Alkaloids from Transannular Iodoaminations

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

by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2009 until October 2012, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

E. Anne Brock
October 2012

Abstract

E. Anne Brock D.Phil. Thesis

St. Catherine's College Michaelmas Term 2012

This thesis is concerned with the development of transannular iodoamination methodology for the synthesis of pyrrolizidine, indolizidine and tropane alkaloids.

Chapter 1 introduces the concept of a 'transannular cyclisation' and outlines the utility of such cyclisations in the synthesis of a range of [x.y.z]-azabicyclic alkaloids.

Chapter 2 describes the development of a three step lithium amide conjugate addition, ring-closing metathesis and transannular iodoamination protocol for the preparation of the pyrrolizidine scaffold ([3.3.0]-azabicycle). Cyclisation of a hexahydroazocine occurs with concomitant *N*-debenzylation to give a single diastereoisomer of the corresponding C(7)-iodopyrrolizidine product, which is then elaborated to the known pyrrolizidine, (−)-7a-*epi*-hyacinthacine A1.

Chapter 3 delineates an extension of the methodology described in Chapter 2, and an investigation into accessing alternate diastereoisomeric pyrrolizidine scaffolds via the transannular iodoamination process. These studies culminate in the synthesis of two pyrrolizidine alkaloids, (−)-hyacinthacine A1 and (−)-hyacinthacine A2.

Chapter 4 details investigations into the further elaboration of the C(7)-iodopyrrolizidine scaffold synthesised in Chapter 2. A nucleophilic displacement reaction with azide leads to the synthesis of novel 7-deoxy-7-aminoalexine analogues, whilst radical-mediated substitution of the iodide by oxygen allows the synthesis and isolation of the pyrrolizidine alkaloid (−)-1-*epi*-alexine.

Chapter 5 outlines the development of the transannular iodoamination reaction to facilitate the synthesis of the tropane architecture ([3.2.1]-azabicycle). A tandem lithium amide conjugate addition and aldol reaction sequence is followed by ring-closing metathesis to give the required aminocycloheptene. Subsequent treatment with iodine results in transannular cyclisation to give a single iodotropane product which, following elaboration culminates in the synthesis of (+)-pseudococaine.

Chapter 6 contains full experimental procedures and characterisation data for all compounds synthesised in Chapters 2, 3, 4 and 5.

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Contents

Abbreviations

The following abbreviations are used throughout this thesis:

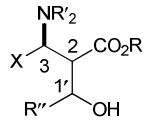
Å	Angstroms
Ac	Acetyl
ACCN	1,1′-Azobis(cyclohexane-1-carbonitrile)
AIBN	2,2′-Azoisobutyronitrile
app	Apparent
aq	Aqueous
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflectance
$[\alpha]_D$	Specific rotation
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
br	Broad
Bu	*n*-Butyl
^{t}Bu	*tert*-Butyl
Bz	Benzoyl
c	Concentration
cat	Catalytic amount
C	Celsius
Cbz	Carboxybenzyl
cm^{-1}	Wavenumber
conc	Concentrated
conv	Conversion
COSY	Correlation spectroscopy
CSA	10-Camphorsulfonic acid
CSI	10-Camphorsulfonylimine
CSO	(10-Camphorsulfonyl)oxaziridine
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Di(*iso*-butyl)aluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dr	Diastereoisomeric ratio
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
δ_H	Proton (^{1}H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
E^+	General electrophile
EDCl	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FI	Field ionisation
Fmoc	Fluorenylmethylcarbonyl
g	Grams
GC	Gas chromatography

GCT	Gas chromatograph/time-of-flight
gem	Geminal
h	Hours
Hal	Halogen
HMBC	Heteronuclear multiple-bond correlation
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple-quantum correlation
HOBt	Hydroxybenzotriazole
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation
Hz	Hertz
i	Ipso
i	Iso
J	Joules
J	Coupling constant
k	Rate constant
KHMDS	Potassium hexamethyldisilazide
lit.	Literature
L	Litres
LDA	Lithium di(*iso*-propyl)amide
LSA	Lithium trimethylsilylamide
m	Meta
m	Metres
m	Milli
m	Multiplet
M	Molar
M	Mega
$[M]^+$	Molecular ion
m-CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
min	Minutes
mol	Moles
mp	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
m/z	Mass to charge ratio
µ	Micro
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
o	Ortho
p	Para
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
ppm	Parts per million
Pr	Propyl
^{i}Pr	*i*-Propyl
py	Pyridine
q	Quartet

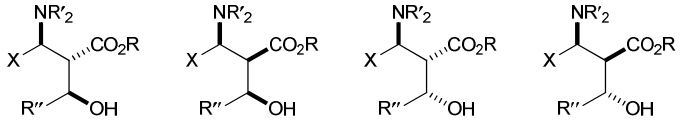
quant	Quantitative
quin	Quintet
R	General alkyl group
Ra-Ni	Raney nickel catalyst
RCM	Ring-closing metathesis
ref.	Reference
R_f	Retention factor
rt	Room temperature
s	Singlet
satd	Saturated
S_N1	Substitution, nucleophilic, unimolecular
S_N2	Substitution, nucleophilic, bimolecular
t	Triplet
t	Time
T	Temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
TEAB	Tetra-ethylammonium bromide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TEOC	Trimethylsilylethyl carbamate
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Triflouroacetic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tr	Trityl
Troc	2,2,2-Trichloroethoxycarbonyl chloride
TPAP	Tetrapropylammonium perruthenate
TPP	Tetraphenylporphyrin
Ts	*p*-Toluenesulfonyl
TSP	Trimethylsilyl propanoic acid
V	Volume
vic	Vicinal
v/v	Volume to volume ratio
ν_{max}	Infra red absorption
w/w	Mass to mass ratio
X	General substituent

Note on Nomenclature

In Chapter 5 of this thesis several enolate aldol reactions of related systems are discussed; these give rise to up to four diastereoisomeric products. In these cases an alternate compound numbering system has been employed to facilitate comparison throughout the chapter. The parent scaffold of each aldol product is given a distinct number (e.g., **999**), and the four possible stereochemical permutations are then assigned a letter (**A**-**D**) according to the stereochemistry at C(2) and C(1′) relative to C(3) within that particular diastereoisomer, as depicted below:



parent scaffold - **999**



999A **999B** **999C** **999D**

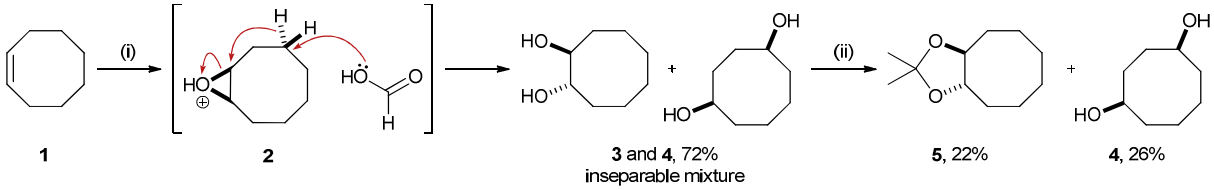
The parent aldol product scaffold **999**, with its four stereochemical permutations **A**, **B**, **C**, and **D**.

Subsequent derivatives of these aldol products are numbered in an analogous manner, with the parent scaffold being given a unique number to indicate the molecular structure, and each diastereoisomer a letter to indicate the relative stereochemistry.

Transannular Cyclisations in the Synthesis of Alkaloids

1.1 Transannular reactions

The phrase "*a transannulation effect*" was coined by Cope in 1952.[1,2] Whilst investigating the dihydroxylation of cyclooctene **1** with performic acid, he observed the formation of 1,4-cyclooctanediol **4** (isolated in 26% yield) which was consistently produced in greater amounts than the expected *trans*-1,2-cyclooctanediol **3**. The formation of **4** was proposed to be the result of a molecular rearrangement of cyclooctene oxide **2** on solvolysis involving a "*1,3-hydride shift in the protonated epoxide, presumably occurring simultaneously with the attack by the solvent at the positively charged carbon in the 4-position.*" Cope suggested that this rearrangement was made possible by the preferred conformation of an 8-membered ring which holds atoms on either side of the ring in close proximity, and it is this conformational effect which gave the name 'transannular reaction' to these transformations (Scheme 1).[1]



Scheme 1 *Reagents and conditions:* (i) 35% H_2O_2, 87% HCO_2H; (ii) $CuSO_4$, acetone, rt, 22 h.

1.2 Transannular cyclisations

Following this study, Prelog investigated the dihydroxylation of cyclodecene **6** and subsequently reported a similar "*chemical transannular effect*".[3] Treatment of *trans*-cyclodecene **6** with performic acid resulted in a number of products being formed, including an unexpected bicyclic product **7**, which was isolated in 10% yield (Fig. 1).[3]

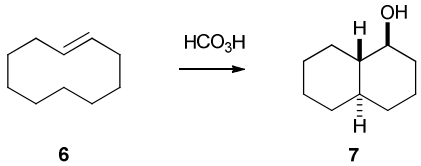


Figure 1 The formation of **7** on treatment of **6** with performic acid.

Transannular cyclisations have therefore been defined as "*those reactions which lead to the formation of a covalent bond between atoms on opposite sides of a ring compound*".[4] The propensity of compounds to undergo such reactions is facilitated by a conformational restriction which brings the two sides of the ring system together, and hence they are most commonly a feature of medium sized (7-10 membered) rings.[5]

1.3 Transannular cyclisations in synthesis

Transannular cyclisations are an extremely valuable tool in the synthesis of polycyclic molecules since they allow the rapid construction of relatively complex systems often with good levels of regio- and stereocontrol. Such processes involving cycloadditions,[6] conjugate additions,[7] radical cascades[8] and aldol reactions[9] have all been applied in the synthesis of carbocyclic natural products. However, these cyclisations are also a common method for the creation of heterocycles through transannular nucleophilic attack of an endo- or exocyclic nitrogen, oxygen[10,11] or sulfur atom.[12,13] In these cases, the cyclisation can be induced in a number of ways,[14] but arguably the most common methods are via a radical-mediated process, via activation of a remote olefin or via an intramolecular displacement reaction.

1.4 Transannular cyclisations in alkaloid synthesis

Transannular cyclisations which involve the attack of a nitrogen atom onto an activated double bond or leaving group have been used in the synthesis of complex alkaloids. They can be broadly classified into two groups of reactions: those in which the nitrogen is contained *within* the ring scaffold (endocyclic nitrogen) or those in which the nitrogen is attached *directly* to the ring (exocyclic nitrogen) (Fig. 2).

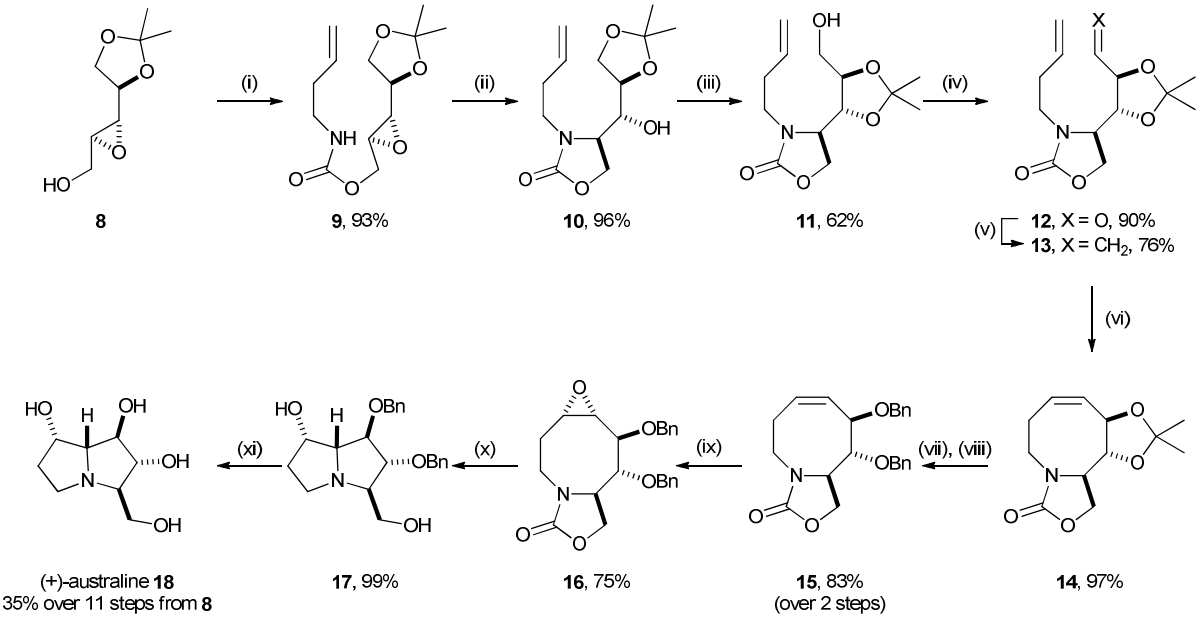
Figure 2 Generic precursors for transannular cyclisation to azabicycles.

1.5 Endocyclic transannular cyclisations

1.5.1 Via epoxide formation

The formation of bicycles by transannular attack of an endocyclic nitrogen atom is found solely in ring systems which are 8-membered or larger, and are generally initiated via double bond activation. One commonly employed method of activation is by the initial formation (and isolation) of an epoxide.[15] The use of this approach was demonstrated by White *et al*. in their asymmetric synthesis of (+)-australine **18**, a tetrahydroxypyrrolizidine alkaloid isolated from the *Castanospermum australe* tree.[16,17] The desired cyclooctene **15**, required for epoxide formation, was synthesised in eight steps from alcohol **8**.[18] Initial reaction of **8** with 4-butenyl isocyanate in the presence of $^{i}Pr_2NEt$ gave **9** in 93% yield; subsequent treatment of **9** with KO^{t}Bu resulted in the cyclisation of the nitrogen atom onto the epoxide to give oxazolidinone

10 in 96% yield. Acetonide migration promoted by Amberlyst-15 resin allowed for oxidation of the resultant primary alcohol **11** to give aldehyde **12**, which was then reacted with methylenetriphenylphosphorane to give **13** in 42% yield over the three steps from **10**. The two terminal olefins within **13** allowed for a ring-closing metathesis reaction with Grubbs I catalyst, which furnished the desired azacycle **14** in 97% yield. Acid-catalysed acetonide deprotection of **14** using HBr and subsequent *O*-benzyl protection gave **15** in 83% yield, and was followed by treatment of **15** with *m*-CPBA in CH_2Cl_2 to give epoxide **16** in 75% yield as a single diastereoisomer. Hydrolysis of the oxazolidinone within **16** with LiOH in EtOH/H_2O was accompanied by transannular attack of the nitrogen onto the epoxide, resulting in the formation of the pyrrolizidine scaffold **17**. Removal of the *O*-benzyl protecting groups from **17** by hydrogenolysis in the presence of $Pd(OH)_2/C$ furnished (+)-australine **18** in 35% overall yield for the eleven step procedure (Scheme 2).[16]

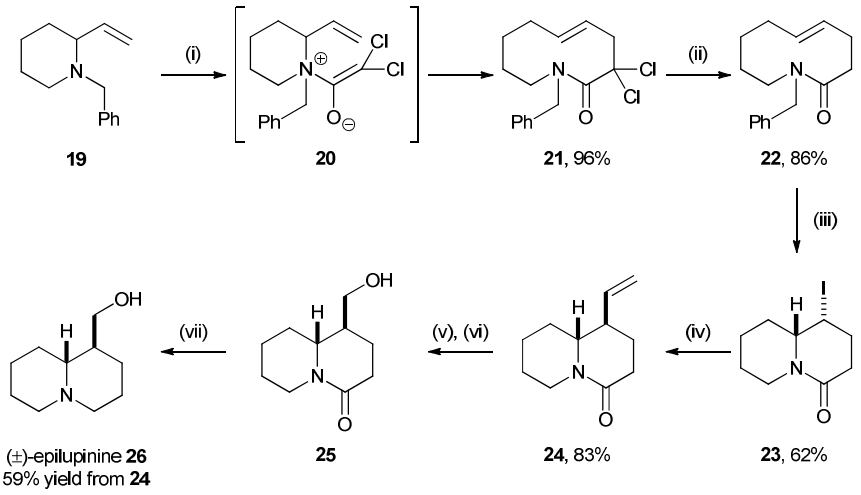


Scheme 2 *Reagents and conditions:* (i) $CH_2{=}CH(CH_2)_2NCO$, $^iPr_2NEt$, C_6H_6, reflux; (ii) KO^{t}Bu, THF, 0 °C; (iii) Amberlyst-15, acetone, rt; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (v) $[Ph_3PMe]^+[Br]^-$, KHMDS, THF, −78 °C to rt; (vi) Grubbs I catalyst, CH_2Cl_2, rt; (vii) HBr, MeCN, rt; (viii) NaH, BnBr, TBAI, THF, 60 °C; (ix) *m*-CPBA, CH_2Cl_2, rt; (x) LiOH, EtOH/H_2O (v/v 1:1), 95 °C; (xi) H_2, 20% $Pd(OH)_2/C$, MeOH, rt.

1.5.2 Via activation with molecular halogen

When molecular halogens such as Br_2 and I_2, are used to activate the double bond to nucleophilic attack, the mechanism either proceeds via direct trapping of a halonium ion[19] by nitrogen or via the dihalide compound which can undergo a subsequent intramolecular S_N2-type displacement.[20] Interestingly, Edstrom has reported the use of I_2 in the transannular cyclisation of a 10-membered azacycle to construct a quinolizidine scaffold, in which he observed the cyclisations occurring with complete regio- and stereocontrol.[21,22] In his reported

synthesis of (±)-epilupinine **26**, macrolactam **22** was synthesised from vinylpiperidine **19** via *N*-acylation with 2,2,2-trichloroacetyl chloride and subsequent aza-Claisen rearrangement of zwitterion **20**, which gave the *gem*-dichloromacrolactam **21** in 96% yield.[22] Reductive dechlorination of **21** gave **22**, which was treated with 2.0 equiv I_2 to induce transannular cyclisation, and the resultant product **23** was isolated in 62% yield. Cu-catalysed substitution of the iodide within **23** using vinyl magnesium bromide occurred with inversion of configuration to give **24** in 83% yield. Ozonolysis of the terminal olefin within **24** and immediate reduction of the resultant aldehyde gave alcohol **25**. Finally, treatment of **25** with AlH_3 completed the synthesis of (±)-epilupinine **26** which was isolated in 59% yield from **24** (Scheme 3).[21]

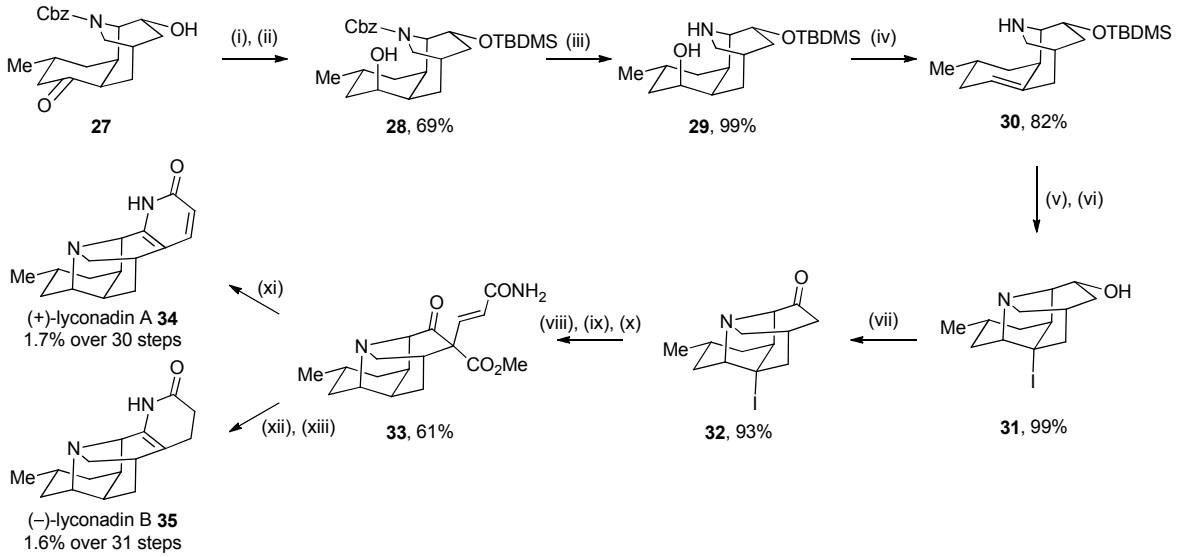


Scheme 3 *Reagents and conditions:* (i) Cl_3CCOCl, Zn-Cu, THF, rt to 62 °C; (ii) Zn-Ag, MeOH/AcOH (v/v 5:1), rt, 18 h; (iii) I_2, MeCN, rt, 2 h; (iv) $CH_2CHMgBr$, CuI (cat.), THF, −35 °C; (v) O_3, MeOH, CH_2Cl_2, −78 °C; (vi) $NaBH_4$, MeOH; (vii) AlH_3, THF, rt.

1.5.3 Via activation using *N*-halo-succinimide

NIS and NBS have both been used as an electrophilic source of a halogen to promote transannular cyclisation.[23] Smith *et al.* used an NIS-promoted transannular reaction to complete the formation of the tetracyclic core of (+)-lyconadin A **34** and (–)-lyconadin B **35**. Intermediate **27** was synthesised in nineteen steps and 9% overall yield from commercially available starting materials. Conversion of **27** into olefin **30** was achieved in four steps, beginning with *O*-TBDMS protection of the free hydroxyl group, followed by reduction of the ketone with L-selectride® and subsequent removal of the *N*-Cbz group to give amino alcohol **29** in 69% yield from **27**. Dehydration of **29** to give olefin **30** was achieved using the Martin sulfurane,[24] and **30** was isolated in 82% yield. Transannular cyclisation was accomplished on treatment of **30** with NIS which, after removal of the *O*-TBDMS group, gave the tetracyclic

core **31** in 92% yield. Dess-Martin oxidation of **31** to ketone **32** was followed by reaction with methyl cyanoformate, reduction of the iodide and conjugate addition to propiolamide to give **33** in 56% overall yield. Heating **33** in MeCN in the presence of Me_4NOAc gave (+)-lyconadin A **34** in 71% yield, 1.7% over the total thirty step synthesis. Meanwhile, reduction of **33** under hydrogenation conditions and subsequent reaction with LiCl in HMPA at 125 °C for 17.5 h gave (–)-lyconadin B **35** in 68% yield, 1.6% yield over thirty-one steps (Scheme 4).[25]

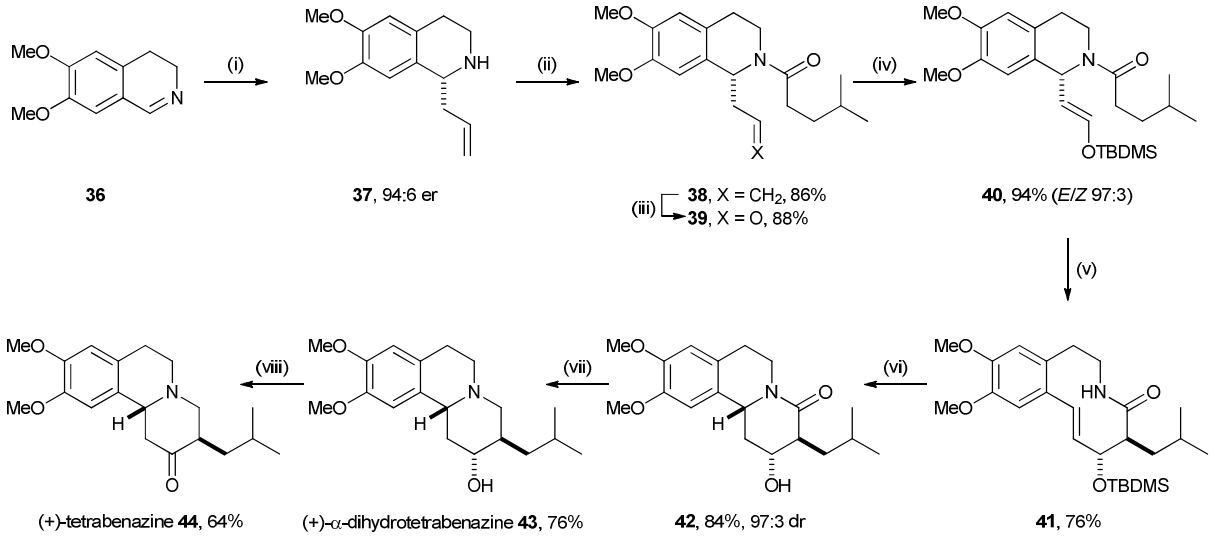


Scheme 4 *Reagents and conditions:* (i) TBDMSOTf, DTBMP, CH_2Cl_2, −78 °C, 1 h; (ii) L-selectride®, CH_2Cl_2, −78 °C to rt, 2 h; (iii) H_2, Pd/C, EtOH, 90 min; (iv) Martin sulfurane, CH_2Cl_2, 0 °C, 20 min; (v) NIS, CH_2Cl_2, rt, 20 min; (vi) HCl, MeOH/H_2O, rt, 18 h; (vii) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 1 h; (viii) LDA, MeOCOCN, HMPA, THF, −78 °C, 1 h; (ix) $PdCl_2$, Et_3SiH, 2,6-lutidine, rt, 2 h; (x) HC≡CCONH$_2$, Cs_2CO_3, DMSO, rt, 24 h; (xi) Me_4NOAc, MeCN, 135 °C, 16 h; (xii) H_2, Pd/C, MeOH, rt, 3 h; (xiii) LiCl, HMPA, 125 °C, 17 h.

1.5.4 Via acid catalysis

The alkaloid (±)-tetrabenazine **44** and its metabolite (±)-α-dihydrotetrabenazine **43** have been identified as highly effective treatments for the debilitating motor symptoms in patients affected by Huntington's chorea. Suh *et al.* reported a total asymmetric synthesis of (+)-tetrabenazine **44** and (+)-α-dihydrotetrabenazine **43** which employed an acid catalysed transannular cyclisation[26] to construct the benzoisoquinolizidine scaffold contained within these alkaloids.[27,28] Macrolactam **41**, required for the transannular reaction, was synthesised in five steps from the commercially available 6,7-dimethoxy-3,4-dihydroisoquinoline **36**. Asymmetric allylation of **36** was achieved under conditions reported by Nakamura,[29] and was followed by coupling of the resultant amine **37** with 4-methylvaleric acid to give **38** in 86% yield over the two steps. Dihydroxylation of the terminal olefin moiety and oxidative cleavage of the diol with $NaIO_4$ gave aldehyde **39** which, when treated with DBU in the

presence of TBDMSCl, gave silyl enol ether **40** in 83% yield (from **38**) as a 97:3 mixture of (*E*)- and (*Z*)-isomers. Aza-Claisen rearrangement of the Mg-enolate derived from **40** gave the desired macrolactam **41** in 76% isolated yield as a single diastereoisomer. When **41** was treated with TsOH at rt for 24 h cyclisation occurred with simultaneous *O*-TBDMS cleavage to give the tricyclic system **42** in 97:3 dr and in 84% yield. Reduction of the carbonyl group within **42** was achieved on treatment with $LiAlH_4$ to give (+)-α-dihydrotetrabenazine **43** in 76% yield. Subsequent oxidation of **43** with TPAP in the presence of NMO gave (+)-tetrabenazine **44** in 64% yield (Scheme 5).[27]

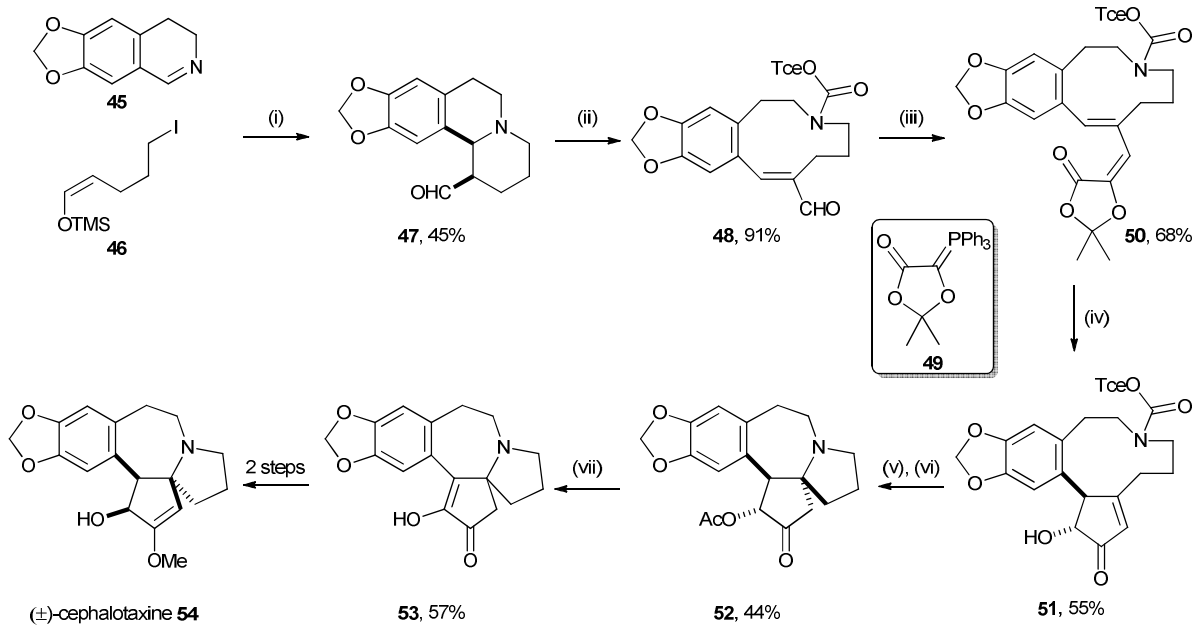


Scheme 5 *Reagents and conditions:* (i) bis(4-isopropyl-4,5-dihydrooxazol-2-yl)methane, 2,2-dipyridyl, BuLi, CH_2CHCH_2ZnBr, THF, −70 °C, 3 h; (ii) 4-methylvaleric acid, EDCl, HOBt, CH_2Cl_2, 0 °C to rt, 12 h; (iii) OsO_4, NMO, acetone/H_2O (v/v 1:1), rt, 12 h then $NaIO_4$, 30 min; (iv) TBDMSCl, DBU, CH_2Cl_2, 40 °C, 5 h; (v) $^{i}PrMgCl$, C_6H_6, 80 °C, 5 h; (vi) TsOH, C_6H_6, rt, 24 h; (vii) $LiAlH_4$, THF, 70 °C, 2 h; (viii) TPAP, NMO, CH_2Cl_2, 0 °C to rt, 2 h.

1.5.5 Via intramolecular conjugate addition

The conjugate addition of an amine, amide or carbamate in a transannular fashion has also been reported.[30] This method of cyclisation was demonstrated by Li *et al.* in their work into the total synthesis of (±)-cephalotaxine **54**, the parent compound of the *Cephalotaxus* alkaloids.[31] Reaction of **45** and **46** gave aldehyde **47** in 45% yield, which then underwent ring-expansion on treatment with TrocCl and $KHCO_3$ to give macrocycle **48** in 91% yield. The presence of the aldehyde component within **48** permitted the installation of the desired dioxolane side chain via Wittig reaction of **48** with 2,2-dimethyl-5-(triphenylphosphoranylidene)-1,3-dioxolan-4-one **49**. Subsequent oxy-Nazarov cyclisation of **50** in the presence of DIBAL-H gave **51** in 55% yield, furnishing the required transannulation precursor. Acetate protection of the free hydroxyl group within **51** was followed by

deprotection of the carbamate; this deprotection was accompanied by the desired transannular cyclisation (via conjugate addition) to give tetracycle **52** in 44% yield over the two steps. Oxidation of **52** gave **53** in 57% yield,[31] and (±)-cephalotaxine **54** has previously been prepared from **53** in two further steps (Scheme 6).[32]

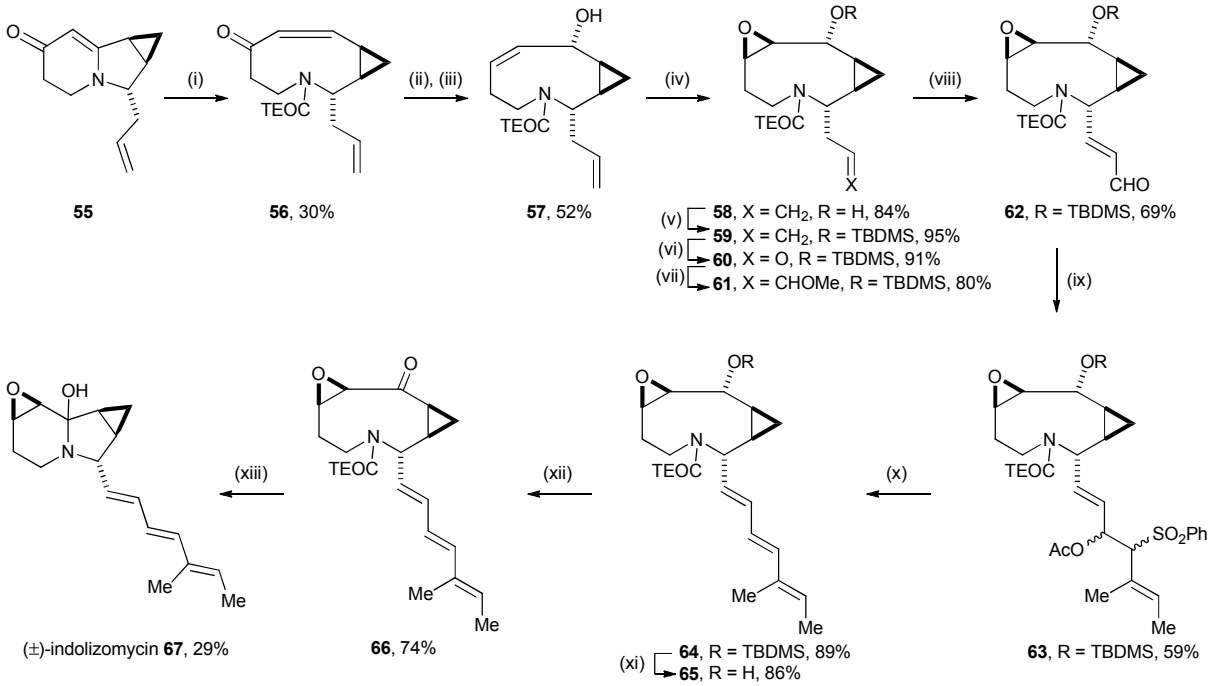


Scheme 6 *Reagents and conditions:* (i) DMF, rt, 24 h; (ii) TrocCl, $KHCO_3$, $CHCl_3$, rt, 48 h; (iii) **49**, PhMe, reflux, 4 h; (iv) DIBAL-H, PhMe, −78 °C, 1 h; (v) Ac_2O, py, rt, 12 h; (vi) Zn, NaH_2PO_4, THF/H_2O (v/v 3:2), rt, 12 h; (vii) KO^{t}Bu, ^{t}BuOH, $P(OEt)_3$, air, 40 °C, 1 h.

1.5.6 Via hemiaminal formation

Bicyclic alkaloids that contain hemiaminal functionality can be accessed via the transannular cyclisation of a macro-azacycle onto a ketone.[33] Danishefsky *et al.* used this approach in their synthesis of the highly unstable bioengineered antibiotic (±)-indolizomycin **67**.[34,35] Treatment of **55**[36] with Me_3OBF_4 resulted in *O*-methylation of the vinylogous lactam, and the resultant iminium was then reduced on addition of $NaBH_4$. Further treatment of this compound with 2-(trimethylsilyl)ethyl chloroformate resulted in *N*-alkoxycarbonylation and subsequent fragmentation to give azonine **56** in 30% yield from **55**. Epoxidation of **56** on treatment with alkaline H_2O_2 was followed by Wharton fragmentation[37] using NH_2NH_2 to give allylic alcohol **57** in 52% yield. Diastereoselective epoxidation of **57** with *m*-CPBA gave *anti*-epoxide **58** as a single product in 84% yield. Subsequent *O*-TBDMS protection of the remaining hydroxyl group, ozonolysis of the terminal alkene and reaction of the resultant aldehyde with (methoxymethylene)triphenylphosphorane gave a 60:40 mixture of enol ethers **61** in 69% yield over the three steps. Photooxygenation of **61** was followed by immediate reduction of the hydroperoxide intermediate with Ph_3P to give **62** in 69% yield. This allowed

for reaction with the lithium anion of (*E*)-2-methyl-2-butenyl phenyl sulfone and acetylation of the resultant compound gave a diastereoisomeric mixture of acetoxy sulfones **63** in 59% yield. Reduction of this mixture with sodium amalgam resulted in the formation of the desired (*E*,*E*,*E*)-triene side chain (i.e., overall Julia-type olefination), and was followed by *O*-desilylation with 1.0 M HIO_4 to give **65** in 77% yield over the two steps. Oxidation of the free hydroxyl group within **65** with TPAP gave ketone **66** in 74% yield. The transannular cyclisation of **66** was then promoted on *N*-deprotection with TBAF, which gave (±)-indolizomycin **67** in 29% yield (Scheme 7).[35]



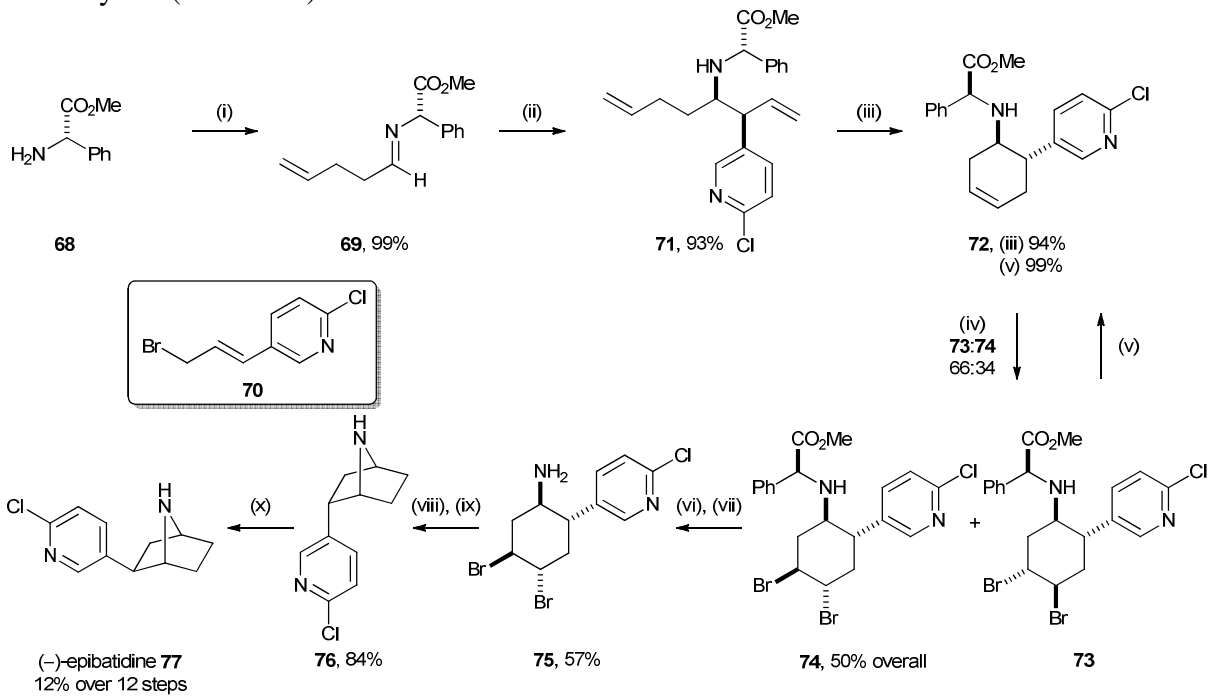
Scheme 7 *Reagents and conditions:* (i) Me_3OBF_4, CH_2Cl_2, 0 °C, 1 h then $NaBH_4$, MeOH, 0 °C to rt, 40 min then $TMS(CH_2)_2OCOCl$, PhH, rt, 4 h; (ii) H_2O_2 (30% wt in H_2O), MeOH, NaOH (3.0 M aq), 0 °C to rt, 5 h; (iii) NH_2NH_2, AcOH, MeOH, rt, 45 min; (iv) *m*-CPBA, CH_2Cl_2, 0 °C, 24 h; (v) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C, 5 min; (vi) O_3, $NaHCO_3$, CH_2Cl_2/MeOH (v/v 1:1), −78 °C then DMS, −78 °C to rt, 19 h; (vii) $[MeOCHPPh_3]^+[Cl]^-$, NaHMDS, THF, 0 °C to rt, 20 min; (viii) TPP, O_2, py, C_6H_6, hν, rt, 8 h then Ph_3P, rt, 1 h; (ix) (*E*)-2-methyl-2-butenyl phenyl sulfone, BuLi, THF, −78 °C, 25 min then Ac_2O, rt, 75 min; (x) 5% sodium amalgam, THF/MeOH (v/v 3:1), −20 °C, 8 h; (xi) HIO_4 (1.0 M aq), THF, rt, 8 h; (xii) TPAP, CH_2Cl_2, rt, 10 min; (xiv) TBAF (1.0 M in THF), THF, 0 °C, 1.5 h.

1.6 Exocyclic transannular cyclisations

1.6.1 In the synthesis of a 7-azabicyclo[2.2.1]heptane ring

The amphibian alkaloid epibatidine **77**[38] is the only example of a naturally occurring 7-azabicyclo[2.2.1]heptane ring,[39,40] and since it has potent analgesic effects it has been a target of many syntheses. To date, a number of these reported syntheses have relied on the cyclisation of an amine, amide or carbamate through intramolecular displacement of a suitable leaving group.[41] Loh *et al.* developed a synthetic strategy which allowed for the gram-scale production of (−)-epibatidine **77**:[42] the synthesis of the amine required for the cyclisation step

was achieved in nine steps from (*S*)-phenylglycine methyl ester **68**. Initial condensation of **68** with 4-pentenal gave **69** in 99% yield, which underwent immediate reaction with **70** (synthesised in four steps from methyl 6-chloronicotinate) in the presence of Zn metal to give **71** in 93% yield as a single diastereoisomer. Ring-closing metathesis of **71** with Grubbs II catalyst gave tetrahydropyridine **72** in 94% yield. Reaction of **72** with Br_2 and TEAB gave a 66:34 mixture of two diastereoisomeric dibromides **73** and **74**, respectively, in 92% yield. Treatment of the major diastereoisomer **73** with Zn in AcOH returned the precursor **72** in quantitative yield, which could then be recycled to give the desired minor diastereoisomer **74** in 50% overall yield. *N*-Deprotection furnished amine **75** in 57% yield. The cyclisation of **75** was achieved by refluxing in MeCN for 48 h, and resulted in the isolation of **76** in 84% yield following removal of the bromide using Bu_3SnH and ACCN. The conditions for effecting the intramolecular cyclisation in such systems are harsh, presumably due to the absence of any favourable conformational effects in a cyclohexane ring. Finally, epimerisation of the chloronicotinyl substituent on treatment of **76** with KO^{t}Bu in ^{t}BuOH gave (–)-epibatidine **77** in 12% overall yield (Scheme 8).[42]

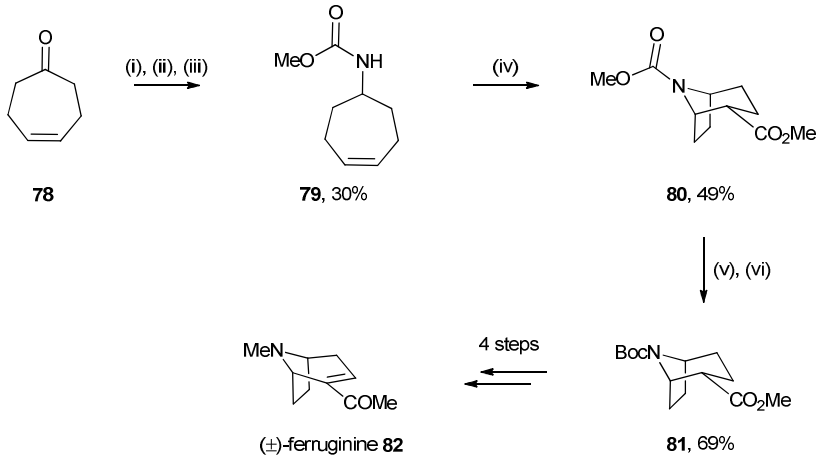


Scheme 8 *Reagents and conditions:* (i) 4-pentenal, Na_2SO_4, CH_2Cl_2, 0 °C, 5 h; (ii) **70** (0.5 M in THF), Zn, THF, 0 °C, 3 h; (iii) Grubbs II catalyst, CH_2Cl_2, 25 °C; (iv) TEAB, CH_2Cl_2, −78 °C, 45 min then Br_2, CH_2Cl_2, −78 °C, 2 h; (v) Zn, AcOH, 25 °C, 4 h; (vi) DIBAL-H, CH_2Cl_2, 0 °C, 30 min; (vii) $Pb(OAc)_4$, CH_2Cl_2/MeOH (v/v 2:1), 0 °C, 20 min; (viii) MeCN, 82 °C, 48 h; (ix) Bu_3SnH, ACCN, C_6H_6, 80 °C, 1.5 h; (x) KO^{t}Bu, ^{t}BuOH, 83 °C, 5 days.

