,4*S*,5*S*)-*N*(1)-benzyl-2-[(triisopropylsilyloxy)methyl]-3,4-dihydroxy-5-(*N*-tosylamino)piperidine 338



337



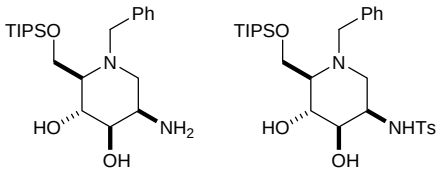
338

Method A: Naphthalene (461 mg, 3.60 mmol) was dissolved in DME (3 mL), then Na (62 mg, 2.70 mmol) was added under nitrogen and the resultant green solution was stirred at rt for 2 h. A solution of **333** (79 mg, 0.12 mmol, >99:1 dr) in DME (3 mL) was added via cannula at –78 °C and the resultant mixture was allowed to warm gradually to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and H_2O (1 mL) was added. The reaction mixture was then allowed to warm to rt and Et_2O (15 mL) was added. The organic layer was washed with satd aq NH_4Cl (15 mL) and brine (15 mL), before being dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/NH_4OH, 95:4:1) gave **338** as a colourless oil (4 mg, 6%, >99:1 dr); $[\alpha]_D^{20}$ –7.1 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3463 (O–H, N–H), 2942, 2866 (C−H), 1159, 1092, 1058 (S=O); δ_H (400 MHz, $CDCl_3$) 0.99–1.12 (21H, m, Si(C*HMe*$_2$)$_3$), 2.35 (1H, dd, *J* 11.2, 10.2, C(6)H_A), 2.39 (3H, s, Ar*Me*), 2.58 (1H, dd, *J* 11.2, 4.5, C(6)H_B), 2.69 (1H, app td, *J* 7.8, 4.3, C(2)*H*), 2.73 (1H, br s, O*H*), 3.40 (1H, d, *J* 14.0, NCH_AH_BPh), 3.45–3.51 (1H, m, C(5)*H*), 3.68–3.77 (4H, m, NCH_AH_BPh, C(2)CH_AH_B, C(3)*H*, C(4)*H*), 4.15 (1H, dd, *J* 9.9, 4.3, C(2)CH_AH_B), 4.49 (1H, br s, O*H*), 5.27 (1H, br s, N*H*), 7.16 (2H, d, *J* 8.0, *Ar*), 7.20–7.22 (2H, m, *Ph*), 7.25–7.33 (3H, m, *Ph*), 7.62 (2H, d, *J* 8.0, *Ar*); δ_H (400 MHz, MeOH-d_4) 1.05–1.12 (21H, m, Si(C*HMe*$_2$)$_3$), 2.11 (1H, app t, *J* 11.0, C(6)H_A), 2.16–2.19 (1H, m, C(6)H_B), 2.37 (3H, s, Ar*Me*), 2.45–2.50 (1H, m, C(2)*H*), 3.13 (1H, d, *J* 13.7, NCH_AH_BPh), 3.25 (1H, ddd, *J* 11.0, 4.7, 2.7, C(5)*H*), 3.42 (1H, dd, *J* 9.5,

3.1, C(3)*H*), 3.78 (1H, app t, *J* 3.1, C(4)*H*), 3.96 (1H, dd, *J* 11.0, 4.7, C(2)CH_AH_B), 4.23 (1H, dd, *J* 11.0, 2.1, C(2)CH_AH_B), 4.31 (1H, d, *J* 13.7, NCH_AH_BPh), 7.13–7.25 (7H, m, *Ar*, *Ph*), 7.53–7.58 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.6 (Si(*C*HMe_2)$_3$), 17.6 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 51.2 (*C*(6)), 51.6 (*C*(5)), 57.7 (N*C*H_2Ph), 60.3 (*C*(2)), 66.0 (C(2)*C*H_2), 68.6 (*C*(3)), 73.6 (*C*(4)), 127.1 (*p-Ph*), 126.7, 128.1, 128.4, 129.7 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 138.2 (*C*(1′)), 138.8 (*i-Ph*), 143.2 (*C*(4′)); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(*C*HMe_2)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 21.7 (Ar*Me*), 50.9 (*C*(6)), 53.7 (*C*(5)), 58.6 (N*C*H_2Ph), 64.3 (C(2)*C*H_2), 64.5 (*C*(2)), 70.3 (*C*(3)), 72.1 (*C*(4)), 128.0 (*p-Ph*), 127.8, 129.4, 130.0, 130.8 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 140.2 (*C*(1′)), 140.6 (*i-Ph*), 144.4 (*C*(4′)); *m/z* (ESI^+) 563 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{47}N_2O_5SSi^+$ ($[M+H]^+$) requires 563.2969; found 563.2955. Further elution gave **337** as a colourless oil (30 mg, 61%, >99:1 dr); $[\alpha]_D^{20}$ –14.7 (*c* 0.3 in MeOH); ν_{max} (ATR) 3337 (O–H, N–H), 2942, 2866 (C−H); δ_H (400 MHz, MeOH-d_4) 1.09–1.14 (21H, m, Si(C*HMe*$_2$)$_3$), 2.53 (1H, dd, *J* 11.9, 7.5, C(6)H_A), 2.83–2.89 (2H, m, C(2)*H*, C(6)H_B), 3.12–3.15 (1H, m, C(5)*H*), 3.59 (1H, d, *J* 13.4, NCH_AH_BPh), 3.81–3.83 (1H, m, C(3)*H*), 3.97 (1H, app t, *J* 3.2, C(4)*H*), 4.03 (1H, dd, *J* 10.9, 4.6, C(2)CH_AH_B), 4.13–4.19 (2H, m, C(2)CH_AH_B, NCH_AH_BPh), 7.21–7.25 (1H, m, *Ph*), 7.29–7.33 (2H, m, *Ph*), 7.38–7.39 (2H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(*C*HMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 50.3 (*C*(6)), 52.1 (*C*(5)), 59.0 (N*C*H_2Ph), 62.2 (C(2)*C*H_2), 65.1 (*C*(2)), 68.6 (*C*(4)), 70.9 (*C*(3)), 128.4 (*p-Ph*), 129.6, 130.1 (*o,m-Ph*), 140.5 (*i-Ph*); *m/z* (ESI^+) 409 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{41}N_2O_3Si^+$ ($[M+H]^+$) requires 409.2881; found 409.2874.

Method B:[53] Naphthalene (118 mg, 0.92 mmol) was dissolved in THF (2 mL), then Na (15 mg, 0.67 mmol) was added under nitrogen and the resultant green solution was stirred at rt for 2 h. A solution of **333** (20 mg, 0.03 mmol, >99:1 dr) in THF (2 mL) was added via cannula at –78 °C, then the resultant mixture was allowed to warm gradually to –10 °C and stirred at –10 °C for 3 h. H_2O (1 mL) was then added and the reaction mixture was allowed to warm to rt. Et_2O (10 mL) was added and the organic layer was washed with satd aq NH_4Cl (10 mL) and brine (10 mL), before being dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 4:1) gave **338** as a colourless oil (10 mg, 60%, >99:1 dr). Further elution (eluent CH_2Cl_2/MeOH, 4:1) gave **337** as a colourless oil (5 mg, 40%, >99:1 dr).

(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-[(triisopropylsilyloxy)methyl]-3,4-dihydroxy-5-aminopiperidine 339 and (*R*,*R*,*R*,*R*)-*N*(1)-benzyl-2-[(triisopropylsilyloxy)methyl]-3,4-dihydroxy-5-(*N*-tosylamino)piperidine 340

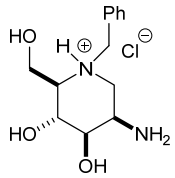


339 **340**

Naphthalene (346 mg, 2.70 mmol) was dissolved in DME (3 mL), then Na (46 mg, 2.02 mmol) was added under nitrogen and the resultant green solution was stirred at rt for 2 h. A solution of **329** (60 mg, 92 μmol, >99:1 dr) in DME (3 mL) was added via cannula at –78 °C, then the resultant mixture was allowed to warm gradually to rt and stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and H_2O (1 mL) was added. The reaction mixture was then allowed to warm to rt and Et_2O (15 mL) was added. The organic layer was washed with satd aq NH_4Cl (15 mL) and brine (15 mL), before being dried and concentrated *in vacuo* to give a 95:5 mixture of **339** and **340**, respectively. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/NH_4OH, 95:4:1) gave **340** as a colourless oil (2 mg, 4%, >99:1 dr); $[\alpha]_D^{20}$ –44.0 (*c* 0.2 in $CHCl_3$); ν_{max} (ATR) 3322 (O–H, N–H), 2940, 2865 (C−H), 1160, 1094, 1070 (S=O); δ_H (400 MHz, MeOH-d_4) 1.08–1.15 (21H, m, Si(C*H*Me$_2$)$_3$), 1.96 (1H, dd, *J* 12.0, 1.9, C(6)H_A), 2.21 (1H, dd, *J* 12.0, 4.6, C(6)H_B), 2.32–2.36 (1H, m, C(2)*H*), 2.34 (3H, s, Ar*Me*), 3.18 (1H, d, *J* 13.4, NCH_AH$_B$Ph), 3.37–3.40 (2H, m, C(4)*H*, C(5)*H*), 3.52–3.55 (1H, m, C(3)*H*), 4.10 (1H, dd, *J* 11.0, 4.7, C(2)CH_AH$_B$), 4.19 (1H, dd, *J* 11.0, 2.7, C(2)CH$_A$$H_B$), 4.23 (1H, d, *J* 13.4, NCH$_A$$H_B$Ph), 7.09 (2H, d, *J* 8.0, *Ar*), 7.24–7.40 (7H, m, *Ar*, *Ph*); δ_C (100 MHz, MeOH-d_4) 13.3 (Si(*C*HMe$_2$)$_3$), 18.7 (Si(CH*Me*$_2$)$_3$), 21.6 (Ar*Me*), 52.2 (*C*(6)), 53.6 (*C*(5)), 58.8 (NCH$_2$Ph), 63.0 (C(2)*C*H$_2$), 69.4 (*C*(2)), 70.9 (*C*(3)), 74.7 (*C*(4)), 128.3 (*p-Ph*), 128.0, 129.7, 130.1, 130.8 (*C*(2′), *C*(3′), *C*(5′), *C*(6′), *o,m-Ph*), 139.1 (*C*(1′)), 141.0 (*i-Ph*), 144.5 (*C*(4′)); *m/z* (ESI$^+$) 563 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{47}N_2O_5SSi^+$ ([M+H]$^+$) requires 563.2969; found 563.2954. Further elution gave **339** as a colourless oil (23 mg, 63%, >99:1 dr); $[\alpha]_D^{20}$ –28.4 (*c* 0.5 in MeOH); ν_{max} (ATR) 3360 (O–H, N–H), 2942, 2865 (C−H); δ_H (400 MHz, MeOH-d_4) 1.10–1.17 (21H, m, Si(C*H*Me$_2$)$_3$), 2.19–2.24 (2H, m, C(6)H_A, C(2)*H*), 2.77 (1H, dd, *J* 12.0, 3.6, C(6)H_B), 2.79–2.83 (1H, m, C(5)*H*), 3.17 (1H, d, *J* 13.4, NCH_AH$_B$Ph), 3.41 (1H, dd, *J* 8.9, 4.0, C(4)*H*), 3.53 (1H, app t, *J* 8.9, C(3)*H*), 4.11 (1H, dd, *J* 11.0, 4.3, C(2)CH_AH$_B$), 4.28 (1H, dd, *J* 11.0, 2.1, C(2)CH$_A$$H_B$), 4.47

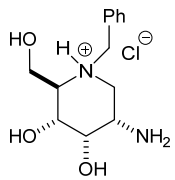
(1H, d, *J* 13.4, NCH_AH_BPh), 7.20–7.36 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 13.4 ($Si(CHMe_2)_3$), 18.7 ($Si(CHMe_2)_3$), 51.6 (*C*(5)), 55.1 (*C*(6)), 58.7 (NCH_2Ph), 63.4 ($C(2)CH_2$), 70.2 (*C*(3)), 70.3 (*C*(2)), 76.7 (*C*(4)), 128.1 (*p-Ph*), 129.5, 130.1 (*o*,*m-Ph*), 141.2 (*i-Ph*); *m/z* (ESI^+) 409 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{41}N_2O_3Si^+$ ($[M+H]^+$) requires 409.2881; found 409.2872.