1.6.2 In the synthesis of an 8-azabicyclo-[3.2.1]-octane ring

The cyclisation of a cyclohept-4-ene-1-amine derivative has been exploited to form the 8-azabicyclo-[3.2.1]-octane system that is characteristic of the tropane alkaloids.[43,44] These

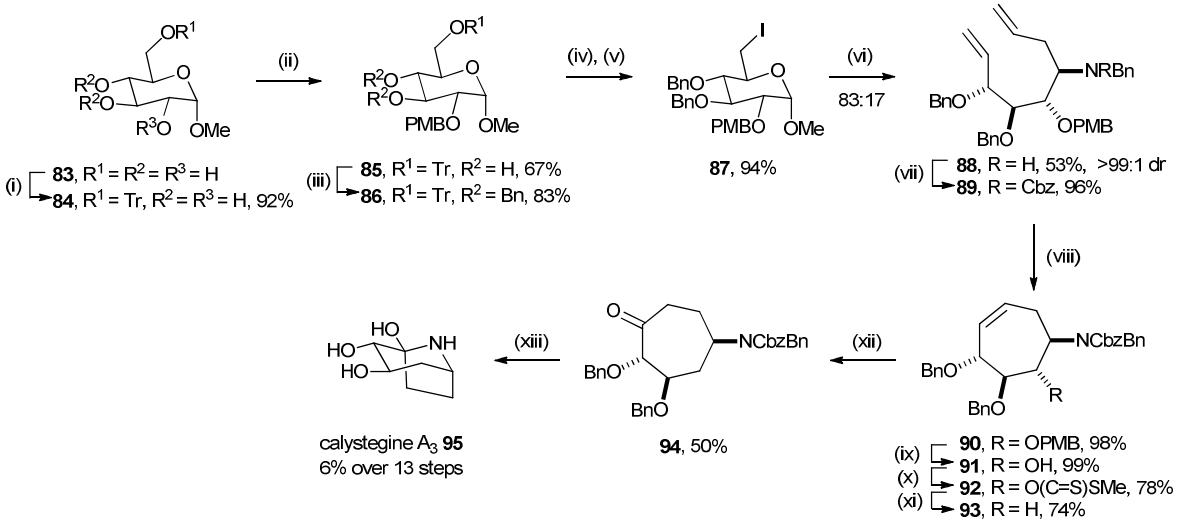
cyclisations occur far more readily than the analogous reactions in the smaller cyclohexene rings due to their ability to adopt a conformation where cyclisation is favoured. For example, a formal synthesis of the tropane alkaloid ferruginine **82** was reported by Ham *et al.*, which made use of an intramolecular aminocarbonylation reaction to promote the transannular cyclisation.[45,46] The reaction of 4-cycloheptenone **78** with hydroxylamine and reduction of the resultant oxime with $LiAlH_4$ was followed by carbamate formation on reaction with methyl chloroformate to give **79** in 30% yield over the three steps. Treatment of **79** with $PdCl_2$ in the presence of $CuCl_2$ and CO gave the desired bicycle **80** in 49% yield,[45] and subsequent *N*-deprotection of **80** with 30% HBr-HOAc, followed by *N*-protection with Boc_2O gave **81** in 69% yield. (±)-Ferruginine **82** was synthesised in a further four steps from **81** (Scheme 9).[47]



Scheme 9 *Reagents and conditions:* (i) $NH_2OH{\cdot}HCl$, Na_2CO_3, MeOH, reflux; (ii) $LiAlH_4$, THF, reflux; (iii) methyl chloroformate, CH_2Cl_2, 0 °C; (iv) $PdCl_2$, $CuCl_2$, CO, MeOH, rt; (v) 30% HBr-HOAc, rt; (vi) Boc_2O, dioxane, rt.

Transannular reactions are an important tool in the total synthesis of the polyhydroxylated nortropane alkaloids such as the calystegines. There are many syntheses of the different members of this family of compounds but, due to their characteristic hemiaminal group, most rely on the reductive amination of an exocyclic nitrogen atom in a transannular process to construct the bicyclic scaffold.[48] A characteristic example of such a synthesis was reported by Madsen *et al.* in the total synthesis of calystegine A_3 **95**.[49] Selective *O*-protection of methyl α-D-glucopyranoside **83** was carried out to install a trityl ether at C(6), an *O*-PMB group at C(2) and an *O*-benzyl group on the two remaining C(3)- and C(4)-hydroxyl groups, which gave **86** in 51% yield over three steps. Deprotection of the C(6)-trityl ether was followed by treatment of the resultant primary alcohol under Appel conditions to give iodide **87** in 94% yield. Reaction of **87** with Zn, $BnNH_2$ and allyl bromide resulted in a tandem ring-opening/imine formation/allylation reaction to give **88** in 90% yield and 83:17 dr.

Chromatographic purification of this diastereoisomeric mixture gave **88** in 53% yield as a single diastereoisomer. Subsequent *N*-Cbz-protection of **88** gave **89** in 96% yield and was followed by treatment with Grubbs II catalyst to effect ring-closing metathesis, which gave **90** in 98% yield. Overall deoxygenation of **90** was achieved via conversion to xanthate ester **92** followed by treatment with Bu_3SnH and AIBN to give **93** in 57% yield over three steps. Hydroboration of **93** and immediate oxidation of the resulting mixture of isomeric alcohols gave a 67:33 mixture of regioisomeric ketones, from which the major regioisomer **94** was isolated in 50% yield. Hydrogenolysis of **94** resulted in *O*- and *N*-deprotection and simultaneous transannular cyclisation to give calystegine A_3 **95** in 6% yield over thirteen steps from **83** (Scheme 10).[49]

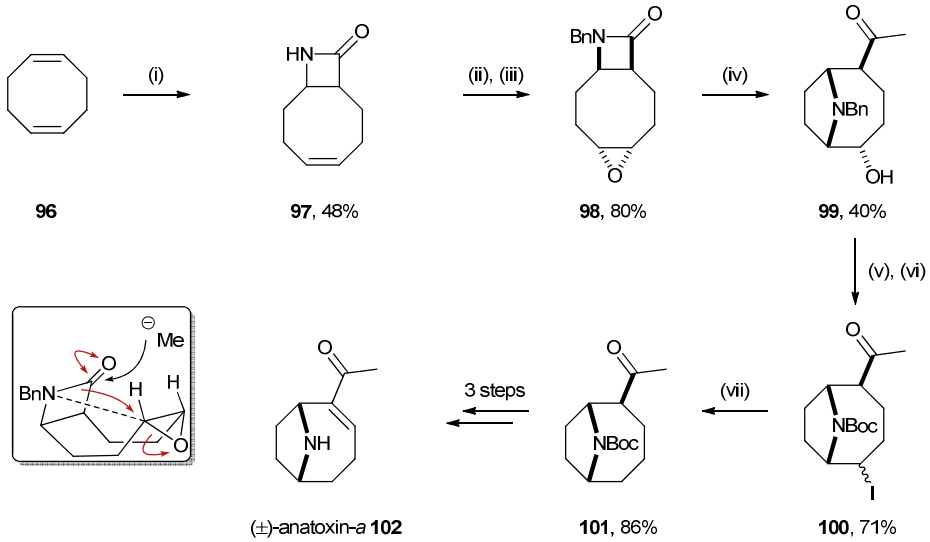


Scheme 10 *Reagents and conditions:* (i) TrCl, py, 90 °C, 3 h; (ii) PMBCl, Bu_2SnO, TBAI, MeCN, 4 Å MS, 82 °C, 16 h; (iii) BnBr, NaH, TBAI, DMF, rt, 12 h; (iv) H_2SO_4, MeOH, rt, 3 h; (v) I_2, PPh_3, imidazole, THF, 67 °C; (vi) Zn, TMSCl, THF, 40 °C, sonication then $BnNH_2$, then CH_2CHCH_2Br, 40 °C, sonication; (vii) CbzCl, $KHCO_3$, H_2O, CH_2Cl_2, 0 °C to rt, 2 h; (viii) Grubbs II catalyst, CH_2Cl_2, rt, 48 h; (ix) DDQ, H_2O, CH_2Cl_2, rt, 2.5 h; (x) imidazole, NaH, CS_2, THF, rt, 3 h then MeI, rt, 12 h; (xi) Bu_3SnH, AIBN, PhMe, 110 °C, 1 h; (xii) BH_3·THF, THF, −40 °C, 3 h then H_2O_2, NaOH, H_2O, rt, 1 h then Dess-Martin periodinane, CH_2Cl_2, rt, 1 h; (xiii) $Pd(OH)_2$/C, H_2, H_2O, dioxane, rt, 15 h.

1.6.3 In the synthesis of a 9-azabicyclo-[4.2.1]-nonane ring

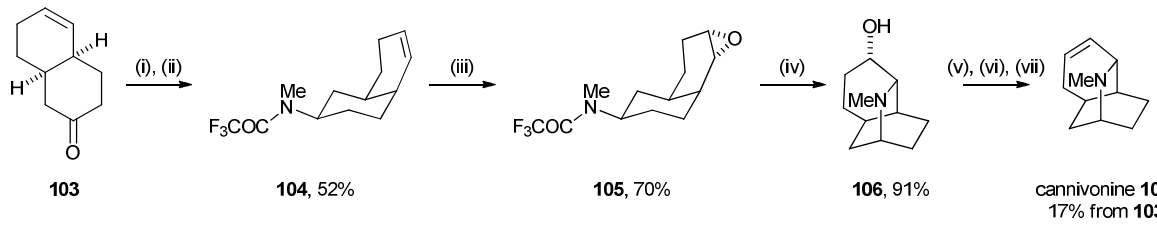
Transannular cyclisation onto an epoxide to form a 9-azabicyclo-[4.2.1]-nonane scaffold[50] has been used by Parsons *et al.* in a formal synthesis of (±)-anatoxin-*a* **102** in ten steps from 1,5-cyclooctadiene **96**.[51,52] Reaction of **96** with chlorosulfonyl isocyanate in the presence of Na_2CO_3 gave β-lactam **97** in 48% yield. *N*-Benzyl protection of **97** followed by epoxidation with *m*-CPBA gave **98** in 80% yield over the two steps. Treatment of **98** with MeLi induced rupture of the 4-membered ring and concomitant cyclisation to form the desired [4.2.1]-azabicycle **99** in 40% yield. Following a tandem *N*-deprotection/*N*-Boc protection, the alcohol could be readily converted to an iodide under Appel conditions, to give iodide **100** in

71% yield over the two steps. Removal of the iodide using Bu_3SnH and AIBN and gave **101** in 86% yield, completing a formal synthesis of (±)-anatoxin-*a* **102** (Scheme 11).[51]



Scheme 11 *Reagents and conditions:* (i) $ClSO_2NCO$, Na_2CO_3, CH_2Cl_2, 0 °C; (ii) BnBr, Bu_4NHSO_4, NaOH (50% aq)/CH_2Cl_2 (v/v 1:1); (iii) *m*-CPBA, CH_2Cl_2, rt, 24 h; (iv) MeLi (1.4 M in Et_2O), THF, −25 °C, 1 h; (v) H_2, 10% Pd/C, MeOH, Boc_2O; (vi) Ph_3P, I_2, imidazole, CH_2Cl_2, rt, 1 h; (vii) Bu_3SnH, AIBN, PhMe, reflux, 30 min.

An epoxide was similarly employed by Kozikowski and Schmiesing in their synthesis of cannivonine **107**,[53] although here the transannular cyclisation took place across the length of a *cis*-decalin system.[54,55] The starting hexahydronapthalenone **103**[56] was treated under reductive amination conditions with $MeNH_2$ and $NaBH_3CN$ which, after subsequent treatment with TFAA, gave triflouroacetate **104** as a 60:40 mixture of diastereoisomers, from which the major diastereoisomer **104** was isolated in 52% overall yield. Epoxidation of **104** was achieved using 2.0 equiv *m*-CPBA and gave a 70:30 mixture of diastereoisomeric epoxides, from which the major diastereoisomer **105** was isolated in 70% yield. Treatment of **105** with K_2CO_3 in MeOH at rt effected *N*-deprotection and resulted in transannular cyclisation of the nitrogen atom onto the epoxide, giving **106** in 91% yield. Finally, the dehydration of **106** was accomplished in three steps (Jones oxidation and the Shapiro procedure),[57] to give cannivonine **107** in 17% yield from **103** (Scheme 12).[53]



Scheme 12 *Reagents and conditions:* (i) $MeNH_2$·HCl, $NaBH_3CN$, MeOH, rt, 24 h; (ii) TFAA, Na_2CO_3, Et_2O/THF (v/v 4:1), rt, 30 min; (iii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 15 h; (iv) K_2CO_3, MeOH, H_2O, rt, 12 h; (v) Jones reagent, acetone, 0 °C to rt, 1 h; (vi) $TsNHNH_2$, TsOH, MeOH, rt, 36 h; (vii) BuLi, THF, −78 °C to rt, 1.5 h.

1.7 Project aims

This project aimed to investigate the use of transannular iodoamination methodology in the synthesis of polyhydroxylated alkaloids. It was proposed that a lithium amide conjugate addition/ring-closing metathesis protocol could be used to access a variety of hexahydroazocine and hexahydroazonine rings, such as **110**, which could then be treated with an electrophile to promote transannular cyclisation to form a polysubstituted bicyclic scaffold. Once this methodology had been developed it was envisaged it could be further elaborated to allow the synthesis of a range of polyhydroxylated pyrrolizidine and indolizidine alkaloid natural products. Furthermore, it was also envisaged that analogous methodology could be applied in an investigation into the transannular cyclisation of an exocyclic nitrogen atom in 7-membered ring systems to form polysubstituted tropanes. The aminocycloheptene **114** required for this study could be accessed via a lithium amide conjugate addition with *in situ* allylation or aldol reaction with acrolein followed by ring-closing metathesis (Fig. 3).

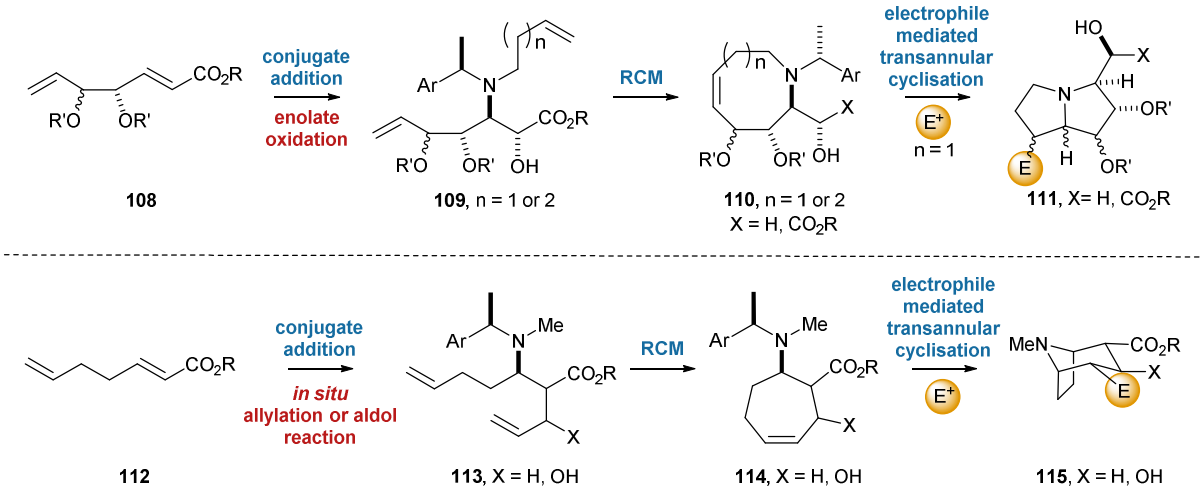


Figure 3 Proposed lithium amide conjugate addition/ring-closing metathesis/transannular cyclisation route through to the pyrrolizidine **111** and tropane **115** scaffolds.

1.8 References and notes

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Transannular Iodoamination in the Asymmetric Synthesis of (–)-7a-*epi*-Hyacinthacine A1

This chapter describes investigations into the iodine-promoted transannular cyclisation of substituted hexahydroazocines **116** and hexahydroazonines **118** in the synthesis of pyrrolizidine **117** and indolizidine **119** scaffolds (Fig. 4).

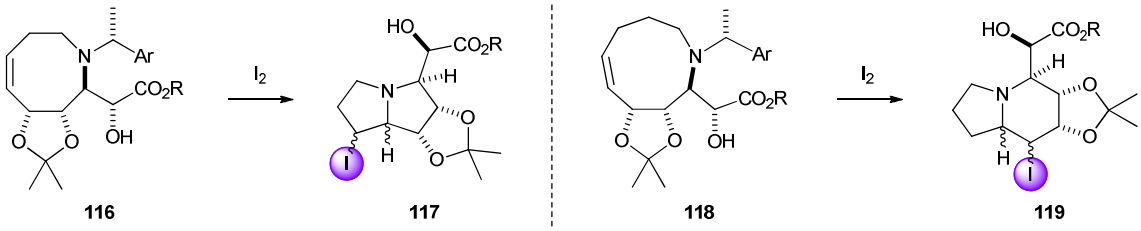


Figure 4 Iodine-promoted transannular cyclisations of substituted hexahydroazocines **116** and hexahydroazonines **118**.

2.1 Polyhydroxylated pyrrolizidine and indolizidine alkaloids

Polyhydroxylated alkaloids are a sub-class of alkaloids found in a wide range of plants and microorganisms.[1] The five main groups contained within this class are the pyrrolidines, piperidines, pyrrolizidines, indolizidines and tropanes. Structurally, they are characterised by a carbocyclic core containing an endocyclic nitrogen, with dense oxygen (hydroxyl) functionality. Many of the alkaloids within these groups have been shown to have desirable and potent biological activity, and hence therapeutic potential, which stems from their ability to act as glycosidase inhibitors. The distribution and orientation of the hydroxyl groups about the carbocyclic core enable these alkaloids to act as specific sugar mimics and give rise to their inhibitory properties.[1] As such, there has been extensive research into their isolation, structural determination and synthesis.[2] Of the pyrrolizidine (hexahydro-1*H*-pyrrolizine) alkaloids, hyacinthacine A1 **120**,[3] alexine **121**[4] or casuarine **122**[5] are representative of three commonly occurring 1,2-dihydroxy-3-hydroxymethyl, 1,2,7-trihydroxy-3-hydroxymethyl or 1,2,6,7-tetrahydroxy-3-hydroxymethyl substitution patterns, respectively.[1] The simplest 1,2-dihydroxy-3-hydroxymethyl substitution pattern gives rise to 16 possible stereoisomers, many of which have been found in the *Muscari armeniacum* and *Scilla campanulata* (Hyacinthaceae) bulbs, and have shown some level of specific glycosidase inhibition (Fig. 5).[6]

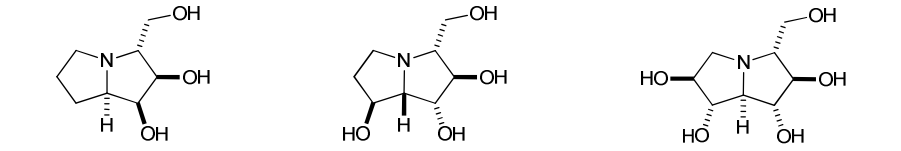


Figure 5 Three characteristic substitution patterns of the pyrrolizidine alkaloids.

The extent to which polyhydroxylated alkaloids can affect biological organisms through interfering with carbohydrate metabolism can be marked. In the western United States, cattle that ingested locoweeds (namely of the type *Astralagus* and *Oxytropis*) began to show signs of a chronic neurological disease known as 'locoism', which ultimately led to their deaths.[7] On investigation into this effect it was found that the locoweeds contained very small amounts of an indolizidine alkaloid called swainsonine **123**.[7] As a result of this swainsonine **123**, alongside another alkaloid castanospermine **124** that had been found to have a similar effect on livestock in Australia,[8] have both had their biological activity extensively evaluated, and been shown to have potent anti-cancer and anti-viral activity, respectively (Fig. 6).[1] Changes in the density of hydroxylation around the bicyclic core can have a marked effect on biological activity. For example, Richardson *et al.* synthesised a number of castanospermine analogues, including (6*R*,7*S*,8a*S*)-6,7-dihydroxyindolizidine **125**, and found that **125** actually *enhanced* the activity of several enzymes including α-glucosidase, α-mannosidase and α-galactosidase.[9] Consequently, any compound, which can be considered a structural analogue of **123** or **124**, has the potential to be a powerful therapeutic agent, and stereoselective synthetic routes to the indolizidines are eagerly sought after.[2]

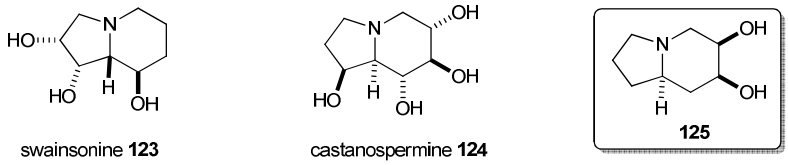


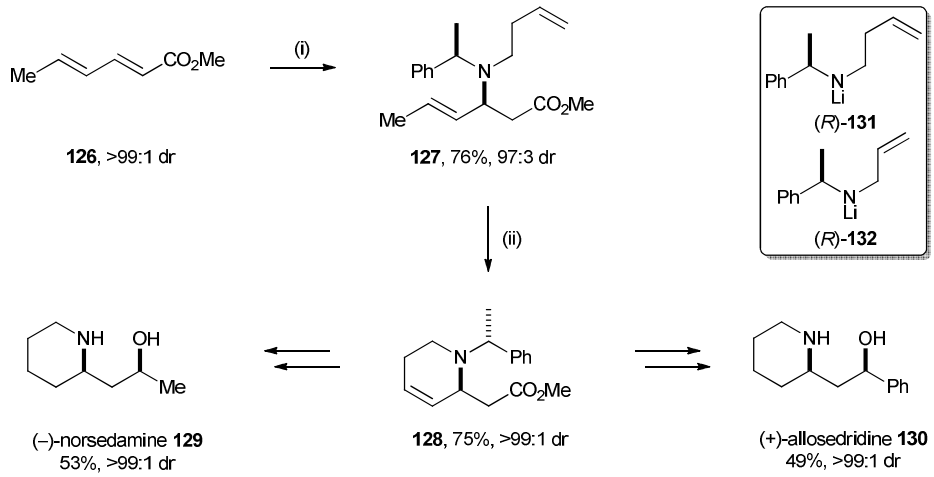
Figure 6 The naturally occurring indolizidine alkaloids swainsonine **123** and castanospermine **124**, and synthetic analogue (6*R*,7*S*,8a*S*)-6,7-dihydroxyindolizidine **125**.

2.2 Background work

2.2.1 Lithium amide conjugate addition: applications in total synthesis

Extensive studies have been carried out by Davies and co-workers into the scope and utility of the diastereoselective conjugate addition of enantiopure secondary lithium amides (derived from α-methylbenzylamine) to α,β-unsaturated esters as a method for the synthesis of β-amino esters.[10] These investigations have shown that this methodology is a versatile tool in

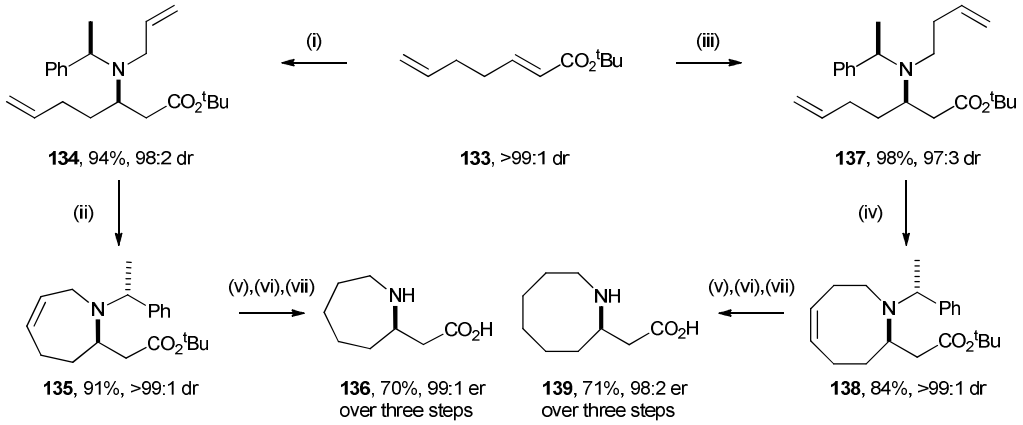
the synthesis of acyclic and cyclic β-amino acids, as well as many alkaloid natural products.[10] To date, a number of total asymmetric syntheses have been reported which all use this conjugate addition protocol as one of the key steps to install the required stereochemistry.[10] While many of these syntheses involve the conjugate addition of either antipode of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide,[11] several have employed lithium amides that have the potential for further functionalisation, for example lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide (*R*)-**131** and lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide (*R*)-**132**, which both contain a terminal olefin within one of their *N*-substituents.[12] In the total synthesis of the *Sedum* alkaloids (–)-norsedamine **129** and (+)-allosedridine **130**, conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide (*R*)-**131** to methyl hexa-2,4-dienoate **126** gave β-amino ester **127** in 76% yield and 97:3 dr. The presence of the two olefinic moieties within **127** enabled ring-closing metathesis upon treatment with 8 mol% Grubbs I catalyst, which resulted in the rapid construction of the azacyclic core: treatment of the unpurified reaction mixture with $P(CH_2OH)_3$ to effect removal of the spent catalyst[13] gave tetrahydropyridine **128** in 75% yield as a single diastereoisomer (>99:1 dr).[14] Tetrahydropyridine **128** was then elaborated to (–)-norsedamine **129** in 53% yield, and (+)-allosedridine **130** in 49% yield (Scheme 13).[14]



Scheme 13 *Reagents and conditions:* (i) (*R*)-**131**, THF, −78 °C, 2 h; (ii) Grubbs I catalyst (8 mol%), CH_2Cl_2, rt, 12 h.

This conjugate addition/ring-closing metathesis approach also proved to be efficacious in the synthesis of seven and eight-membered cyclic β-amino acids. Conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide (*R*)-**131** and lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide (*R*)-**132** to α,β-unsaturated ester **133** (derived from the olefination of 4-pentenal)[14] gave **137** in 98% yield and 97:3 dr, and **134** in 94% yield and 98:2 dr,

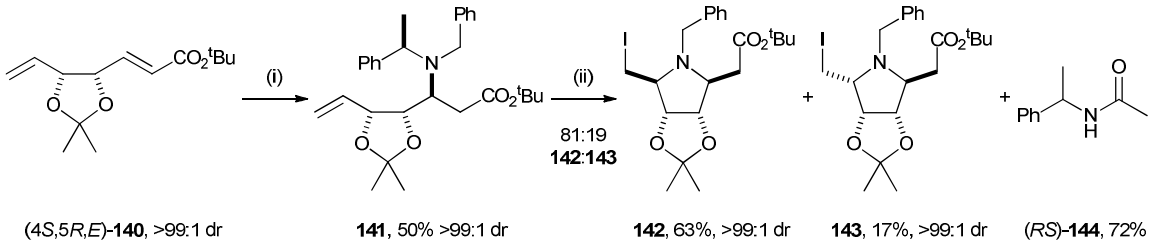
respectively. Ring-closing metathesis of **134** using 8 mol% of Grubbs I catalyst at rt gave tetrahydroazepine **135** in 91% yield and >99:1 dr, although reaction of **137** under the same conditions resulted in only 65% conversion to the desired hexahydroazocine **138**; nonetheless an increase in reaction temperature to 30 °C gave complete conversion to hexahydroazocine **138** which was isolated in 84% yield and >99:1 dr. Hydrogenation of both **135** and **138** with Wilkinson's catalyst [$RhCl(PPh_3)_3$], followed by hydrogenolysis in the presence of Pearlman's catalyst [$Pd(OH)_2/C$] and subsequent hydrolysis of the *tert*-butyl ester moieties led to the isolation (after ion exchange chromatography) of β-amino acids **136** and **139** in 70 and 71% yield, respectively (Scheme 14).[15]



Scheme 14 *Reagents and conditions:* (i) (*R*)-132, THF, −78 °C, 2 h; (ii) Grubbs I catalyst (8 mol%), CH_2Cl_2, rt, 12 h; (iii) (*R*)-131, THF, −78 °C, 2 h; (iv) Grubbs I catalyst (8 mol%), CH_2Cl_2, 30 °C, 12 h; (v) H_2 (4 atm), $RhCl(PPh_3)_3$ (5 mol%), EtOAc, rt, 12 h; (vi) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), EtOAc, rt, 12 h; (vii) TFA, CH_2Cl_2, rt, 12 h, then HCl (6.0 M aq), then DOWEX 50WX8-200.

2.2.2 Iodoamination reactions in the synthesis of pyrrolidines

Davies and co-workers have also reported an iodine-mediated ring-closing iodoamination reaction of an unsaturated amine that proceeds with concomitant *N*-debenzylation to generate a pyrrolidine scaffold.[16] For example, unsaturated amine **141** was obtained by conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**145** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** (which was synthesised in four steps and 45% overall yield from D-ribose):[17] this gave the required β-amino ester **141** in 50% yield and >99:1 dr. Subsequent treatment of **141** with I_2 and $NaHCO_3$ in MeCN gave an 81:19 mixture of diastereoisomeric iodomethyl pyrrolidines from which the major diastereoisomer **142** was isolated in 63% yield and >99:1 dr, and the minor diastereoisomer **143** was isolated in 17% yield and >99:1 dr, along with racemic α-methylbenzyl acetamide **144** in 72% yield (Scheme 15).[16]



Scheme 15 *Reagents and conditions:* (i) (*R*)-145, THF, −78 °C, 2 h; (ii) I_2, $NaHCO_3$, MeCN, −20 °C to rt, 20 h.

The mechanism of this transformation was proposed to involve reversible iodonium ion formation from **141**, followed by preferential cyclisation of iodonium **147** to give ammonium **148**. S_N1-Type loss of the α-methylbenzyl group (in preference to the benzyl group) from the sterically congested nitrogen atom within **148** gives the major diastereoisomer **142**.[16] Presumably the minor diastereoisomer **143** is formed from cyclisation of iodonium **146**. The isolation of racemic α-methylbenzyl acetamide **145** is consistent with trapping of the α-methylbenzyl cation **149** by MeCN in a Ritter-type reaction (Fig. 7).

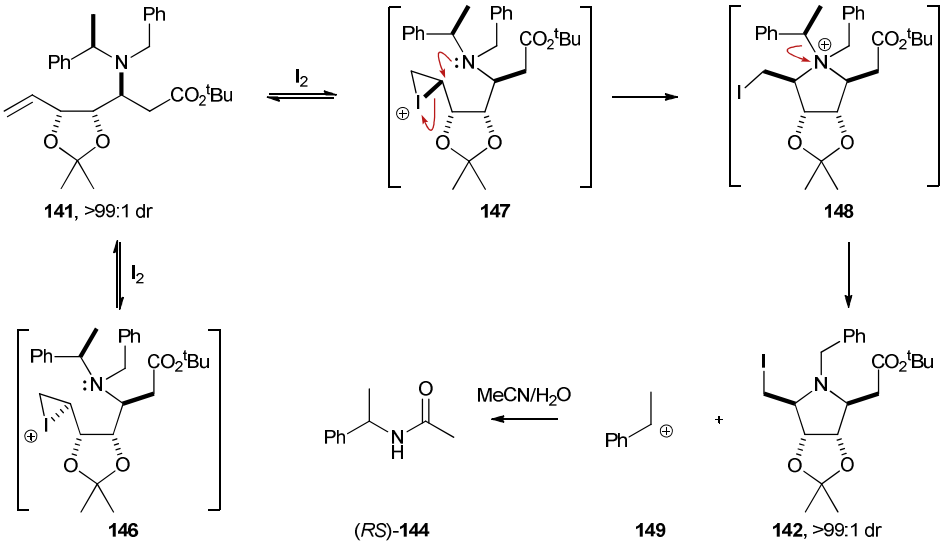


Figure 7 Proposed mechanism of cyclisation of **141** to pyrrolidine **142**.

2.3 Aims: proposed route to the pyrrolizidine scaffold

Building on both these investigations, it was anticipated that the iodoamination methodology could be applied in the synthesis of polyhydroxylated pyrrolizidines using transannular cyclisation of a hexahydroazocine scaffold (such as **116**), which was expected to proceed with concomitant *N*-debenzylation.[16] Furthermore, the hexahydroazocine **116** required for this study should be readily prepared by conjugate addition of a butenyl-substituted lithium amide to α,β-unsaturated ester (4*S*,5*R*,*E*)-**150**, coupled with *in situ* enolate oxidation to give **151**; subsequent ring-closing metathesis of **151** would then give **116**.[14] Treatment of hexahydroazocine **116** with iodine was predicted to result in transannular cyclisation[18] with concomitant loss of the *N*-α-methylbenzyl protecting group to form the 5,5-fused bicyclic

pyrrolizidine skeleton **117**. This system could then undergo further elaboration to access a range of polyhydroxylated pyrrolizidine alkaloid natural products, and their diastereoisomers (Fig. 8).[19]

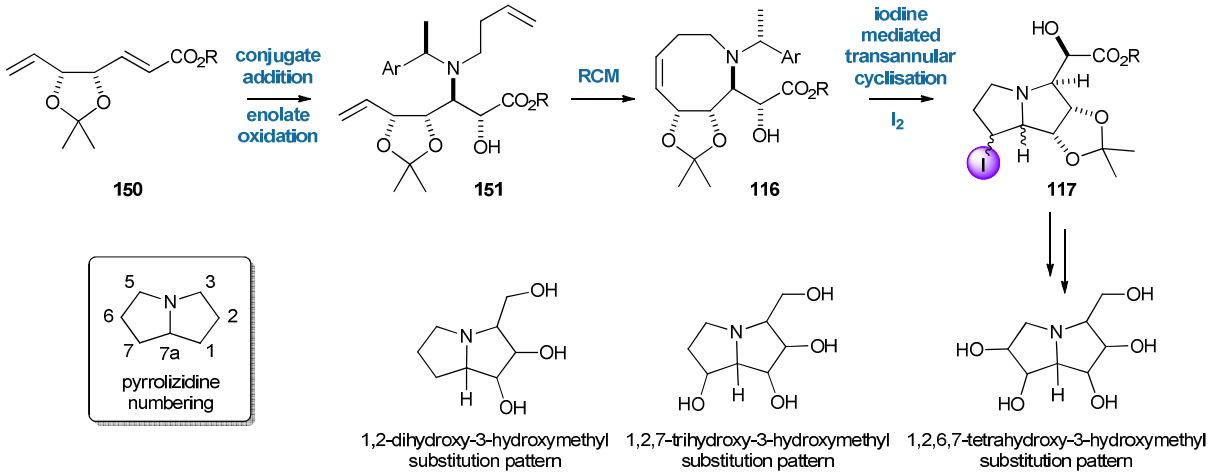
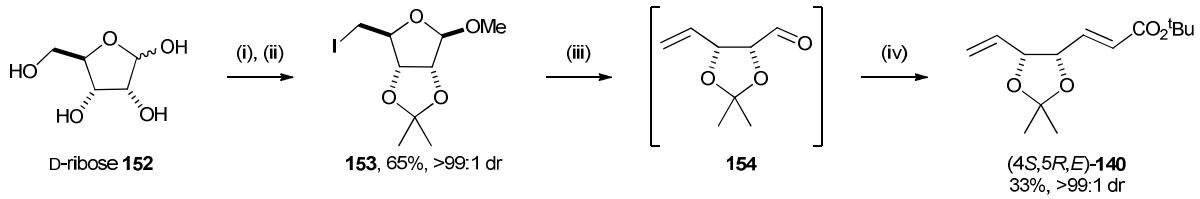


Figure 8 Proposed route through to three characteristic substitution patterns of the pyrrolizidine alkaloids from (4*S*,5*R*,*E*)-**150** via transannular iodoamination of hexahydroazocine **116**.

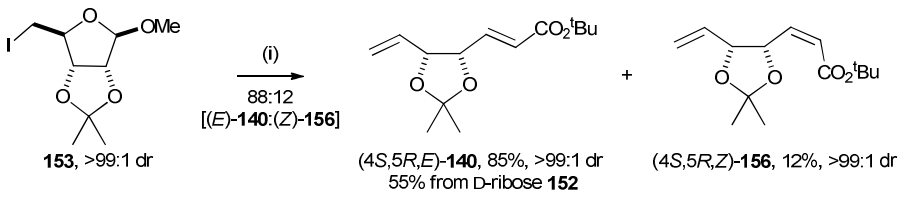
2.4 Preparation of the requisite α,β-unsaturated esters

The previously reported synthesis of *tert*-butyl (4*S*,5*R*,*E*)-4,5-*O*-isopropylidenehepta-2,6-dienoate **140** was achieved from D-ribose **152** in 45% yield and >99:1 dr over four steps (on a 200 mg scale).[17,20] Following this literature procedure, treatment of D-ribose **152** with acetone in acidic methanol to give the corresponding 2,3-*O*-isopropylidene protected methyl glycoside, was followed by reaction with I_2, imidazole and PPh_3 to give iodide **153** in 65% yield and >99:1 dr over the two steps.[21] Aldehyde **154** was then generated by treatment of iodide **153** with activated Zn in MeOH and, without purification, subjected to Horner-Wadsworth-Emmons reaction[20] with phosphonate **155** to afford (4*S*,5*R*,*E*)-**140** in 33% yield and >99:1 dr over the two steps. It was postulated that the low yield of this reaction was due to the difficulty in completely removing MeOH from the volatile aldehyde **154**, and indicated that the original method was not amenable to scale-up.[22] Overall, the most efficient large scale synthesis [that enabled preparation of >5 g of (4*S*,5*R*,*E*)-**140**] using this method gave (4*S*,5*R*,*E*)-**140** in 21% overall yield and in >99:1 dr (Scheme 16).



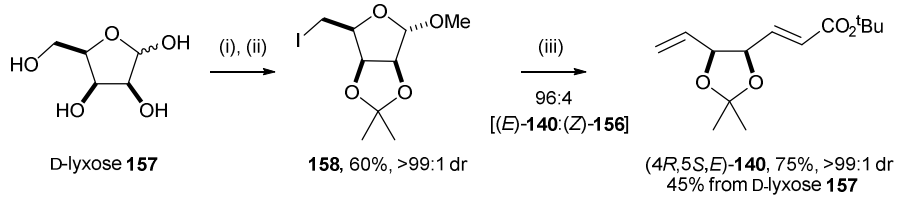
Scheme 16 *Reagents and conditions:* (i) acetone/MeOH (v/v 1:1), HCl (aq, cat.), reflux, 1 h; (ii) I_2, PPh_3, imidazole, PhMe/MeCN (v/v 5:1), 60 °C, 1 h; (iii) Zn, MeOH, reflux, 1 h; (iv) $(EtO)_2P(O)CH_2CO_2{}^tBu$ **155**, MeMgBr, THF, rt, 15 min then **154**, reflux, 2.5 h.

The conversion of iodide **153** to aldehyde **154** has been achieved in quantitative yield by Jäger *et al.*, using 1.5 equiv of BuLi in THF to effect the transformation.[23] Since the use of BuLi in Horner-Wadsworth-Emmons reactions is well documented,[24] it was envisaged that these two processes could occur in tandem and development of a 'one-pot' transmetallation/ring-opening/Horner-Wadsworth-Emmons[17,23] strategy was investigated to facilitate the synthesis of (4*S*,5*R*,*E*)-**140** by avoiding the need to isolate the intermediate aldehyde **154**. Thus, treatment of a 1:1 mixture of **153** and *tert*-butyl diethylphosphonoacetate **155** in Et_2O with 2.0 equiv of BuLi resulted in the formation of an 88:12 mixture of olefins (4*S*,5*R*,*E*)-**140** and (4*S*,5*R*,*Z*)-**156**, with chromatographic separation giving (4*S*,5*R*,*E*)-**140** in >99:1 dr and 55% overall yield in three steps from D-ribose **152**. This procedure could reliably be used for the production of (4*S*,5*R*,*E*)-**140** in >25 g batches (Scheme 17).



Scheme 17 *Reagents and conditions:* (i) BuLi (2.0 equiv), **155** (1.0 equiv), Et_2O, −78 °C to rt, 4 h.

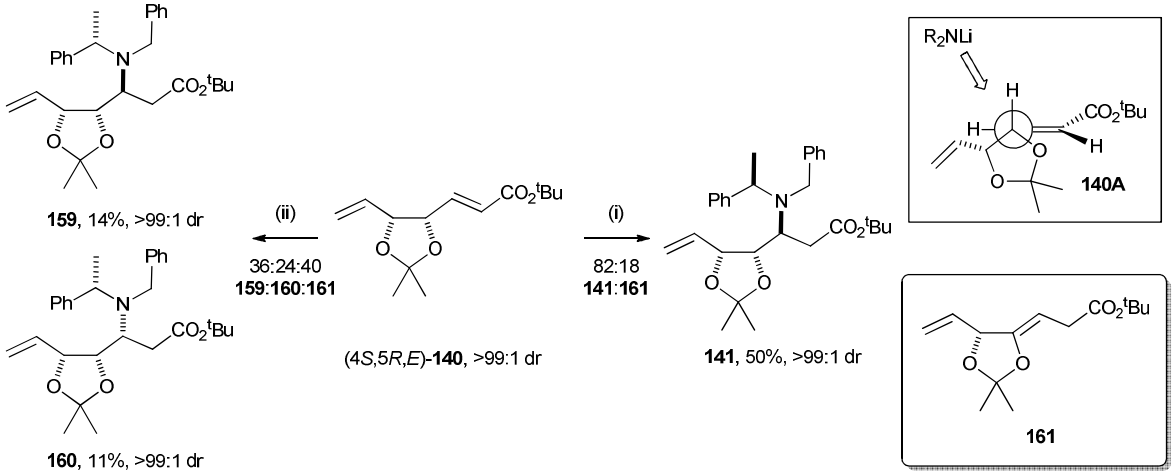
It was anticipated that the enantiomeric α,β-unsaturated ester (4*R*,5*S*,*E*)-**140** would result from the 'one-pot' transmetallation/ring-opening/Horner-Wadsworth-Emmons strategy starting from iodide **158**, which can be derived from D-lyxose **157**. This would then enable preparation of either enantiomer of any substituted pyrrolizidine product. Indeed, treatment of D-lyxose **157** with acetone in acidic methanol followed by reaction with I_2, imidazole and PPh_3 gave iodide **158** in 60% yield and >99:1 dr. Reaction of a 1:1 mixture of **158** and **155** with 2.0 equiv BuLi gave a 96:4 mixture of (4*R*,5*S*,*E*)-**140** and (4*R*,5*S*,*Z*)-**156** from which the major diastereoisomer (4*R*,5*S*,*E*)-**140**[25] was isolated in 45% overall yield and >99:1 dr over three steps from D-lyxose **157** (Scheme 18).



Scheme 18 *Reagents and conditions:* (i) acetone/MeOH (v/v 1:1), HCl (aq, cat.), reflux, 1 h; (ii) I_2, PPh_3, imidazole, PhMe/MeCN (v/v 5:1), 60 °C, 1 h; (iii) BuLi (2.0 equiv), **155** (1.0 equiv), Et_2O, −78 °C to rt, 4 h.