(*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-(hydroxymethyl)-3,4-dihydroxy-5-aminopiperidine hydrochloride 341·HCl



339 (30 mg) was dissolved in 6.0 M aq HCl (1 mL) and MeOH (1 mL) at rt and the resultant mixture was stirred at 40 °C for 16 h before being concentrated *in vacuo* to give **341**·HCl as a yellow oil (20 mg); $[\alpha]_D^{20}$ +31.8 (*c* 1.0 in MeOH); ν_{max} (ATR) 3350 (O–H, N–H), 2942, 2865 (C−H); δ_H (400 MHz, MeOH-d_4) 3.51–3.58 (2H, m, C(2)*H*, C(6)H_A), 3.65–3.76 (2H, m, C(2)CH_AH_B, C(6)H_B), 4.00–4.08 (1H, m, C(4)*H*), 4.09–4.14 (2H, m, C(2)CH_AH_B, C(3)*H*), 4.25–4.39 (1H, m, C(5)*H*), 4.54–4.68 (1H, m, NCH_AH_BPh), 5.00–5.09 (1H, m, NCH_AH_BPh), 7.45–7.53 (3H, m, *Ph*), 7.61–7.71 (2H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 44.6 (*C*(5)), 45.3 (*C*(6)), 57.9 ($C(2)CH_2$), 60.9 (NCH_2Ph), 64.7 (*C*(2)), 67.6 (*C*(3)), 69.0 (*C*(4)), 130.5, 131.3 (*o*,*m-Ph*), 132.7 (*p-Ph*), 132.8 (*i-Ph*); *m/z* (ESI^+) 253 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{21}N_2O_3^+$ ($[M+H]^+$) requires 253.1547; found 253.1545.

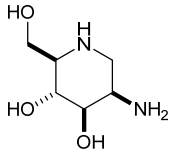
(2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-(hydroxymethyl)-3,4-dihydroxy-5-aminopiperidine hydrochloride 342·HCl



337 (30 mg) was dissolved in 6.0 M aq HCl (1 mL) and MeOH (1 mL) at rt and the resultant mixture was stirred at 40 °C for 16 h before being concentrated *in vacuo* to give **342**·HCl as a yellow oil (19 mg); $[\alpha]_D^{20}$ −16.8 (*c* 0.2 in MeOH); ν_{max} (ATR) 3360 (O–H, N–H), 2942, 2865 (C−H); δ_H (400 MHz, MeOH-d_4) 3.20 (1H, dd, *J* 11.7, 4.3, C(6)H_A), 3.25–3.30 (1H, m, C(6)H_B), 3.41–3.46 (1H, m, C(2)*H*), 3.62–3.66 (1H, m, C(5)*H*), 3.96 (1H, app d, *J* 9.8,

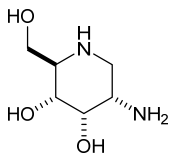
C(3)*H*), 4.16–4.18 (1H, m, C(4)*H*), 4.23–4.26 (2H, m, C(2)CH_2), 4.32 (1H, d, *J* 11.8, NCH_AH$_B$Ph), 4.86 (1H, d, *J* 11.8, NCH$_A$$H_B$Ph), 7.50–7.66 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 46.7 (*C*(6)), 48.0 (*C*(5)), 54.9 (C(2)*C*H$_2$), 58.7 (N*C*H$_2$Ph), 63.8 (*C*(2)), 66.5 (*C*(3)), 67.7 (*C*(4)), 130.7, 131.7, 133.0 (*o,m,p-Ph*), 133.5 (*i-Ph*); *m/z* (ESI$^+$) 253 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{21}N_2O_3^+$ ([M+H]$^+$) requires 253.1547; found 253.1540.

(*R*,*R*,*R*,*R*)-2-Amino-1,2,5-trideoxy-1,5-imino-D-mannose [(–)-2-amino-1-deoxymannojirimycin (ADMJ)] 112



Pd(OH)$_2$/C (10 mg) was added to a stirred solution of the residue of **341**·HCl (20 mg) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt for 48 h under an atmosphere of H_2 (5 atm). HCl (1.0 M in Et_2O, 1 mL) was then added and the resultant suspension was stirred for a further 5 min before being filtrated through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **112** as a white solid (12 mg, quant, >99:1dr);[54] mp >250 °C; $[\alpha]_D^{20}$ –11.5 (*c* 0.3 in H_2O); {lit[54] $[\alpha]_D^{20}$ –14 (*c* 0.4 in H_2O)}; ν_{max} (ATR) 3360 (O–H, N–H); δ_H (400 MHz, D_2O) 2.50 (1H, ddd, *J* 9.7, 5.8, 3.0, C(5)*H*), 2.84 (1H, dd, *J* 14.0, 2.4, C(1)H_A), 3.00 (1H, dd, *J* 14.0, 2.4, C(1)H_B), 3.29–3.33 (1H, m, C(2)*H*), 3.44 (1H, t, *J* 9.7, C(4)*H*), 3.63–3.68 (2H, m, C(3)*H*, C(6)H_A), 3.77 (1H, dd, *J* 11.7, 3.0, C(6)H_B); δ_C (100 MHz, D_2O) 46.4 (*C*(1)), 51.2 (*C*(2)), 60.9 (*C*(5)), 60.9 (C(6)), 68.0 (*C*(4)), 73.1 (*C*(3)); *m/z* (ESI$^+$) 163 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{15}N_2O_3^+$ ([M+H]$^+$) requires 163.1077; found 163.1078.