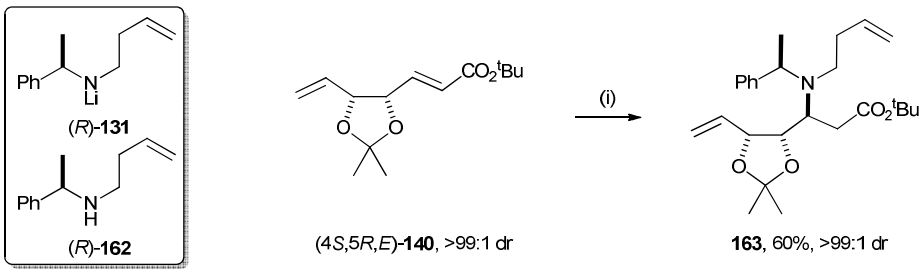
2.5 Doubly diastereoselective conjugate additions to chiral α,β-unsaturated esters

The stereochemical outcome of a doubly diastereoselective conjugate addition reaction26 between an enantiopure lithium amide [such as (*R*)-**145**] and an enantiopure α,β-unsaturated ester [such as (4*S*,5*R*,*E*)-**140**] is a result of the combined stereocontrol of both the lithium amide reagent and the α,β-unsaturated ester substrate. If substrate and reagent both favour the same stereochemical outcome then a high level of diastereoselectivity is often observed and the pairing is termed 'matched'. In the case where the substrate and reagent favour different stereochemical outcomes, then the agent (reagent or substrate) with the dominant stereocontrol dictates which is the major diastereoisomeric product, although the diastereoselectivity of the reaction tends to be low and the pairing is termed 'mismatched'.[26a] There has been significant investigation by Davies *et al.* into this phenomenon; of particular relevance to the present study is the previously reported conjugate addition of both enantiomers of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **145** to (4*S*,5*R*,*E*)-**140**.[17] Conjugate addition of (*R*)-**145** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** gave an 82:18 mixture of β-amino ester **141** (as a single diastereoisomer) and β,γ-unsaturated ester **161** (resulting from a competing γ-deprotonation pathway), from which **141** was isolated in 50% yield and >99:1 dr. However, when the reaction between (*S*)-**145** and (4*S*,5*R*,*E*)-**140** was carried out, the conjugate addition reaction was not only accompanied by γ-deprotonation but also gave a very poor diastereoisomeric ratio of the two possible conjugate addition products **159** and **160**. From the 36:24:40 unpurified reaction mixture of **159**, **160** and **161**, β-amino esters **159** and **160** were isolated in 14 and 11% yield, respectively. These product distributions are consistent with the pairing of (*R*)-**145** and (4*S*,5*R*,*E*)-**140** being the doubly diastereoselective 'matched' case, and the pairing of (*S*)-**145** and (4*S*,5*R*,*E*)-**140** being the 'mismatched' case. Davies *et al.* surmised that these observations are consistent with reaction proceeding with the substrate in conformation **140A**: in this conformation, approach of the lithium amide reagent to the *Si* face at C(3) would be expected to be favoured [i.e., approach *syn* to the C(4)-hydrogen atom and opposite the bulky C(4)-alkoxyalkyl substituent], "matched" with the inherent diastereofacial bias of lithium amide (*R*)-**145**. However, the C(4)-hydrogen atom is also well placed to undergo competitive deprotonation leading, after kinetic protonation of the resultant dienolate, to (*Z*)-**161** (Scheme 19).[17]



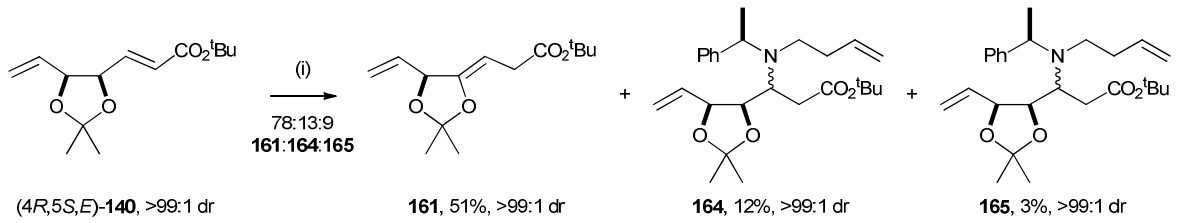
Scheme 19 *Reagents and conditions:* (i) (*R*)-**145**, THF, −78 °C, 2 h; (ii) (*S*)-**145**, THF, −78 °C, 2 h.

Following these results, it was predicted that the conjugate addition of lithium (*R*)-*N*-but-3-en-yl-*N*-(α-methylbenzyl)amide (*R*)-**131** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** would also be 'matched'. The synthesis of amine (*R*)-**162** was achieved using a literature procedure whereby treatment of 2.5 equiv (*R*)-*N*-(α-methylbenzyl)amine with 1.0 equiv of commercially available 4-bromo-but-1-ene at 60 °C for 12 h, gave (*R*)-**162** in 75% yield after chromatographic purification.[14] Conjugate addition of lithium amide (*R*)-**131** [generated from amine (*R*)-**162** by addition of BuLi] to (4*S*,5*R*,*E*)-**140** was carried out under the standard conditions (reaction in THF at −78 °C for 2 h followed by addition of satd aq NH_4Cl)27 to give exclusively β-amino ester **163** in >99:1 dr, which was isolated in 60% yield. The (*S*)-configuration of the newly formed C(3)-stereogenic centre within **163** was initially assigned by reference to the lithium amide conjugate addition 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.[28] This assignment was later confirmed unambiguously by single crystal X-ray diffraction analysis of a derivative (*vide infra*). This result supported the hypothesis that the pairing of (*R*)-**131** with (4*S*,5*R*,*E*)-**140** was the 'matched' case, and was consistent with the previous investigations by Davies *et al.*[17] Interestingly, no evidence of the formation of β,γ-unsaturated ester **161** was observed, suggesting that the γ-deprotonation pathway does not compete with conjugate addition in this case (Scheme 20).



Scheme 20 *Reagents and conditions:* (i) (*R*)-**131**, THF, −78 °C, 2 h then satd aq NH_4Cl.

To thoroughly investigate double asymmetric induction in this system, the assumed 'mismatched' conjugate addition of lithium amide (*R*)-**131** to the enantiomeric α,β-unsaturated ester (4*R*,5*S*,*E*)-**140** was attempted. Treatment of (4*R*,5*S*,*E*)-**140** under standard conditions gave a 78:13:9 mixture of β,γ-unsaturated ester **161** and β-amino esters **164** and **165**. Purification of this mixture allowed the isolation of **161** in 51% yield and >99:1 dr, along with β-amino esters **164** and **165** in 12 and 3% yield, respectively, and in >99:1 dr. β-Amino esters **164** and **165** were assigned as epimers at their C(3)-stereogenic centre, but the absolute configurations within these compounds were not assigned (Scheme 21).

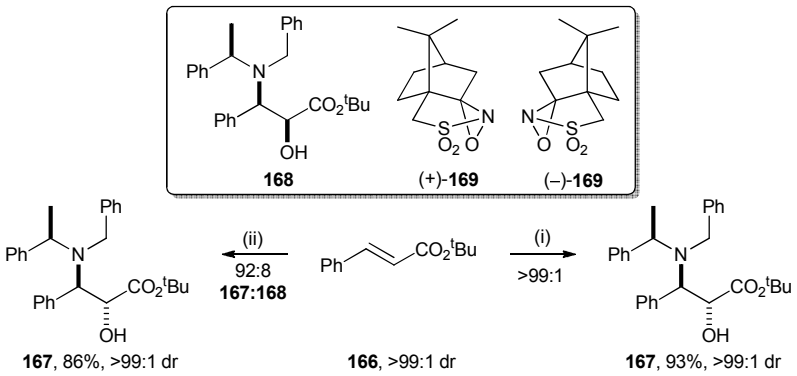


Scheme 21 *Reagents and conditions:* (i) (*R*)-**131**, THF, −78 °C, 2 h.

2.6 Aminohydroxylation

Davies *et al*. have developed a method for the *in situ* oxidation of lithium (*Z*)-β-amino enolates (formed from an α,β-unsaturated ester upon conjugate addition of a lithium amide) using (10-camphorsulfonyl)oxaziridine [CSO] **169** as the oxidant, which results in the selective formation of an α-hydroxy-β-amino ester.[29] Although the stereochemical outcome in this (doubly diastereoselective) oxidation procedure is usually under the dominant stereocontrol of the chiral lithium (*Z*)-β-amino enolate, with the formation of the corresponding *anti*-α-hydroxy-β-amino ester being favoured, a slight dependency on the chirality of CSO **169** is observed. For instance, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**145** to *tert*-butyl cinnamate **166** followed by *in situ* enolate oxidation with (−)-CSO **169** gave *anti*-α-hydroxy-β-amino ester **167** in >99:1 dr.[30] Meanwhile, conjugate addition of (*R*)-**145** to **166** followed by *in situ* enolate oxidation with

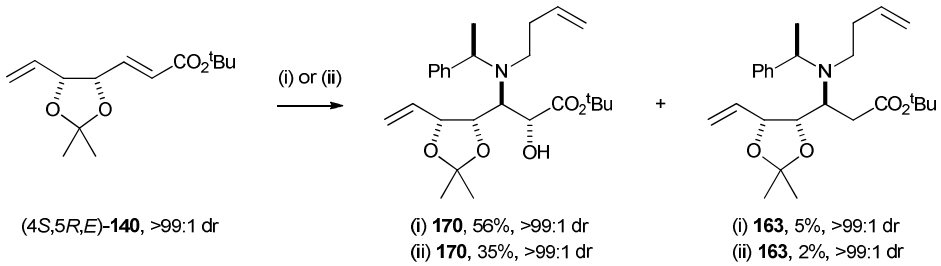
(+)-CSO **169** gave α-hydroxy-β-amino esters **167** and **168** in a 92:8 mixture, from which **168** was isolated in 86% yield as a single diastereoisomer (Scheme 22).[29] Hence, the use of lithium amide (*R*)-**145** is conventionally paired with (−)-CSO **169**, whilst use of lithium amide (*S*)-**145** is paired with (+)-CSO **169** upon conjugate addition to achiral α,β-unsaturated esters.



Scheme 22 *Reagents and conditions:* (i) (*R*)-**145**, THF, −78 °C, 2 h then (−)-CSO **169**, −78 °C to rt, 12 h; (ii) (*R*)-**145**, THF, −78 °C, 2 h then (+)-CSO **169**, −78 °C to rt, 12 h.

Following this precedent, the aminohydroxylation of α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** using the doubly diastereoselective 'matched'[26] conjugate addition of 1.6 equiv of lithium amide (*R*)-**131** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** in THF at −78 °C followed by the addition of (−)-CSO **169**[31] was investigated.[29b,32] This reaction resulted in the formation of a mixture of β-amino ester **163** and α-hydroxy-β-amino ester **170**, although due to the presence of excess (−)-CSO **169**, (+)-CSI and excess amine (*R*)-**162** in the ^{1}H NMR spectrum of the unpurified reaction mixture neither a product ratio nor a reaction diastereoselectivity for the formation of **163** or **170** could be evaluated. Attempted removal of the excess amine (*R*)-**162** using an aqueous citric acid wash[27] was unsuccessful, as it resulted in the formation of a persistent emulsion. Attempted removal of the (−)-CSO **169** and (+)-CSI by trituration of the unpurified reaction mixture with cold Et_2O[29a] was similarly ineffective, resulting in the formation of thick, viscous emulsion from which only 50% of the expected mass could be retrieved after filtration. However, chromatographic purification of the reaction mixture directly (without an aqueous work-up) gave **170** in 56% yield and >99:1 dr and **163** in 5% yield and >99:1 dr. The configurations of the C(2)- and C(3)-stereogenic centres within **170** were initially assigned by reference to the well-established stereochemical outcome of this aminohydroxylation process,[33] and this assignment was later confirmed unambiguously by single crystal X-ray diffraction analysis of a derivative (*vide infra*). The alternative reaction, the conjugate addition of lithium amide (*R*)-**131** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** followed by addition of (+)-CSO **169**[34] was also investigated, and resulted in the formation of

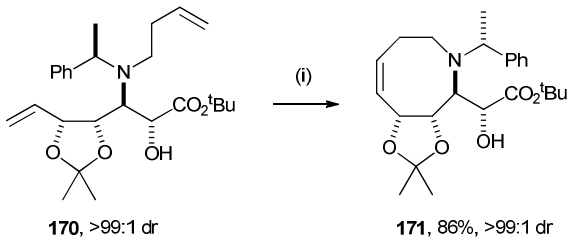
a mixture of β-amino ester **163** and α-hydroxy-β-amino ester **170** (as before), from which **170** and **163** were isolated in 35 and 6% yield, respectively, and in >99:1 dr in both cases (Scheme 23). The superior yield obtained when using (−)-CSO **169** suggested that this reaction was more efficacious, and consequently all future conjugate addition reactions with lithium amide (*R*)-**131** that were followed by *in situ* enolate oxidation employed (−)-CSO **169** (i.e., 'the conventional pairing').



Scheme 23 *Reagents and conditions:* (i) (*R*)-**131**, THF, −78 °C, 2 h then (−)-CSO **169**, −78 °C to rt, 12 h; (ii) (*R*)-**131**, THF, −78 °C, 2 h then (+)-CSO **169**, −78 °C to rt, 12 h.

2.7 Ring-closing metathesis

Ring-closing metathesis of **170** upon treatment with Grubbs I in CH_2Cl_2 at 30 °C (the conditions used previously for the ring-closure of the related β-amino ester **137**)[14] resulted in the formation of hexahydroazocine **171** as a single diastereoisomer. However, in contrast to the literature precedence,[14] reaction of **170** with Grubbs I at rt also gave complete conversion to **171**, which was isolated in 86% yield and >99:1 dr (Scheme 24). This result could be explained by the presence of the *cis*-acetonide group which may ensure a facile ring-closure by enforcing a more favourable conformation.[35]

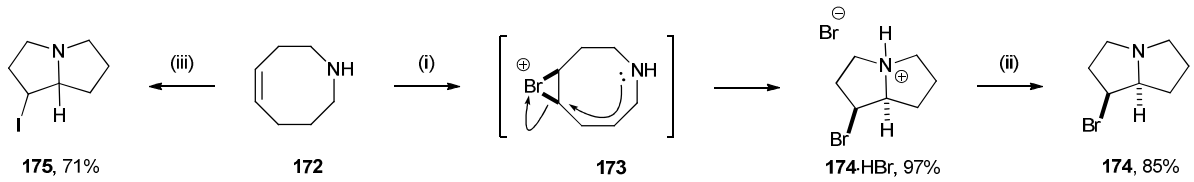


Scheme 24 *Reagents and conditions:* (i) Grubbs I catalyst (10 mol%), CH_2Cl_2, rt, 12 h.

2.8 Transannular cyclisations

There are a few reported examples of electrophile-mediated transannular cyclisations of hexahydroazocines, and fewer still that can be classed as 'one-pot' reactions. Indeed, at the outset of this investigation, there were two previous studies which were of significance. In 1978, Wilson and Sawicki reported that the treatment of 1,4-aza-*cis*-cyclooctene **172** with a number of electrophiles (Br_2, I_2, $HgCl_2$, PhSBr, PhSeBr) resulted in the formation of C(7)-substituted pyrrolizidines.[18] For example, treatment of 1,4-aza-*cis*-cyclooctene **172**

(synthesised in four steps from the commercially available 4-cycloheptenone) with Br_2 in CH_2Cl_2 at rt for 12 h resulted in the formation of **174**·HBr which was isolated in 97% yield. The relative configuration within **174**·HBr was established by single crystal X-ray diffraction analysis, and suggested that the cyclisation had occurred via trapping of bromonium ion **173** by the endocyclic nitrogen. Treatment of **174**·HBr with 1.0 M aq NaOH allowed isolation of pyrrolizidine **174** in 85% yield. Following this result, **172** was also treated with iodine, which led to the isolation of **175** in 71% yield, although no comment as to the stereochemistry within **175** was made by the authors (Scheme 25).



Scheme 25 *Reagents and conditions:* (i) Br_2, CH_2Cl_2, rt, 12 h; (ii) NaOH (1.0 M aq), Et_2O; (iii) I_2, CH_2Cl_2/Et_2O (v/v 2:1), rt, 12 h then NaOH (1.0 M aq), Et_2O.

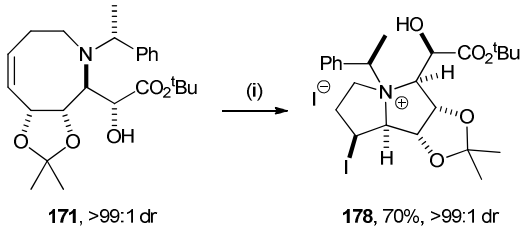
More recently, Fox *et al*. reported the photochemical synthesis of several functionalised 4-aza-*trans*-cyclooctenes from their 4-aza-*cis*-cyclooctene counterparts, and subsequently investigated their transannular cyclisations. For example, the 4-aza-*trans*-cyclooctene derivative **176** was reacted with Br_2 to give pyrrolizidine scaffold **177** with 86% mass return and >90:10 dr (unfortunately their attempts at purification of the reaction mixture resulted in extensive decomposition). Here, the cyclisation proceeded with concomitant *N*-deprotection, although no comment was made concerning either the mechanism of deprotection or the fate of the *N*-Boc group. This stereochemical outcome is consistent with a stereospecific process occurring (Scheme 26).[36]

Scheme 26 *Reagents and conditions:* (i) Br_2, CH_2Cl_2, rt, 12 h then NaOH (1.0 M aq), Et_2O.

2.8.1 Transannular iodoamination of hexahydroazocine 171

Initially, the iodoamination of hexahydroazocine **171** was attempted under the conditions previously reported by Davies *et al.* in their investigations into the synthesis of pyrrolidine scaffolds.[16] Reaction of **171** with 3.0 equiv I_2 and 3.0 equiv $NaHCO_3$ in MeCN at −20 °C followed by an aqueous $Na_2S_2O_3$ work-up resulted in low mass return, and the ^1H NMR spectrum of the unpurified reaction mixture was broad and complex. Attempted chromatographic purification gave no identifiable products, and repetition of these conditions

followed by washing the unpurified reaction mixture with 1.0 M aq KOH (to remove any salts that were present) resulted in almost complete loss of mass. Likewise, under the conditions reported by Wilson and Sawicki [1.2 equiv I_2 in CH_2Cl_2/Et_2O (v/v 2:1) at rt for 16 h], low mass return was encountered and no recognisable species could be discerned in the similarly broad ^{1}H NMR spectrum of the unpurified reaction mixture.[18] At this point, extensive investigations were carried out to determine the effect of changing the reaction stoichiometry, solvent, time and temperature: the results from these studies enabled the identification of conditions that allowed the isolation of a cyclised product. Thus, reaction of hexahydroazocine **171** with 3.0 equiv I_2 and 3.0 equiv $NaHCO_3$ in $CHCl_3$, followed by the addition of solid $Na_2S_2O_3$ gave ammonium salt **178** which, upon direct crystallisation from the unpurified reaction mixture (using 30-40 °C petroleum ether), was isolated in 70% yield as a single diastereoisomer (Scheme 27). An analogous reaction was carried out without the addition of the 3.0 equiv $NaHCO_3$, which gave the same result.



171, >99:1 dr **178**, 70%, >99:1 dr

Scheme 27 *Reagents and conditions:* (i) I_2, $NaHCO_3$, $CHCl_3$, rt, 12 h.

The relative configuration within **178** was unambiguously established by single crystal X-ray diffraction analysis, with the absolute configuration being assigned from the known configurations of the C(1)- and C(2)-stereocentres (derived from D-ribose **152**), and from the known (*R*)-configuration of the *N*-α-methylbenzyl group. This analysis confirmed the identity of the iodide counter-ion and also unambiguously established the absolute configurations within the synthetic precursors hexahydroazocine **171** and α-hydroxy-β-amino ester **170**, and hence in β-amino ester **163** (Fig. 9).[37]

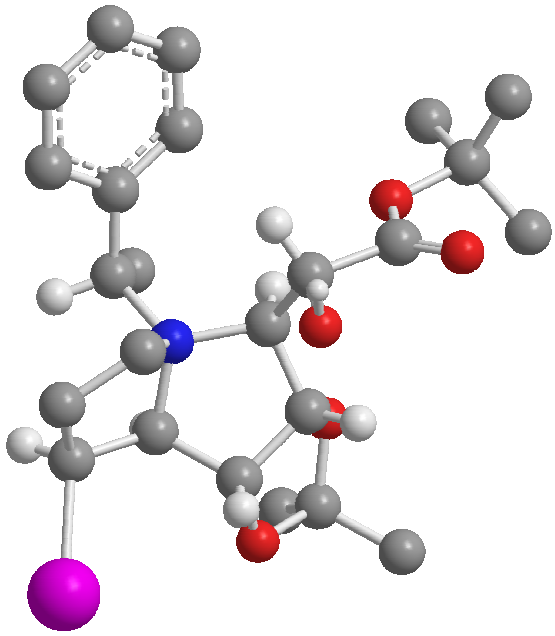


Figure 9 Chem3D representation of the single crystal X-ray structure of (1*R*,2*S*,3*S*,4*R*,7*S*,7a*S*,1′*R*,α*R*)-**178** (selected H atoms and the iodide counter-ion have been omitted for clarity).

The stereochemical outcome of this cyclisation protocol can be rationalised by reversible iodonium ion formation from hexahydroazocine **171**, followed by preferential cyclisation of one of the diastereoisomeric iodonium ions **179** and **181**. Ring-closure of **179** is expected to be disfavoured due to the high degree of 1,2-strain experienced between the α-branched *N*-protecting group and the α-branched C(3)-substituent (pyrrolizidine numbering); ring-closure of **181** does not suffer from such a severe steric interaction and gives the corresponding ammonium ion **178** (Fig. 10).

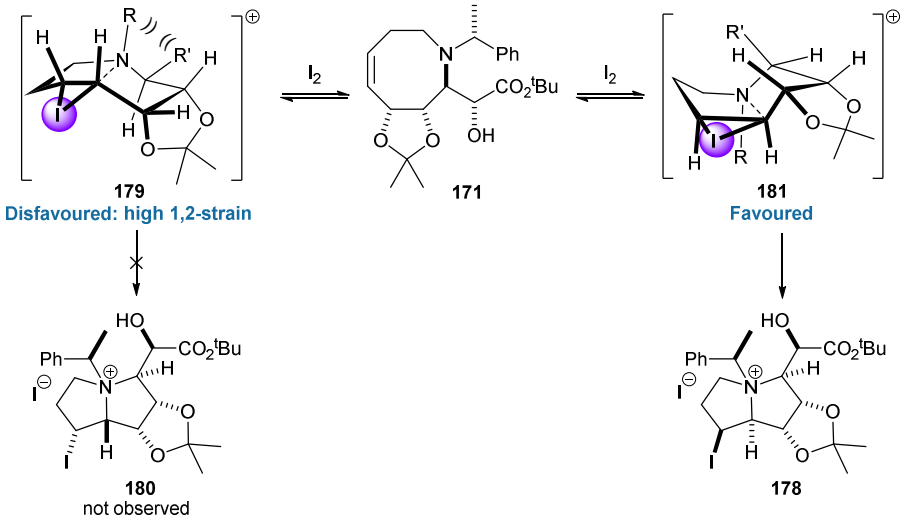


Figure 10 Postulated mechanistic rationale for transannular cyclisation of **171** [R = (*R*)-CHMePh, R′ = (*R*)-CH(OH)$CO_2{}^t$Bu].

In an attempt to provide some insight into the reaction mechanism, the iodocyclisation reaction was monitored by 400 MHz ^{1}H NMR spectroscopy. Iodine was added to

hexahydroazocine **171** in $CDCl_3$ and ^1H NMR spectra were recorded at regular intervals over 12 h. Between 0 h and 1 h, a gradual conversion of **171** into **178** was observed. After 1 h, complete consumption of hexahydroazocine **171** had occurred to give ammonium **178** as the only product (spectrum **B**). However, as the reaction progressed the peaks in the ^1H NMR spectrum broadened and shifted upfield (spectra **C** and **D**), before sharpening to give a spectrum of a previously unseen species, **182**, as a single diastereoisomer (spectrum **E**). Full ^1H NMR spectroscopic analysis of **182**, including a ^1H-^1H 2D NOESY study, coupling constant and chemical shift analyses, concluded that **182** was an ammonium with identical connectivity and relative configuration to those of ammonium **178**. Thus, the averaging of the two signals between the first and the last recorded spectra might be explained by the slow dissolution of the iodine into the solvent; at saturation level the counter-ion for the ammonium is no longer a single iodide ion, but a poly-iodide (Fig. 11).[38]

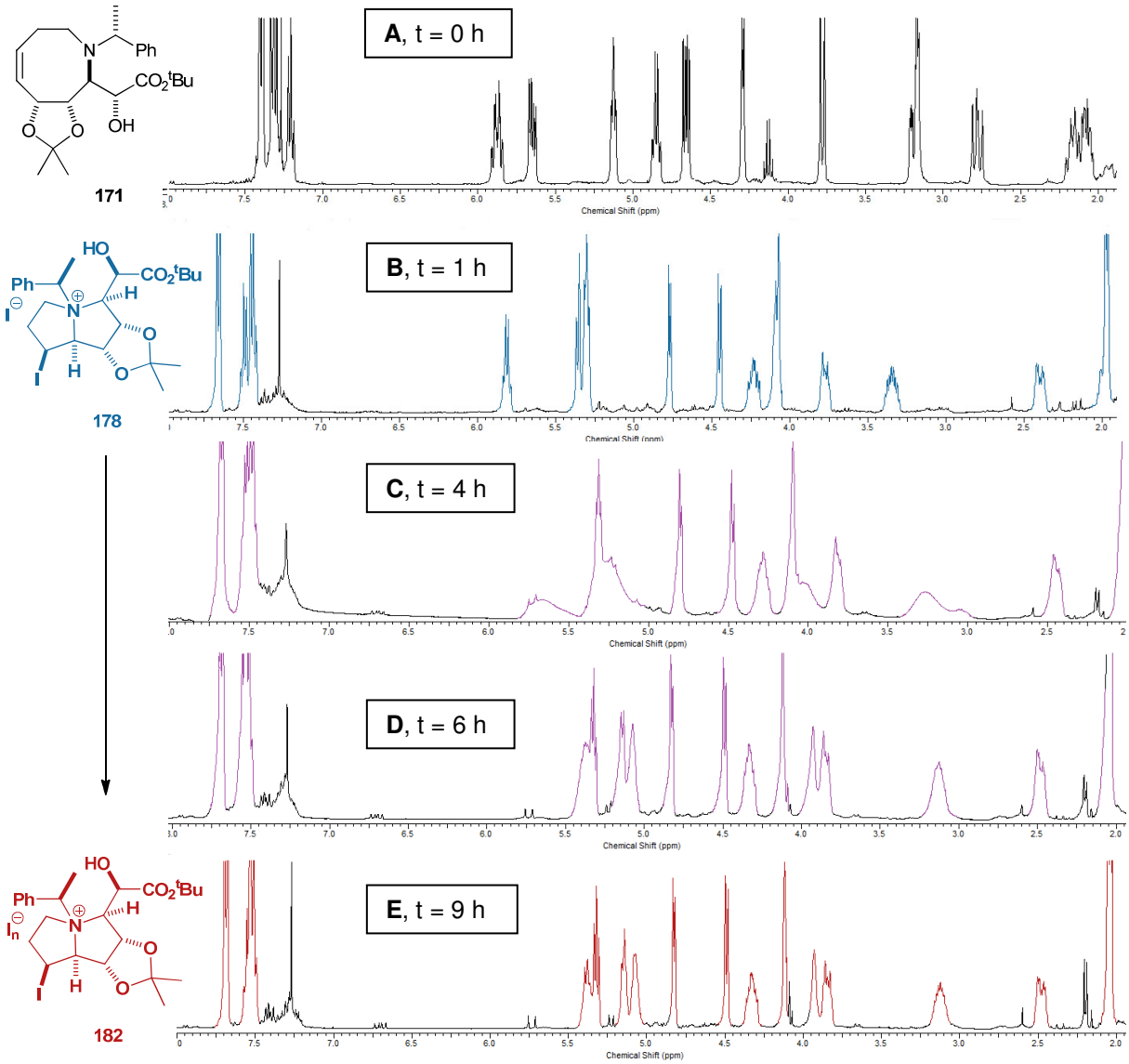


Figure 11 The ^1H NMR spectra of the iodocyclisation of **171** at t = 0, 1, 4, 6 and 9 h, respectively.

In order to test this theory, a second experiment was carried out whereby hexahydroazocine **171** was added to a homogeneous mixture of I_2 and $CDCl_3$, and the subsequent reaction was monitored by 400 MHz ^{1}H NMR spectroscopy. Direct formation of ammonium **182** was observed after 15 min, and no evidence of ammonium iodide **178** was noted, supporting the hypothesis that it is the slow dissolution of I_2 that causes the changes in the spectrum over time, as **178** becomes **182**. The faster rate of complete conversion to **182** here is consistent with the slow dissolution of I_2 in the previous case. Furthermore, on work-up of **182** with solid $Na_2S_2O_3$, ammonium **178** was isolated as the sole product (Fig. 12).

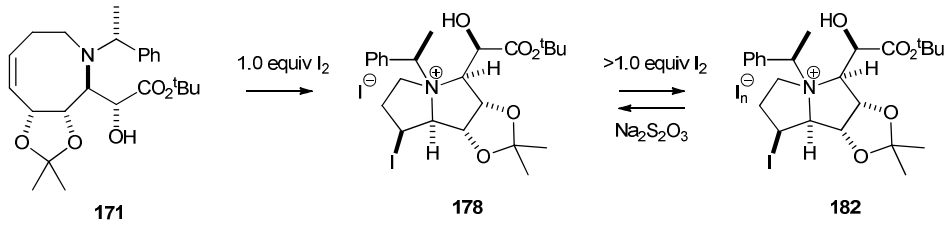
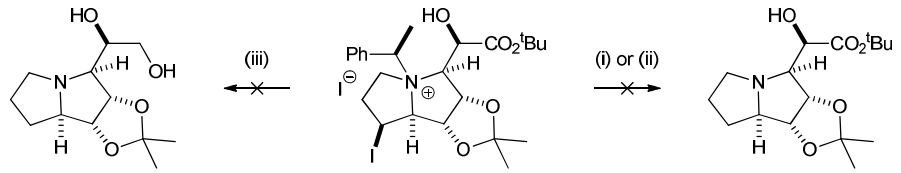


Figure 12 Formation of polyiodide **182** from **171** and **178**.

2.8.2 Attempted *N*-debenzylation

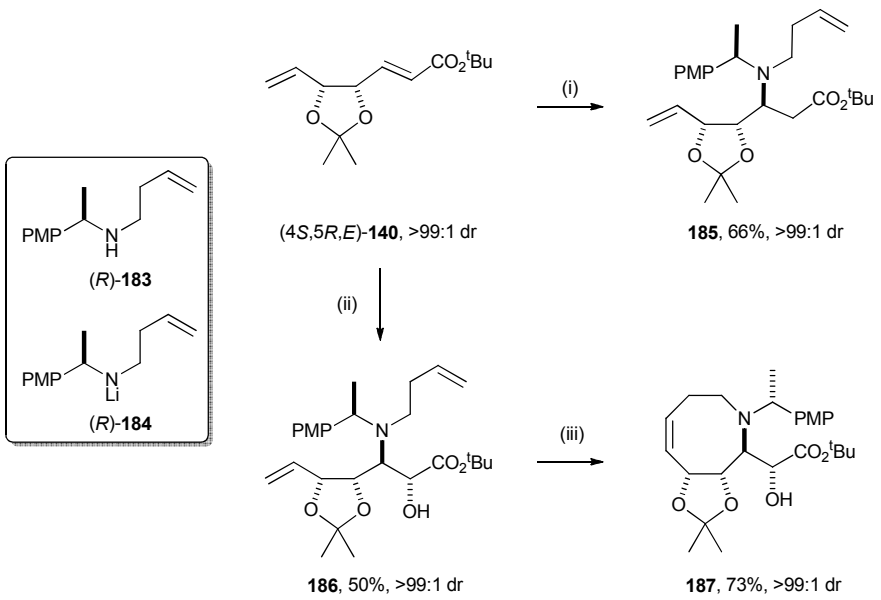
Although *N*-debenzylation had not occurred as expected, the isolation of the stable quaternary ammonium salt **178** was encouraging. Furthermore, on inspection of the ^{1}H NMR spectrum of ammonium salt **182** small peaks that could correspond to the formation of styrene species were noted, suggesting that slow *N*-debenzylation may be occurring. Following this observation, it was proposed that ammonium salt **178** should be subjected to conditions that would favour an S_N1-type process, hence **178** was heated in an array of polar protic solvent mixtures (e.g., MeCN/H_2O) to try to complete the *N*-debenzylation, all of which resulted in the formation of complex mixtures of products. Nevertheless, the successful hydrogenolytic removal of *N*-α-methylbenzyl groups from related ammonium salts is known;[39] and reaction of **178** under these literature conditions [5 atm H_2 in the presence of 5% Pd/C, 10% Pd/C or $Pd(OH)_2$ for 12 h] was attempted, which all resulted in returned starting material. Wright *et al.* used transfer hydrogenation conditions to effect debenzylation of a bicyclic ammonium salt,[39a] but attempted use of these conditions for **178** resulted only in the formation of complex mixtures of products. Finally, attempted simultaneous reduction of the ester, the C–I bond and removal of the *N*-protecting group using $LiAlH_4$ was investigated but also gave a complex mixture of products (Scheme 28).



Scheme 28 *Reagents and conditions:* (i) H_2 (5 atm), 5% Pd/C (50% w/w), MeOH, rt, 12 h; (i) H_2 (5 atm), $Pd(OH)_2$/C (50% w/w), MeOH, rt, 12 h; (ii) 10% Pd/C (50% w/w), cyclohexene, EtOH, reflux, 4 h; (iii) $LiAlH_4$ (1.0 M in THF), THF, −78 °C to rt, 12 h.

2.8.3 Promoting *N*-debenzylation

Following the failure of ammonium ion **178** to undergo *N*-debenzylation under any of the conditions investigated, it was anticipated that promotion of the S_N1-type loss of the α-methylbenzyl group (without recourse to yet further modification of the cyclisation conditions) through structural adaptation of hexahydroazocine **171** would prove successful. An increase in the stability of the carbocation (formed during the iodoamination reaction) would encourage the desired *N*-debenzylation, and to this end it was decided to incorporate an (α-methyl-*p*-methoxy)benzyl group within the hexahydroazocine substrate. Thus, the requisite amine (*R*)-**183** was prepared in an analogous manner to (*R*)-**162** [from (*R*)-(α-methyl-*p*-methoxy)benzylamine and 4-bromobut-1-ene] in 73% yield after chromatographic purification. The synthesis of α-hydroxy-β-amino ester **186** was achieved by the doubly diastereoselective 'matched' conjugate addition of 1.6 equiv of lithium amide (*R*)-**184** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** in THF at −78 °C followed by the addition of 2.0 equiv of (−)-CSO **169**. This reaction resulted in the formation of a mixture of β-amino ester **185** and α-hydroxy-β-amino ester **186**;[40] chromatographic purification of the reaction mixture directly (with no aqueous work-up) gave **186** in 50% yield and >99:1 dr and **185** in 8% yield and >99:1 dr. An authentic sample of β-amino ester **185** was prepared by the conjugate addition of lithium amide (*R*)-**184** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** in THF at −78 °C followed by quenching with satd aq NH_4Cl (which gave **185** in 66% yield and >99:1 dr).[41] The stereochemical outcome of these conjugate addition reactions (for the formation of both **185** and **186**) were initially assigned by reference to the transition state mnemonic,[28] and the established stereochemical outcome of the aminohydroxylated process,[33] these assignments were later confirmed by single crystal X-ray diffraction analysis of a derivative of **186** (*vide infra*). Subsequent ring-closing metathesis of α-hydroxy-β-amino ester **186** with Grubbs I catalyst in CH_2Cl_2 at rt gave (α-methyl-*p*-methoxy)benzyl-protected hexahydroazocine **187** in 73% yield and >99:1 dr (Scheme 29).



Scheme 29 *Reagents and conditions:* (i) (*R*)-**184**, THF, −78 °C, 2 h; (ii) (*R*)-**184**, THF, −78 °C, 2 h then (−)-CSO **169**, −78 °C to rt, 12 h; (iii) Grubbs I catalyst (10 mol%), CH_2Cl_2, rt, 12 h.

2.8.4 Transannular iodoamination of 187

Cyclisation of hexahydroazocine **187** was carried out under the optimised conditions (3.0 equiv I_2, 3.0 equiv $NaHCO_3$ in $CHCl_3$ for 12 h), and resulted in the formation of a cyclised product, which was tentatively assigned as the HI salt of the iodopyrrolizidine **189**, indicating that the desired *N*-debenzylation had occurred. However, loss of the (α-methyl-*p*-methoxy)benzyl group (as the corresponding cation), resulted in the formation of a mixture of products, which were identified as styrene **190**, alcohol **191** and iodide **192**, and that rendered purification (and hence isolation of a pure sample) problematic (Fig. 13).

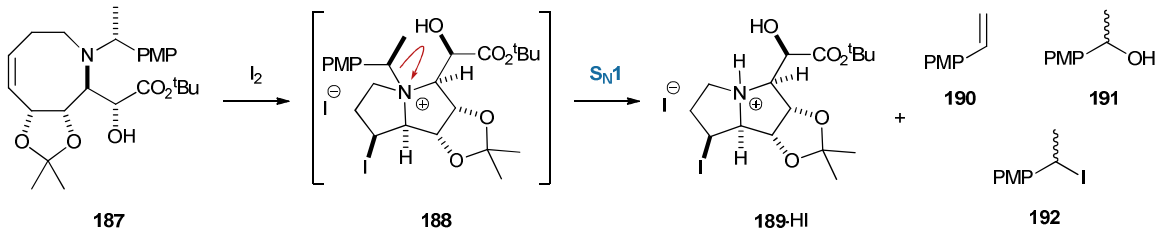
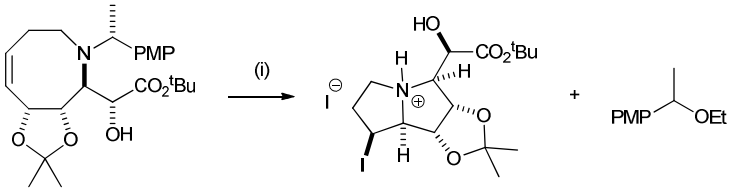


Figure 13 Reaction of hexahydroazocine **187** with iodine in $CHCl_3$ resulting in concomitant *N*-debenzylation.

In the original Davies iodoamination reaction, the α-methylbenzyl carbocation, formed as a result of the S_N1-type process, was efficiently scavenged by MeCN in a Ritter reaction to give *N*-α-methylbenzylacetamide **144**.[16a] However, investigations into the use of MeCN in this system showed that (α-methyl-*p*-methoxy)benzyl alcohol **191** was formed in preference to the desired acetamide, and hence attention was turned to identification of an alternate solvent system in which the reaction could be carried out but that would allow efficient scavenging to give a more easily separable product. It was proposed that reaction of **187** in the presence of an alcohol, such as EtOH, could result in the formation of (α-methyl-*p*-methoxy)benzyl ether

193, which would be of significantly different polarity to **189** and therefore allow further purification attempts. The reaction was repeated in CH_2Cl_2 in the presence of 3.0 equiv EtOH, which resulted in the formation of **189**·HI and (α-methyl-*p*-methoxy)benzyl ether **193**. Now **189**·HI could be readily separated from ether **193** by its direct recrystallisation from 30-40 °C petroleum ether. Furthermore, it was discovered that use of commercially available CH_2Cl_2 stabilised by EtOH (rather than the more commonly encountered amylene) allowed isolation of **189**·HI in >99:1 dr and 79% yield after direct crystallisation from the unpurified reaction mixture, along with (α-methyl-*p*-methoxy)benzyl ethyl ether **193**, which was isolated in 95% yield from the mother liquors (Scheme 30).



187 **189**·HI, 79%, >99:1 dr **193**, 95%, 3% ee

Scheme 30 *Reagents and conditions:* (i) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h.

The relative configuration within **189**·HI was unambiguously established by single crystal X-ray diffraction analysis, with the absolute configuration within **189**·HI being assigned from the known configurations of the C(1)- and C(2)-stereogenic centres (derived from D-ribose **152**). This analysis also unambiguously established the absolute configurations within the synthetic precursors hexahydroazocine **187** and α-hydroxy-β-amino ester **186**, and hence within β-amino ester **185** (Fig. 14).

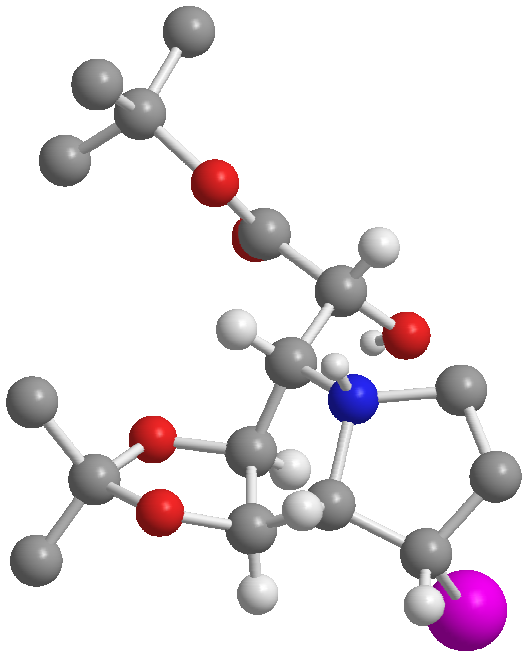


Figure 14 Chem3D representation of the single crystal X-ray structure of (1*R*,2*S*,3*S*,4*S*,7*S*,7a*S*,1′*R*)-**189**·HI (selected H atoms and the iodide counter-ion have been omitted for clarity).

The homochirality of **178** and **189**·HI suggested that the transannular cyclisation had occurred via the same pathway in each case. However, facile S_N1-type loss of the (α-methyl-*p*-methoxy)benzyl cation from ammonium **188** gave **189** which underwent salt formation to give **189**·HI upon reaction with *in situ* generated HI (Fig. 15).

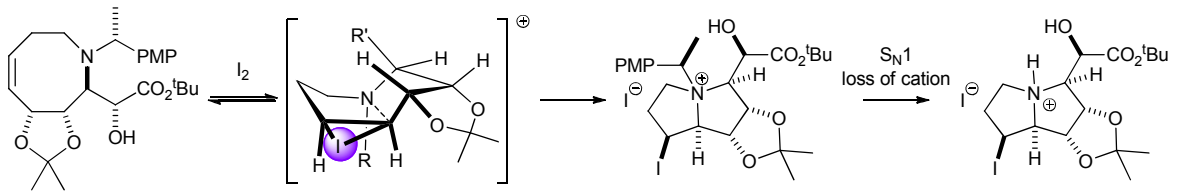


Figure 15 Postulated mechanistic rationale for transannular cyclisation of **187** and formation of **189**·HI [R = (*R*)-CHMePMP, R′ = (*R*)-CH(OH)CO_2^{t}Bu].

In order to help confirm this mechanistic proposal, the iodoamination reaction was monitored by 400 MHz ^{1}H spectroscopy with $CDCl_3$ as the solvent; it was hoped that the intermediate ammonium **188** would be observable. So that peak broadening or changes in chemical shifts were avoided, hexahydroazocine **187** was added to a homogeneous mixture of I_2 and $CDCl_3$. After 5 min, complete consumption of starting material had occurred to give a compound, which was assigned as ammonium salt **188** (spectra **B**); this was followed by loss of the *N*-(α-methyl-*p*-methoxy)benzyl group, which can be observed in spectra **C** and **D**. From here, signals appear at δ_H 2.79, 4.72 and 5.18 ppm, that are consistent with the production of **189**·HI, and the ^{1}H NMR peaks at δ_H 3.06, 4.10 and 5.30 ppm corresponding to ammonium **188** begin to decrease in intensity. Moreover, the peak that appears at δ_H 6.22 ppm shows the formation of styrene. After 5 h the *N*-debenzylation is complete as seen in spectra **E** (Fig. 16).