(2*S*,3*S*,4*R*,5*R*)-2-Amino-1,2,5-trideoxy-1,5-imino-D-allose [(+)-2-amino-1-deoxyallonojirimycin (ADANJ)] 263



Pd(OH)$_2$/C (10 mg) was added to a stirred solution of the residue of **342**·HCl (19 mg) in degassed MeOH (2 mL) and the resultant suspension was stirred at rt for 48 h under an atmosphere of H_2 (5 atm). HCl (1.0 M in Et_2O, 1 mL) was then added and the resultant

suspension was stirred for a further 5 min before being filtrated through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **263** as a white solid (12 mg, quant from **337**, >99:1dr); mp >250 °C; $[\alpha]_D^{20}$ +16.3 (*c* 0.3 in H_2O); ν_{max} (ATR) 3360 (O–H, N–H); δ_H (400 MHz, D_2O) 2.52 (1H, app t, *J* 11.8, C(1)H_A), 2.69 (1H, ddd, *J* 10.4, 5.8, 2.8, C(5)*H*), 2.76 (1H, dd, *J* 12.3, 4.8, C(1)H_B), 2.79–2.85 (1H, m, C(2)*H*), 3.42 (1H, dd, *J* 10.4, 2.8, C(4)*H*), 3.59 (1H, dd, *J* 11.7, 5.8, C(6)H_A), 3.76 (1H, dd, *J* 11.7, 2.8, C(6)H_B), 3.93–3.95 (1H, m, C(3)*H*); δ_C (100 MHz, D_2O) 44.6 (*C*(1)), 50.1 (*C*(2)), 54.5 (*C*(5)), 61.5 (C(6)), 69.1 (*C*(4)), 71.4 (*C*(3)); *m/z* (ESI^+) 163 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{15}N_2O_3^+$ ($[M+H]^+$) requires 163.1077; found 163.1076.

5.5. References and notes for Chapter 5

[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[2] Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.

[3] Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655.

[4] Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem-Eur. J.* **2000**, *6*, 1840.

[5] Yoon, N. M.; Lee, H. J.; Kim, H. K.; Kang, J. *J. Korean Chem. Soc.* **1976**, *20*, 59.

[6] Evans, D. A.; Welch, D. S.; Speed, A. W. H.; Moniz, G. A.; Reichelt, A.; Ho, S. *J. Am. Chem. Soc.* **2009**, *131*, 3840.

[7] Noji, M.; Konno, Y.; Ishii, K. *J. Org. Chem*. **2007**, *72*, 5161.

[8] Srihari, P.; Bhunia, D. C.; Sreedhar, P.; Yadav, J. S. *Synlett* **2008**, 1045.

[9] The ee of (*R*)-**186** was determined from the 400 MHz ^{1}H NMR spectrum in the presence of the chiral solvating agent (*R*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample.

[10] Foster, E. M. *D.Phil Thesis*, University of Oxford, **2012**.

[11] Abraham, E.; Davies, Brock, E. A.; Candela-Lena, J. I., Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sanchez-Fernandez, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665.

[12] (a) Davies, S. G.; Fletcher, A. M; Foster, E. M; Lee, J. A; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 2500. (b) Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8885.

[13] Asano, N.; Yamauchi, T.; Kagamifuchi, K.; Shimizu, N.; Takahashi, S.; Takatsuka, H.; Ikeda, K.; Kizu, H.; Chuakul, W.; Kettawan, A.; Okamoto, T. *J. Nat. Prod.* **2005**, *68*, 1238.

[14] Donohoe, T. J.; Cheeseman, M. D.; O'Riordan, T. J. C.; Kershaw, J. A. *Org. Biomol. Chem.* **2008**, *6*, 3896.

[15] Blanco, O.; Pato, C.; Ruiz, M.; Ojea, V. *Org. Biomol. Chem.* **2008**, *6*, 3967.

[16] Kumar, V.; Ramesh, N. G. *Tetrahedron* **2006**, *62*, 1877.

[17] Kim, I.-S.; Kim, S.-J.; Lee, J. K.; Li, Q.-R; Jung, Y.-H. *Carbohydrate Research* **2007**, *342*, 1502.

[18] Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929.

[19] Characterisation data for **203** were reported in section 5.2.

[20] Dieskau, A. P.; Begouin, J. M.; Plietker, B.; *Eur. J. Org. Chem*. **2011**, 5291.

[21] Chakraborti. A. K.; Chankeshwara. S. V.; *J. Org. Chem*. **2009**, *74*, 1367.

[22] Characterisation data for **205** were reported in section 5.2.

[23] Xu, X.-M.; Zhou, W.-S. *Tetrahedron Lett.* **1996**, *37*, 1461.

[24] Asano, N.; Oseki, K.; Kizu, H.; Matsui, K. *J. Med. Chem.* **1994**, *37*, 3701.

[25] Broxterman, H. J. G.; Neefjes, J. J.; Van der Marel, G. A.; Ploegh, H. L.; Van Boom, J. H. *J. Carbohydr. Chem.* **1988**, *7*, 593.

[26] Concia, A. L.; Lozano, C.; Castillo, J. A.; Parella, T.; Joglar, J.; Clapés, P. *Chem. Eur. J.* **2009**, *15*, 3808.

[27] Kim, I. S.; Lee, H. Y.; Jung, Y. H. *Heterocycles* **2007**, *71*, 1787.

[28] Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036.

[29] Singh, A.; Kim, B.; Lee, W.; Ha, H.-J. *Org. Biomol. Chem*. **2011**, *9*, 1372.

[30] Sridhar, R.; Srinivas, B.; Rao, K. *Tetrahedron* **2009**, *65*, 70701.

[31] Hong, B.-C.; Chen, Z.-Y.; Nagarajan, A.; Kottani, R.; Chavan, V.; Chen, W.-H.; Jiang, Y.-F.; Zhang, S.-C.; Liaoa, J.-H.; Sarsharb, S. *Carbohydr. Res.* **2005**, *340*, 2457.

[32] Ikota, N.; Hirano, J.-I.; Gamage, R.; Nakagawa, H.; Hama-Inaba, H. *Heterocycles* **1997**, 46, 637.

[33] Chesney, A.; Marko, I. E. *Synlett* **1992**, 275.

[34] Chesney, A.; Marko, I. E. *Synth. Commun.* **1990**, *20*, 3167.

[35] Almiento, G. M.; Balducci, D.; Bottoni, A.; Calvaresi, M.; Porzi, G. *Tetrahedron: Asymmetry* **2007**, *18*, 2695.

[36] Cook, P. D. US Patent, 9810286, **1998**.

[37] Khamrai, U.; Karak, S. K.; Ronsheim, M.; Saha, A. K. US Patent, 0168080 A1 20100701, **2010**.

[38] Solé, D.; Garcia-Rubio, S.; Bosch, J.; Bonjoch, J. Heterocycles **1996**, *43*, 2415.

[39] Ortiz, A.; Young, I. S.; Sawyer, J. R.; Hsiao, Y.; Singh, A.; Sugiyama, M.; Corbett, R. M.; Chau, M.; Shi, Z.; Conlon, D. A. *Org. Biomol. Chem.* **2012**, *10*, 5253.

[40] Csatayová, K.; Davies, S. G.; Ford, J. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 12397.

[41] Pavlova, M.; Hoenke, C.; Christoffers, J. *Synthesis* **2009**, 1659.

[42] Grishina, G. V.; Borisenko, A. A.; Veselov, I. S.; Petrenko, A. M. *Russ. J. Org. Chem.* **2005**, *41*, 272.

[43] Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762.

[44] Terentiev, P. B.; Zilberstein, T. M.; Borisenko, A. A.; Shmorgunov, V. A.; Piskunkova, N. F.; Grishina, G. V. *Chem. Heterocycl. Compd.* **2003**, *39*, 885.

[45] The product underwent degradation upon column chromatography attempt. The crude sample was therefore characterised as a 50:50 mixture of **287** and DMAP.

[46] Data in $CDCl_3$ at rt were unable to confirm the structure (broad or missing peaks). VT (363 K) in PhMe-d_8 was necessary to resolve all peaks.

[47] C(4)*H* could not be observed in the spectrum (rt, $CDCl_3$).

[48] *C*(3) at 39.9 ppm and *C*(6) at 48.3 ppm were observed as extremely broad peaks.

[49] The product could not be isolated due to degradation.

[50] Rives, A.; Génisson, Y.; Faugeroux, V.; Zedde, C.; Lepetit, C.; Chauvin, R.; Saffon, N.; Andrieu-Abadie, N.; Colié, S.; Levade, T.; Baltas, M. *Eur. J. Org. Chem.* **2009**, 2474.

[51] Roush, W. R.; Gustin, D. *Tetrahedron Lett.* **1994**, *35*, 4931.

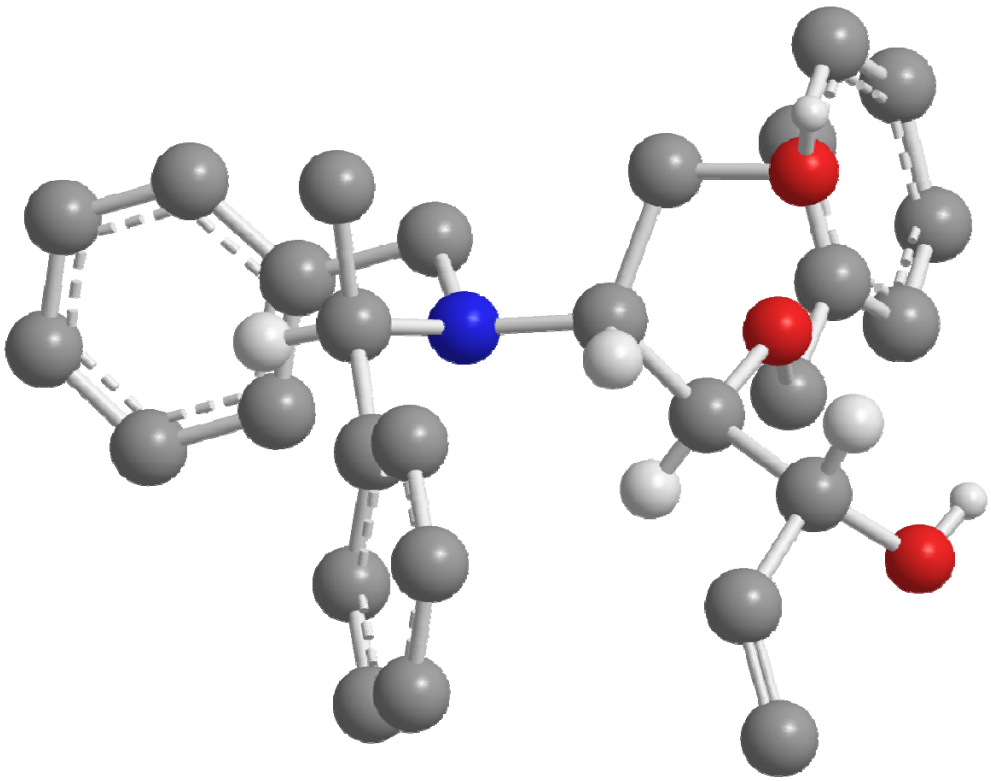
[52] The product was characterised as a crude mixture (>80% purity). VT NMR (DMSO, 363 K) was necessary to overcome the broadness of the sample at rt.

[53] Llaveria J.; Beltran A.; Sameera W. M. C.; Locati A.; Mar Diaz-Requejo M.; Matheu M. I.; Castillon S.; Maseras F.; Perez P. J. *J. Am. Chem. Soc.* **2014**, *136*, 5342.

[54] Le Merrer Y.; Poitout L.; Depezay J.; Dosbaa I.; Geoffroy S.; Foglietti M. *Bioorg. Med. Chem.* **1997**, *5*, 519.