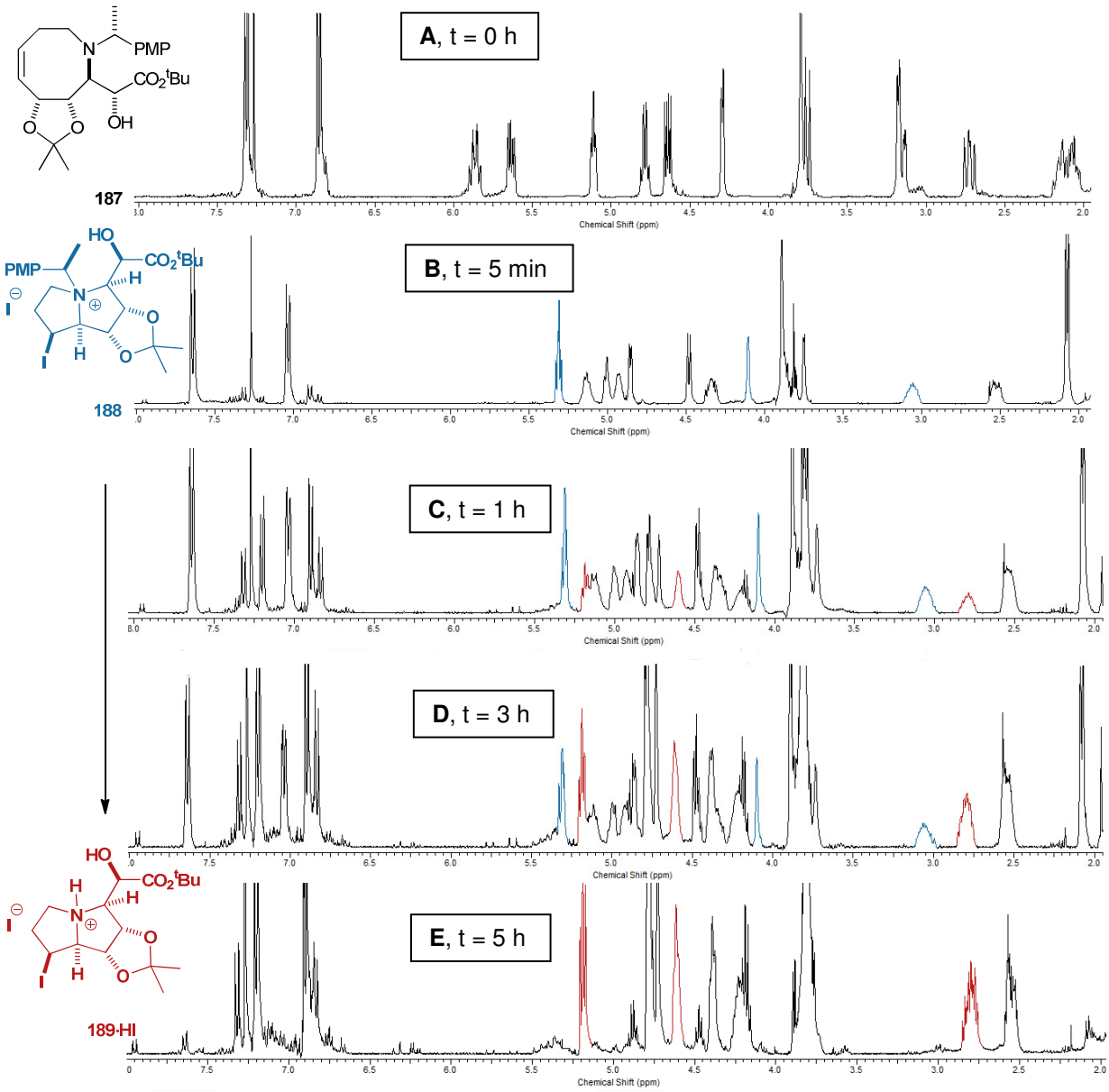
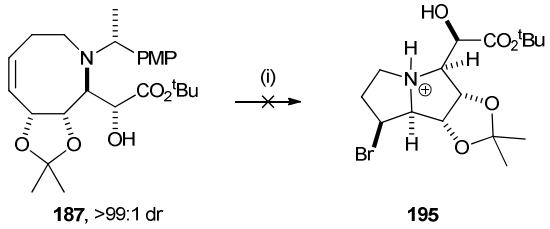


Figure 16 ^{1}H NMR spectra of the iodocyclisation of **187** at t = 0, 5 min, 1, 3 and 5 h, showing the formation of ammonium **188** and the loss of the (α-methyl-*p*-methoxy)benzyl group.

2.8.5 Transannular cyclisation of 187 induced by alternative electrophiles

With an efficient procedure for iodine-promoted transannular cyclisation in hand, the effect of a range of electrophiles on reaction with hexahydroazocine **187** was next investigated. Using the conditions previously reported by Wilson and Sawicki,[18] reaction of **187** with 1.2 equiv Br_2 in CH_2Cl_2 at rt gave a complex mixture of unidentifiable products, with no evidence of any transannular cyclisation or remaining starting material. Reaction of **187** with Br_2 under conditions that matched the developed iodocyclisation protocol (3.0 equiv Br_2 and 3.0 equiv $NaHCO_3$ in EtOH-stabilised CH_2Cl_2) resulted in a mixture of products that showed no evidence of residual starting material in the ^{1}H NMR spectrum of the unpurified reaction mixture. If an HBr salt was present then it was not possible to recrystallise it and hence

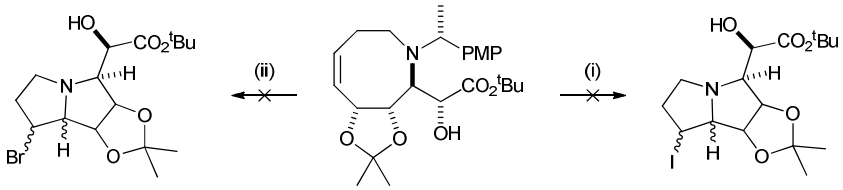
chromatographic purification (following treatment with base) was attempted. Repeated efforts gave a number of complex fractions and no cyclised product was isolated (Scheme 31)



187, >99:1 dr **195**

Scheme 31 *Reagents and conditions:* (i) Br_2 (3.0 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2 (EtOH-stabilised), rt, 12 h; (ii) Br_2 (1.2 equiv), CH_2Cl_2, rt, 12 h.

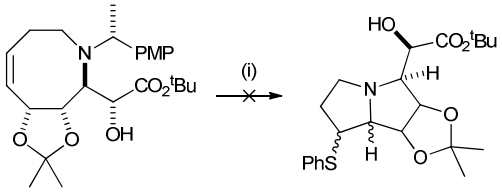
In light of these results, it was proposed that a reagent such as NBS would enable the isolation of the C(7)-bromo substituted pyrrolizidine **195**. There is significant literature precedence for carrying out haloaminations using NIS and NBS.[42] Reaction of hexahydroazocine **187** with either NIS or NBS resulted in the formation of complex mixtures from which no evidence of cyclisation could be gleaned (Scheme 32).



187, >99:1 dr

Scheme 32 *Reagents and conditions:* (i) NIS, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h; (ii) NBS, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h.

Wilson and Sawicki also reported the successful transannular cyclisation of 1,4-aza-*cis*-cyclooctene **172** with PhSBr and PhSeBr leading to the corresponding C(7)-sulfenyl and C(7)-selenyl substituted pyrrolizidine scaffolds in 71 and 63% yields, respectively.[18] Reaction of hexahydroazocine **187** with PhSCl[43] resulted in apparent cyclisation, however attempted chromatographic purification of pyrrolizidine **196** was unsuccessful (Scheme 33).



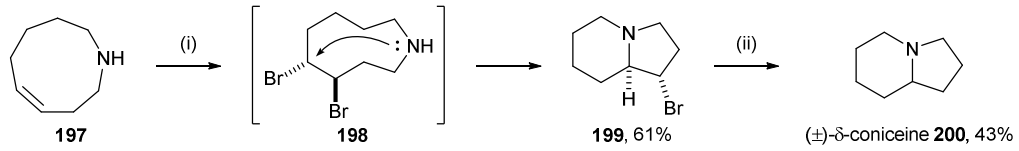
187, >99:1 dr **196**

Scheme 33 *Reagents and conditions:* (i) PhSH, NCS, CH_2Cl_2, rt, 12 h.

2.9 Larger ring size – formation of an indolizidine scaffold

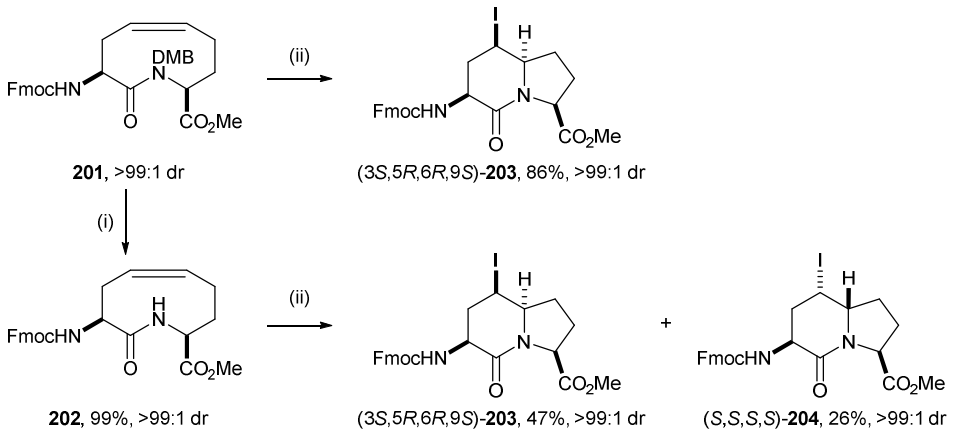
Alongside their investigation into the cyclisation of 1,4-aza-*cis*-cyclooctene **172**, Wilson and Sawicki reported the transannular cyclisation of hexahydroazonine **197** upon treatment with bromine,[44] which resulted in the formation of a single compound **199** that was isolated in 61%

yield. The regio- and stereochemistry of **199** was confirmed by single crystal X-ray diffraction analysis and suggested that, in this instance, transannular cyclisation had occurred via formation of the dibromide **198** instead of via direct trapping of the corresponding bromonium ion by the nitrogen atom.[44] Having isolated **199** successfully, a total synthesis of (±)-δ-coniceine **200** was completed by reduction of the C–Br bond with $LiAlH_4$ to give (±)-**200** in 43% yield (Scheme 34).



Scheme 34 *Reagents and conditions:* (i) Br_2, CH_2Cl_2/Et_2O (v/v 1:1), rt, 12 h; (ii) $LiAlH_4$, THF, reflux, 12 h.

Other studies into the transannular cyclisation of 9-membered azacycles to their corresponding 5,6-fused indolizidines have focused on the cyclisation of macrolactams. It has been reported that in such systems the presence of the carbonyl group controls the regiochemical outcome of ring-closure to place the carbonyl (and hence the electrophile) on the 6-membered ring.[45] For example, in their investigations into the synthesis of the efficient peptide mimics that contain the general azabicyclo[X.Y.0]alkanone structure, Surprenant and Lubell investigated the iodine-promoted transannular cyclisation of macrocyclic dipeptides **201** and **202**. Here, reaction of tertiary amide **201** occurred with concomitant *N*-debenzylation to give **203** in 86% yield and >99:1 dr. However, transannular cyclisation of secondary amide **202** resulted in the isolation of the diastereoisomeric products **203** and **204** in 47 and 26% yield, respectively; in each case the regiochemistry of cyclisation was such that the carbonyl group was placed on the 6-membered ring (Scheme 35).[46] The authors did not comment on the difference in the stereoselectivity between the cyclisation of the tertiary and secondary amines.



Scheme 35 *Reagents and conditions:* (i) TFA/CH_2Cl_2 (v/v 1:1); (ii) I_2, THF, reflux, 2 h.

2.9.1 Proposed route to the indolizidine scaffold

It was envisaged that the conjugate addition/ring-closing metathesis approach to the hexahydroazocine **187** would allow access to the analogous 9-membered ring **118** if the initial conjugate addition employed lithium (*R*)-*N*-pent-4-enyl-*N*-(α-methyl-*p*-methoxybenzyl) amide (*R*)-**205**.[47] Transannular cyclisation of hexahydroazonine **118** could occur to give rise to either of two polysubstituted indolizidine scaffolds: **119** or **206** (Fig. 17).

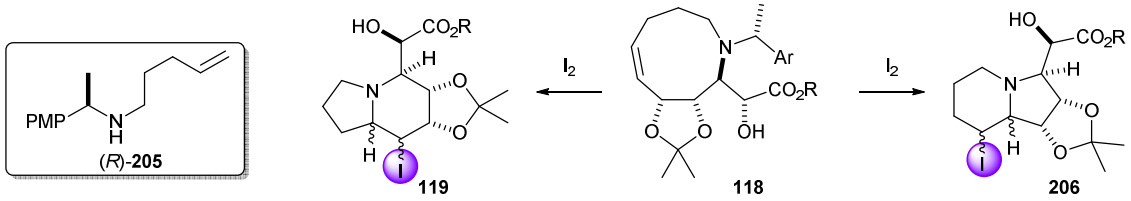
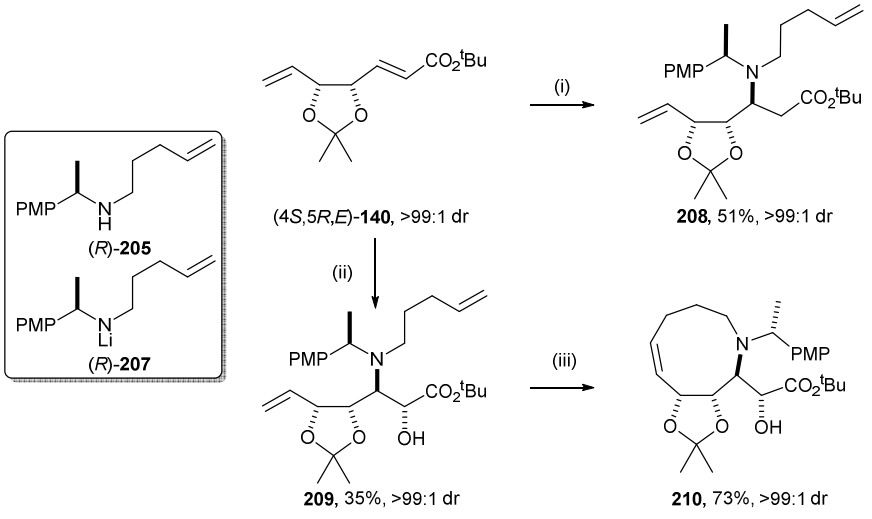


Figure 17 The two possible products from iodocyclisation of hexahydroazonine **118**.

2.9.2 Conjugate addition of (*R*)-207 to (4*S*,5*R*,*E*)-140

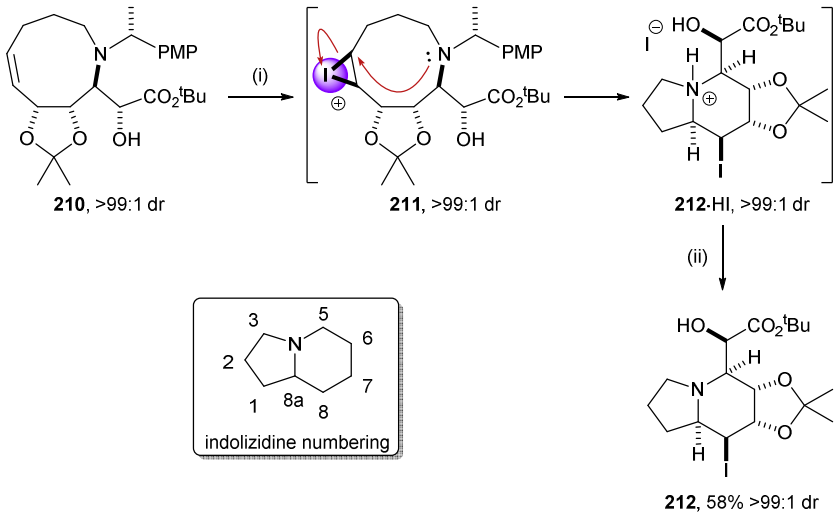
The pentenyl substituted amine (*R*)-**205** was prepared from (*R*)-*N*-(α-methyl-*p*-methoxybenzyl)amine by alkylation with 5-bromo-1-pentene. Conjugate addition of lithium amide (*R*)-**207** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** in THF at −78 °C gave β-amino ester **208** in 51% yield and >99:1 dr, and the configuration within **208** was confidently assigned by reference to the transition state mnemonic.[28] The preparation of α-hydroxy-β-amino ester **209** was achieved in 35% yield and >99:1 dr after conjugate addition of (*R*)-**207** to (4*S*,5*R*,*E*)-**140** with *in situ* enolate oxidation using (−)-CSO **169** (the low yield in this case was due to difficulties encountered during purification). The relative C(2)-C(3) configuration within **209** was assigned as *anti*.[33] Ring-closing metathesis of **209** with Grubbs I catalyst in CH_2Cl_2 was carried out under the literature conditions of 30 °C for 12 h, and gave **210** in 73% yield and >99:1 dr (Scheme 36).[14]



Scheme 36 *Reagents and conditions:* (i) (*R*)-**207**, THF, −78 °C, 2 h; (ii) (*R*)-**207**, THF, −78 °C, 2 h then (−)-CSO **169**, −78 °C to rt, 12 h; (iii) Grubbs I catalyst (10 mol%), CH_2Cl_2, 30 °C, 12 h.

2.9.3 Transannular iodoamination of 210

Treatment of **210** under the previously optimised transannular cyclisation conditions resulted in the formation of a single cyclised product that was tentatively assigned as **212**·HI along with ether **193**. Unfortunately in this case direct recrystallisation did not enable the purification and isolation of **212**·HI, and instead **212** was isolated in 58% yield and >99:1 dr following an aqueous base wash and subsequent chromatographic purification (Scheme 37). Transannular cyclisation of **210** occurred to give the single regio- and diastereoisomer **212**. The regiochemistry of **212** was established by ^{1}H-^{1}H 2D COSY NMR spectroscopic analysis, which indicated that the ring-closure had occurred selectively to form a 6,5-system placing the iodine substituent on the larger ring. The relative configuration of the C(5)-C(7) and C(8a) stereogenic centres were established by nOe analysis of a derivative (*vide infra*) and the relative configuration at C(8) within **212** was subsequently assigned on the basis of an analogous mechanism of cyclisation, which proceeds via iodonium **211**. Within this mechanistic proposal, it is apparent that the regiochemical outcome is consistent with an attack of the nitrogen atom onto the iodonium **211** at the carbon furthest from the oxygen substituent at C(7) to minimise its destabilising electron withdrawing effect on the transition state.[48]



Scheme 37 *Reagents and conditions:* (i) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h; (ii) KOH (1.0 M aq), CH_2Cl_2.

2.10 Synthesis of polyhydroxylated alkaloids

With the iodo-substituted pyrrolizidine and indolizidine scaffolds (**189**·HI and **212**, respectively) in hand, attention was turned to the elaboration of these compounds to the corresponding azacycles. It was proposed that this could rapidly be achieved in four facile steps: reduction of the C–I bond and C(1′)-ester moiety, cleavage of the diol, reduction of the

resultant aldehyde and then acid-deprotection. This would lead to the known pyrrolizidine 7a-*epi*-hyacinthacine A1 **216** in the case of **189**·HI, and to a novel indolizidine **215** in the case of **212** (Fig. 18).

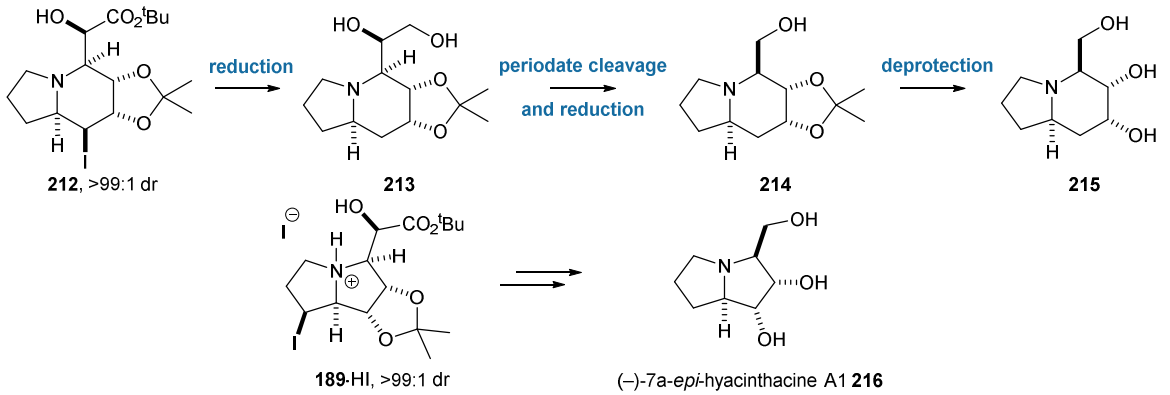
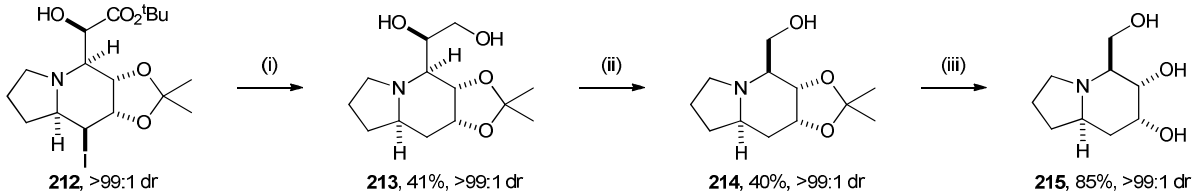


Figure 18 Proposed route through to a novel polyhydroxylated indolizidine **215** and 7a-*epi*-hyacinthacine A1 **216**.

2.10.1 (5*S*,6*S*,7*R*,8a*R*)-6,7-dihydroxy-5-(hydroxymethyl)hexahydro-1*H*-indolizidine 215

As expected, treatment of **212** with $LiAlH_4$ in THF for 12 h resulted in the simultaneous reduction of the C–I bond as well as the *tert*-butyl ester to give diol **213** in 41% yield and >99:1 dr. Oxidative cleavage of the diol using $NaIO_4$ in MeOH/H_2O was followed by immediate reduction of the resultant aldehyde with $NaBH_4$ to give **214** in 40% yield as a single diastereoisomer. Finally acid-catalysed deprotection of the dioxolane group using 3.0 M aq HCl in MeOH and subsequent ion exchange chromatography gave the novel indolizidine **215** in 85% yield and >99:1 dr (Scheme 38).



Scheme 38 *Reagents and conditions:* (i) $LiAlH_4$ (1.0 M in THF), THF, −78 °C to rt 12 h; (ii) $NaIO_4$, MeOH/H_2O (v/v 5:1), rt, 4 h then $NaBH_4$, MeOH, rt, 12 h; (iii) HCl (3.0 M aq), MeOH, 60 °C, 2 h.

^{1}H NMR nOe analysis was instigated to determine the relative configuration within **215**, and hence within the precursors **209** to **214**. Irradiation of the protons around the bicyclic system within **215** resulted in a series of enhancements linking C(6)*H*, C(7)*H*, C(8)H_A and C(1′)H_2, which suggested that they occupied the same face of the bicyclic system. Most importantly, a reciprocal interaction between C(8a)*H* and C(5)*H* was also observed, along with a reciprocal interaction between C(8a)*H* and C(8)H_B, suggesting that these protons also occupied the same face. This allowed assignment of the relative configuration within **215**. The absolute (*S*)-configuration at C(5) was assigned by reference to the diastereofacial selectivity of the

conjugate addition of lithium amide (*R*)-**207** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** and the (6*S*,7*R*)-configuration derived from D-ribose **152**, which allowed the absolute (5*S*,6*S*,7*R*,8a*R*)-configuration to be assigned to **215** (Fig. 19).

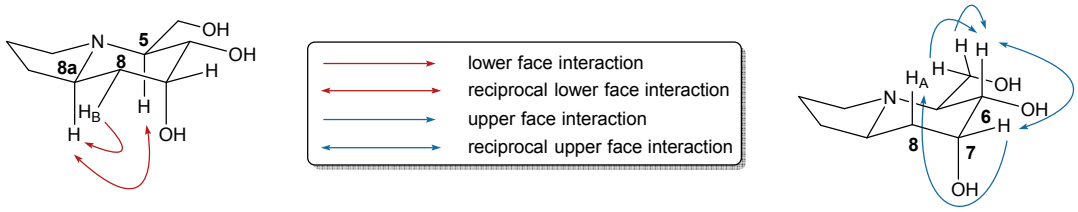
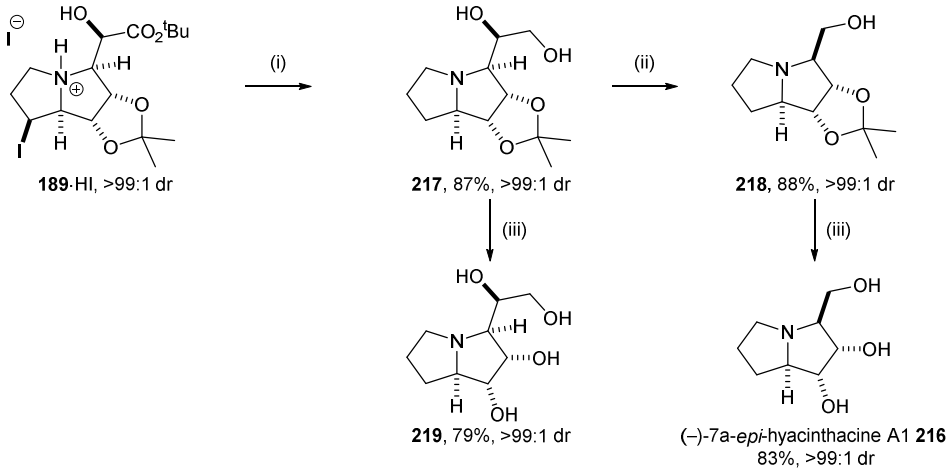


Figure 19 ^{1}H NMR nOe correlations within polyhydroxylated indolizidine **215**.

2.10.2 Synthesis of (–)-7a-*epi*-hyacinthacine A1 216

The planned elaboration of the C(7)-iodo-substituted pyrrolizidine scaffold **189**·HI would result in a concise and stereoselective synthesis of 7a-*epi*-hyacinthacine A1 **216**, a known diastereoisomer of the alkaloid hyacinthacine A1 **120**. Reduction of the ester moiety and the C–I bond with $LiAlH_4$ in THF gave diol **217** in 87% yield. Acid-catalysed hydrolysis of diol **217** gave a novel C(1′)-hydroxymethyl substituted analogue of 7a-*epi*-hyacinthacine A1 **216**, (1*R*,2*S*,3*S*,7a*R*,1′*R*)-7a-*epi*-1′-(hydroxymethyl)hyacinthacine A1 **219**, which was isolated in 79% yield and >99:1 dr after ion exchange chromatography. Oxidative cleavage of **217** was followed immediately by addition of $NaBH_4$ (to avoid the need to isolate the resultant aldehyde), which gave **218** in 88% yield and >99:1 dr. Acid deprotection of the acetonide group and purification by ion exchange chromatography afforded (–)-7a-*epi*-hyacinthacine A1 **216** in 10% yield over nine steps from D-ribose **152** (Scheme 39). [49,50]



Scheme 39 *Reagents and conditions:* (i) $LiAlH_4$ (1.0 M in THF), THF, −78 °C to rt 12 h; (ii) $NaIO_4$, MeOH/H_2O (v/v 5:1), rt, 4 h then $NaBH_4$, MeOH, rt, 12 h; (iii) HCl (3.0 M aq), MeOH, 60 °C, 2 h.

The specific rotation and ^{1}H and ^{13}C NMR spectra of this sample of (–)-7a-*epi*-hyacinthacine A1 **216** {$[\alpha]_D^{25}$ –45.9 (*c* 0.2 in H_2O)} were in excellent agreement with those previously reported for (–)-7a-*epi*-hyacinthacine A1 **216** {$[\alpha]_D^{22}$ –45.3 (*c* 1.5 in H_2O)} by Clapés *et al.*,[49d]

(+)-7a-*epi*-hyacinthacine A1 **216** by Izquierdo *et al.* {$[\alpha]_D^{27}$ +47.0 (*c* 0.65 in H_2O)}[49b] and for racemic (±)-7a-*epi*-hyacinthacine A1 **216** by Affolter *et al.*[49a] (Tables 1 and 2).

^{1}H data for 7a-*epi*-hyacinthacine A1 **216**					
H	δ_H (500 MHz, D_2O [TSP])		δ_H (500 MHz, MeOH-d_4)		
	Clapés[49d]	This study	Izquierdo[49b]	Affolter[49a]	This study
C(1)H	4.00 (dd, *J* 5.0, 1.8)	3.93 (dd, *J* 5.0, 2.3)	3.76 (dd)	3.75 (dd, *J* 5.4, 2.7)	3.81 (dd, *J* 5.3, 2.3)
C(2)H	4.08 (dd, *J* 10.0, 4.9)	4.02 (dd, *J* 9.5, 5.0)	3.88 (dd, *J* 9.0, 5.5)	3.79-3.89 (m)	3.93 (dd, *J* 8.8, 5.3)
C(3)H	3.41 (ddd, *J* 10.0, 8.5, 4.5)	3.25, (ddd, *J* 9.5, 6.6, 6.6)	3.21 (dt)	3.19 (ddd, *J* 8.5, 8.2, 4.2)	3.29 (app td, *J* 8.8, 4.1)
C(5)H_A	2.91 (td, *J* 10.7, 5.7)	2.76 (td, *J* 10.4, 5.7)	2.91 (ddd, *J* 9.0, 2.1)	2.76 (ddd, *J* 10.3, 9.5, 5.8)	2.86 (td, *J* 10.1, 6.0)
C(5)H_B	3.13 (m)	2.94-2.97 (m)	2.79 (dt, *J* 9.8, 5.8)	2.88 (ddd, *J* 9.5, 6.6, 2.7)	2.97-3.01 (m)
C(6)H_A	1.73 (m)	1.63-1.73 (m)	1.87 (m)	1.64-1.74 (m)	1.69-1.70 (m)
C(6)H_B	1.99 (m)	1.89-1.94 (m)	1.69 (m)	1.83-1.89 (m)	1.89-1.95 (m)
C(7)H_A	1.58 (m)	1.49-1.57 (m)	1.50 (ddt, *J* 10.4, 7.6)	1.49 (ddt, *J* 12.6, 10.6, 7.7)	1.50-1.58 (m)
C(7)H_B	2.25 (m)	2.17-2.23 (m)	2.14 (ddt, *J* 12.6, 7.6, 2.5)	2.11-2.17 (m)	2.16-2.22 (m)
C(7a)H	3.63 (td, *J* 8.5, 1.7)	3.43 (td, *J* 8.2, 2.3)	3.39 (app dd, *J* 7.9, 2.4)	3.36 (dt, *J* 7.7, 2.7)	3.57 (dt, *J* 8.2, 2.3)
C(1′)H_2	3.91 (m)	3.89 (d, *J* 6.6)	3.81-3.84 (m)	3.79-3.89 (m)	3.84-3.91 (m)

Table 1 Comparison of ^{1}H NMR data of 7a-*epi*-hyacinthacine A1 **216** [Chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

^{13}C data for 7a-*epi*-hyacinthacine A1 **216**					
C	δ_C (125 MHz, D_2O [TSP])		δ_C (125 MHz, MeOH-d_4)		
	Clapés[49d]	This study	Izquierdo[49b]	Affolter[49a]	This study
C(1)	77.3	78.2	76.9	77.4	77.0
C(2)	72.8	73.6	72.5	72.7	72.4
C(3)	66.7	67.3	67.1	67.0	66.9
C(5)	50.0	50.1	49.1	48.6	46.5
C(6)	28.0	28.6	27.4	27.3	27.3
C(7)	31.6	32.2	30.9	31.0	30.9
C(7a)	72.7	72.6	72.1	71.3	71.7
C(1′)	61.3	62.3	60.9	61.3	60.9

Table 2 Comparison of ^{13}C NMR data of 7a-*epi*-hyacinthacine A1 **216** [Chemical shifts (δ_C) are reported in ppm].

2.11 Summary

Doubly diastereoselective 'matched' conjugate addition of lithium amides (*R*)-**131** and (*R*)-**184** to α,β-unsaturated ester (4*S*,5*R*,*E*)-**140** with *in situ* enolate oxidation by (−)-CSO **169** was followed by ring-closing metathesis with Grubbs I catalyst to enable rapid construction of hexahydroazocines **171** and **187** in a highly diastereoselective manner. Treatment of **171** with I_2 resulted in transannular cyclisation to allow the isolation of ammonium salt **178**. A similar ammonium salt formation was also observed in the reaction of **187** with I_2, although in this instance it was followed by rapid S_N1-type loss of the (α-methyl-*p*-methoxy)benzyl group to give iodopyrrolizidine **189**·HI.[51] Elaboration of **189**·HI allowed the synthesis of the known pyrrolizidine (−)-7a-*epi*-hyacinthacine A1 **216**, which was completed in nine steps from D-ribose **152** and in 10% overall yield (Fig. 20).

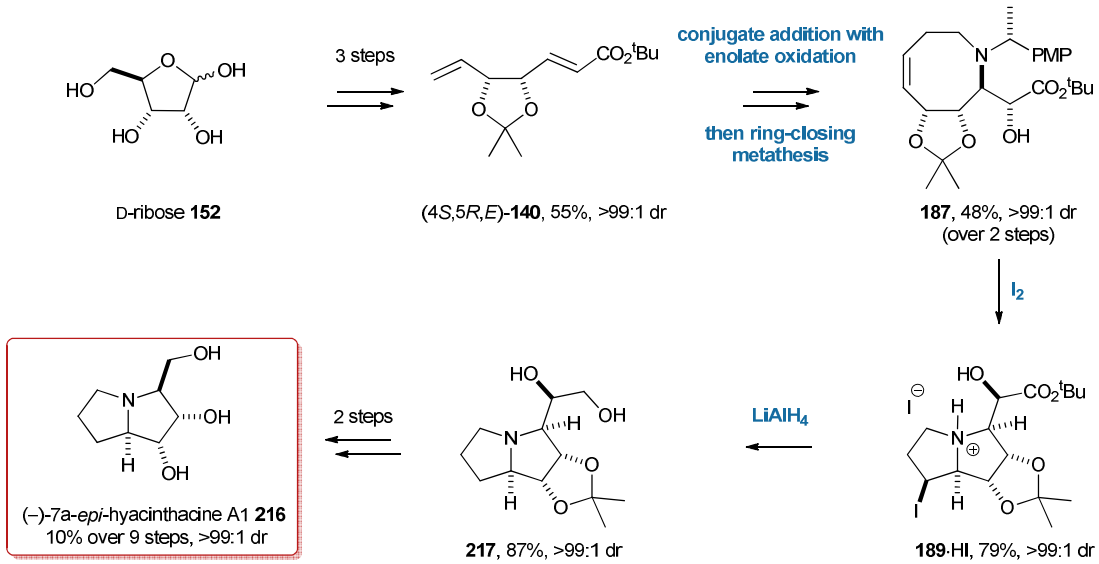


Figure 20 The total asymmetric synthesis of (−)-7a-*epi*-hyacinthacine A1 **216** using an iodine-mediated transannular cyclisation as the key step.

This methodology was also successfully applied in an analogous hexahydroazonine system for the preparation of a novel polysubstituted indolizidine **215**. Further investigations into the scope of this protocol and its application in the synthesis of polysubstituted pyrrolizidines that are more densely functionalised or that differ in stereochemistry are described in the next chapters.

2.12 References and notes

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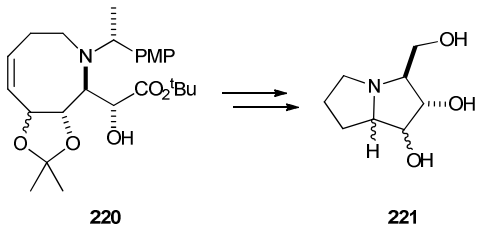
Further Application of Transannular Iodoaminations: Synthesis of (−)-Hyacinthacine A1 and (−)-Hyacinthacine A2

This chapter describes the further development of the transannular iodoamination methodology and its application in the asymmetric synthesis of diastereoisomers of the 1,2-dihydroxy-3-hydroxymethyl pyrrolizidine family of compounds (Fig. 21).



220 **221**

Figure 21 Elaboration of hexahydroazocines **220** to diastereoisomeric pyrrolizidines **221**.

3.1 Polyhydroxylated pyrrolizidines

Polyhydroxylated pyrrolizidines that share the 1,2-dihydroxy-3-hydroxymethyl motif around their scaffold are distinguished by the relative stereochemistry at their four stereogenic centres, as illustrated by the structures of the three known pyrrolizidine alkaloids, hyacinthacine A1 **120**,[1] hyacinthacine A2 **222**[2] and 7-deoxyalexine **223**,[3] which differ only in their relative stereochemistry at C(1), C(2) and/or C(3) (Fig. 22). There are 16 possible stereoisomeric pyrrolizidines that have this particular substitution pattern (8 pairs of enantiomers) and, of these 8 diastereoisomers, only one, 7a-*epi*-hyacinthacine A1 **216**, has been prepared via the original route (*vide supra*). It was anticipated that further investigation into the transannular iodoamination approach may allow access to some of the other 7 diastereoisomers.

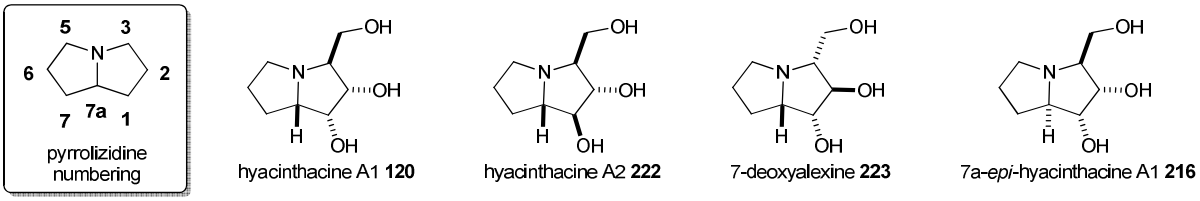
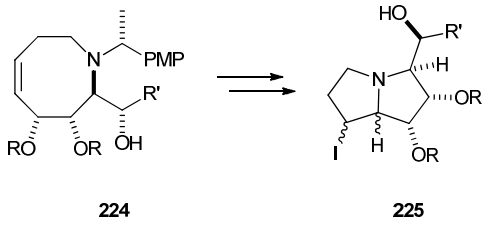


Figure 22 Three known diastereoisomeric pyrrolizidine alkaloids: hyacinthacine A1 **120**, hyacinthacine A2 **222**, 7-deoxyalexine **223**, 7a-*epi*-hyacinthacine A1 **216**.

3.2 Structural effects on the diastereoselectivity of the iodocyclisation

In order to expand the utility of this synthetic approach to the pyrrolizidine family of alkaloids, it was envisaged that modifying the structure of hexahydroazocine **187** and subjecting the resulting structural analogues to the optimised transannular iodocyclisation conditions may provide some insight into the origin of the diastereoselectivity of the process,

as well as providing further iodopyrrolizidines for elaboration to polyhydroxylated pyrrolizidines (Fig. 23).

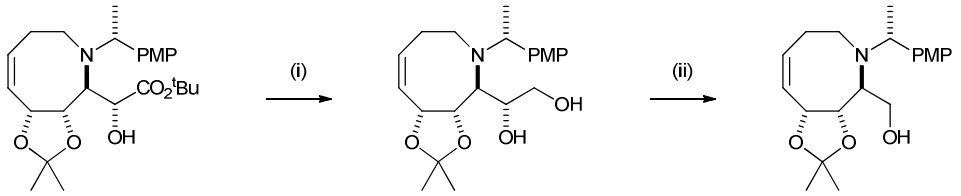


224 **225**

Figure 23 The proposed route to alternate iodopyrrolizidines **225**.

3.2.1 Iodoamination of 227

At first, an investigation into the effect of performing an oxidative cleavage of diol **226**, prior to the iodocyclisation, was carried out. Treatment of **187** with $LiAlH_4$ resulted in the reduction of the ester to give diol **226** in 89% yield and >99:1 dr. Oxidative cleavage of this diol upon treatment with $NaIO_4$ and then reduction with $NaBH_4$ proved to be somewhat problematic, and several attempts produced either a white solid or a dark brown oil, which both gave intractable ^1H NMR spectra in an range of solvents. However, mass spectrometric analyses of these products revealed a signal at m/z = 303 corresponding to $[M+H]^+$ of the desired product **227**. Thus, purification by column chromatography was carried out which allowed the isolation of **227** in >99:1 dr, albeit in only 15% yield (Scheme 40).

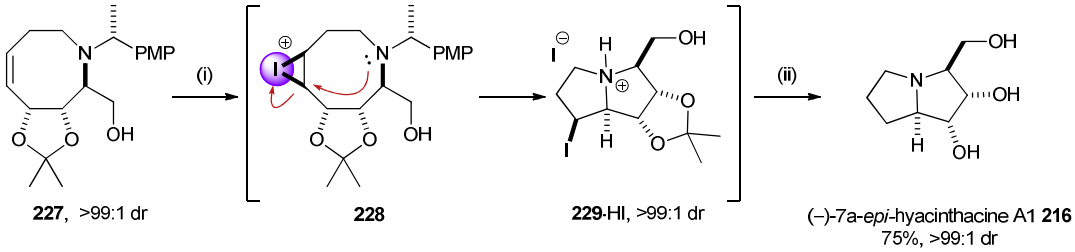


187, >99:1 dr **226**, 89% >99:1 dr **227**, 15% >99:1 dr

Scheme 40 *Reagents and conditions:* (i) $LiAlH_4$ (1.0 M in THF), THF, −78 °C to rt, 12 h; (ii) $NaIO_4$, MeOH, rt, 4 h then $NaBH_4$, MeOH, rt, 12 h.

Cyclisation of **227** under the optimised conditions (3.0 equiv I_2 and 3.0 equiv $NaHCO_3$ in CH_2Cl_2 for 12 h) was next investigated and gave a single compound, assigned as iodopyrrolizidine **229**·HI. Immediate hydrogenolysis of **229**·HI under 1 atm H_2 in the presence of Et_3N and 10% Pd/C (to effect reduction of the C–I bond), was followed by acid-catalysed hydrolysis on treatment with 3.0 M HCl (to hydrolyse the dioxolane ring). Purification via ion exchange chromatography gave (–)-7a-*epi*-hyacinthacine A1 **216** in 75% yield and >99:1 dr. The identity of **216** was confirmed by comparison of its ^1H and ^{13}C NMR spectrum and specific rotation $\{[\alpha]_D^{20}$ –39.5 (*c* 0.3 in H_2O)$\}$ with the sample prepared previously (*vide supra*). Assuming in this case an analogous mechanism for transannular cyclisation (i.e., via iodonium ion formation and subsequent attack by the nitrogen atom) the

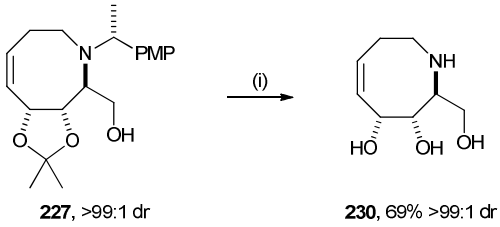
C(7)-configuration within iodopyrrolizidine **229**·HI was also assigned. Thus, the stereochemical outcome of this transannular cyclisation is in accordance with that for hexahydroazocine **187** (Scheme 41).



Scheme 41 *Reagents and conditions:* (i) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h; (ii) H_2 (1 atm), 10% Pd/C (50% w/w), Et_3N, MeOH, rt, 12 h then HCl (6.0 M aq), MeOH.

3.2.2 Synthesis of (−)-hyacinthacine A1 120

Next, the cyclisation of the fully deprotected hexahydroazocine **230** was investigated. Hydrolysis of the dioxolane unit within hexahydroazocine **227** on heating with 3.0 M aq HCl in MeOH simultaneously removed the *N*-(α-methyl-*p*-methoxy)benzyl group and the acetal protecting group, to give **230** in 69% yield after purification by ion-exchange chromatography (Scheme 42).



Scheme 42 *Reagents and conditions:* (i) HCl (3.0 M aq), MeOH, 60 °C, 2 h.

The relative configuration within **230** was confirmed by single crystal X-ray diffraction analysis, with the (2*S*,3*S*,4*R*)-absolute configuration within **230** being assigned from the known (2*R*,2′*S*,3′*S*,4′*R*,α*R*)-absolute configuration within hexahydroazocine **187** (Fig. 24).

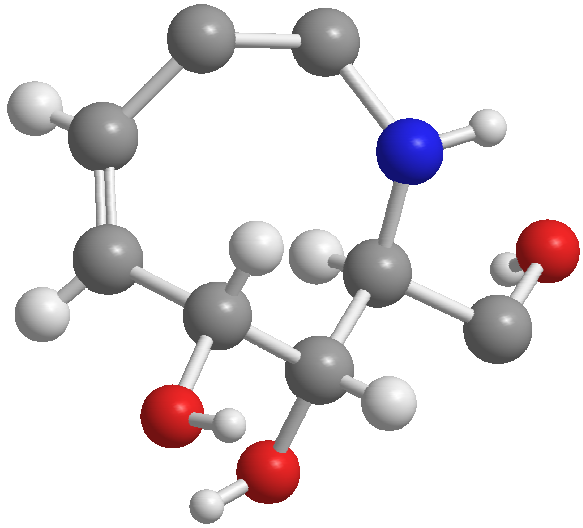
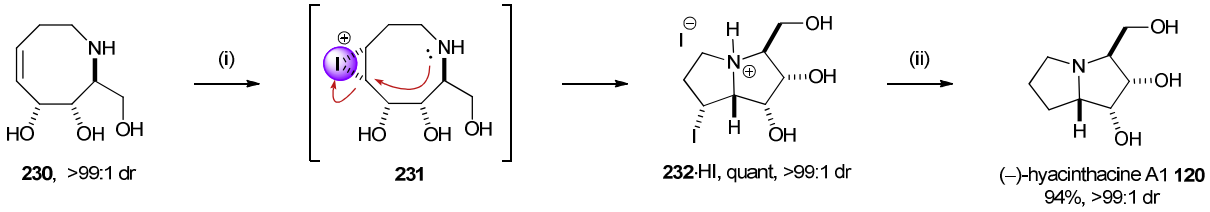


Figure 24 Chem3D representation of the single crystal X-ray diffraction structure of (2*S*,3*S*,4*R*)-230 (selected H atoms have been omitted for clarity).