X-Ray crystal structure data for (*R*,*R*,*R*,*R*)-193

(selected H atoms are omitted for clarity)



X-Ray crystal structure determination for 193

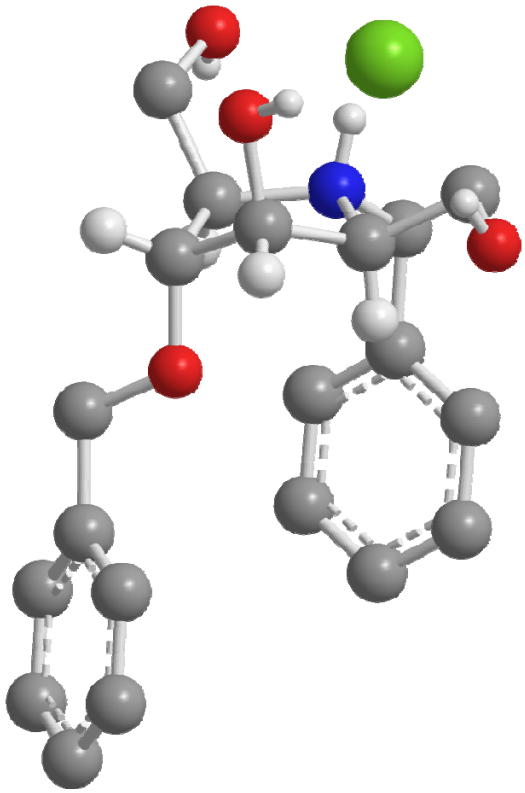
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-Ray crystal structure data for **193** [$C_{28}H_{33}NO_3$]: M = 431.57, monoclinic, space group $P\,2_1$, a = 12.8417(4) Å, b = 6.6522(1) Å, c = 14.8628(5) Å, β = 109.357(4)°, V = 1197.89(6) Å^3, Z = 2, μ = 0.605 mm^{-1}, colourless block, crystal dimensions = 0.05 × 0.06 × 0.19 mm. A total of 4855 unique reflections were measured for $3 < \theta < 80$ and 4265 reflections were used in the refinement. The final parameters were wR_2 = 0.110 and R_1 = 0.047 [$I>-3.0\sigma(I)$]. X-Ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (2*R*,3*R*,4*R*,5*S*)-204·HCl·H_2O

(H_2O and selected H atoms are omitted for clarity)



X-Ray crystal structure determination for 204·HCl·H_2O

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.[2]

X-Ray crystal structure data for **204**·HCl·H_2O [$C_{20}H_{28}ClNO_5$]: M = 397.90, monoclinic, space group $P\ 2_1$, a = 16.4392(3) Å, b = 7.4924(2) Å, c = 16.8150(4) Å, β = 93.3685(19)°, V = 2067.51(8) Å^3, Z = 4, μ = 1.886 mm^{-1}, colourless plate, crystal dimensions = 0.12 × 0.22 × 0.25 mm. A total of 8578 unique reflections were measured for 4 < θ < 76 and 7291 reflections were used in the refinement. The final parameters were wR_2 = 0.158 and R_1 = 0.047 [I>−3.0σ(I)], with Flack enantiopole = –0.057(13).[3] X-Ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

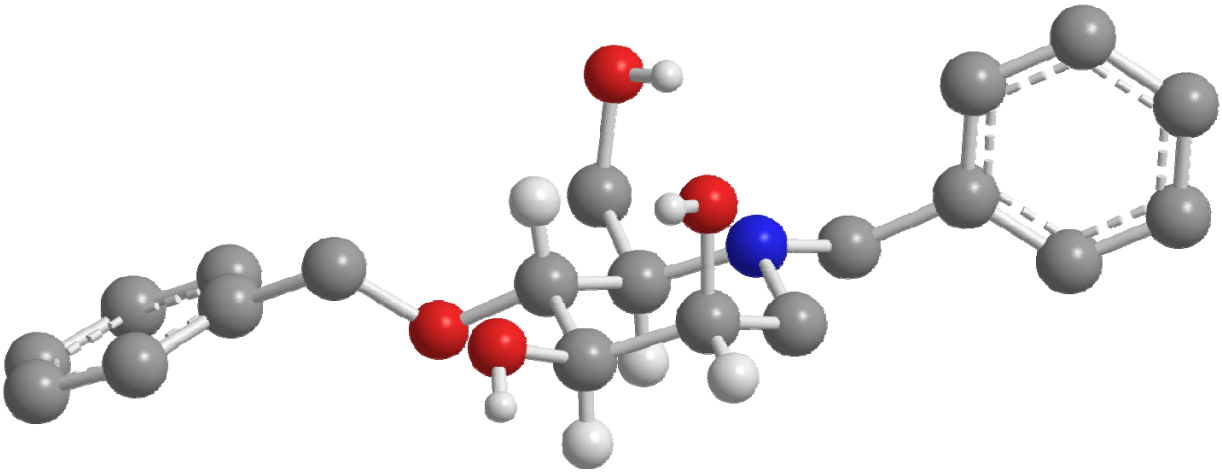
---

[2] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[3] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (*R*,*R*,*R*,*R*)-205·$CHCl_3$

($CHCl_3$ and selected H atoms are omitted for clarity)



X-Ray crystal structure determination for 205·$CHCl_3$

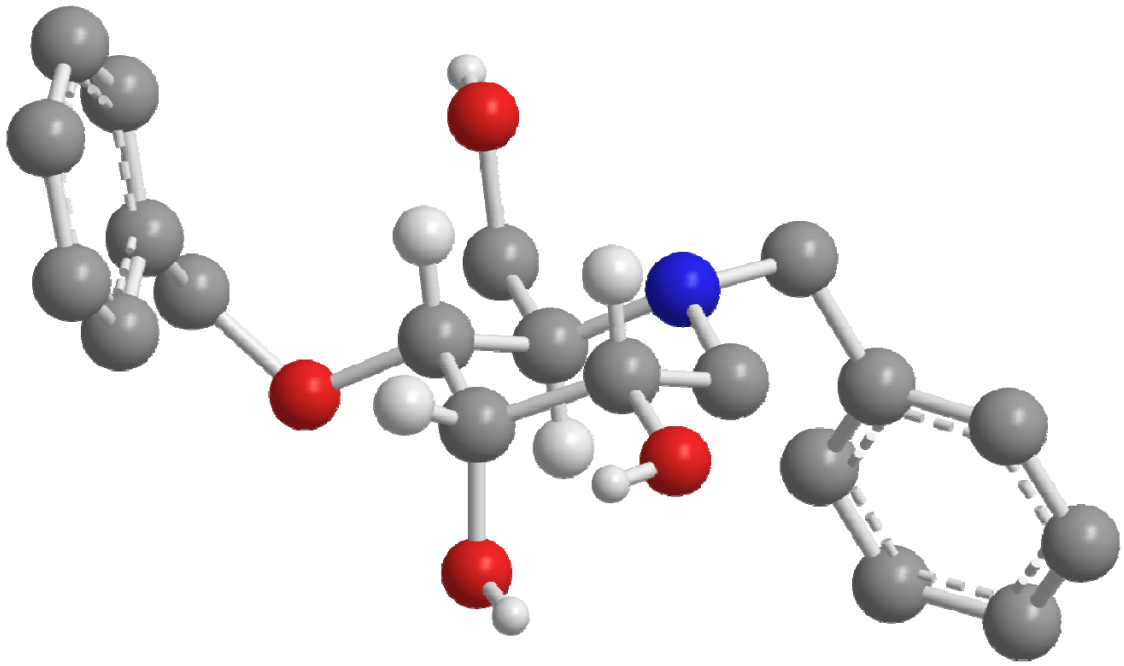
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[4]