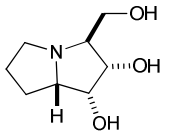
Due to the inherent insolubility of triol **230** in CH_2Cl_2 and $CHCl_3$, the transannular iodoamination reaction was performed in MeOH. In order to avoid partial dissolution of $NaHCO_3$ or $Na_2S_2O_3$ (used during work-up), a new procedure was designed whereby no $NaHCO_3$ was used (*vide infra*) and only 1.0 equiv of I_2 was employed to ensure that there was no excess reagent left to quench at the end of the reaction. After stirring the mixture for 12 h at rt the solvent was removed *in vacuo* to give a single product, assigned as iodopyrrolizidine **232**·HI in >99:1 dr. Subsequent hydrogenolysis and purification of the resultant product by ion exchange chromatography gave a single polyhydroxylated pyrrolizidine, identified as (−)-hyacinthacine A1 **120** by comparison of its specific rotation and ^{1}H and ^{13}C NMR spectra with those previously reported in the literature (*vide infra*),[1,4] which was isolated in 94% yield and >99:1 dr. As before, by invoking a mechanism which involves reversible iodonium ion formation and subsequent attack of the nitrogen, the isolation of (−)-**120** from this sequence of reactions suggested that the transannular cyclisation had occurred onto iodonium ion **231** to give iodopyrrolizidine **232**·HI (Scheme 43). The stereochemical outcome of this transannular cyclisation is therefore in contrast to that seen in the transannular cyclisation of hexahydroazocines **187** and **227**.



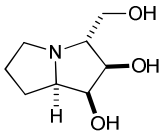
230, >99:1 dr — **231** — **232**·HI, quant, >99:1 dr — (−)-hyacinthacine A1 **120** 94%, >99:1 dr

Scheme 43 *Reagents and conditions:* (i) I_2 (1.0 equiv), MeOH, rt, 12 h; (ii) H_2 (1 atm), 10% Pd/C (50% w/w), Et_3N, MeOH, rt, 12 h.

Comparison of the ^{1}H and ^{13}C NMR data of this synthetic sample of (−)-hyacinthacine A1 **120** {$[\alpha]_D^{20}$ −34.1 (*c* 0.4 in H_2O)} with those reported for (+)-hyacinthacine A1 **120** {$[\alpha]_D^{20}$ +38.2 (*c* 0.23 in H_2O)} isolated from *Muscari armeniacum* by Asano *et al.*,[1] and those reported for a synthetic sample of (+)-hyacinthacine A1 **120** {$[\alpha]_D^{20}$ +43.5 (*c* 0.23 in H_2O)} by Donohoe *et al.*[4f] showed excellent agreement (Tables 3 and 4).



(–)-hyacinthacine A1 **120**



(+)-hyacinthacine A1 **120**

^{1}H NMR data for hyacinthacine A1 **120** (in MeOH-d_4)			
H	Asano *et al.*[1] (400 MHz)	Donohoe *et al.*[4f] (400 MHz)	This study (500 MHz)
C(1)H	3.87 (t, *J* 4.0)	3.90 (m)	3.87-3.90 (m)
C(2)H	3.88 (dd, *J* 9.0, 4.0)	3.88 (m)	3.87-3.90 (m)
C(3)H	2.76 (ddd, *J* 9.0, 6.4, 3.4)	2.81 (m)	2.75-2.79 (m)
$C(5)H_A$	2.65 (ddd, *J* 10.0, 8.1, 6.1)	2.69 (ddd, *J* 10.0, 8.1, 6.2)	2.63-2.68 (m)
$C(5)H_B$	3.05 (ddd, *J* 10.0, 6.4, 4.9)	3.10 (ddd, *J* 10.4, 5.6, 5.6)	3.05-3.09 (m)
$C(6)H_A$	1.74 (m)	1.78 (m)	1.75-1.82 (m)
$C(6)H_B$	1.93 (m)	1.96 (m)	1.92-1.99 (m)
$C(7)H_A$	1.68 (m)	1.70 (m)	1.66-1.72 (m)
$C(7)H_B$	2.08 (m)	2.11 (m)	2.06-2.13 (m)
C(7a)H	3.47 (ddd, *J* 8.1, 6.6, 4.0)	3.52 (ddd, *J* 7.8, 6.6, 3.5)	3.46 (td, *J* 7.6, 2.8)
$C(1')H_A$	3.58 (dd, *J* 11.3, 6.4)	3.60 (dd, *J* 11.2, 6.6)	3.60 (dd, *J* 11.0, 6.6)
$C(1')H_B$	3.78 (dd, *J* 11.3, 3.4)	3.81 (dd, *J* 11.2, 3.3)	3.81 (dd, *J* 11.0, 3.5)

Table 3 Comparison of ^{1}H NMR data for hyacinthacine A1 **120** [Chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

^{13}C NMR data for hyacinthacine A1 **120** (in MeOH-d_4)			
C	Asano *et al.*[1] (100 MHz)	Donohoe *et al.*[4f] (100 MHz)	This study (125 MHz)
C(1)	73.7	72.9	72.9
C(2)	77.5	76.6	76.8
C(3)	71.9	71.2	71.1
C(5)	57.5	57.0	56.8
C(6)	28.8	28.1	28.1
C(7)	26.0	25.3	25.2
C(7a)	69.7	67.4	66.9
C(1')	65.2	64.2	64.7

Table 4 Comparison of ^{13}C NMR data for hyacinthacine A1 **120** [Chemical shifts (δ_C) are reported in ppm].

3.3 Exploring the flexibility of the transannular iodoamination reaction

The configuration at C(3) within the final pyrrolizidines **120** and **216** is a result of the doubly diastereoselective 'matched' conjugate addition of (*R*)-**184** to (4*S*,5*R*,*E*)-**140**, and the

configuration at C(7a) is a result of the diastereoselectivity of the transannular iodocyclisation of **187** so, as such both may be considered inherent to the system and less readily operator controlled (Fig. 25). However, to increase the synthetic value of the transannular iodoamination approach to polyhydroxylated pyrrolizidines, it was desirable to be able to access the corresponding 1,2-*anti* configured diastereoisomers, and since these stereocentres result from the α,β-unsaturated ester, it was proposed that the conjugate addition/ring-closing metathesis approach could allow access to the relative *trans*-stereochemistry at C(1) and C(2) in the hexahydroazocine scaffold if α,β-unsaturated ester (*S*,*S*,*E*)-**233** was employed in the place of (4*S*,5*R*,*E*)-**140**.

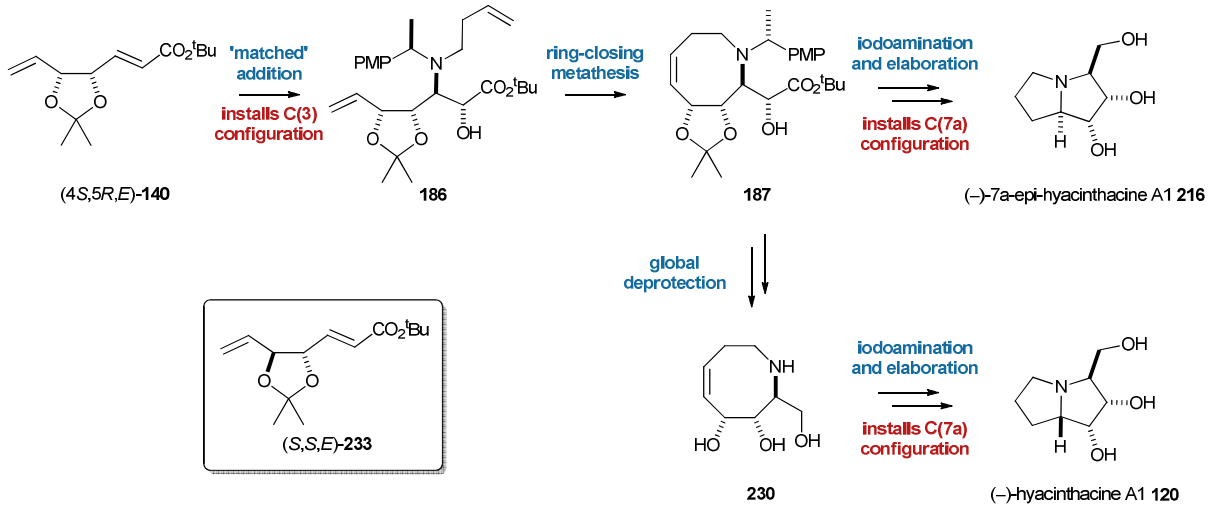
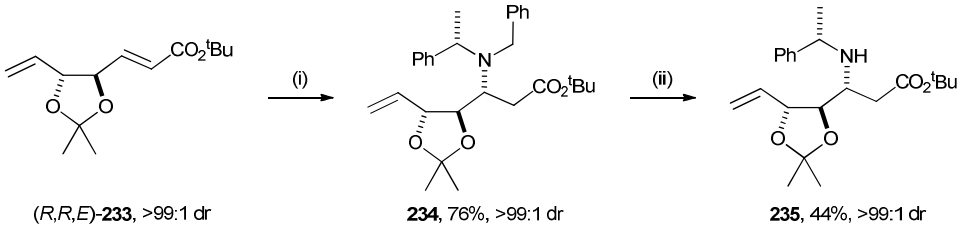


Figure 25 Installation of the stereochemistry within 7a-*epi*-hyacinthacine A1 **216** and hyacinthacine A1 **120**.

Ester (*R*,*R*,*E*)-**233** has been reported by Davies *et al.* in their investigation into the synthesis of polyhydroxylated pyrrolidines via iodoamination. In this study, conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **145** to α,β-unsaturated ester (*R*,*R*,*E*)-**223** revealed that the conjugate addition of (*S*)-**145** to (*R*,*R*,*E*)-**233** was the doubly diastereoselective 'matched' pairing of chiral reagents, giving only β-amino ester **234** in 76% isolated yield and >99:1 dr.[5,6] Investigations into the use of iodocyclisation of the *trans*-dioxolane containing β-amino ester **234** to access the corresponding pyrrolidine scaffold did not result in cyclisation; in fact treatment of **234** with I_2 resulted solely in the formation of the *N*-debenzylation product **235** which was isolated in 44% yield (Scheme 44).[7]



Scheme 44 *Reagents and conditions:* (i) (*S*)-**145**, THF, −78 °C, 2 h; (ii) I_2, $NaHCO_3$, MeCN, −20 °C to rt, 20 h.

Building on this precedent, it was envisaged that the conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amide (*R*)-**184** to α,β-unsaturated ester (*S*,*S*,*E*)-**236** would be the doubly diastereoselective 'matched' pairing, and when coupled with *in situ* oxidation with (–)-CSO **169**, would give the corresponding α-hydroxy-β-amino ester, which may be cyclised via metathesis to give hexahydroazocine **237**. Although iodocyclisation of **237** would also result in the formation of a 5,5-*trans*-fused bicyclic system **238**, it was envisaged that the presence of transannular interactions in this medium ring system may promote the attack of the nitrogen atom onto the iodonium ion. Once this has occurred, loss of the *N*-(α-methyl-*p*-methoxy)benzyl group would prevent the reversal of the process. Moreover, if cyclisation did not occur, it was predicted that it would be possible to remove the dioxolane group and cyclise the resultant hexahydroazocine to access the pyrrolizidine scaffold (comparable to the route investigated for the *cis*-system). Additionally the cyclisation of a *trans*-dioxolane containing hexahydroazonine **239** would also be attempted, which it was envisaged may be more readily cyclised due to the flexibility introduced into the system by the extra carbon in the ring, this would result in the formation of a 6,5-*trans*-fused bicycle **240** (Fig. 26).

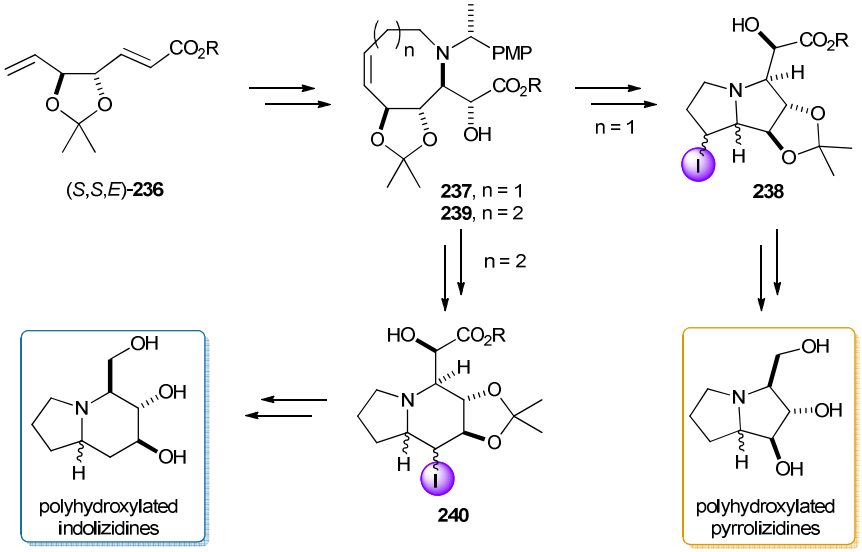
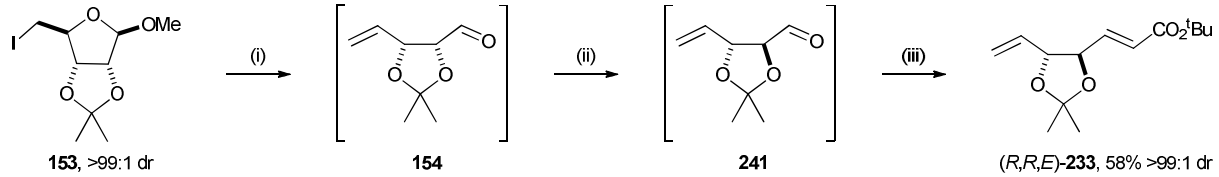


Figure 26 The proposed conjugate addition/ring-closing metathesis/iodoamination approach to incorporate *trans*-stereochemistry at C(1) and C(2) in the pyrrolizidine scaffold and C(6) and C(7) in the indolizidine scaffold.

3.3.1 Preparation of *tert*-butyl (*S*,*S*,*E*)-4,5-*O*-isopropylidenehepta-2,6-dienoate 233

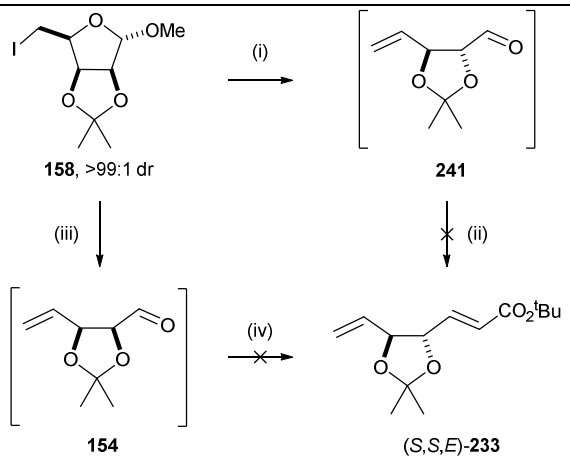
Sharpless *et al.* have noted the base catalysed epimerisation of *cis*-dioxolane containing aldehydes to their corresponding *trans*-dioxolane isomer on treatment with K_2CO_3 in MeOH.8 This procedure was used by Davies *et al.* in their original synthesis of (*R*,*R*,*E*)-**233**: D-ribose-derived iodide **153** was treated with activated Zn in MeOH to give *cis*-aldehyde **154**,

which, on treatment with K_2CO_3 in MeOH for 2.5 h, gave *trans*-aldehyde **241**. This was followed by olefination of **241** with the magnesium anion of phosphonate ester **155**, which gave (*R*,*R*,*E*)-**233** in 58% yield and in >99:1 dr (Scheme 45).[6]



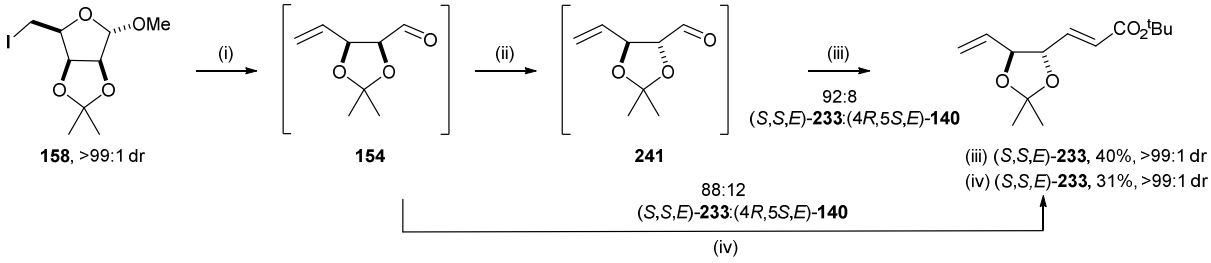
Scheme 45 *Reagents and conditions:* (i) Zn, MeOH, reflux, 1 h; (ii) K_2CO_3, MeOH, rt, 2.5 h; (iii) $(EtO)_2P(O)CH_2CO_2{}^tBu$ **155**, MeMgBr, THF, rt, 15 min then **241**, reflux, 2 h.

It was proposed that the enantiomeric α,β-unsaturated ester (*S*,*S*,*E*)-**233** could be accessed in an analogous manner starting from D-lyxose **157**. Iodide **158** had been previously prepared in two steps from D-lyxose **157**, and in 60% yield (*vide supra*). In order to provide a scalable route to (*S*,*S*,*E*)-**233**, it was anticipated that *cis*-aldehyde **154** could be generated from **158** using BuLi, and a method by which the epimerisation and olefination could be performed in tandem, avoiding the need to isolate the intermediate *trans*-aldehyde **241**, would be developed. At first **158** was treated with BuLi to generate *cis*-aldehyde **154**, which was followed immediately by reaction with phosphonoacetate **155** and K_2CO_3 in MeOH. Analysis of the ^{1}H NMR spectrum of the unpurified reaction mixture showed the presence of returned phosphonoacetate **155** only and no sign of any signals characteristic of an aldehyde or an olefin. This approach was altered so that the generation of the aldehyde and its epimerisation could be carried out in a 'one-pot' reaction by following the satd aq NH_4Cl quench with addition of 1.1 equiv of K_2CO_3 and leaving the mixture to stir for a further 2 h. After drying the mixture and filtering through Celite®, BuLi and **155** in Et_2O were added to attempt the olefination. Again the ^{1}H NMR spectrum of the unpurified reaction mixture showed the presence of the unreacted **155** only (Scheme 46).



Scheme 46 *Reagents and conditions:* (i) BuLi, Et_2O, −78 °C, 2 h then NH_4Cl, K_2CO_3, rt, 2 h; (ii) BuLi, **155**, Et_2O, −78 °C to rt, 12 h; (iii) BuLi, Et_2O, −78 °C, 2 h; (iv) K_2CO_3, **155**, MeOH, rt, 12 h.

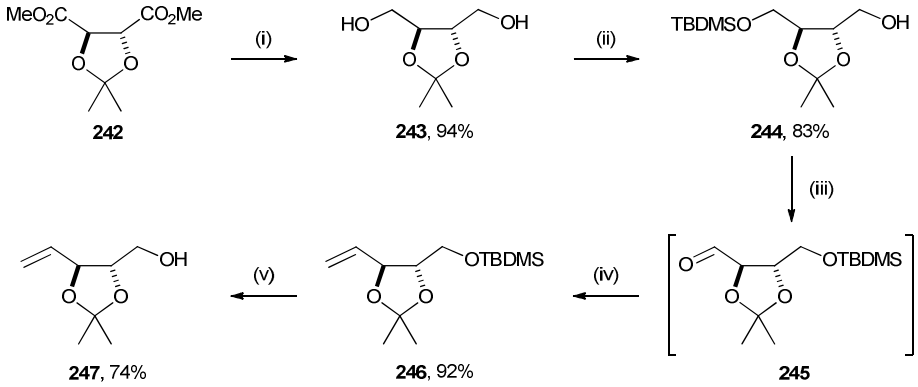
Following these results an alternative approach was attempted, the *cis*-aldehyde **154** was still generated using BuLi but the Et_2O was then carefully removed *in vacuo* before both the epimerisation and the olefination under Masamune-Roush conditions9 were carried out in 'one pot'. This gave an 88:12 mixture of (*S*,*S*,*E*)-**233** and (4*R*,5*S*,*E*)-**140** from which (*S*,*S*,*E*)-**233** was isolated in 31% yield and >99:1 dr. To ensure that the epimerisation of the *cis*-aldehyde **154** went to completion, a second approach was tried: generation of *cis*-aldehyde **154** with BuLi and removal of the Et_2O was followed by treatment of the residue with K_2CO_3 in MeOH. After stirring for 4 h the MeOH was diluted with MeCN and phosphonoacetate **155**, $^iPr_2NEt$ and LiCl were added. This gave a 92:8 mixture of (*S*,*S*,*E*)-**233** and (4*R*,5*S*,*E*)-**140**, from which **233** was isolated in 40% yield (Scheme 47).



Scheme 47 *Reagents and conditions:* (i) BuLi, Et_2O, −78 °C, 2 h; (ii) K_2CO_3, MeOH, rt, 4 h; (iii) **155**, $^iPr_2NEt$, LiCl, MeCN, rt, 12 h; (iv) K_2CO_3, **155**, $^iPr_2NEt$, LiCl, MeCN/MeOH (v/v 10:1), rt, 12 h.

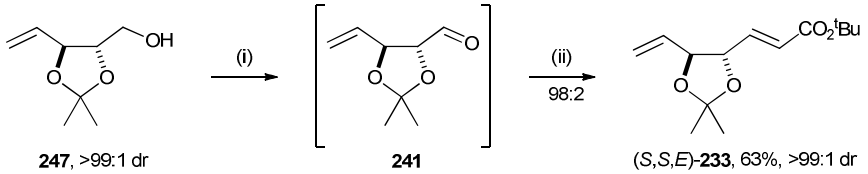
Unfortunately, when these conditions were employed to facilitate production of (*S*,*S*,*E*)-**233** on scale (~10 g) the extent to which the epimerisation occurred became unreliable, decreasing the amount of isolated (*S*,*S*,*E*)-**233**. In support of this, direct reduction of the intermediate aldehyde **241** with $NaBH_4$ to the corresponding alcohol gave a mixture of products. At this point, it was decided that the tandem/ring-opening/epimerisation approach to (*S*,*S*,*E*)-**223** was not practical on the scale required to produce synthetically useful quantities of material, and an alternate (stepwise) approach was instigated. Thus, **242** (prepared by acetonide protection

of dimethyl L-tartrate)[10] was treated with $LiAlH_4$ to reduce both ester moieties, which gave diol **243** in 94% yield. Selective mono-*O*-TBDMS protection of one of the hydroxyl groups within **243** on treatment with 1.0 equiv TBDMSCl and 1.0 equiv NaH gave **244** in 83% yield.[11] This was followed by Swern oxidation of the remaining (free) hydroxyl group within **244** to give the corresponding aldehyde **245**, which was immediately subjected to Wittig reaction with the ylid derived from triphenylmethylphosphonium iodide and BuLi. This gave alkene **246** in 92% yield and >99:1 dr.[12] Removal of the *O*-TBDMS group from within alkene **246** upon treatment with TBAF gave alcohol **247** in 74% yield (51% yield over five steps from dimethyl L-tartrate) and in >10 g batches (Scheme 48).[13]



Scheme 48 *Reagents and conditions:* (i) $LiAlH_4$, THF, reflux, 16 h; (ii) NaH, THF, 0 °C to rt, 45 min, then TBDMSCl, rt, 16 h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, −78 °C to rt, 30 min; (iv) KO^{t}Bu, $[MePh_3P]^+[I]^-$, THF, rt, 1 h; (v) TBAF, THF, 0 °C, 2.5 h.

The final step of this approach was a 'one-pot' Swern/Wittig reaction, which again circumvented the need to isolate the intermediate *trans*-aldehyde **241**. Thus, treatment of **247** under standard Swern oxidation conditions followed by the addition of 1.0 equiv **248** into the reaction mixture gave (*S*,*S*,*E*)-**233** in 98:2 dr. α,β-Unsaturated ester (*S*,*S*,*E*)-**233** was then isolated in 63% yield and >99:1 dr after chromatographic purification. This route was amenable to the synthesis of >5 g batches of (*S*,*S*,*E*)-**233** (Scheme 49).

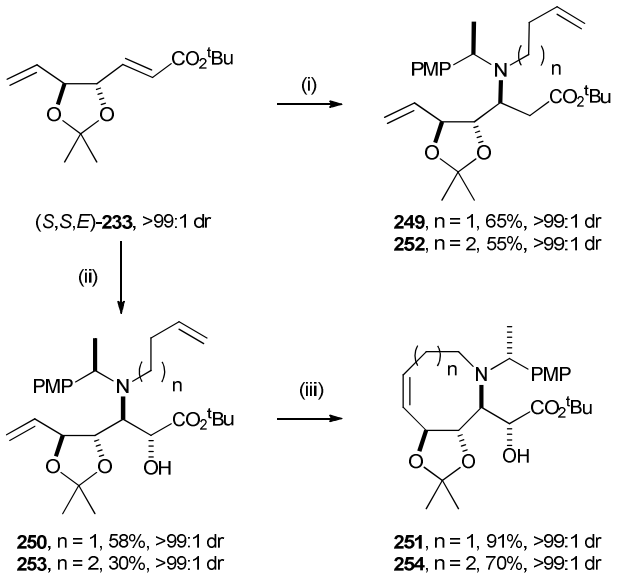


Scheme 49 *Reagents and conditions:* (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, −78 °C to rt, 30 min; (ii) $Ph_3PCHCO_2{}^tBu$ **248**, CH_2Cl_2, rt, 12 h.

3.3.2 Conjugate Addition of (*R*)-184 and (*R*)-207 to (*S*,*S*,*E*)-233

Conjugate addition of lithium amide (*R*)-**184** to α,β-unsaturated ester (*S*,*S*,*E*)-**233** in THF at −78 °C gave β-amino ester **249** in >99:1 dr. This result was consistent with this addition being the doubly diastereoselective 'matched' case, since no minor diastereoisomer was observed in

the ^{1}H NMR spectrum of the unpurified reaction mixture.[14] On this basis, the absolute (*S*,*S*,*S*)-configuration within β-amino ester **249** was confidently assigned.[15] The synthesis of α-hydroxy-β-amino ester **250** was next achieved by conjugate addition of lithium amide (*R*)-**184** to α,β-unsaturated ester (*S*,*S*,*E*)-**233** in THF at −78 °C, followed by the addition of (−)-CSO **169**, which gave **250** in 58% yield and >99:1 dr.[16] Again, the absolute (2*R*,3*S*,4*S*,5*S*)-configuration within **250** was assigned by reference to the well-established stereochemical outcome of this aminohydroxylation procedure.[17] Subsequent ring-closing metathesis of **250** proved less amenable with the presence of the *trans*-dioxolane group hindering cyclisation. Reaction of **250** at rt with 10 mol% catalyst gave 95% conversion to **251**, increasing the temperature to 30 °C at this catalyst loading resulted in complete conversion to **251**, which was isolated in 91% yield and >99:1 dr. The relative configuration within **251** was unambiguously established by single crystal X-ray diffraction analysis, with the absolute (2*R*,2′*S*,3′*S*,4′*S*,α*R*)-configuration being assigned from the known dimethyl L-tartrate **242** C(1)- and C(2)-stereocentres, and the known (*R*)-configuration of the *N*-(α-methyl-*p*-methoxy)benzyl group. This analysis also unambiguously established the absolute configurations within **250** and hence **249** (Fig. 27). Hexahydroazonine **254** was next prepared in a directly analogous manner: conjugate addition of lithium amide (*R*)-**207** to α,β-unsaturated ester (*S*,*S*,*E*)-**233** followed by addition of (−)-CSO **169** gave *anti*-α-hydroxy-β-amino ester **253** in 30% yield,[17,18] and was followed by treatment of **253** with Grubbs I catalyst to effect ring-closing metathesis giving **254** in 70% isolated yield (Scheme 50).



Scheme 50 *Reagents and conditions:* (i) (*R*)-**184** (n = 1) or (*R*)-**207** (n = 2), THF, −78 °C, 2 h; (ii) (*R*)-**184** (n = 1) or (*R*)-**207** (n = 2), THF, −78 °C, 2 h then (−)-CSO **169**, −78 °C to rt, 12 h; (iii) Grubbs I catalyst (10 mol%), CH_2Cl_2, 30 °C, 12 h.

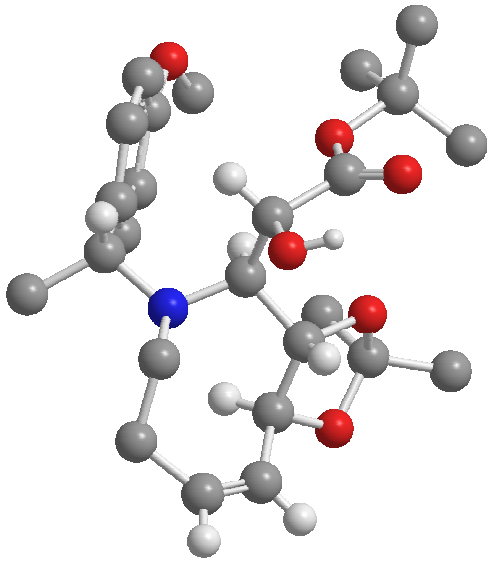
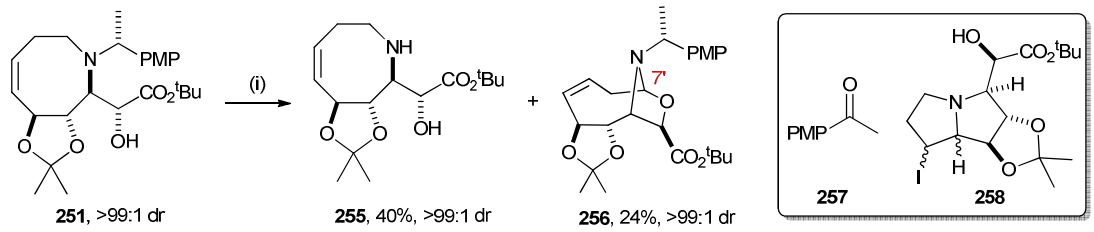


Figure 27 Chem3D representation of the single crystal X-ray diffraction structure of (2*R*,2′*S*,3′*S*,4′*S*,α*R*)-**251** (selected H atoms have been omitted for clarity).

3.3.3 Attempted transannular iodoamination of 251

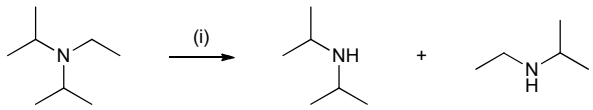
Treatment of **251** under the previously optimised conditions to promote transannular iodoamination resulted in the formation of a 9:62:29 mixture of three products which were identified as ketone **257**, secondary amine **255** and a tricyclic compound **256**, with no evidence of the desired pyrrolizidine **258**. Chromatographic purification gave **255** in 40% yield and >99:1 dr, and **256** in 24% yield and >99:1 dr although ketone **257** was not isolated. The structure of **256** was determined by ^{1}H-^{1}H 2D COSY and HMBC spectroscopic analyses: in particular the ^{1}H and ^{13}C NMR chemical shifts corresponding to C(7′)*H* (δ_H 5.10 ppm and δ_C 94.5 ppm) were characteristic of the formation of an N–O acetal (Scheme 51). Despite efforts to force the desired transannular cyclisation by increasing the temperature of the reaction to 30 °C or to 80 °C (with the reaction solvent changed to PhMe/EtOH) no evidence of **258** was observed.[19,20]



Scheme 51 *Reagents and conditions:* (i) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h.

The halogen promoted *N*-debenzylation of tertiary amines has been previously reported, and has been proposed to involve initial *N*-oxidation followed by the formation of an iminium ion, which is hydrolysed under the aqueous work-up conditions to give a secondary amine product and an aldehyde or ketone.[21] Deno and Fruit Jr. studied this process by treating a range of

acylic unsymmetrical amines with bromine.[22] The observed product distributions from these reactions were explained as a result of two competing effects: firstly, that the alkyl group that forms the most stable carbocation (iminium ion) is more readily lost; and secondly, that the least sterically encumbered imine is formed which results in the cleavage of the least branched substituent. The latter effect seemed to dominate and, for example, the amine products resulting from the oxidative cleavage of diisopropylpropylamine **259** with aqueous bromine at 25 °C were diisopropylamine **260** and propylisopropylamine **261**, isolated in 72 and 28% yield, respectively (Scheme 52).[22,23]



259 **260**, 72% **261**, 28%

Scheme 52 *Reagents and conditions:* (i) Br_2, 0.40 M acetate buffer, aq HCl, pH ~5-6, 25 °C, 30 min.

The observed chemoselectivity of the iodine-promoted oxidation of hexahydroazocine **251** is consistent with either formation of an imine between N(1′)–C(8′) [least substituted imine **262**] followed by trapping of imine **262** by the C(2)-hydroxyl group which gives tricyclic hemiaminal ether **256**, or formation of an imine between N(1′)–C(α) [most substituted/stable imine **263**] followed by hydrolysis which results in the formation of the secondary amine **255** and ketone **257** (Fig. 28).

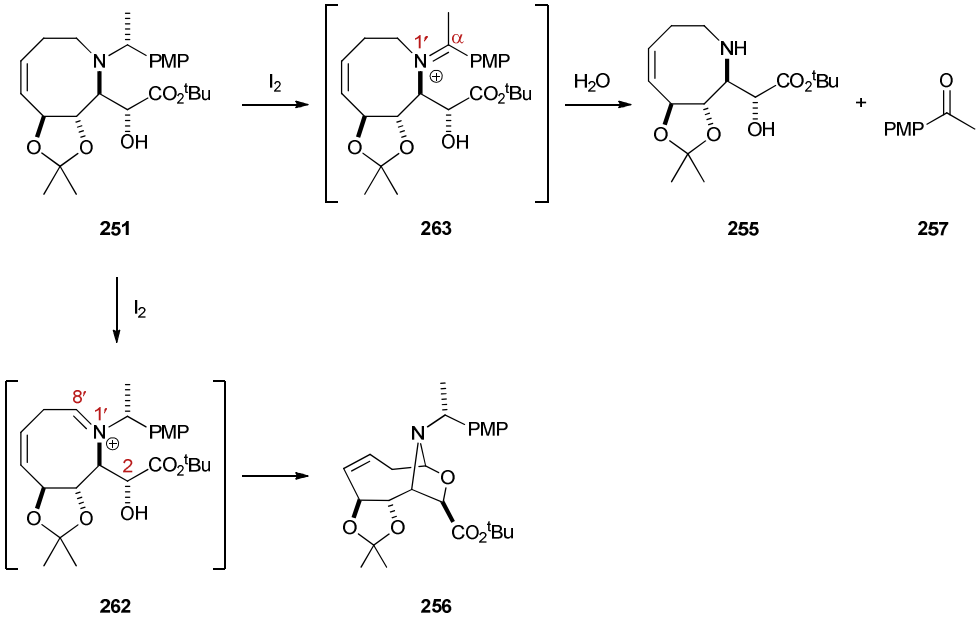
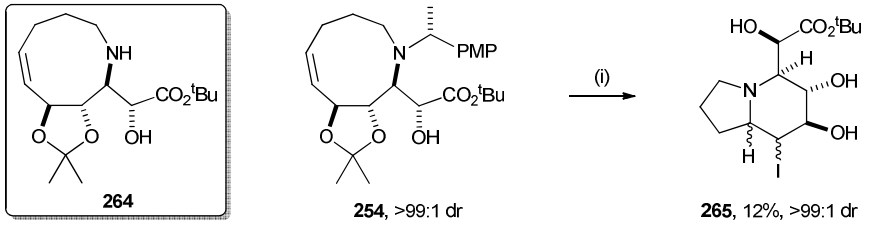


Figure 28 The formation of imines **262** and **263** leading to the observed products **256** and **255**, respectively.

Having established that hexahydroazocine **251** did not undergo transannular cyclisation, the behaviour of the corresponding 9-membered ring system **254** under analogous conditions was examined.

3.3.4 Iodoamination of 254

Treatment of **254** under the optimised conditions for transannular iodoamination resulted in the formation of a complex mixture of products, from which only a sample of **265** was isolated in 12% yield (Scheme 53). Analysis of the unpurified reaction mixture by mass spectrometry showed the presence of *N*-debenzylated hexahydroazonine **264** (*m*/*z* = 328, $[M+H]^+$), although this compound was not isolated.

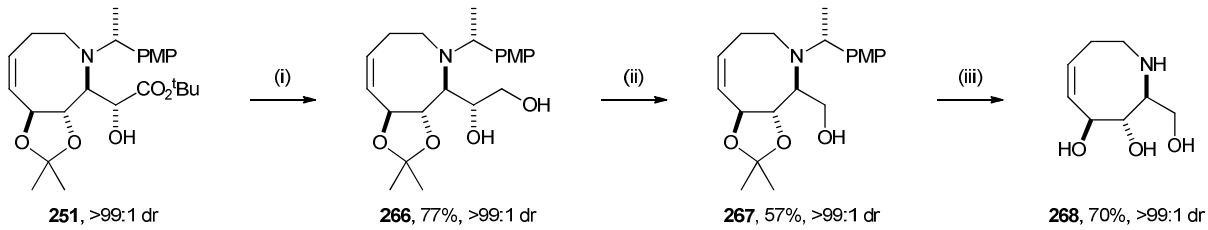


Scheme 53 *Reagents and conditions:* (i) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h.

This result indicated that the introduction of extra flexibility into the system was not enough to overcome the strain that resulted from the incorporation of the *trans*-dioxolane unit. In fact, the only cyclised product isolated (iodoindolizidine **265**) had no dioxolane unit and, although the origin of this species is unclear, may indicate that hydrolysis of the dioxolane group is prerequisite to transannular cyclisation. It was therefore proposed that further investigation of the *trans*-dixolane system would involve the hydrolysis of the dioxolane unit from hexahydroazocine **251** prior to any cyclisation attempts.

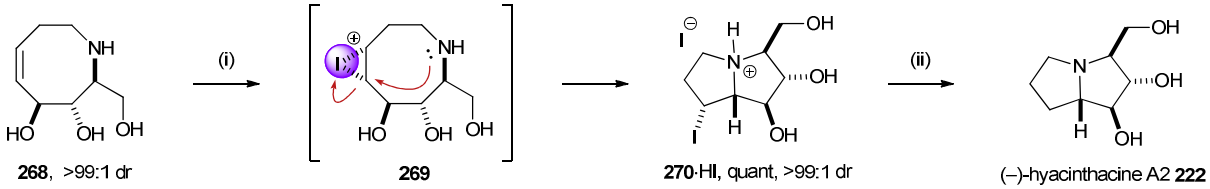
3.3.5 Synthesis of (−)-hyacinthacine A2 222

Following the procedure developed for the synthesis of hexahydroazocine **230** (*vide supra*), reduction of hexahydroazocine **251** with $LiAlH_4$ gave diol **266** in 77% yield. Subsequent oxidative cleavage of the 1,2-diol unit within **266** upon treatment with $NaIO_4$ and immediate reduction of the resultant aldehyde with $NaBH_4$ gave the required C(2)-hydroxymethyl substituted hexahydroazocine **267** in 57% yield. Acid-catalysed hydrolysis of the dioxolane group in **267** proceeded with simultaneous *N*-debenzylation to give triol **268** in 70% yield after purification by ion exchange chromatography (Scheme 54).



Scheme 54 *Reagents and conditions:* (i) $LiAlH_4$ (1.0 M in THF), THF, −78 °C to rt, 12 h; (ii) $NaIO_4$, $MeOH/H_2O$ (v/v 5:1), rt, 1 h then $NaBH_4$, MeOH, rt, 12 h; (iii) HCl (3.0 M aq), MeOH, reflux, 2 h.

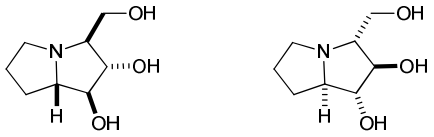
Treatment of **268** with 1.0 equiv of I_2 in MeOH for 12 h at rt followed by removal of the solvent *in vacuo* gave a single compound, which was assigned as iodopyrrolizidine **270**·HI, in >99:1 dr. Subsequent hydrogenolysis and purification of the resultant product by ion exchange chromatography gave (−)-hyacinthacine A2 **222** in 95% yield and >99:1 dr; the identity of (−)-**222** was confirmed by comparison of its specific rotation and ^{1}H and ^{13}C NMR spectra to those previously reported in the literature (Scheme 55).[24,25] As before, invoking a cyclisation mechanism which involved the attack of the nitrogen atom onto an iodonium ion allowed the assignment of the configuration at C(7) within iodopyrrolizidine **270**·HI.



268, >99:1 dr — **269** — **270**·HI, quant, >99:1 dr — (−)-hyacinthacine A2 **222** 95%, >99:1 dr

Scheme 55 *Reagents and conditions:* (i) I_2 (1.0 equiv), MeOH, rt, 12 h; (ii) H_2 (1 atm), 10% Pd/C (50% w/w), Et_3N, MeOH, rt, 12 h.

A comparison of the ^{1}H NMR and ^{13}C NMR data of this sample of (−)-hyacinthacine A2 **222** with the data reported for the natural product (+)-hyacinthacine A2 **222** isolated by Asano *et al.*,[2] along with other reported data for synthetic samples of either enantiomer showed excellent agreement (Tables 5 and 6).



(−)-hyacinthacine A2 **222** (+)-hyacinthacine A2 **222**

^{13}C NMR data for hyacinthacine A2 **222** (in D_2O)								
C	Asano *et al.*[2] (100 MHz)	Izquierdo *et al.*[24i] (100 MHz)	Vallée *et al.*[24e] (75 MHz)	Blechert *et al.*[24g] (125 MHz)	Clapés *et al.*[24a] (125 MHz)	Marco *et al.*[24j] (125 MHz)	Zheng *et al.*[24d] (100 MHz)	This study (125 MHz)
C(1)	82.9	81.1	83.1	80.9	82.1	82.2	83.0	83.0
C(2)	79.8	77.7	80.2	78.0	79.0	79.0	80.0	80.0
C(3)	72.1	71.5	72.0	69.9	71.4	72.1	71.9	72.1
C(5)	57.7	57.1	57.6	55.6	57.0	57.7	57.6	57.7
C(6)	27.3	26.3	27.3	25.2	26.7	27.1	27.3	27.4
C(7)	32.5	31.2	32.6	30.5	31.9	32.1	32.6	32.6
C(7a)	69.2	69.4	68.8	66.7	68.3	69.7	68.8	69.0
C(1′)	65.3	62.2	66.0	63.8	64.5	63.9	65.9	65.7

Table 5 Comparison of ^{13}C NMR data of hyacinthacine A2 **222** [Chemical shifts (δ_C) are reported in ppm].

^{1}H NMR data for hyacinthacine A2 **222** (in D_2O)							
H	Asano *et al.*[2] (400 MHz)	Izquierdo *et al.*[24i] (400 MHz)	Vallée *et al.*[24e] (300 MHz)	Blechert *et al.*[24g] (500 MHz)	Clapés *et al.*[24a] (500 MHz)	Marco *et al.*[24j] (500 MHz)	This study (500 MHz)
C(1)H	3.76 dd *J* 8.8, 7.1	3.71-3.79 m	3.61-3.81 m	3.62 br t *J* 8.0	3.78 br s	3.78-3.87 m	3.72-3.81 m
C(2)H	3.81 t *J* 8.8	3.71-3.79 m	3.61-3.81 m	3.54-3.61 m	3.74 t *J* 8.0	3.78-3.87 m	3.72-3.81 m
C(3)H	2.77 ddd *J* 8.8, 6,5, 3.9	2.85-2.93 m	2.66-2.77 m	2.42-2.64 m	2.75 br s	2.85-2.95 m	2.71-2.74 m
C(5)H_A	2.81 dt *J* 5.6	2.85-2.93 m	2.66-2.77 m	2.42-2.64 m	2.80 br s	2.85-2.95 m	2.75-2.79 m
C(5)H_B	2.96 ddd *J* 11.0, 7.3, 5.9	3.04 br t *J* 11.7, 6.5	2.85-2.93 m	2.42-2.64 m	2.94 br s	3.06 br t *J* 11.4, 6.3	2.89-2.94 m
C(6)H_A	1.82 m	1.72-1.96 m	1.70-2.00 m	1.49-1.75 m	1.79 m	1.80-1.90 m	1.73-1.81 m
C(6)H_B	1.90 m	1.72-1.96 m	1.70-2.00 m	1.49-1.75 m	1.88 m	1.90-2.00 m	1.84-1.91 m
C(7)H_A	1.77 m	1.72-1.96 m	1.70-2.00 m	1.49-1.75 m	1.76 m	1.80-1.90 m	1.73-1.81 m
C(7)H_B	1.97 m	1.72-1.96 m	1.70-2.00 m	1.49-1.75 m	1.96 m	2.00-2.05 m	1.93-1.99 m
C(7a)H	3.32 m	3.37 m	2.96-2.90 m	2.90-2.96 m	3.20 m	3.36 m	3.17 app td *J* 7.9, 4.7
C(1′)H_A	3.67 dd *J* 11.8, 6.7	3.63 dd *J* 12.1, 6.0	3.61-3.81 m	3.44 dd *J* 11.0, 6.8	3.65 dd *J* 11.8, 6.5	3.70 dd *J* 12.0, 6.0	3.65 dd *J* 12.0, 6.6
C(1′)H_B	3.80 dd *J* 11.8, 3.9	3.71-3.79 m	3.61-3.81 m	3.54-3.61 m	3.79 dd *J* 12.2, 8.2	3.78-3.87 m	3.72-3.81 m

Table 6 Comparison of ^{1}H NMR data of hyacinthacine A2 **222** [Chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

The specific rotation of this synthetic sample of (−)-hyacinthacine A2 **222** {$[\alpha]_D^{25}$ −11.2 (*c* 0.83 in MeOH); $[\alpha]_D^{25}$ −11.0 (*c* 0.43 in H_2O)} was not consistent with the value reported for the isolated natural product (+)-hyacinthacine A2 **222** {$[\alpha]_D^{25}$ +20.1 (*c* 0.44 in H_2O)}.[2] However, this seemed to be the case for most values reported for synthetic samples of this alkaloid in the literature. In fact, the value recorded for this sample was in excellent agreement with the other reported values of synthetic (+)-hyacinthacine A2 **222** {lit.[25] $[\alpha]_D^{25}$ +12.5 (*c* 0.4 in H_2O)}; {lit.[24h] $[\alpha]_D^{25}$ +12.7 (*c* 0.13 in H_2O)}; {lit.[24g] $[\alpha]_D^{25}$ +10.5

(*c* 0.6 in H_2O)}; {lit.[24f] $[\alpha]_D^{20}$ +11.2 (*c* 0.52 in H_2O)}; {lit.[24c] $[\alpha]_D^{20}$ +10.6 (*c* 1.64 in H_2O)}. The origin of this difference is unclear.

3.4 Rationale for the stereochemical outcomes of the transannular iodoamination reactions

The stereochemical outcomes of the transannular iodoamination reactions of hexahydroazocines **187**, **227**, **230** and **232** can, in all cases, be rationalised by invoking a mechanism involving the reversible formation of two diastereoisomeric iodonium ions. In the case of **187** and **227**, where the *N*-(α-methyl-*p*-methoxy)benzyl group is adjacent to the C(3)-substituent, the 1,2-strain present in iodonium ions **271** and **272** is very large which disfavours transannular cyclisation (*vide supra*); the reaction proceeds via iodonium ions **194** and **273** to give **189**·HI and **229**·HI, respectively. In the case of **230** and **232**, where there is little 1,2-strain between the *N*-H and the C(3)-substituent, the transannular strain present in iodonium ions **274** and **275** disfavours this cyclisation pathway, and hence the reaction proceeds via iodonium ions **276** and **278** to give **232**·HI and **270**·HI, respectively (Fig. 29). These results suggest that this diastereodivergent transannular process is governed either by the presence of 1,2-strain between the *N*-protecting group and the C(3)-substituent, or by the transannular strain between the C(3)-substituent and the distal ring substituents.

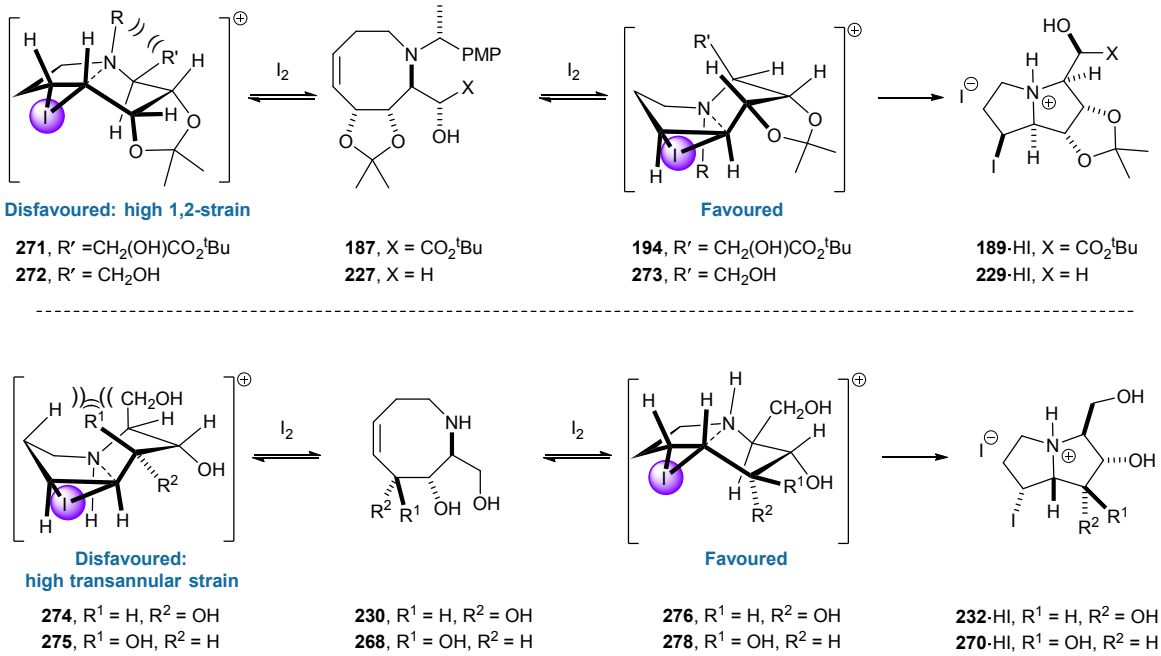


Figure 29 Postulated mechanistic rationale for the observed stereochemical outcomes of transannular iodoamination of **187**, **230**, **268** [R = CHMePMP].

3.5 Summary

The asymmetric synthesis of two naturally occurring polyhydroxylated pyrrolizidine alkaloids (−)-hyacinthacine A1 **120** and (−)-hyacinthacine A2 **222** was achieved by global deprotection of hexahydroazocines **187** and **251** to give **230** and **268**, respectively. Treatment of both these compounds with I_2 resulted in transannular cyclisation and was immediately followed by hydrogenolysis of the resulting iodopyrrolizidines **232**·HI and **270**·HI to give (−)-hyacinthacine A1 **120** and (−)-hyacinthacine A2 **222**, respectively (Fig. 29).

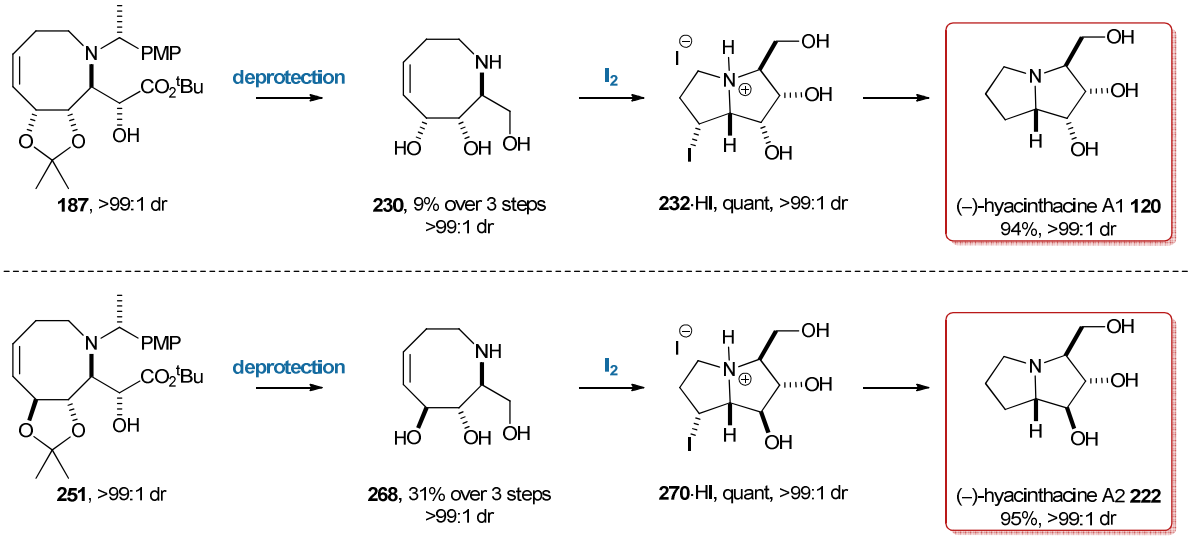


Figure 30 The total asymmetric syntheses of (−)-hyacinthacine A1 **120** and (−)-hyacinthacine A2 **222**.

Following this successful investigation into the applicability of the iodoamination methodology in the asymmetric synthesis of diastereoisomers of the 1,2-dihydroxy-3-hydroxymethyl pyrrolizidine family of compounds, the transformation of iodopyrrolizidine **189** into the 1,2,7-trihydroxy-3-hydroxymethyl and 1,2,6,7-tetrahydroxy-3-hydroxymethyl pyrrolizidine families was explored. The results of these investigations will be described in the next chapter.

3.6 References and notes

[1] For the reported isolation of the naturally occurring pyrrolizidine alkaloid (+)-hyacinthacine A1 **120**, see: Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1.

[2] For the reported isolation of the naturally occurring pyrrolizidine alkaloid (+)-hyacinthacine A2 **222**, see: Ref 1.

[3] (a) Izquierdo, I; Plaza, M. T.; Robles, R.; Franco, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2481. (b) Yoda, H.; Asai, F.; Takabe, K. *Synlett* **2000**, 1001.

[4] For a previous synthesis of (±)-hyacinthacine A1 **120**, see: (a) Donohoe, T. J.; Sintim, H. O.; Hollinshead, J. *J. Org. Chem.* **2005**, *70*, 2005. For previous syntheses of (+)-hyacinthacine A1 **120**, see: (a) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A.; Sanchez-Cantalejo, F. *Eur. J. Org. Chem.* **2007**, 6078. (b) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587. (c) Venkatram, R. P.; Amael, V.; Koos, P.; Bayle, A.; Greene, A. E.; Delair, P. *Org. Biomol. Chem.* **2008**, *6*, 1170. (d) Chandrasekhar, S.; Parida, B. B.; Rambabu, C. *J. Org. Chem.* **2008**, *73*, 7826. (e) D'Adamio, G.; Goti, A.; Parmeggiani, C.; Cardona, F.; Moreno-Clavijo, E.; Robina, I. *Eur. J. Org. Chem.* **2011**, 7155. (f) Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Linney, I. D.; Bhalay, G. *Org. Lett.* **2008**, *10*, 3615.

[5] Upon conjugate addition of (*R*)-**145** the minor diastereoisomer was also observed and isolated indicating that this was the 'mismatched' case.

[6] Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J. *Org. Biomol. Chem.* **2009**, *7*, 761.

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

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[10] A sample of **242** was kindly supplied by T. Lorkin.

[11] Davies, S. G.; Foster, E. M.; Frost, A. B.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Biomol. Chem.* **2012**, *10*, 6186.

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[14] The assumed 'mismatched' conjugate addition of (*S*)-**184** to (*S*,*S*,*E*)-**223** was not attempted.

[15] For the lithium amide conjugate addition transition state mnemonic that is used to predict the stereochemical outcome of these reactions, see: Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *10*, 1999.

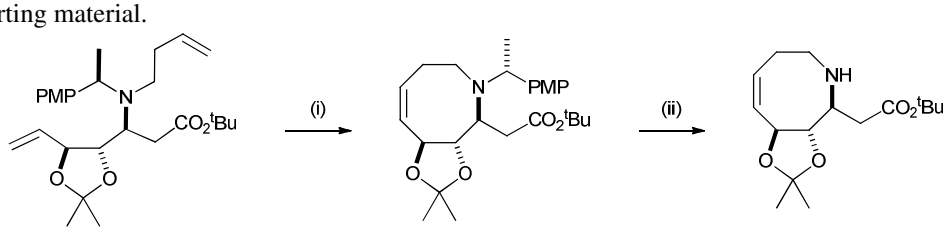
[16] A sample of **249** was also isolated from this reaction in 9% yield and >99:1 dr.

[17] For previous examples of this stereochemical outcome see: (a) 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. (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. (c) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. (d) 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] A sample of **252** was also isolated in 4% yield.

[19] Chang, S.; McNally, D.; Shary-Tehrany, S.; Hickey, M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109.

[20] When hexahydroazocine **279**, resulting from ring-closing metathesis of **249** (isolated in 67% yield and >99:1 dr), was treated with I_2 a similar *N*-debenzylation occurred to give the corresponding secondary amine **280** as the sole product which was isolated in 72% yield and >99:1 dr. Resubjection of **280** to the iodoamination conditions returned starting material.



249 **279**, 67%, >99:1 dr **280**, 72%, >99:1 dr

Reagents and conditions: (i) Grubbs I catalyst (10 mol%), CH_2Cl_2, 30 °C, 12 h; (ii) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h.

[21] Horner, L. *Angew. Chem.* **1950**, *62*, 359.

[22] Deno, N. C.; Fruit Jr., R. E. *J. Am. Chem. Soc.* **1968**, *90*, 3502.

[23] The corresponding carbonyl compounds, propionaldehyde and acetone were isolated in 50 and 21% yield, respectively.

[24] For previous syntheses of (−)-hyacinthacine A2 **222**, see: (a) Calveras, J.; Casas, J.; Parella, T.; Joglar, J.; Clapés, P. *Adv. Synth. Catal.* **2007**, *349*, 1661. (b) Garrabou, X.; Gómez, L.; Joglar, J.; Gil, S.; Parella, T.; Bujons, J.; Clapés, P. *Chem. Eur. J.* **2010**, *16*, 10691. For previous syntheses of (+)-hyacinthacine A2 **222**, see: (c) Liu, W.-J.; Ye, J.-L.; Huang, P.-Q. *Org. Biomol. Chem.* **2010**, *8*, 2085. (d) Liu, X.-K.; Qiu, S.; Xiang, Y.-G.; Ruan, Y.-P.; Zheng, X.; Huang, P.-Q. *J. Org. Chem.* **2011**, *76*, 4952. (e) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459. (f) Delso, I.; Tejero, T.; Goti, A.; Merino, P. *Tetrahedron* **2010**, *66*, 1220. (g) Dewi-Wülfing, P.; Blechert, S. *Eur. J. Org. Chem.* **2006**, 1852. (h) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron: Asymmetry* **2003**, *44*, 2315. (i) Cardona, F.; Faggi, E.; Ligouri, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315. (j) Ribes, C.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2009**, *65*, 6965.

[25] For the first total synthesis of (+)-hyacinthacine A2, see: Rambaud, L.; Compain, P.; Martin, O. R. *Tetrahedron: Asymmetry* **2001**, *12*, 1807. ^{1}H NMR data was not given in this paper; δ_C (D_2O) 27.4 (*C*(6)), 32.6 (*C*(7)), 57.7 (*C*(5)), 65.8 (*C*(1′)), 68.8 (*C*(7a)), 72.0 (*C*(3)), 80.1 (*C*(2)), 83.0 (*C*(1)).

Synthesis of (–)-1-*epi*-Alexine

This chapter describes investigations into the further elaboration of iodopyrrolizidine **189** to facilitate the asymmetric synthesis of a range of polyfunctionalised pyrrolizidines **281** (Fig. 31).

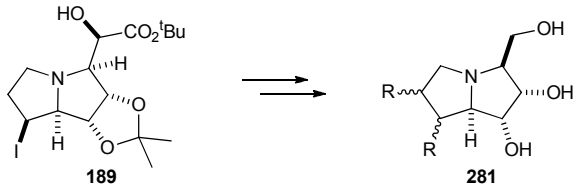


Figure 31 Elaboration of **189** to polyfunctionalised pyrrolizidines **281**.

4.1 Polyhydroxylated pyrrolizidines – the alexines and casuarines

The successful preparation of the known 1,2-dihydroxy-3-(hydroxymethyl)pyrrolizidines (–)-7a-*epi*-hyacinthacine A1 **216**, (–)-hyacinthacine A1 **120** and (–)-hyacinthacine A2 **222** (*vide supra*) instigated a study into the synthesis of other, more densely hydroxylated pyrrolizidine scaffolds. Pyrrolizidines which contain the 1,2,7-trihydroxy-3-hydroxymethyl or the 1,2,6,7-tetrahydroxy-3-hydroxymethyl substitution patterns are diastereoisomers of the naturally occuring pyrrolizidine alkaloids alexine **121** and casuarine **122**, respectively.[1] It was envisaged that the C(7)-iodo functionality within **189** could be used as a synthetic handle to allow access to both of these substitution patterns. For example, regioselective base-promoted elimination of HI and ensuing dihydroxylation of the resultant dihydropyrrole **282** would result in the formation of the casuarine substitution pattern **283**, whilst displacement of the iodide with a nucleophilic source of 'O' would allow the synthesis of the alexine substitution pattern **284** (Fig. 32).

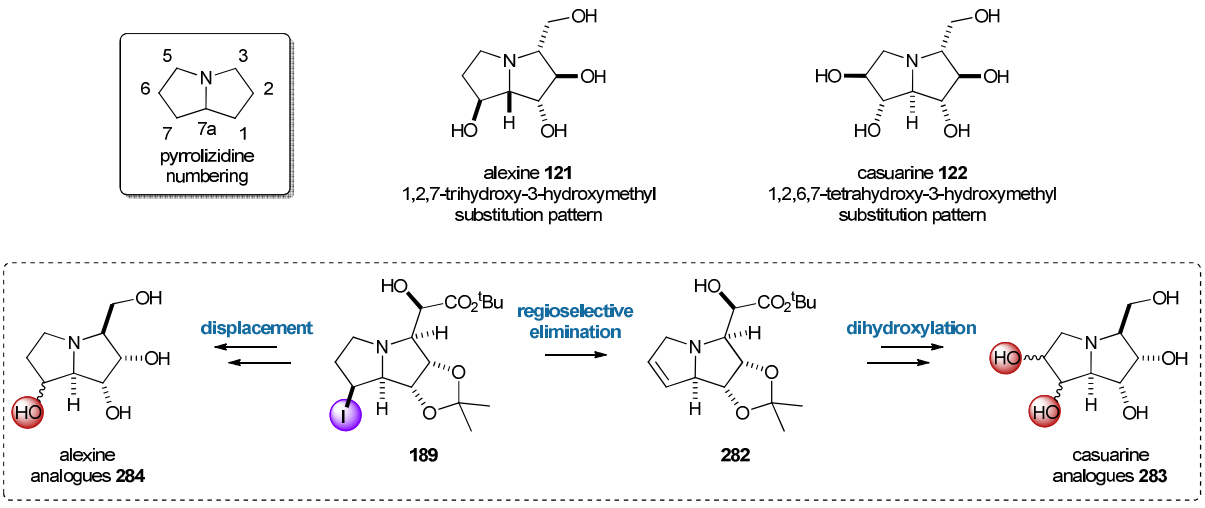
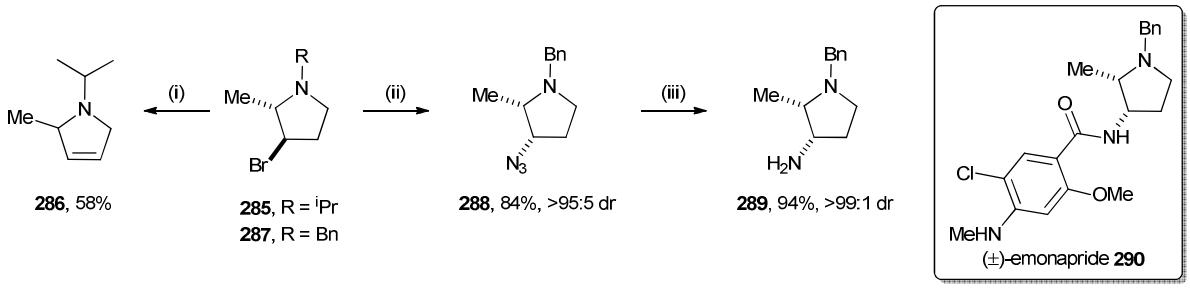


Figure 32 Proposed synthesis of alexine **121** and casuarine **122** analogues **284** and **283**.

4.2 Background

A search of the literature revealed little precedent for the base-promoted dehydrohalogenation of a 3-halopyrrolidine resulting in the isolation of a dihydropyrrole, although there are several examples of the successful nucleophilic displacement of a group from within a pyrrolidine scaffold. One particularly relevant study described both transformations. In their investigations into the synthesis of *cis*-2-methyl-3-aminopyrrolidines, De Kimpe *et al*. probed the substitution and elimination reactions of *trans*-2-methyl-3-bromopyrrolidines **285** and **287**.[2] They found that reaction of **285** with KO^{t}Bu in THF resulted in dehydrobromination to give dihydropyrrole **286** in 58% isolated yield. Pyrrolidine **287** underwent successful displacement of bromide on reaction with NaN_3 to give *cis*-2-methyl-3-azidopyrrolidine **288** in 84% yield and >95:5 dr. Reduction of **288** with $LiAlH_4$ gave **289** in 94% yield, completing a formal synthesis of the antipsychotic (±)-emonapride **290** (Scheme 56).[2]



286, 58%

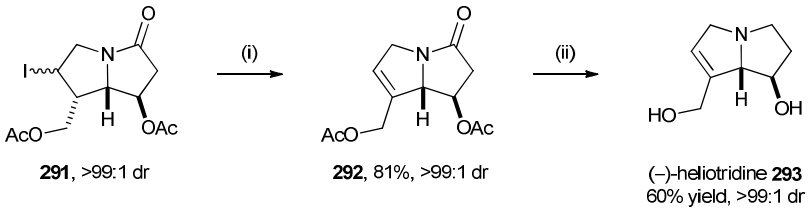
285, R = ^{i}Pr
287, R = Bn

288, 84%, >95:5 dr

289, 94%, >99:1 dr

Scheme 56 *Reagents and conditions:* (i) KO^{t}Bu, THF, reflux, 1 h; (ii) NaN_3, DMSO, 80-90 °C, 8-18 h; (ii) $LiAlH_4$, THF, reflux, 1 h.

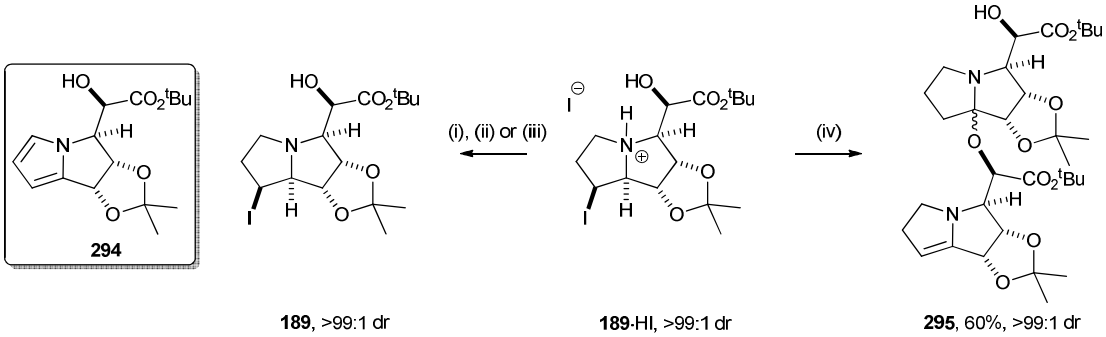
Related dehydrohalogenations have, however, proved a useful synthetic tool in the synthesis of dihydropyrrolones, dihydroxypyrroles, pyrrolizidines and maleimides,[3] although all of these successful eliminations have one common factor in that the lone pair of the endocyclic nitrogen atom is conjugated with an adjacent carbonyl group, either through *N*-Boc or *N*-Cbz protection, or as part of a lactam. For example, in 1985 Hart *et al.* reported a total synthesis of the pyrrolizidine (−)-heliotridine **293**, the penultimate step of which involved the base promoted elimination of iodide from lactam **291**, which was achieved using DBU in C_6H_6 at rt to give the dihydropyrrolizinone **292** in 81% yield. This was followed by treatment of **292** with $LiAlH_4$ which simultaneously effected reduction of the lactam and acetyl groups to give (−)-heliotridine **293** in 60% yield (Scheme 57).[4]



Scheme 57 *Reagents and conditions:* (i) DBU, C_6H_6, rt, 3.5 h; (ii) $LiAlH_4$, THF, reflux, 30 min.

4.3 Regioselective elimination reactions of 189·HI

The dehydroiodination of **189**·HI was first investigated using the reported conditions by De Kimpe *et al*. However, reaction of **189**·HI with KO^{t}Bu in THF for 1 h returned only the free base **189** quantitively.[2] Following this result, a screen of conditions was carried out to test the tolerance of the system to a basic environment, beginning with reaction under mild conditions, for example at rt with Et_3N or K_2CO_3 for up to 36 h, which only resulted in the formation of the free base **189**. Next, incrementally more forcing conditions were trialled. The use of DBU is prevalent in dehydrohalogenations,[5] and hence reaction of **189**·HI with DBU in CH_2Cl_2 at rt and 30 °C was attempted, but both conditions returned **189** only. The reaction was then repeated in PhMe at 60 °C, which resulted in the formation of a complex mixture of products by ^{1}H NMR spectroscopic analysis, although the major product was identified as pyrrole **294**. The formation of **294** was encouraging as it suggested that elimination of HI was occurring, but with subsequent oxidation of the resultant dihydropyrrole. If this reaction was carried out under an Ar atmosphere, no oxidation to pyrrole **294** was observed, but instead it resulted in the formation of a single compound, which was assigned as dimer **295** and isolated in 60% yield and >99:1 dr after chromatographic purification (Scheme 58). Despite efforts to hinder the dimerisation process by reducing the reaction time or temperature, the attempted elimination of HI unremittingly resulted in dimer **295** even under very dilute conditions.



Scheme 58 *Reagents and conditions:* (i) KO^{t}Bu, THF, rt, 1 h; (ii) Et_3N/K_2CO_3/DBU, CH_2Cl_2, rt, 1 to 36 h; (iii) DBU, PhMe, 30 °C, 12 h; (iv) DBU, PhMe, 60 °C, 12 h.

The persistent formation of dimer **295** as the major elimination product suggested regioselective elimination of HI across the C(7)–C(7a) bond to give enamine **296**, rather than

across the C(6)–C(7) bond to give the desired alkene **282**. The formation of dimer **295** when the reaction was carried out under an Ar atmosphere, could be explained by the tautomerisation of **296** to give imine **297**; the subsequent trapping of **297** by **296** would give dimer **295** (Fig. 33). In light of these results this particular strategy was not pursued further, and attention next turned to nucleophilic displacement reactions of **189**·HI.

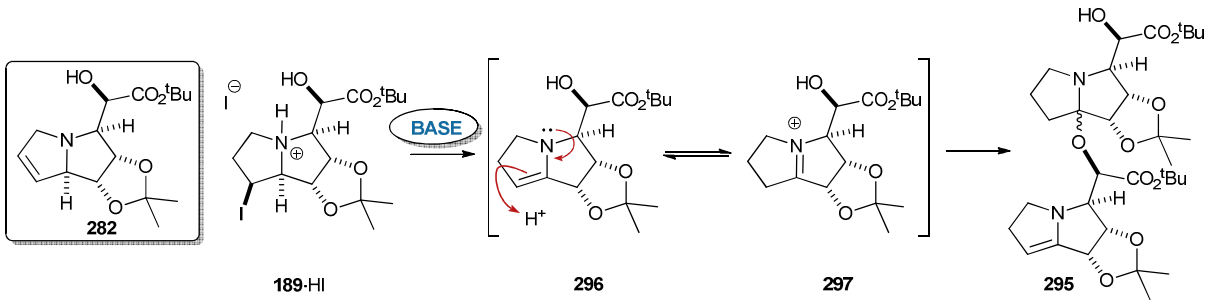
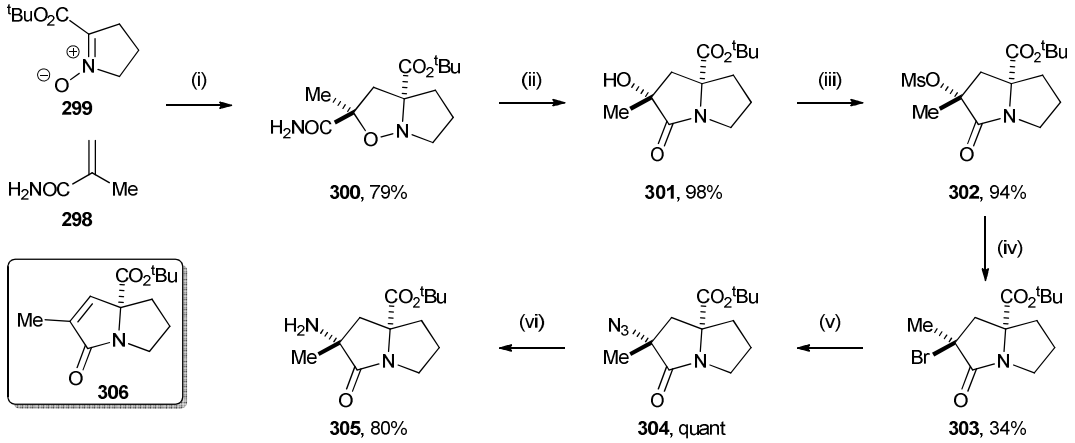


Figure 33 Rationale for the formation of dimer **295** during the base-promoted dehydroiodination reaction.

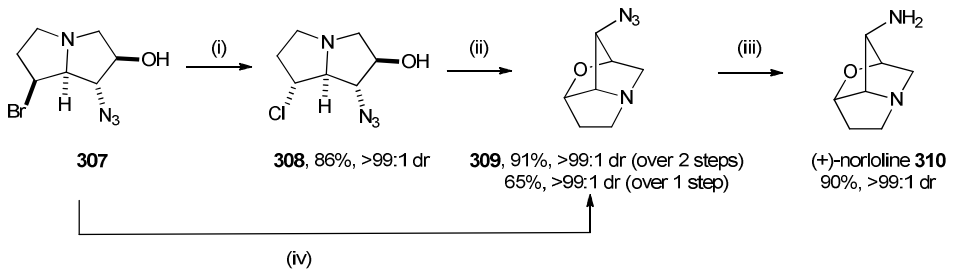
4.4 Nucleophilic displacement reactions of 189·HI

Displacement reactions of halogen containing compounds are a common synthetic tool,6 although there are few examples of displacement reactions from halogenated pyrrolizidines, especially those which do not occur intramolecularly.[7] Whilst investigating the synthesis of new dipeptide isoteres containing an aminopyrrolizidinone scaffold, Salvati *et al.* introduced the requisite amino-substitution via displacement of bromide with azide.8 Pyrrolizidinone **305** was synthesised from methacrylamide **298** via cycloaddition with nitrone **299**, which gave a single regio- and diastereoisomer **300** in 79% yield. Hydrogenolysis of **300** in the presence of $Pd(OH)_2$ and 10 mol equiv of AcOH gave **301** in 98% yield, and treatment of **301** with MsCl gave **302** in 94% yield. The halogen displacement of **302** was then attempted, but proved difficult with reaction of **302** with KBr under phase transfer conditions affording a 1:1 mixture of **303** and the elimination product **306**. The desired bromide **303** was isolated in 34% yield and subsequent reaction with NaN_3 gave the azide product **304** in quantitative yield. Reduction of **304** gave the amino-substituted pyrrolizidinone **305** in 80% yield (Scheme 59).[8]



Scheme 59 *Reagents and conditions:* (i) H_2O, 60 °C, 12 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, AcOH, MeOH, rt, 15 h; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h; (iv) KBr, $[(C_{12}H_{25})Me_3N]^+[Br]^-$, CH_2Cl_2, H_2O, rt, 48 h; (v) NaN_3, DMF, rt, 12 h; (vi) Ra-Ni, MeOH, rt, 2 h.

During the course of these studies into the elimination and displacement reactions of the iodopyrrolizidine **189**, Trauner *et al.* reported using an intermolecular-intramolecular displacement sequence to synthesise the core structure of the loline alkaloids, which resulted in a total synthesis of (+)-norloline **310**.[9] Finkelstein reaction of bromopyrrolizidine **307** using LiCl in DMF achieved displacement and selective inversion of the stereochemistry at C(7) to give chloropyrrolizidine **308** in 86% yield. Heating **308** in a microwave apparatus in the presence of K_2CO_3 resulted in an intramolecular displacement of chloride by the C(2)-hydroxyl group to give tricycle **309** in 91% yield. Subsequent hydrogenation reduced the azide functionality within **309** to give (+)-norloline **310** in three steps and 70% yield from pyrrolizidine **307**. The two steps were also realised in a 'one pot' reaction, which gave **309** in 65% yield (Scheme 60).[9]

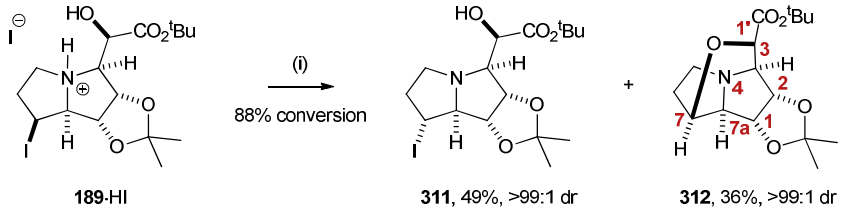


Scheme 60 *Reagents and conditions:* (i) LiCl, DMF, 105 °C, 6 h; (ii) K_2CO_3, MeOH, 150 °C/300W, 10 min; (iii) H_2 (1 atm), 10% Pd/C, MeOH, rt, 4 h; (iv) LiCl, DMF, 85 °C, 4 h then KO^{t}Bu, rt, 12 h.

4.4.1 Formation of epimer 311

It was observed that reaction of **189**·HI with KI in DMF at 100 °C for 23 h resulted in 88% conversion to a 57:43 mixture of **311** and **312**. Epimer **311** was isolated in 49% yield and >99:1 dr along with tricyclic bridged ether **312** in 36% yield and >99:1 dr (Scheme 61).[10] The relative configuration within **311** was unambiguously established by single crystal X-ray

diffraction analysis, with the absolute (1*R*,2*S*,3*S*,4*S*,7*R*,7a*S*,1′*R*)-configuration being assigned from the known configuration of **189**·HI (Fig. 34).



189·HI **311**, 49%, >99:1 dr **312**, 36%, >99:1 dr

Scheme 61 *Reagents and conditions:* (i) KI, DMF, 100 °C, 23 h.

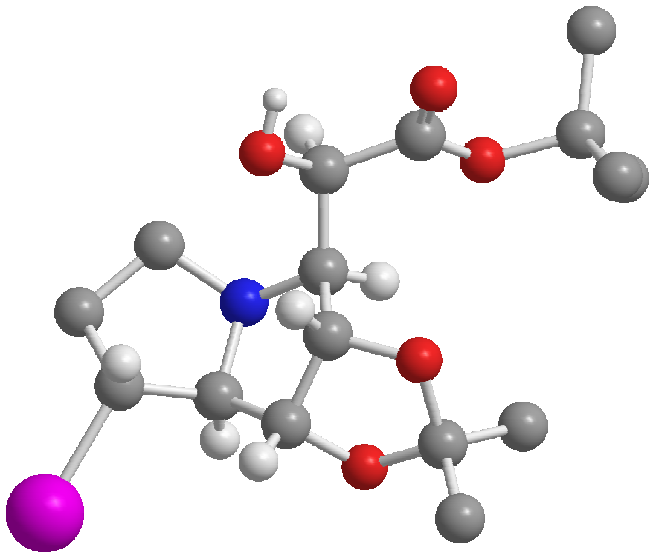
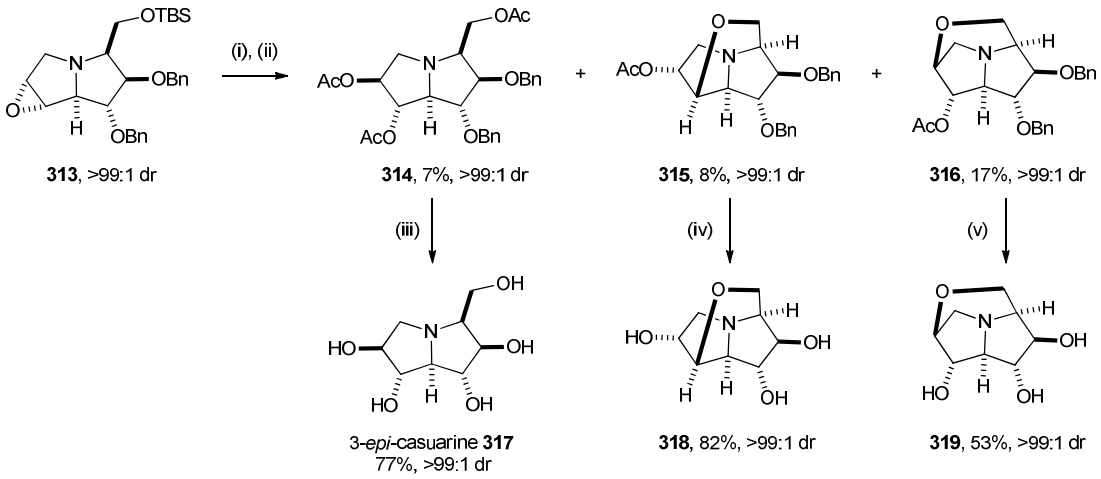


Figure 34 Chem3D representation of the single crystal X-ray structure of (1*R*,2*S*,3*S*,4*S*,7*R*,7a*S*,1′*R*)-**311** (selected H atoms have been omitted for clarity).

A comparable intramolecular reaction to form a bicyclic ether has been reported: Pyne *et al.* observed a competing intramolecular displacement in their reported synthesis of 3-*epi*-casuarine **317**.[11] Their proposed route to **317** involved the regioselective ring-opening of epoxide **313**, although reaction of **313** with $NaHSO_4$ actually resulted in the formation of a complex mixture of products from which, following acetylation to enable their separation, **314**, **315** and **316** were isolated in 7, 8 and 17% yield, respectively. Unfortunately, efforts to avoid intramolecular displacement and to improve the yield of **314** were unsuccessful. 3-*epi*-Casuarine **317** was finally isolated following the hydrolysis and hydrogenolysis of **314**, in 77% yield and >99:1 dr from **314**, and in 0.4% yield over thirteen steps from L-xylose (Scheme 62).[11]



Scheme 62 *Reagents and conditions:* (i) $NaHSO_4$, CH_2Cl_2, 50 °C, 7 days; (ii) Ac_2O, py, DMAP, 24 h; (iii) $PdCl_2$, H_2 (1 atm), MeOH, 4 days; (iv) Amberlyst (OH^-), MeOH, rt, 12 h then $PdCl_2$, H_2 (1 atm), MeOH, 24 h; (v) Amberlyst (OH^-), MeOH, rt, 16 h then $PdCl_2$, H_2 (1 atm), MeOH, 12 h.

The solid state structures of **189**·HI and **311** allowed a comparison of the respective nucleophile approach trajectories: it was proposed that the solid state conformation of each compound would give an approximation of their solution phase conformations, and could allow a prediction of their respective behaviours towards nucleophiles. It was apparent that the solid state conformation of **189**·HI was such that the approach to C(7) was relatively unhindered. In contrast, in the epimer **311**, the α-branched substituent at C(3) hinders the attack of nucleophiles at C(7). In fact, the C(1′)-hydroxyl group is in a position to readily effect intramolecular displacement of the iodide, which rationalised formation of ether **312** during the attempted epimerisation of **189**·HI (Fig. 35). From this, it was hypothesised that displacement of the iodide would occur more readily from **189**·HI than its epimer **311**. To test this hypothesis, the proposed displacement of **189**·HI with NaN_3 was accompanied by an investigation into the reaction of epimer **311** with NaN_3.

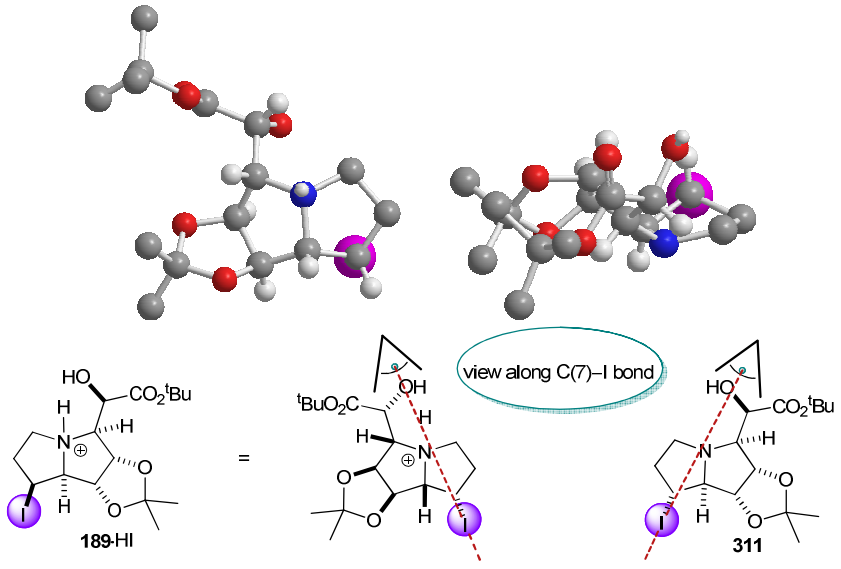
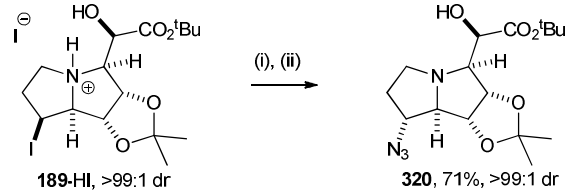


Figure 35 The nucleophile approach trajectory in both **189**·HI and **311**.

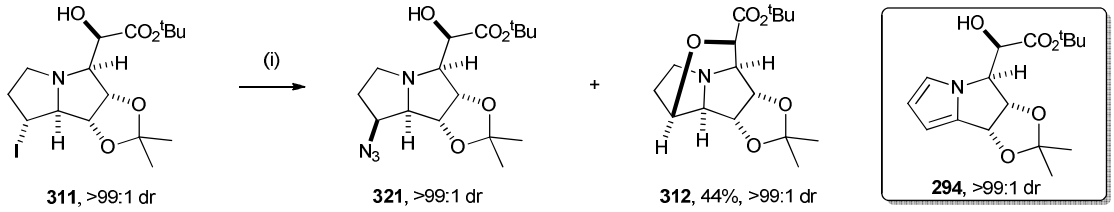
4.4.2 Displacement reactions with NaN_3

Reaction of **189**·HI with NaN_3 in DMF at 50 °C proceeded to give the C(7)-azidopyrrolizidine product **320** in >99:1 dr which was subsequently purified and isolated in 71% yield and >99:1 dr (Scheme 63). The absolute configuration at C(7) within **320** was assigned on the basis of an S_N2-type displacement reaction occurring with inversion of configuration.



Scheme 63 *Reagents and conditions:* (i) KOH (1.0 M aq), $CHCl_3$; (ii) NaN_3, DMF, 50 °C, 12 h.

In contrast, reaction of the epimer **311** under the same conditions gave an approximate 50:50 mixture of C(7)-azidopyrrolizidine **321** and tricyclic bridged ether **312**, along with trace amounts of other species. A 90:10 mixture of **321** and pyrrole **294** was isolated on purification, as well as tricyclic ether **312** which was isolated in 44% yield and >99:1 dr (Scheme 64).

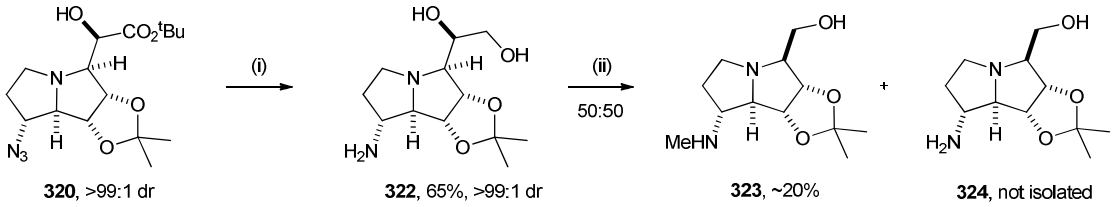


Scheme 64 *Reagents and conditions:* (i) NaN_3, DMF, 50 °C, 12 h.