X-Ray crystal structure data for **205**·$CHCl_3$ [$C_{21}H_{26}Cl_3NO_4$]: M = 462.80, monoclinic, space group $P\ 2_1$, a = 11.1676(4) Å, b = 8.2551(3) Å, c = 12.4524(5) Å, β = 90.8174(16)°, V = 1147.87(7) Å^3, Z = 2, μ = 0.425 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.26 × 0.27 mm. A total of 5050 unique reflections were measured for 5 < θ < 27 and 2656 reflections were used in the refinement. The final parameters were wR_2 = 0.062 and R_1 = 0.051 [I>−3.0$\sigma(I)$], with Flack enantiopole = –0.09(12).[5] X-Ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[4] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
[5] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (2*R*,3*R*,4*S*,5*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.[6]

X-Ray crystal structure data for **260** [$C_{20}H_{25}NO_4$]: M = 343.43, monoclinic, space group $P\,2_1$, a = 10.3223(3) Å, b = 6.9861(2) Å, c = 12.9927(3) Å, β = 101.708(3)°, V = 917.44(4) Å^3, Z = 2, μ = 0.698 mm^{-1}, colourless block, crystal dimensions = 0.07 × 0.09 × 0.16 mm. A total of 3813 unique reflections were measured for 3 < θ < 77 and 3796 reflections were used in the refinement. The final parameters were wR_2 = 0.064 and R_1 = 0.033 [I>−3.0σ(I)], with Flack enantiopole = –0.05(16).[7] X-Ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

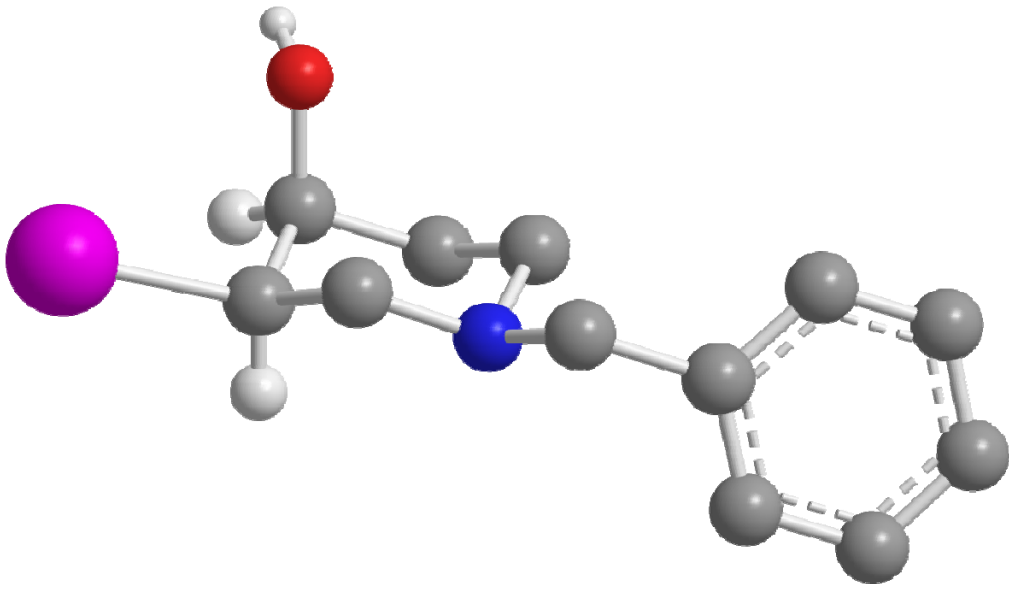
---

[6] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[7] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (*RS*,*SR*)-288

(selected H atoms are omitted for clarity)



X-Ray crystal structure determination for 288

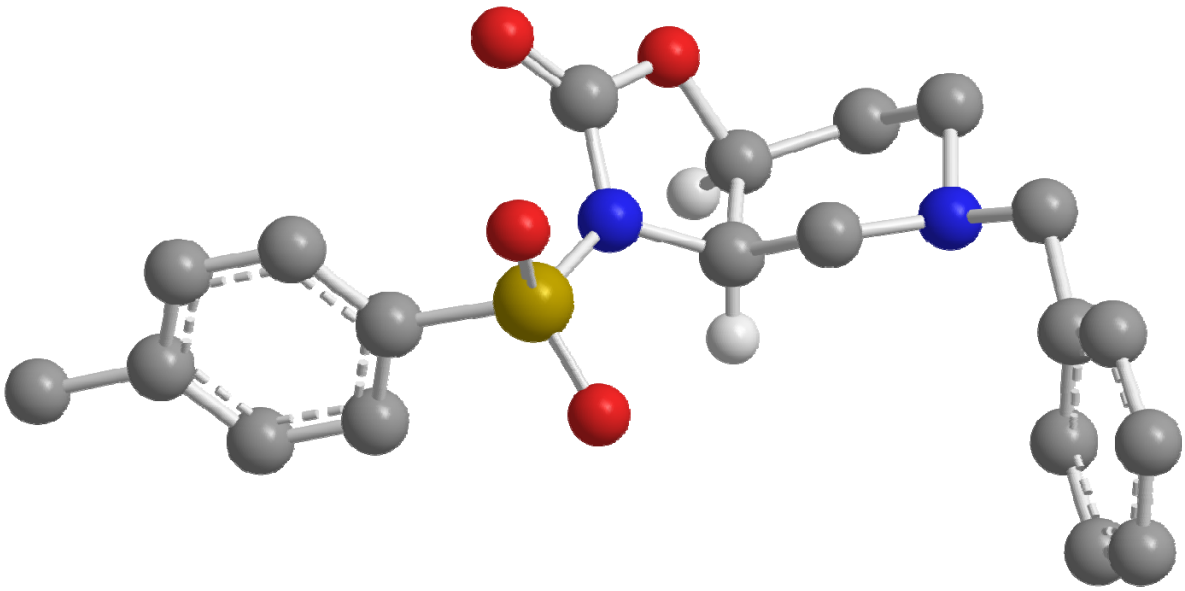
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[8]