4.4.3 Towards 7-deoxy-7-amino alexine analogues

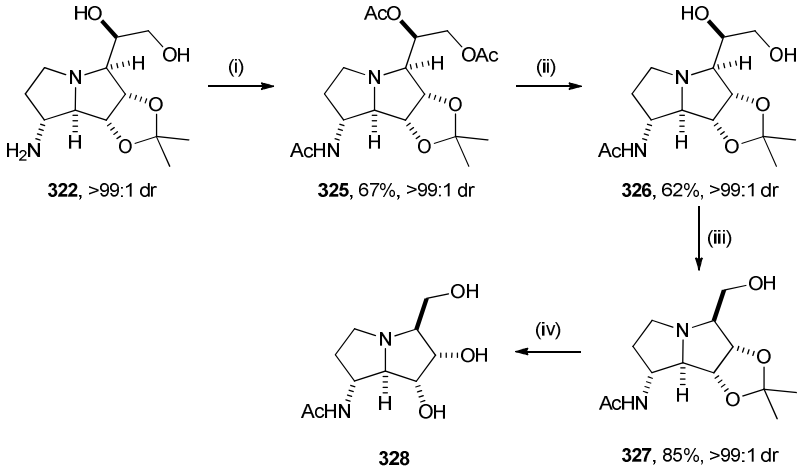
Replacement of an endo- or exocyclic oxygen atom of a biologically active sugar-derived compound with a nitrogen atom is known to change its activity and, for this reason, deoxy-amino analogues of biologically active compounds are of great interest to medicinal chemists.[12] By extension, deoxy-amino pyrrolizidines could prove to be more powerful glycosidase inhibitors than their parent alkaloids. Thus, the elaboration of the azidopyrrolizidine **320** to the corresponding deoxy-amino pyrrolizidine (7-deoxy-7-amino-alexine) was investigated. Reaction of **320** with $LiAlH_4$ gave diol **322** in 65% yield and >99:1 dr. Oxidative cleavage of **322** with $NaIO_4$ followed by addition of $NaBH_4$ gave a 50:50 mixture of two products, from which an impure sample of *N*-methyl amine **323** was isolated in 20% yield upon chromatographic purification. The desired product **324** was tentatively assigned as the other product of this reaction, but none was isolated. The formation of **323** was presumed to result from reductive *N*-methylation of the amine moiety within **324** by

formaldehyde, formed as a by-product during cleavage of the diol **322** by $NaIO_4$. In an effort to avoid this undesirable side reaction the oxidative cleavage was attempted in the presence of a large excess of benzylamine which, it was hoped, would act as a formaldehyde scavenger. Unfortunately, this reaction resulted in the formation of a complex mixture of products (Scheme 65).



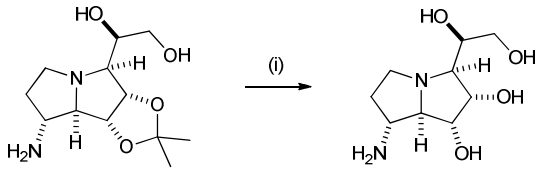
Scheme 65 *Reagents and conditions*: (i) $LiAlH_4$ (1.0 M in THF), THF, −78 °C to rt, 12 h; (ii) $NaIO_4$, $MeOH/H_2O$ (v/v 5:1), rt, 4 h then $NaBH_4$, MeOH, rt, 12 h.

In order to achieve oxidative cleavage in this particular system it was decided to effect protection of the C(7)-amine group of **322**. Hence, treatment of **322** with Ac_2O gave *N*,*O*,*O*-triacetate **325** in 67% yield and >99:1 dr. Selective removal of the *O*-acetyl groups initiated by a catalytic amount of KOH in MeOH gave diol **326** in 62% yield, which underwent oxidative cleavage with $NaIO_4$ and immediate reduction with $NaBH_4$ to give **327**, which was isolated in 85% yield. Acid-catalysed hydrolysis of **327** gave an impure sample of **328**, which proved difficult to purify (Scheme 66).



Scheme 66 *Reagents and conditions*: (i) Ac_2O, DMAP, py, rt, 12 h; (ii) KOH, MeOH, rt, 2 h; (iii) $NaIO_4$, $MeOH/H_2O$ (v/v 5:1), rt, 4 h; (iv) HCl (3.0 M aq), MeOH, 60 °C, 2 h.

Despite the difficulties encountered isolating **328**, this route did allow the isolation of a novel C(7)-aminopyrrolizidine in good yield and purity. Acid-catalysed hydrolysis of the acetonide group within **322** with 3.0 M aq HCl in MeOH gave the densely functionalised pyrrolizidine **329** in 76% yield and >99:1 dr after ion exchange chromatography (Scheme 67).



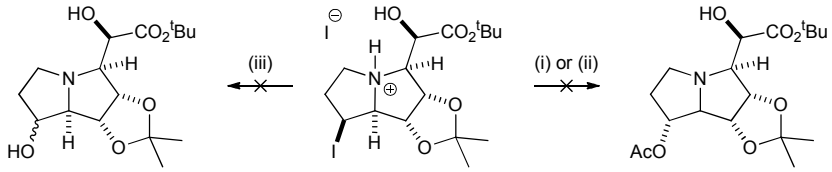
322, >99:1 dr **329**, 76%, >99:1 dr

Scheme 67 *Reagents and conditions*: (i) HCl (3.0 M aq), MeOH, 60 °C, 2 h.

Following the successful displacement with NaN_3, it was decided to attempt the displacement using a nucleophilic source of 'O', which would give access to the pyrrolizidine scaffold bearing the alexine substitution pattern.

4.4.4 Displacement reactions with nucleophilic 'O'

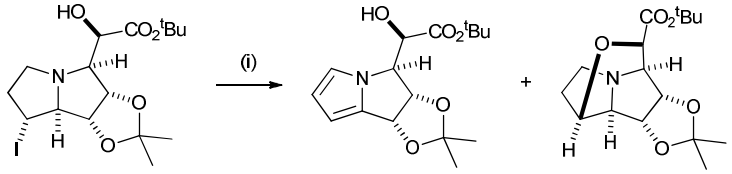
Using representative literature conditions,[13] reaction of **189**·HI with KOAc in DMF at 100 °C for 23 h resulted in the formation of a complex mixture of products by ^{1}H NMR spectroscopic analysis. Analysis of the mass spectrum of the unpurified product showed no sign of the desired acetate **330**, and attempted chromatographic purification resulted in the isolation of mixtures of unidentifiable products. Similarly, reaction of **189**·HI with AgOAc in AcOH at rt for 6 h gave a complex mixture of products. Lautens *et al*. reported the nucleophilic displacement of a primary iodide with H_2O in the presence of $AgNO_3$,[14] unfortunately replication of their reaction conditions on **189**·HI returned only starting materials (Scheme 68).



331 **189**·HI, >99:1 dr **330**

Scheme 68 *Reagents and conditions:* (i) KOAc, DMF, 100 °C, 23 h; (ii) AgOAc, AcOH, rt, 6 h; (iii) $AgNO_3$, acetone/H_2O (v/v 4:1), rt, 12 h.

When epimer **311** was reacted with KOAc in DMF to attempt an oxygen displacement, analysis of the complex ^{1}H NMR spectrum of the unpurified reaction mixture revealed the presence of ether **312**, pyrrole **294** and other pyrrole-containing and dimeric species. Chromatographic purification allowed isolation of pyrrole **294** and ether **312** in 7 and 65% yield, respectively, and in >99:1 dr in both cases (Scheme 69). No other identifiable species were returned from the column.

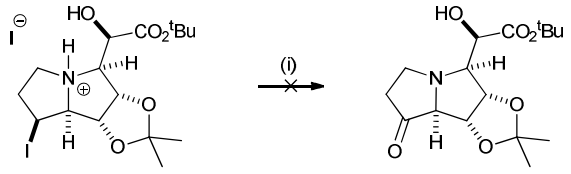


Scheme 69 *Reagents and conditions:* (i) KOAc, DMF, 100 °C, 23 h.

As these initial results were not promising, the investigation turned to alternative methods for introducing oxygen to the pyrrolizidine skeleton.

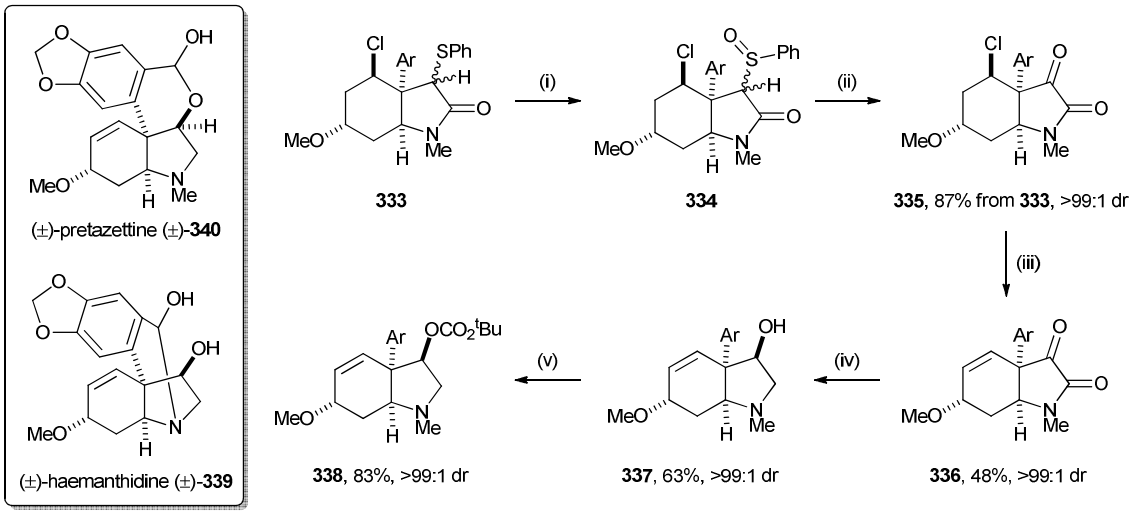
4.5 Installation of ketone functionality at C(7)

Other literature examples showed the use of the oxidation of alkyl halides to give ketones;[15] subjecting **189**·HI to these conditions was predicted to result in the formation of pyrrolizidinone **332** which could then undergo diastereoselective reduction[16] to give the desired C(7)-hydroxyl substituent. Reaction of **189**·HI under conditions reported by Bonjoch *et al.*, whereby **189**·HI was stirred at rt with $AgBF_4$ and DMSO (a modification of Kornblum's original conditions)[17] returned starting materials (Scheme 70).[18]



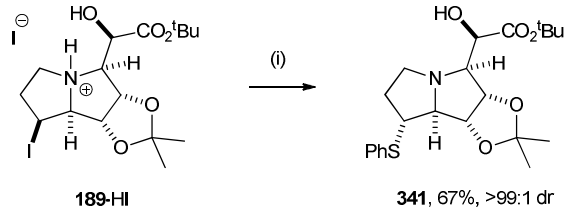
Scheme 70 *Reagents and conditions:* (i) $AgBF_4$, DMSO, rt, 12 h then Et_3N, rt, 1 h.

The presence of sulfur in a compound has often been used as a gateway for introducing ketone functionality into a system by using the Pummerer rearrangement.[19] In their formal synthesis of (±)-haemanthidine **339** and (±)-pretazettine **340**, Ishibashi *et al.* used a Pummerer-type rearrangement to install the desired oxygen functionality within **338**.[20] Oxidation of sulfide **333** with *m*-CPBA gave sulfoxide **334**, which subsequently rearranged on treatment with TFAA to afford dioxo species **335** in 87% yield over two steps. Dehydrochlorination was achieved with DBU in MeCN at 160 °C to give alkene **336** in 48% yield. Stereoselective reduction of **336** with $LiAlH_4$ was followed by acylation of **337** with pivaloyl chloride to give ester **338** in 52% yield from alkene **336**, and as a single diastereoisomer. Ester **338** had previously been reported as the key intermediate in total syntheses of (±)-**339** and (±)-**340** (Scheme 71).[20]



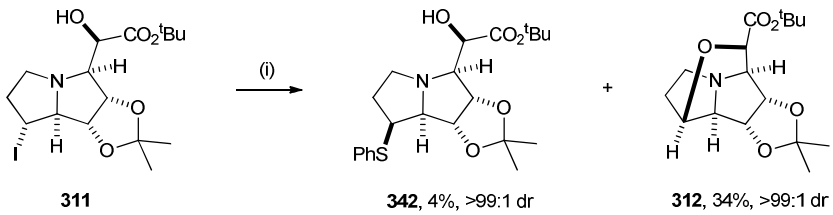
Scheme 71 *Reagents and conditions:* (i) *m*-CPBA, CH_2Cl_2; (ii) TFAA, 2,6-lutidine, CH_2Cl_2, reflux then satd aq $NaHCO_3$; (iii) DBU, MeCN, 160 °C, 3 h; (iv) $LiAlH_4$, THF, reflux; (v) ^{t}BuCOCl, py, 30 °C to 40 °C.

Reaction of **189**·HI with PhSH and K_2CO_3 resulted in the selective formation of C(7)-phenylthiopyrrolizidine **341** which was isolated in 67% yield and in >99:1 dr (Scheme 72). Again the observed configuration at C(7) within **341** was assigned on the basis of an S_N2-type substitution reaction proceeding with inversion of configuration at C(7).



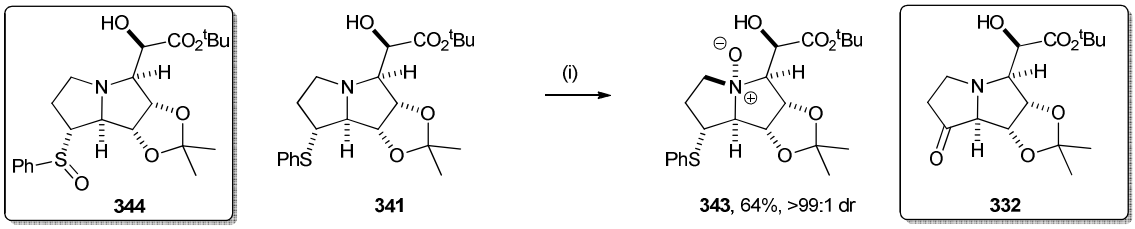
Scheme 72 *Reagents and conditions:* (i) PhSH, K_2CO_3, THF, rt, 28 h.

This successful displacement prompted investigation of the analogous reaction with epimer **311**, and as expected this reaction occurred much less-readily: after 12 h there was no sign of displacement. However, if the reaction mixture was left to stir for 1 week at rt, formation of a trace amount (<5%) of the desired displaced product was observed, with the major product being tricyclic ether **312**. Chromatographic purification allowed the isolation of C(7)-phenylthiopyrrolizidine **342** in 4% yield and >99:1 dr and **312** in 34% yield and >99:1 dr (Scheme 73).



Scheme 73 *Reagents and conditions:* (i) PhSH, K_2CO_3, THF, rt, 1 week.

Oxidation of **341** and subsequent Pummerer rearrangement was anticipated to result in the formation of pyrrolizidinone **332**, which could subsequently be reduced selectively to give the required C(7)-hydroxyl substituent. Reaction of **341** with *m*-CPBA for 30 min unfortunately gave complete conversion to the *N*-oxide **343** in 64% yield as a single diastereoisomer in preference to sulfoxide **344** (Scheme 74). The relative configuration within **343** was unambiguously established by single crystal X-ray analysis, with the absolute (1*R*,2*S*,3*S*,4*R*,7*R*,7a*R*,1′*R*)-configuration being assigned from the known configuration within **189**·HI. This analysis also confirmed the absolute (1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-configuration within **341** and this stereochemical outcome is consistent with an S_N2-type mechanism upon reaction of **189**·HI with PhSH (Fig. 36). This result demonstrated that oxidation occurred more readily at nitrogen rather than sulfur, and further studies within this area were not pursued.



Scheme 74 *Reagents and conditions:* (i) *m*-CPBA, CH_2Cl_2, −78 °C, 30 min.

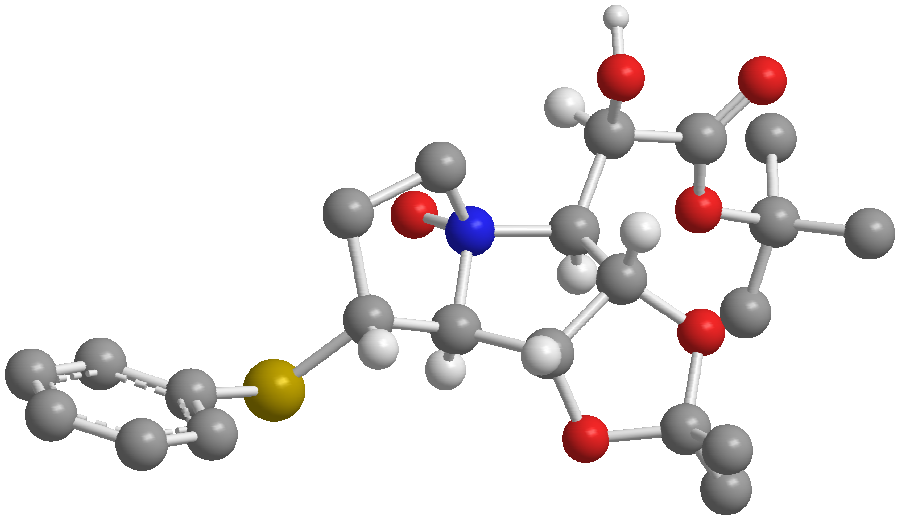
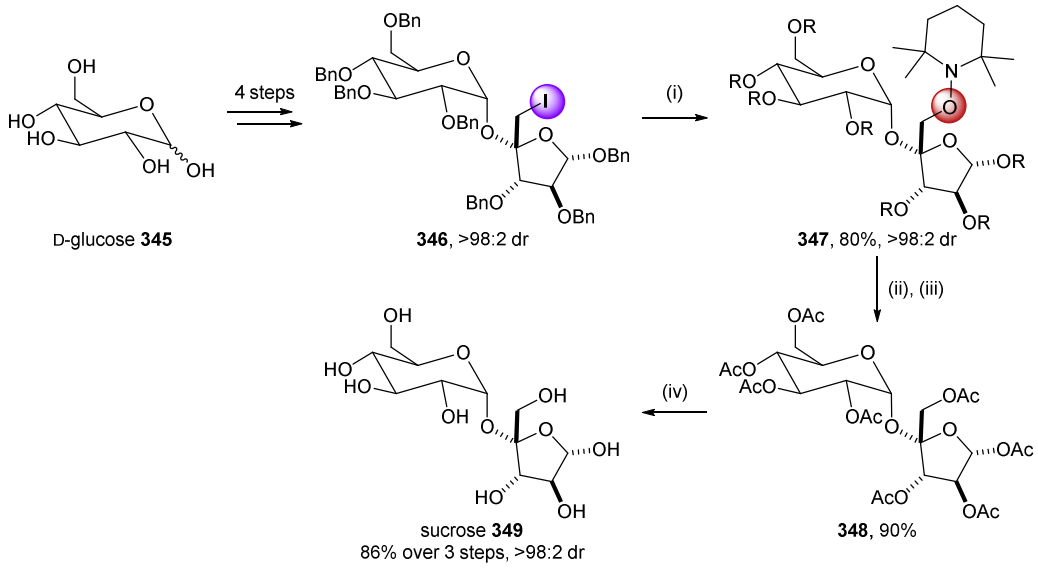


Figure 36 Chem3D representation of the single crystal X-ray structure of (1*R*,2*S*,3*S*,4*R*,7*R*,7a*R*,1′*R*)-**343** (selected H atoms have been omitted for clarity).

4.6 Radical-mediated substitution of iodide

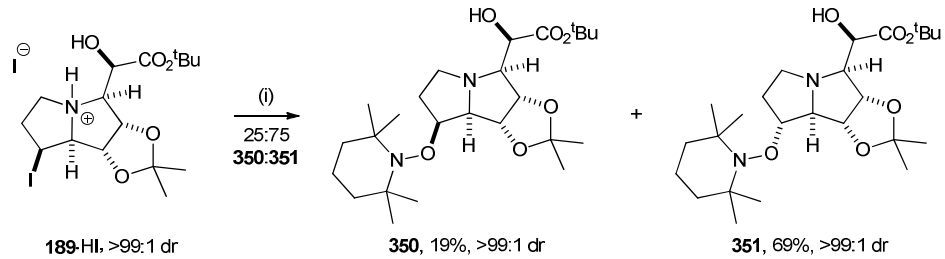
In 1990 Barrett *et al.* reported a stereoselective synthesis of sucrose **349** from D-glucose **345** which proceeded via iodide **346**.[21] Their proposed route involved an S_N2-type displacement of the iodide with an oxygen nucleophile, although **346** proved to be resistant to all displacement attempts, even at high temperatures. Ultimately, they achieved the desired iodine-to-oxygen transformation via radical-mediated substitution, when **346** was treated with Bu_3SnH in the

presence of TEMPO to give hydroxylamine **347** in 80% yield. Global deprotection of **347** with Na metal was accompanied by N–O bond cleavage, and was followed by acetate protection of the free hydroxyl groups to facilitate purification, which gave **348** in 90% yield. Sucrose **349** was then isolated in 95% yield by basic hydrolysis of the acetate protecting groups within **348**, in eight steps from D-glucose **345** (Scheme 75).[21]



Scheme 75 *Reagents and conditions:* (i) TEMPO, Bu_3SnH, PhH, *hv*; (ii) Na, NH_3, THF; (iii) Ac_2O, py; (iv) NaOMe, MeOH.

It was decided to apply this procedure to **189**·HI. Accordingly, reaction of **189**·HI with Bu_3SnH in the presence of TEMPO gave a 25:75 mixture of two diastereoisomeric hydroxylamines **350** and **351**.[22] Chromatographic purification on silica doped with 10% KF[23] gave **351** in 69% yield, and an impure sample of **350** in 19% yield, as single diastereoisomers in both cases (Scheme 76). The configuration within both **350** and **351** were assigned by chemical correlation (*vide infra*).

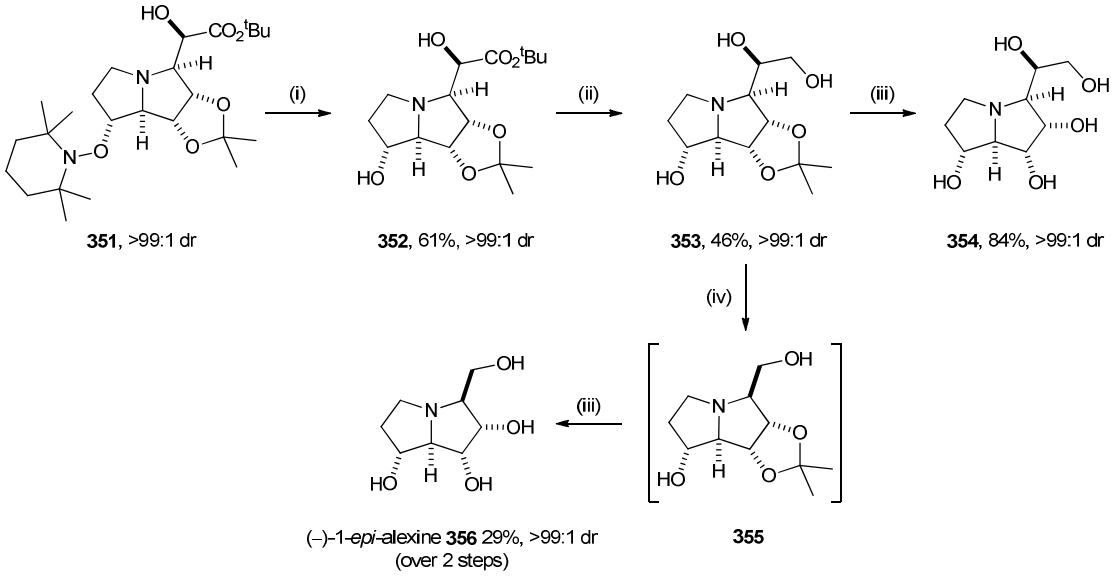


Scheme 76 *Reagents and conditions:* (i) Bu_3SnH, TEMPO, PhMe, 70 °C, 1.5 h.

4.6.1 Synthesis of (–)-1-*epi*-alexine 356

Subsequent cleavage of the N–O bond within **351** was achieved by reaction with activated Zn in AcOH to give the corresponding C(7)-hydroxypyrrolizidine **352** in 61% yield and >99:1 dr. Reduction of **352** with $LiAlH_4$ gave **353** in 46% yield and >99:1 dr. Acid-catalysed hydrolysis of the acetonide group within **353** allowed the isolation of polyhydroxylated pyrrolizidine **354**

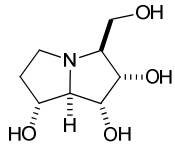
in 84% yield as a single diastereoisomer. Unfortunately, as with hexahydroazocine **226**, treatment of **353** with $NaIO_4$ and immediate reduction of the resultant aldehyde with $NaBH_4$ proved problematic and resulted in a reaction mixture that produced a complex ^1H NMR spectrum. Attempted chromatographic purification did not allow the isolation of any identifiable species. However, since mass spectrometric analysis of the unpurified product showed a signal at m/z = 230, which corresponds to the desired product **355** ($[M+H]^+$), it was decided to subject the mixture to acid-catalysed hydrolysis conditions and subsequent ion-exchange chromatography. In fact, ion exchange chromatography with DOWEX 1X8-200 (OH^- form) ion exchange resin, followed by DOWEX 50WX8 (H^+ form) allowed the isolation of the pyrrolizidine alkaloid (**–**)-1-*epi*-alexine **356**24 in 29% yield from **353**. The identity of (**–**)-**356** was confirmed by comparison of its specific rotation and ^1H and ^{13}C NMR data with those previously reported in the literature (Scheme 77).[25,26] The conversion of hydroxylamine **351** into (**–**)-1-*epi*-alexine **356** allowed the assignment of the C(7)-configuration within **351**, and hence that within **350**.



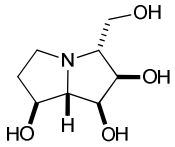
Scheme 77 *Reagents and conditions*: (i) Zn, AcOH/THF/H_2O (v/v/v 3:1:1), 70 °C, 2 h; (ii) $LiAlH_4$ (1.0 M in THF), THF, −78 °C to rt, 12 h; (iii) HCl (3.0 M aq), MeOH, 60 °C, 2 h; (iv) $NaIO_4$, MeOH/H_2O (v/v 5:1), rt, 4 h, then $NaBH_4$, MeOH, 12 h.

A comparison of the ^1H and ^{13}C NMR data of this synthetic sample of (–)-1-*epi*-alexine **356** {$[\alpha]_D^{20}$ −48 (*c* 0.03 in H_2O); $[\alpha]_D^{20}$ −60 (*c* 0.03 in MeOH)} with data reported for (+)-1-*epi*-alexine **356** {$[\alpha]_D$ +59.7 (*c* 0.58 in H_2O)} isolated from *Castanospermum australe* by Asano *et al.*,[25a] the data reported for (+)-1-*epi*-alexine **356** {$[\alpha]_D^{25}$ +53.4 (*c* 0.43 in H_2O)} isolated from *Castanospermum australe* by Nash *et al.*,[25b] and the data reported for a synthetic

sample of (–)-1-*epi*-alexine **356** {$[\alpha]_D^{20}$ –51.0 (*c* 0.51 in H_2O)} reported by Donohoe *et al.*[26a] showed excellent agreement (Tables 7, 8 and 9).



(–)-1-*epi*-alexine **356**



(+)-1-*epi*-alexine **356**

^{1}H data for 1-*epi*-alexine **356**			
H	Asano *et al.*[25a] δ_H (400 MHz, D_2O [TSP])	Donohoe *et al.*[26a] δ_H (500 MHz, D_2O [TSP])	This study δ_H (500 MHz, D_2O [TSP])
C(1)H	4.06 (dd, *J* 5.3, 2.5)	4.06 (dd, *J* 5.2, 2.4)	4.05 (dd, *J* 5.4, 2.4)
C(2)H	3.95 (dd, *J* 9.3, 5.3)	3.95 (dd, *J* 9.5, 5.4)	3.93 (dd, *J* 9.5, 5.4)
C(3)H	3.21 (ddd, *J* 9.3, 6.0, 6.0)	3.21 (m)	3.15-3.18 (m)
C(5)H_A	2.90 (ddd, *J* 10.6, 10.3, 5.8)	2.90 (ddd, *J* 10.3, 10.1, 6.3)	2.85 (td, *J* 10.4, 5.7)
C(5)H_B	3.01 (ddd, *J* 10.3, 6.8, 3.4)	3.00 (ddd, *J* 10.1, 7.3, 3.5)	2.96 (ddd, *J* 10.1, 6.9, 3.2)
C(6)H_A	1.76 (m)	1.76 (m)	1.71-1.78 (m)
C(6)H_B	2.14 (m)	2.14 (m)	2.09-2.16 (m)
C(7)H	4.14 (ddd, *J* 8.0, 5.9, 5.9)	4.14 (ddd, *J* 8.0, 6.2, 6.0)	4.12 (ddd, *J* 8.2, 6.3, 6.0)
C(7a)H	3.19 (dd, *J* 5.9, 2.5)	3.19 (dd, *J* 5.5, 2.4)	3.13 (dd, *J* 5.7, 2.4)
C(1′)H_2	3.87 (d)	3.87 (d)	3.86 (d, *J* 1.6) 3.87 (d, *J* 4.1)

Table 7 Comparison of ^{1}H NMR data of 1-*epi*-alexine **356** [Chemical shifts (δ_H) are reported in ppm relative to TSP as an internal standard (Me_3Si δ_H = 0.00) and coupling constants (*J*) in Hz].

^{1}H data for 1-*epi*-alexine **356** δ_H (500 MHz, D_2O)		
H	Nash *et al.*[25b]	This study
C(1)H	4.00 (dd, *J* 5.4, 2.5)	3.96 (dd, *J* 5.2, 2.2)
C(2)H	3.88 (dd, *J* 9.5, 5.0)	3.85 (dd, *J* 9.8, 5.2)
C(3)H	3.13 (ddd, *J* 9.5, 7.3, 5.0)	3.07-3.12 (m)
C(5)H_A	2.83 (m)	2.80 (td, *J* 10.5, 5.8)
C(5)H_B	2.93 (m)	2.88-2.91 (m)
C(6)H_A	1.70 (m)	1.62-1.70 (m)
C(6)H_B	2.09 (m)	2.02-2.07 (m)
C(7)H	-	4.02-4.06 (m)
C(7a)H	3.10 (dd, *J* 6.0, 2.5)	3.07-3.12 (m)
C(1′)H_2	3.81 (m)	3.76 (s) 3.78 (d, *J* 1.9)

Table 8 Comparison of ^{1}H NMR data of 1-*epi*-alexine **356** [Chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

^{13}C data for 1-*epi*-alexine **356**					
C	δ_C (100 MHz, D_2O [TSP])	δ_C (125 MHz, D_2O [TSP])		δ_C (125 MHz, D_2O)	
	Asano *et al.*[25a]	Donohoe *et al.*[26a]	This study	Nash *et al.*[25b]	This study
C(1)	76.4	76.5	76.7	73.8	73.6
C(2)	73.8	73.8	73.9	71.0	70.9
C(3)	67.4	67.3	67.3	64.4	64.4
C(5)	47.7	47.7	47.5	44.6	44.7
C(6)	36.3	36.3	36.4	33.5	33.4
C(7)	77.0	77.0	77.2	74.3	74.2
C(7a)	78.7	78.6	78.5	75.6	75.7
C(1′)	61.8	61.8	62.0	59.1	58.9

Table 9 Comparison of ^{13}C NMR data of 1-*epi*-alexine **356** [Chemical shifts (δ_C) are reported in ppm].

4.7 Summary

Investigations into the displacement of the iodide from within **189**·HI resulted in the formation of several C(7)-substituted pyrrolizidines: for example, reaction with NaN_3 led to the synthesis of the aminopyrrolizidine **329**. Displacement reactions of **189**·HI with nucleophilic sources of 'O', in an attempt to access the alexine substitution pattern, were hindered by the propensity of the nucleophile to act as a base, and resulted in the formation of several undesirable side products. Nonetheless, radical-mediated substitution allowed access to hydroxylamine **351**, which subsequently led to the isolation of the known pyrrolizidine alkaloid (**–**)-1-*epi*-alexine **356** in 10 steps from D-ribose **152** (Fig. 37).

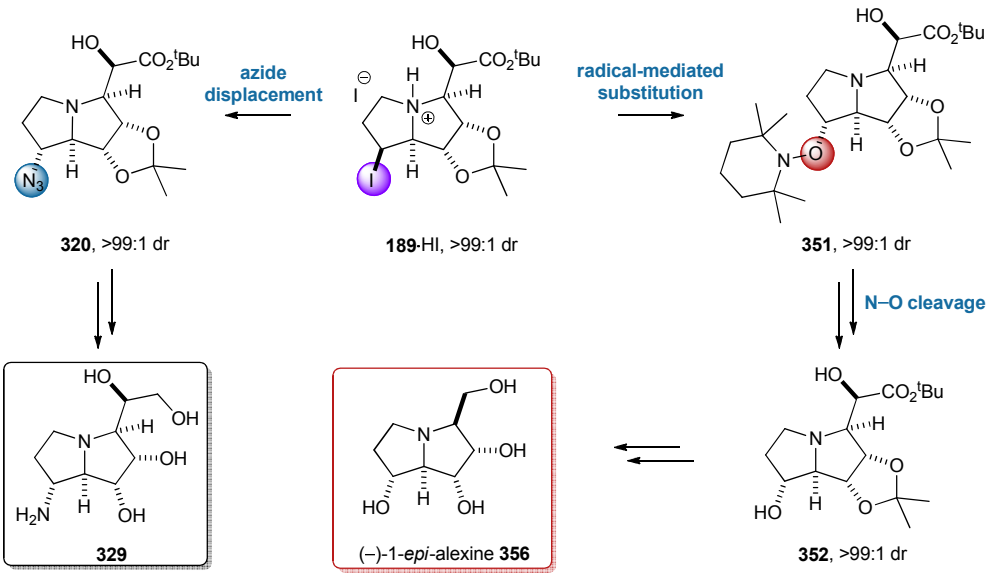


Figure 37 Elaboration of **189**·HI to aminopyrrolizidine **329** and hydroxypyrrolizidine (**–**)-1-*epi*-alexine **356**.

4.8 References and notes

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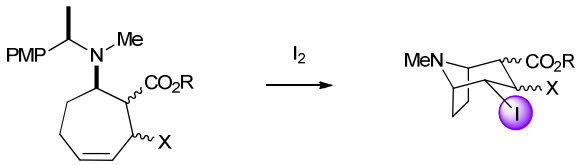
Transannular Iodoamination in the Asymmetric Synthesis of (+)-Pseudococaine

This chapter details an investigation into the development of a transannular ring-closing iodoamination procedure for the synthesis of the [3.2.1]-azabicyclic scaffold of the tropane alkaloids (Fig. 38).

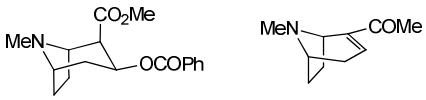


357, X = H, OH **358**, X = H, OH

Figure 38 Formation of the [3.2.1]-azabicyclic scaffold on reaction of **357** with I_2.

5.1 The tropane alkaloids

The tropane alkaloids are naturally occurring plant alkaloids that contain a characteristic 8-azabicylo-[3.2.1]-octane ring and which have an array of biological activities. The most notorious of these alkaloids is cocaine **359**,[1] a highly addictive narcotic due to its ability to act as a serotonin, norepinephrine and dopamine reuptake inhibitor.[2,3] Another distinctive example of this family of compounds is (−)-*ent*-ferruginine **82**, whose antipode is found in the plants *Darlingia ferruginea* and *Darlingia darlingiana*,[4] which has been shown to be a potent agonist for the nicotinic acetylcholine receptor [nAchR] (Fig. 39).[5] Since compounds which contain this [3.2.1]-azabicyclic structure have potential as cocaine antagonists in the treatment of cocaine addiction and as radiopharmaceuticals, they are of great interest to medicinal chemists and are commonly lead compounds in drug discovery.[6]



(–)-cocaine **359** (–)-ferruginine **82**

Figure 39 The tropane alkaloids (–)-cocaine **359** and (–)-ferruginine **82**.

5.2 Synthetic approaches to the 8-azabicyclo-[3.2.1]-octane ring

The distinctive bicyclic scaffold of the tropane alkaloids has made them an intriguing total synthesis target for many synthetic chemists since the birth of natural product synthesis in the mid-19th century. In fact, members of the tropane alkaloid family were among the first alkaloids to be synthesised despite the difficulties encountered in the elucidation of their core structure, which was only secured in 1901 by Willstätter.[7] As part of this seminal structural elucidation work, Willstätter also reported the first total syntheses of tropinone **362**, tropine and cocaine **359**.[7,8,9] Although not as elegant as the Robinson synthesis,[10] Willstätter's

approach to tropinone **359** involved the first reported example of transannular cyclisation of an exocyclic nitrogen atom to form the [3.2.1]-azabicyclic structure (Fig. 40).[11]

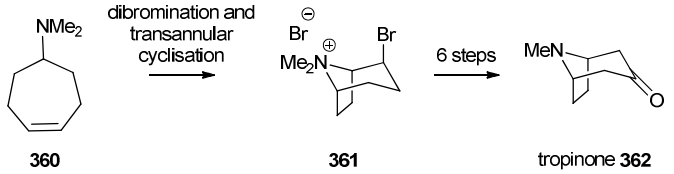


Figure 40 The first total synthesis of tropinone **359** by Willstätter.

Following this, Willstätter also reported the synthesis of (±)-cocaine **359** by elaboration of tropinone **362**, and subsequent resolution of (±)-**359** with D-tartaric acid completed the first total synthesis of (−)-cocaine **359**.[8,9] To date many synthetic approaches to a chiral tropane scaffold, such as (−)-cocaine **359**, rely on the resolution of a racemic mixture as Willstätter did over 100 years ago (Fig. 41).[12] Asymmetric approaches to the scaffold can generally be defined as those that are enantiospecific chiral pool syntheses,[13] asymmetric syntheses (e.g., using chiral auxiliaries and chiral catalysts)[14] and those which rely on enzymatic resolutions.[15]

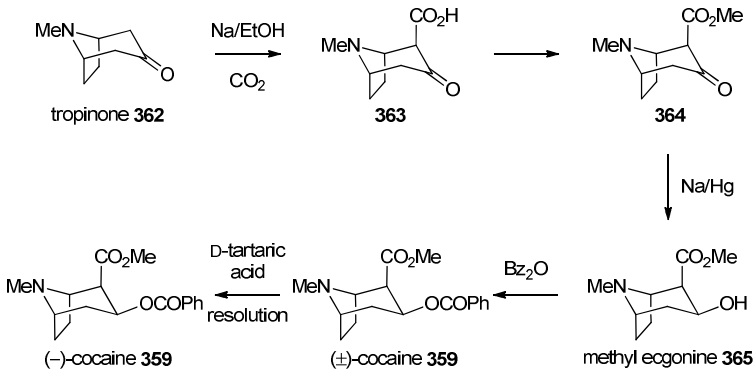


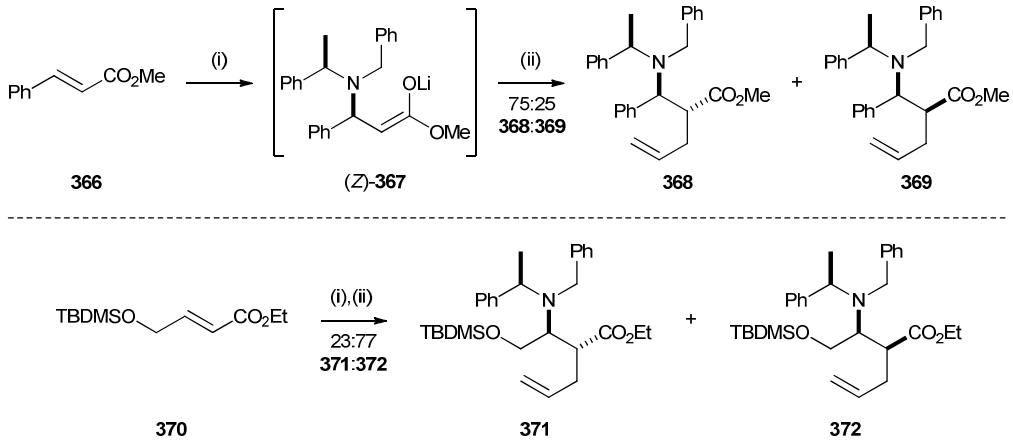
Figure 41 The first total synthesis of (−)-cocaine **359**.

5.3 Background

5.3.1 Tandem lithium amide conjugate addition and alkylation reactions

Davies *et al.* have investigated the stereochemical outcome of the reaction of lithium (*Z*)-enolates (formed on conjugate addition of an enantiopure lithium amide to an α,β-unsaturated ester) with alkylating agents.[16,17] For example, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (*R*)-**145** to methyl cinnamate **366** followed by addition of allyl bromide gave a 75:25 mixture of *anti*-α-allyl-β-amino ester **368** and *syn*-α-allyl-β-amino ester **369**, respectively.[16] In fact, the result of such reactions is generally the formation of the *anti*-α-alkyl-β-amino ester with moderate to good levels of diastereoselectivity.[16] However, when the analogous reaction was carried out on

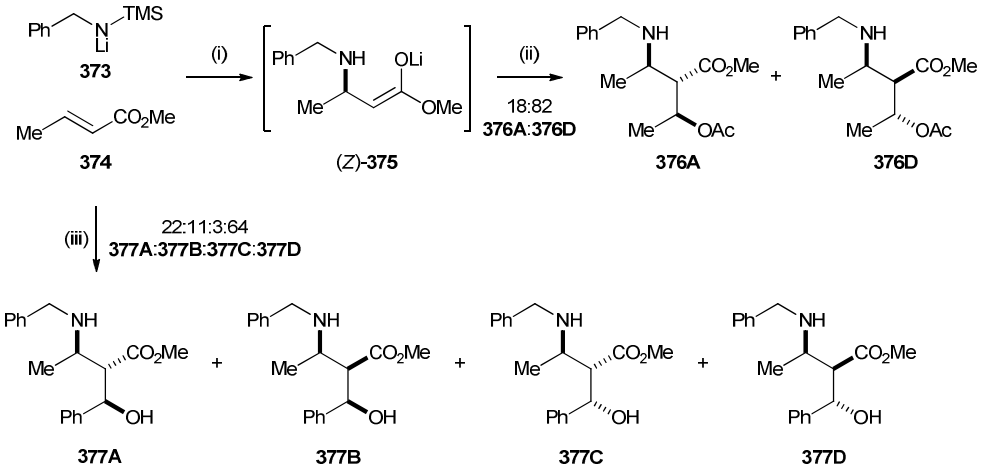
α,β-unsaturated ester **370**, a 77:23 mixture of *syn*-**372** to *anti*-**371** was isolated in 55% yield. This suggests that the diastereoselectivity of the allylation process is highly dependent on the structure of the substrate (Scheme 78).[17c]



Scheme 78 *Reagents and conditions:* (i) (*R*)-**145**, THF, −78 °C, 2 h; (ii) allyl bromide, −78 °C to rt, 15 h.

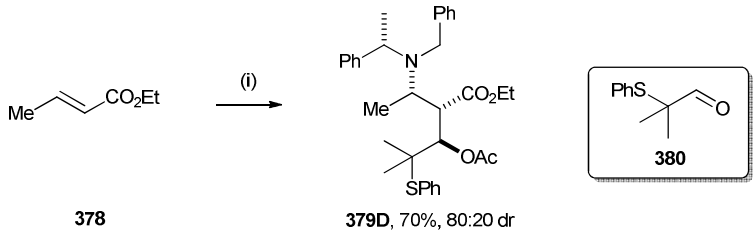
5.3.2 Tandem lithium amide conjugate addition and aldol reactions

Yamamoto *et al.* have investigated the stereoselectivity of the aldol reaction between the lithium (*Z*)-enolate (*Z*)-**375**, formed on conjugate addition of LSA **373** to methyl crotonate **374**, with either acetaldehyde or benzaldehyde. The diastereofacial selectivity of each condensation was reasonably high, giving predominantly diastereoisomers **376D** and **377D** in 82:18 and 64:22:11:3 dr, respectively (Scheme 79).[18]



Scheme 79 *Reagents and conditions:* (i) THF, −78 °C, 30 min; (ii) acetaldehyde, −78 °C to rt, 12 h then AcCl; (iii) THF, −78 °C, 30 min then benzaldehyde, −78 °C to rt, 12 h then H_2O.