X-Ray crystal structure data for **288** [$C_{12}H_{16}INO$]: M = 317.17, orthorhombic, space group $P\,c\,2_1\,n$, a = 9.9626(2) Å, b = 14.5776(4) Å, c = 17.0821(4) Å, V = 2480.85(10) Å^3, Z = 8, μ = 1.698 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.28 × 0.30 mm^3. A total of 5148 unique reflections were measured for $5 < \theta < 27$ and 5148 reflections were used in the refinement. The final parameters were wR_2 = 0.062 and R_1 = 0.038 [I>–3.0σ(I)], with Flack enantiopole = 0.40(2).[9] X-Ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[8] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
[9] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (*RS*,*SR*)-312

(selected H atoms are omitted for clarity)



X-Ray crystal structure determination for 312

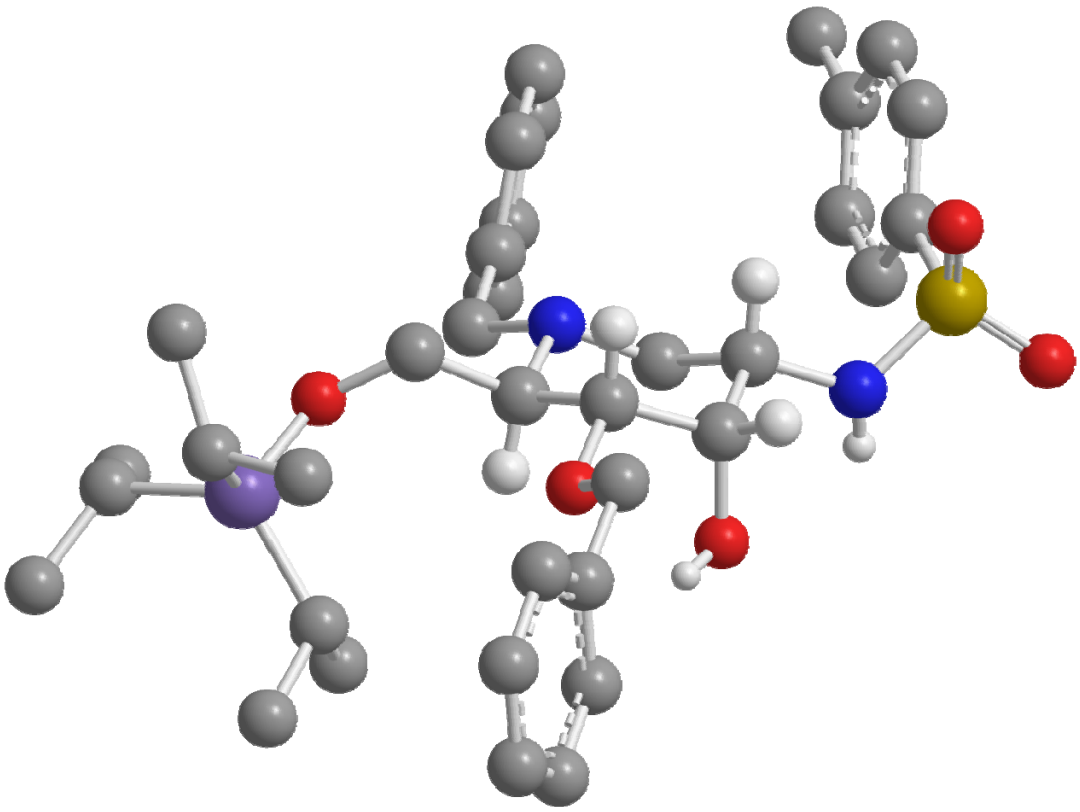
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[10]

X-Ray crystal structure data for **312** [$C_{20}H_{22}N_2O_4S$]: M = 386.47, monoclinic, space group $P2_1/c$, a = 20.4099(4) Å, b = 5.74096(12) Å, c = 16.7887(4) Å, β = 106.159(2)°, V = 1889.46(7) Å^3, Z = 4, μ = 1.767 mm^{-1}, colourless prism, crystal dimensions = 0.03 × 0.04 × 0.12 mm^3. A total of 3915 unique reflections were measured for 5 < θ < 76 and 3902 reflections were used in the refinement. The final parameters were wR_2 = 0.097 and R_1 = 0.043 [I>–3.0σ(I)]. X-Ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[10] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (2*R*,3*R*,4*S*,5*S*)-333

(selected H atoms are omitted for clarity)



X-Ray crystal structure determination for 333

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.[11]

X-Ray crystal structure data for **333** [$C_{36}H_{52}N_2O_5SSi$]: M = 652.97, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 14.6607(2) Å, b = 15.61716(19) Å, c = 31.7110(4) Å, V = 7260.51(16) Å^3, Z = 8, μ = 1.441 mm^{-1}, colourless plate, crystal dimensions = 0.10 × 0.20 × 0.20 mm^3. A total of 15165 unique reflections were measured for $3 < \theta < 77$ and 15107 reflections were used in the refinement. The final parameters were wR_2 = 0.092 and R_1 = 0.037 [I>–3.0σ(I)], with Flack enantiopole = –0.004(9).[12] X-Ray crystal structure determination was performed by Dr J. E. Thomson, Chemistry Research Laboratory, University of Oxford, U.K.

[11] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
[12] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.