Similarly, Warren *et al.* carried out the conjugate addition of lithium amide (*S*)-**145** to ethyl crotonate **378** followed by the addition of aldehyde **380**. The stereochemical outcome of this tandem reaction was analogous to that reported by Yamamoto, with **379D** being formed in 80:20 dr, although no comment was made on the stereochemistry of the minor diastereoisomer in this case (Scheme 80).[19]



Scheme 80 *Reagents and conditions:* (i) (*S*)-**145**, THF, –78 °C, 1 h then **380**, –78 °C, 1 h.

5.4 Proposed route

Building on this precedent, it was proposed that a tandem lithium amide conjugate addition/alkylation (with allyl bromide) or aldol reaction (with acrolein) could be followed by ring-closing metathesis to synthesise aminocycloheptenes, such as **357**. Lithium (*R*)-*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amide (*R*)-**383** was chosen for the initial conjugate addition reaction to import an *N*-methyl group to the synthesis, which is characteristic of many members of the tropane alkaloid family. Subsequent iodoamination with concomitant *N*-debenzylation of **357** would give the rapid and diastereoselective construction of the corresponding [3.2.1]-azabicylic scaffold **358**. Further functionalisation of the scaffold **358** could give access to a number of known tropanes, such as (–)-cocaine **359** or (–)-ferruginine **82** (Fig. 42).

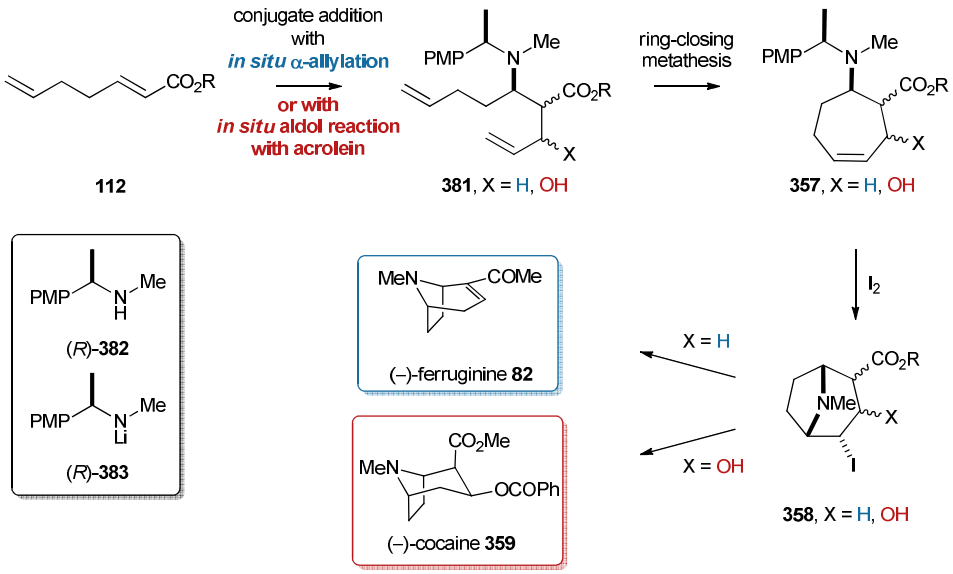
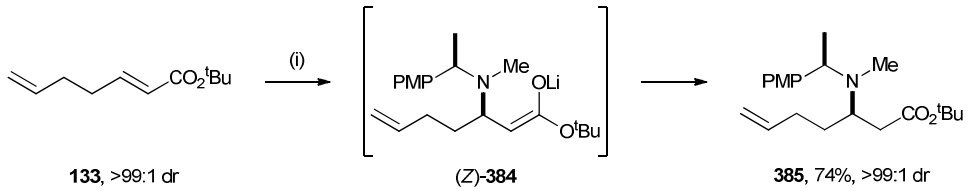


Figure 42 Proposed route to tropanes using the iodoamination of aminocycloheptene **357**.

5.5 Synthesis of aminocycloheptenes 389 and 391A

(*R*)-*N*-Methyl-*N*-(α-methyl-*p*-methoxybenzyl)amine (*R*)-**382** was synthesised in two steps: reaction of (*R*)-*N*-(α-methyl-*p*-methoxybenzyl)amine with ethyl chloroformate gave the corresponding carbamate which was reduced with $LiAlH_4$ to give (*R*)-**382** when required.[20] Conjugate addition of lithium *N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amine (*R*)-**383** to

α,β-unsaturated ester **133** (which was prepared in 81% yield and >99:1 dr from commercially available 4-pentenal)[21] followed by the addition of satd aq NH_4Cl allowed the isolation of β-amino ester **385** in 74% yield as a single diastereoisomer (Scheme 81). The absolute (*R*,*R*)-configuration within **385** was assigned by reference to the well-established transition state mnemonic for this class of conjugate addition reactions.[22]



133, >99:1 dr (*Z*)-**384** **385**, 74%, >99:1 dr

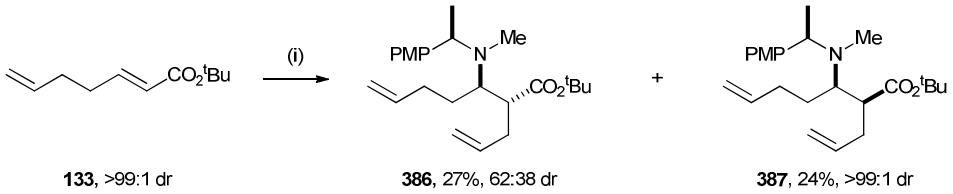
Scheme 81 *Reagents and conditions:* (i) (*R*)-**383**, THF, −78 °C, 2 h.

Since the conjugate addition of lithium amide (*R*)-**383** to α,β-unsaturated ester **133** resulted in the formation of **385** as a single diastereoisomer it was expected that in the tandem processes (allylation or aldol reaction) the resulting diastereoisomeric products would all have the (*R*,*R*)-configuration: the configuration at C(3) would remain solely a result of the conjugate addition of (*R*)-**383**, and would be independent of the allylation or aldol step, resulting in the formation of up to two possible diastereoisomers in the tandem alkylation reaction, and up to four possible diastereoisomers in the case of the tandem aldol reaction.

5.5.1 α-Allylation

Conjugate addition of (*R*)-**383** to **133** followed by the addition of allyl bromide to the resultant lithium (*Z*)-β-amino enolate (*Z*)-**384** gave a mixture of β-amino esters **385**, *anti*-**386** and *syn*-**387**. Due to significant peak overlap in the ^{1}H NMR spectrum of the unpurified reaction mixture neither a product ratio nor a reaction diastereoselectivity could be evaluated. Purification of this mixture gave **387** in 24% yield and >99:1 dr, along with **386** in 27% yield and 62:38 dr; β-amino ester **385** was also isolated in 20% yield as a single diastereoisomer (Scheme 82). The configurations at C(2) within both **386** and **387** could not be unambiguously assigned at this point; however it was envisaged that a mixture of the two diastereoisomers **386** and **387** could be reacted on under metathesis conditions, and treatment of the corresponding mixture of aminocycloheptenes with base was predicted to effect epimerisation of the C(1)-stereocentre to give a single *anti*-aminocycloheptene, and thus facilitate the configurational assignment of **386** and **387**. A subsequent repeat of this tandem conjugate addition/allylation reaction gave a mixture of **385**, **386** and **387** from which a 68:32

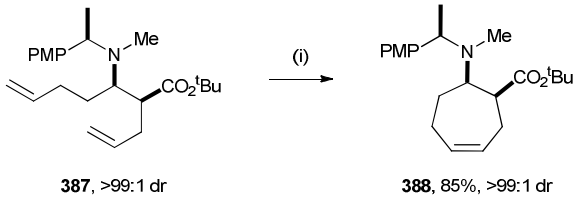
mixture of **387** and **386** was isolated in an improved 64% yield after purification; no effort was made to separate the two diastereoisomers **386** and **387** on this occasion.

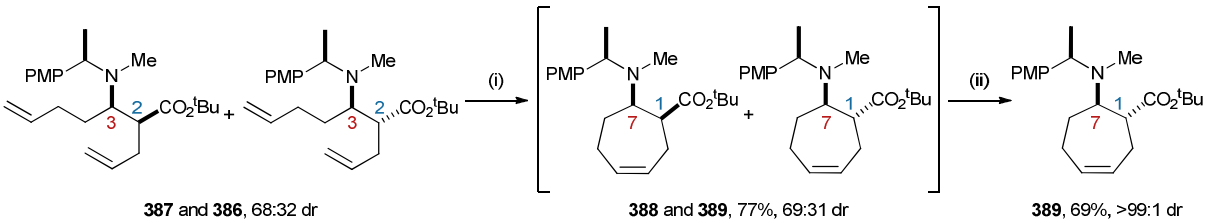


Scheme 82 *Reagents and conditions:* (i) (*R*)-**383**, THF, −78 °C, 2 h then allyl bromide, −78 °C to rt, 12 h.

5.5.2 Ring-closing metathesis

Ring-closing metathesis of the major diastereoisomer **387** from the allylation step with Grubbs I catalyst led to the isolation of aminocycloheptene **388** in 85% yield and >99:1 dr. Treatment of the 68:32 mixture of **387** and **386** resulted in complete conversion to a 61:39 mixture of diastereoisomers **388** and **389**. On heating this mixture with KO^{t}Bu in ^{t}BuOH, complete epimerisation of the C(1)-stereocentre within **388** occurred to give **389** in 69% yield as a single diastereoisomer (Scheme 83). This result permitted the assignment of the configuration at C(1) in both **388** and **389** (on the basis of **389** being the more thermodynamically stable, *trans*-isomer)[23] and hence the configuration at C(2) in their acyclic precursors **387** and **386**.



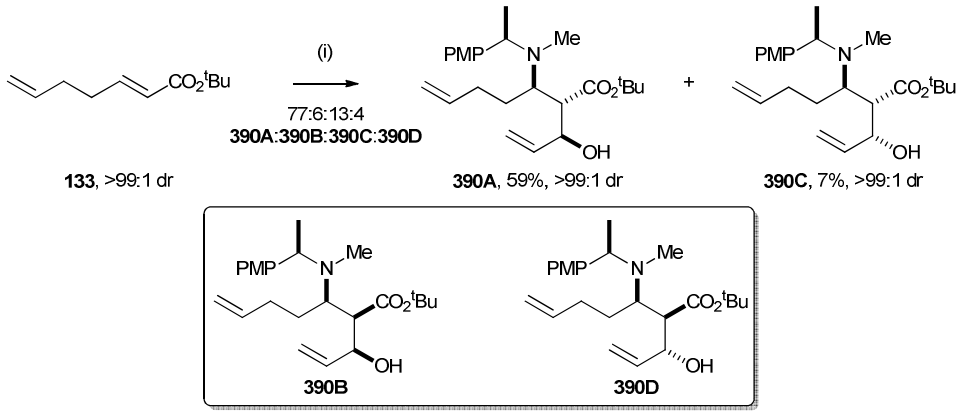


Scheme 83 *Reagents and conditions:* (i) Grubbs I catalyst (20 mol%), CH_2Cl_2, 30 °C, 12 h; (ii) KO^{t}Bu, ^{t}BuOH, 80 °C, 3 h.

5.5.3 Tandem aldol reaction

Following the successful synthesis of aminocycloheptene **389**, the conjugate addition/aldol reaction was next investigated. Conjugate addition of (*R*)-**383** to **133** followed by addition of 2.0 equiv acrolein to the resultant lithium (*Z*)-enolate (*Z*)-**384** resulted in 89% conversion to the aldol product **390** as a 77:6:13:4 mixture of diastereoisomers **390A**, **390B**, **390C** and **390D**,24 from which only **390A** and **390C** were isolated in 59 and 7% yields respectively and in >99:1 dr (Scheme 84). The relative configuration within **390A** was unambiguously

established by single crystal X-ray analysis, with the absolute (2*S*,3*R*,1′*S*,α*R*)-configuration being assigned from the known (*R*)-configuration of the *N*-(α-methyl-*p*-methoxy)benzyl group (Fig. 43). This result also confirms that the formation of the (3*R*)-stereocentre is under the control of the *N*-(α-methyl-*p*-methoxy)benzyl group, as expected. The absolute configurations within **390B**, **390C** and **390D** were not assigned at this point, but were later established either by chemical correlation (**390B** and **390D**) or by single crystal X-ray diffraction analysis of a derivative (**390C**). The formation of **390A** as the major diastereoisomer from this reaction is in contrast to the previously reported stereochemical outcomes of the aldol reactions of lithium (*Z*)-β-amino enolates reported by Yamamoto and Warren (*vide supra*).[18a,19] In fact, none of the observed stereochemical outcomes of these reactions can be rationalised by a standard Zimmerman-Traxler transition state involving a lithium (*Z*)-enolate in which the aldehydic alkyl substituent is positioned pseudoequatorial.[25] It is clear, however, that the overall stereochemical outcome of these reactions is highly dependent on the nature of the substrate and may be a result of the requirement to minimise several unfavorable steric interactions involving some or all of the ester alkoxy group, the aldehydic alkyl and C(3)-substituents.



Scheme 84 *Reagents and conditions:* (i) (*R*)-**383**, THF, −78 °C, 2 h then acrolein, −78 °C to rt, 2 h.

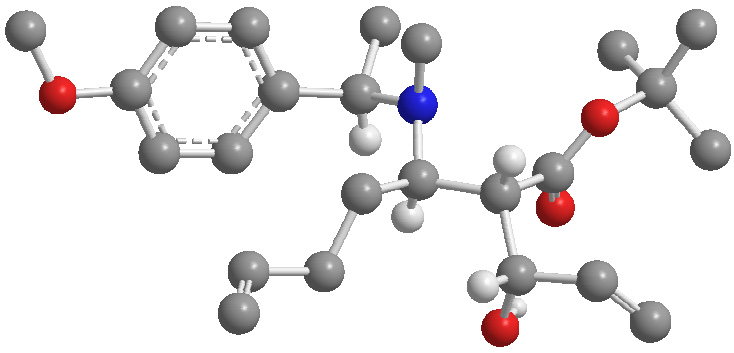
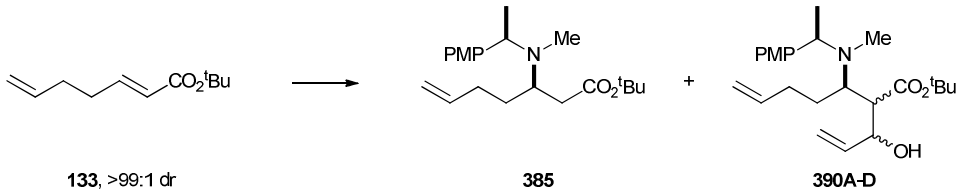


Figure 43 Chem3D representation of the single crystal X-ray structure of (2*S*,3*R*,1′*S*,α*R*)-**390A** (selected H atoms have been omitted for clarity).

A brief investigation was then carried out to attempt to increase the overall conversion or diastereoselectivity of the aldol reaction. Increasing the amount of acrolein used to 3.0 and 5.0 equiv did not change the overall conversion to **390** rather than **385**; in fact the large excess of aldehyde underwent polymerisation which introduced difficulties on work-up and resulted in low mass return. It was observed that the overall diastereoselectivity of this reaction had a slight dependancy on the concentration of the reaction mixture (with respect to **133**). As the concentration of **133** decreased, so too did the amount of **390B**, **390C** and **390D** observed, resulting in a greater percentage of the major diastereoisomer **390A**. In each case, the reaction displayed a high diastereofacial selectivity with respect to the enolate, with the resultant diastereoisomeric mixture remaining >90:10 in favour of **390A** and **390C** with respect to **390B** and **390D**. Unfortunately, this effect was also accompanied by a decrease in the overall percentage of aldol product **390** in the reaction mixture (Table 10).



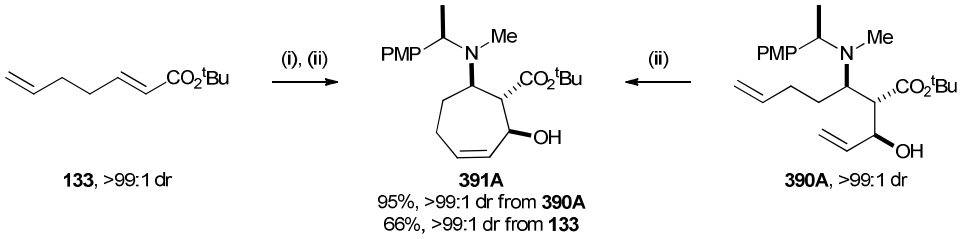
133, >99:1 dr **385** **390A-D**

c **133***	% **390**†	**390A**:**390B**:**390C**:**390D**
0.13	60	97:0:2:1
0.24	80	89:1:8:2
0.5	88	77:6:13:4

Table 10 Effect of reaction concentration on the diastereoselectivity of the tandem conjugate addition/aldol reaction [**c* = mmol/mL **133**] [† remaining mass balance is comprised of **385**].

5.5.4 Ring-closing metathesis

Treatment of **390A** with 20 mol% Grubbs I catalyst gave complete conversion to the desired aminocycloheptene **391A**, which was isolated in 95% yield as a single diastereoisomer. The yield of **391A** (56% over the two steps from α,β-unsaturated ester **133**) could be increased by reacting the unpurified mixture of **390A**-**390D** under metathesis conditions, followed by column chromatography to give **391A** in 66% yield and >99:1 dr over the two steps (Scheme 85). The relative configuration within **391A** was confirmed by single crystal X-ray diffraction analysis, with the absolute (1*S*,2*S*,7*R*,α*R*)-configuration being assigned from the known (2*S*,3*R*,1′*S*,α*R*)-configuration of **391A** and that of the *N*-(α-methyl-*p*-methoxy)benzyl stereocentre (Fig. 44).[26]



Scheme 85 *Reagents and conditions:* (i) (*R*)-**383**, THF, −78 °C, 2 h then acrolein, −78 °C to rt, 2 h; (ii) Grubbs I catalyst (20 mol%), CH_2Cl_2, 30 °C, 12 h.

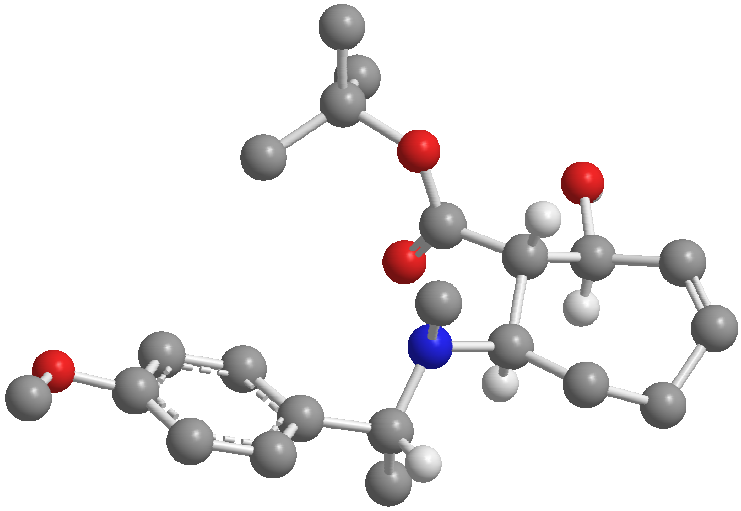
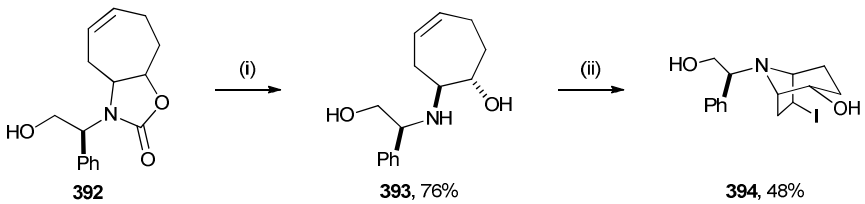


Figure 44 Chem3D representation of the single crystal X-ray structure of (1*S*,2*S*,7*R*,α*R*)-**391A** (selected H atoms have been omitted for clarity).

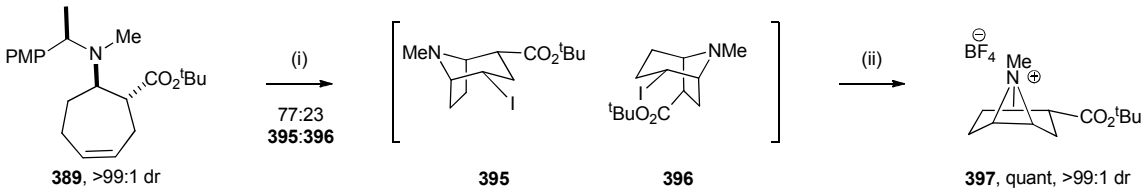
5.6 Transannular iodoamination of 389 and 391A

With both **389** and **391A** in hand, attention turned to the study of their transannular iodoamination reactions. Transannular cyclisations are a popular method for the construction of the tropane architecture (*vide supra*), although a search of the available literature showed that employing a molecular halogen to induce the transannular process in 'one pot' had not been previously reported. Nonetheless, Couty *et al.* have reported the use of an NIS-promoted transannular process in the synthesis of "*new tropanic alkaloids*" from cyclohept-3-ene-1-amine **393**.[27] Oxazolidinone **392** was subjected to base-catalysed hydrolysis conditions which furnished **393** in 76% yield. Amino alkene **393** was then treated with NIS in CH_2Cl_2 at −78 °C which resulted in transannular cyclisation to give iodotropane **394**, which was isolated in 48% yield (Scheme 86).[27]



Scheme 86 *Reagents and conditions:* (i) KOH, EtOH, reflux; (ii) NIS, CH_2Cl_2, −78 °C to rt.

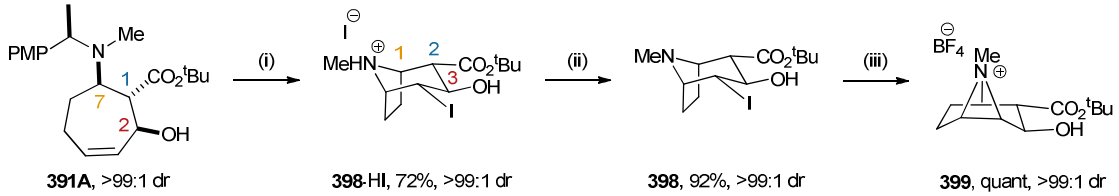
Iodoamination of **389** was carried out without the addition of $NaHCO_3$: treatment of **389** with I_2 in CH_2Cl_2 for 12 h gave a 77:23 mixture of two products, which were tentatively assigned as regioisomers **395** and **396**, along with (α-methyl-*p*-methoxy)benzyl ethyl ether **193**. An aqueous basic work-up and column chromatography allowed the isolation of a 77:23 mixture of **395** and **396**, respectively, in 57% combined yield. Reaction of this mixture with $AgBF_4$ for 2 h resulted in the formation of aziridinium **397** in quantitative yield and as a single diastereoisomer, supporting the assignment of **395** and **396** as regioisomers (Scheme 87).



389, >99:1 dr **395** **396** **397**, quant, >99:1 dr

Scheme 87 *Reagents and conditions:* (i) I_2, CH_2Cl_2 (EtOH-stabilised), rt, 12 h then KOH (1.0 M aq), CH_2Cl_2; (ii) $AgBF_4$, CH_2Cl_2, rt, 2 h.

The formation of the two regioisomeric products **395** and **396** was not ideal; however it did confirm that transannular processes would readily occur in such systems and were accompanied by the desired *N*-debenzylation, which was encouraging. So, aminocycloheptene **391A** was also subjected to iodoamination conditions, which resulted in the formation of a single product, assigned as **398**·HI, along with ether **193**. Direct crystallisation of the unpurified reaction mixture using CH_2Cl_2/Et_2O allowed the isolation of **398**·HI in 72% yield and >99:1 dr. Treatment of **398**·HI with K_2CO_3 in THF allowed isolation of **398** in 92% yield,[28] and subsequent treatment of **398** with $AgBF_4$ in CH_2Cl_2 resulted in the formation of a single species assigned as aziridinium **399**, in quantitative yield as a single diastereoisomer (Scheme 88).



391A, >99:1 dr **398**·HI, 72%, >99:1 dr **398**, 92%, >99:1 dr **399**, quant, >99:1 dr

Scheme 88 *Reagents and conditions:* (i) I_2, CH_2Cl_2 (EtOH-stabilised), rt, 18 h; (ii) K_2CO_3, THF, rt, 4 h; (iii) $AgBF_4$, CH_2Cl_2, rt, 2 h.

The relative configuration within **398**·HI was unambiguously established by single crystal X-ray diffraction analysis, with the absolute (1*R*,2*S*,3*R*,4*R*,5*S*)-configuration being assigned from the known (1*S*,2*S*,7*R*,α*R*)-configuration of **391A**, and confirmed by the determination of a Flack *x* parameter[29] of −0.01(7) for this crystal structure (Fig. 45). The stereochemical outcome of this reaction is consistent with a mechanism in which formation of an iodonium

ion is followed by transannular attack of the nitrogen atom at C(5), distal to the C(3)-hydroxyl group, supporting the hypothesis that an allylic hydroxyl group influences the regioselectivity of attack of the nitrogen atom onto the iodonium ion (*vide supra*).[30]

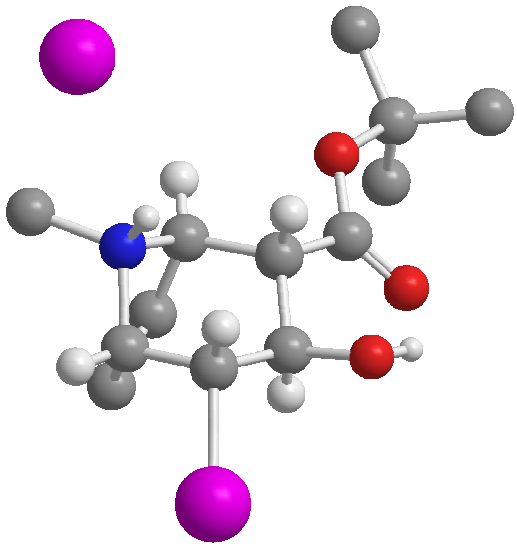


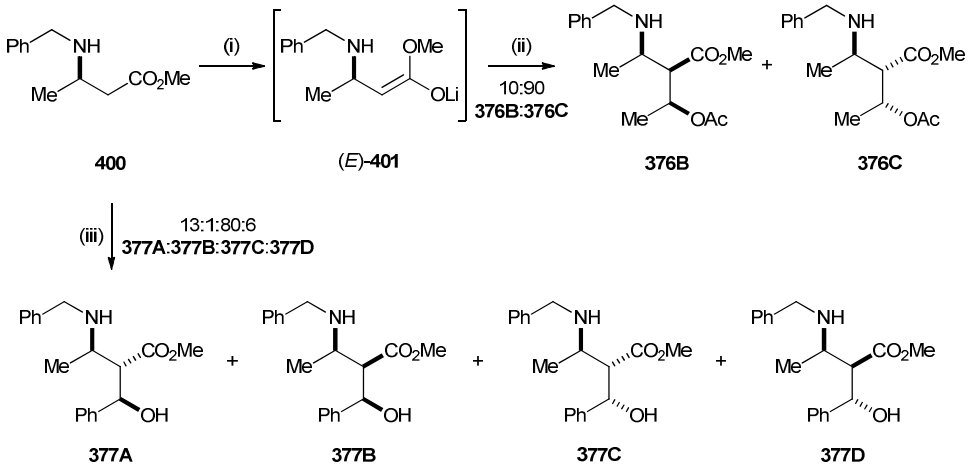
Figure 45 Chem3D representation of the single crystal X-ray structure of (1*R*,2*S*,3*R*,4*R*,5*S*)-**398**·HI (selected H atoms have been omitted for clarity).

5.7 Determination of the stereochemistry of 390B, 390C and 390D

The tandem lithium amide conjugate addition and aldol reaction had resulted in the formation of four diastereoisomeric products although only **390A** and **390C** were isolated. It was anticipated that further investigation into this reaction could allow the isolation of a sample of each of the remaining diastereoisomers **390B** and **390D**, and hence allow their subsequent configurational assignment.

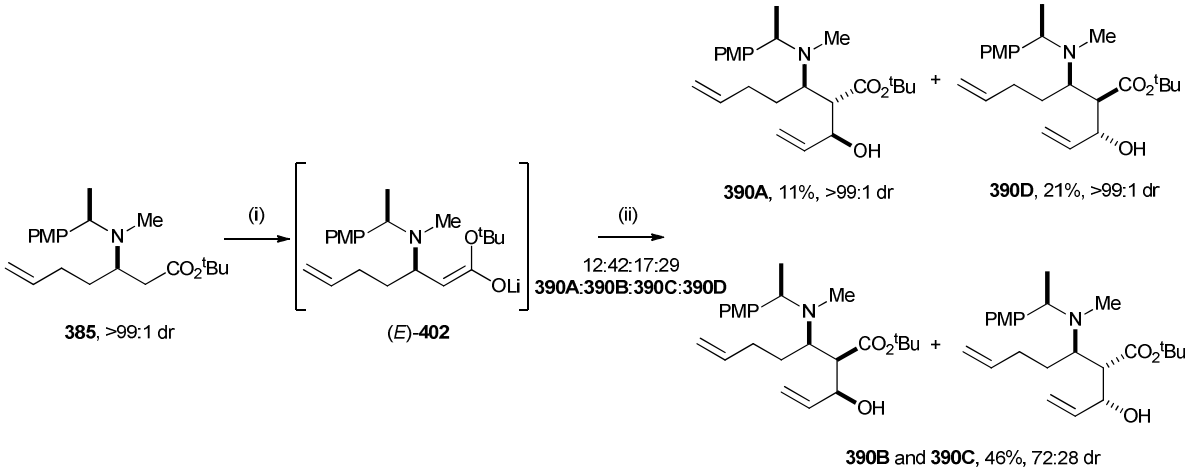
5.7.1 Stepwise aldol reactions

Yamamoto *et al.* have investigated the addition of either acetaldehyde or benzaldehyde to the lithium (*E*)-enolate (*E*)-**401** formed on treatment of β-amino ester **400** with LDA.1[8a] Addition of acetaldehyde was followed by addition of AcCl, and resulted in the isolation of a 90:10 mixture of diastereoisomeric products **376C** and **376B**, in contrast to the 82:18 mixture of **376D** and **376A** observed in the tandem process. Meanwhile, reaction with benzaldehyde gave **377C** as the major diastereoisomer, but as a mixture with the other three possible diastereoisomers: **377A**, **377B**, **377C** and **377D** were observed as a 13:1:80:6 mixture (Scheme 89).



Scheme 89 *Reagents and conditions:* (i) LDA, THF, −78 °C, 2 h; (ii) acetaldehyde, −78 °C to rt, 12 h then AcCl; (iii) LDA, THF, −78 °C, 2 h, then benzaldehyde, −78 °C to rt, 12 h.

Following this precedent, treatment of β-amino ester **385** with LDA, to form the lithium (*E*)-enolate (*E*)-**402**, was followed by addition of acrolein to give a 12:42:17:29 ratio of **390A**, **390B**, **390C** and **390D**, from which **390A** and **390D** were isolated in 11 and 21% yield as single diastereoisomers, along with an inseparable 72:28 mixture of **390B** and **390C** in 46% yield (Scheme 90).

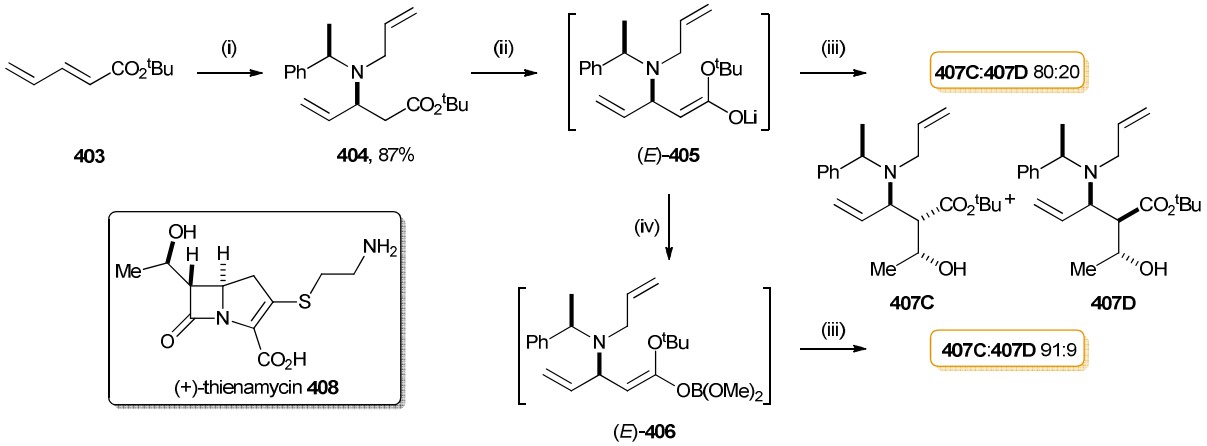


Scheme 90 *Reagents and conditions:* (i) LDA, THF, −78 °C, 2 h; (ii) acrolein, −78 °C to rt, 12 h.

5.7.2 Transmetallation of lithium (*E*)-enolates

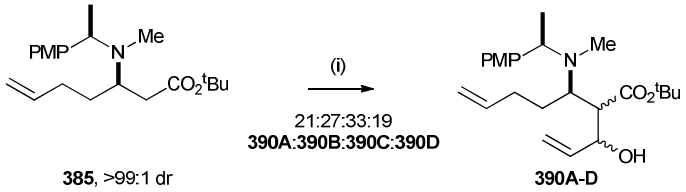
Transmetallation of lithium (*E*)-enolates with $B(OMe)_3$ can result in comparatively higher levels of C(2)-C(1′) *syn*-diastereoselectivity in subsequent aldol reactions.[31,32] Davies *et al.* have reported a formal asymmetric synthesis of (+)-thienamycin **408**, in which the synthesis of a key intermediate β-lactam was completed using a stepwise lithium amide conjugate addition and aldol reaction protocol.[33] Conjugate addition of (*R*)-**132** to α,β-unsaturated ester **403** gave β-amino ester **404** in 87% yield and >99:1 dr. Treatment of **404** with LDA, to form the lithium (*E*)-enolate (*E*)-**405**, was followed by addition of acetaldehyde to give two diastereoisomeric products **407C** and **407D** in 80:20 dr. Further investigation discovered that

transmetallation of the lithium enolate (*E*)-**405** to form the corresponding boron enolate (*E*)-**406** resulted in an improved 91:9 mixture of **407C** and **407D** (Scheme 91).[33]



Scheme 91 *Reagents and conditions:* (i) (*R*)-**132**, THF, −78 °C, 2 h; (ii) LDA, THF, 0 °C, 2 h; (iii) acetaldehyde, −78 °C to rt, 12 h; (iv) $B(OMe)_3$, −78 °C, 1 h.

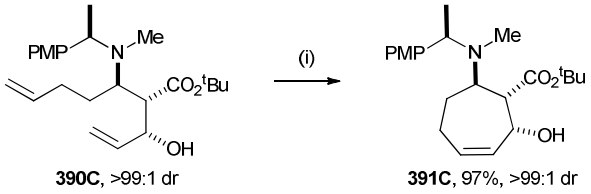
It was now decided to apply a transmetallation procedure to the lithium (*E*)-enolate (*E*)-**402**, formed on the addition of LDA to β-amino ester **385**, to investigate the effect on the stereochemical outcome of the aldol reaction. Treatment of enolate (*E*)-**402** with $B(OMe)_3$ and subsequent aldol reaction with acrolein, unfortunately gave a 21:27:33:19 mixture of **390A**, **390B**, **390C** and **390D** (Scheme 92).[34] Given the low overall selectivity of both of these stepwise aldol reactions further investigations in this area were not pursued.



Scheme 92 *Reagents and conditions:* (i) LDA, THF, −78 °C, 2 h, then $B(OMe)_3$, −78 °C, 1 h, then acrolein, −78 °C to rt, 12 h.

5.7.3 Ring-closing metathesis

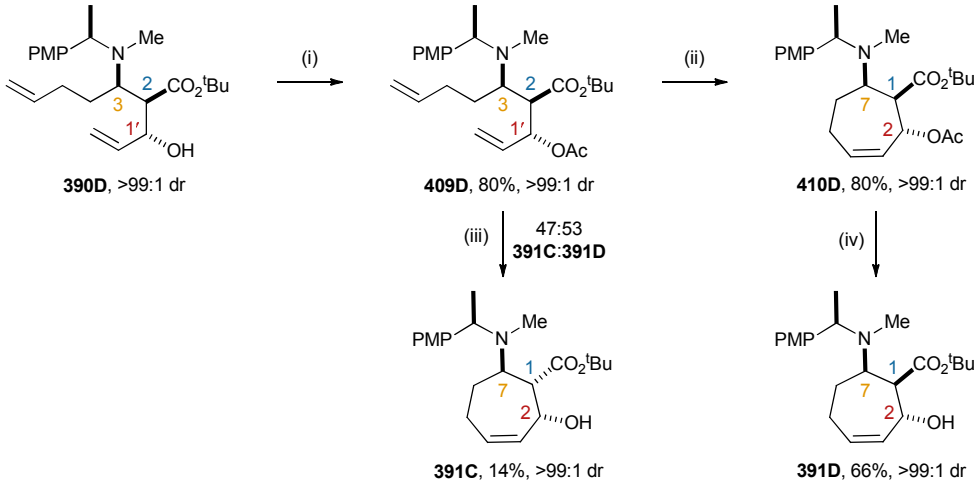
Although the diastereoselectivity of the aldol reaction could not be biased to favour production of one of the diastereoisomers **390B**-**390D** as the major product in synthetically useful yield, the isolation of **390C** and **390D** meant that it would be possible to access two more of the four possible corresponding aminocycloheptenes **391C** and **391D**. As in the case of **388** and **389** derived from allylation, it was anticipated that base-promoted epimerisation would facilitate the stereochemical assignment of **390B**-**390D**. Reaction of **390C** with Grubbs I catalyst at 30 °C resulted in complete conversion to the ring-closed product **391C**, allowing the isolation of **391C** in 97% yield and in >99:1 dr (Scheme 93).



390C, >99:1 dr **391C**, 97%, >99:1 dr

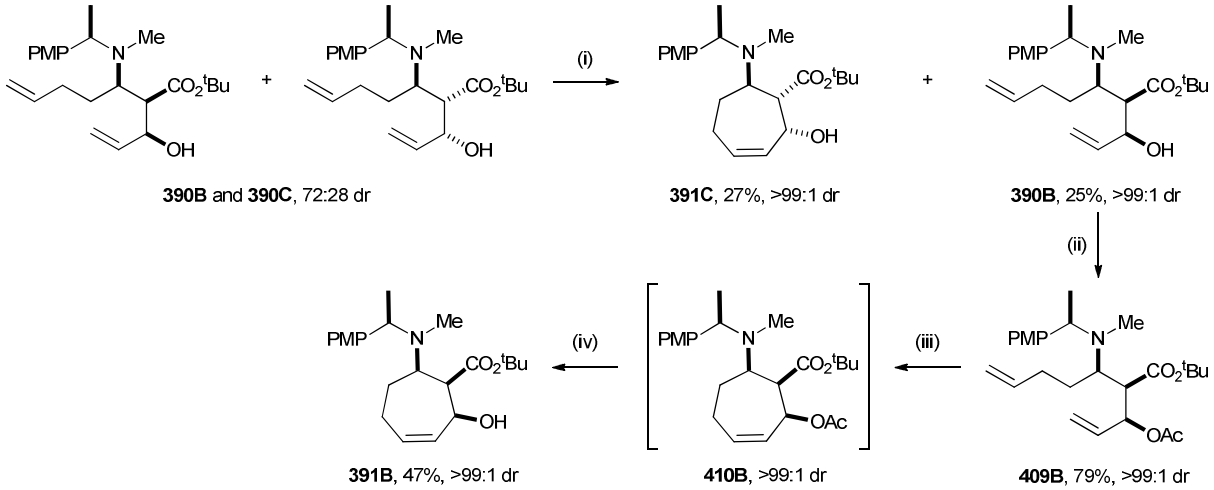
Scheme 93 *Reagents and conditions:* (i) Grubbs I catalyst (20 mol%), CH_2Cl_2, 30 °C, 12 h.

Surprisingly, attempted ring-closing metathesis of **390D** with Grubbs I or Grubbs II catalyst in CH_2Cl_2 at 30 °C and in PhMe at 80 °C returned starting material. Acetate protection of a free hydroxyl group in a system that is resistant to ring-closing metathesis has been previously shown to result in the success of subsequent metathesis attempts.[35] In order to investigate this possibility here, **390D** was treated with Ac_2O in pyridine, to give **409D** in 80% yield. Treatment of **409D** with Grubbs I catalyst at 30 °C gave complete conversion to **410D**, which was isolated in 80% yield and >99:1 dr. Hydrolysis of **410D** with KOH in CH_2Cl_2/MeOH at rt led to the isolation of **391D** in 66% yield as a single diastereoisomer. Furthermore, when **410D** was treated with K_2CO_3 in MeOH at 60 °C (immediately after ring-closing metathesis), epimerisation of the C(1)-stereocentre occurred to give a 47:53 mixture of **391C** and **391D**. Chromatographic purification gave **391C** and **391D** in 14 and 17% yield, respectively, and in >99:1 dr in each case (Scheme 94). This correlation suggested that **391C** and **391D** were related as epimers at C(1), with **391C** having the more stable C(1)-C(7) *trans*-configuration, and hence also suggested that the aldol products **390C** and **390D** were related as C(2)-epimers. It follows, therefore, that **390A** and **390B** are likely related as epimers at C(2), and, given the known absolute (2*S*,3*R*,1′*S*,α*R*)-configuration within **390A**, the absolute configurations within **390B**-**390D** could be tentatively assigned at this stage: (2*R*,3*R*,1′*S*,α*R*)-**390B**, (2*S*,3*R*,1′*R*,α*R*)-**390C** and (*R*,*R*,*R*,*R*)-**390D**.36 Corroboration of this hypothesis was next sought by preparation of an authentic sample of **391B** from **390B**, and subjection of **391B** to base-promoted epimerisation.



Scheme 94 *Reagents and conditions:* (i) Ac_2O, DMAP, py, rt, 12 h; (ii) Grubbs I catalyst (20 mol%), CH_2Cl_2, 30 °C, 12 h; (iii) Grubbs I catalyst (20 mol%), CH_2Cl_2, 30 °C, 12 h, then K_2CO_3, MeOH, 60 °C, 2 h; (iv) KOH, CH_2Cl_2/MeOH (v/v 30:1), rt, 2 h.

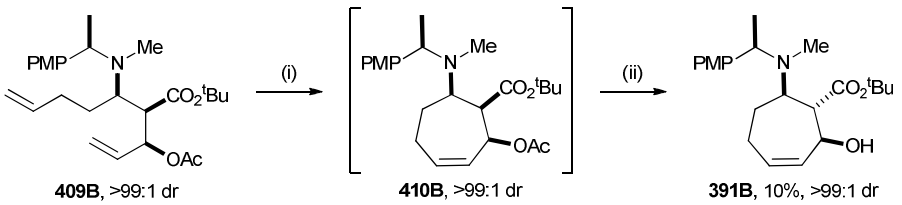
Treatment of the inseparable 72:28 mixture of **390B** and **390C** with Grubbs I catalyst, to attempt the isolation of the final aminocycloheptene **391B**, resulted in the ring-closing metathesis of **390C** only, but fortuitously did allow the subsequent separation of cyclic **391C** and acyclic **390B** by column chromatography to give **390B** in 25% yield and >99:1 dr and **391C** in 27% yield and >99:1 dr. *O*-Acetyl protection of **390B** and repetition of the metathesis reaction conditions resulted in the formation of the ring-closed product **410B**, which unfortunately decomposed on attempted purification. Reaction of the unpurified sample of **410B** with KOH in CH_2Cl_2/MeOH at rt for 2 h allowed the isolation of **391B** in 47% yield and >99:1 dr in two steps from **409B** (Scheme 95).



Scheme 95 *Reagents and conditions:* (i) Ac_2O, DMAP, py, rt, 12 h; (ii) Grubbs I catalyst (20 mol%), CH_2Cl_2, 30 °C, 12 h; (iii) KOH, CH_2Cl_2/MeOH (v/v 30:1), rt, 2 h.

Attempted hydrolysis of the acetate group within **410B** with K_2CO_3 in MeOH at 60 °C immediately after the metathesis step resulted in extensive decomposition of the reaction mixture. However, on careful examination of the ^{1}H NMR spectrum of the unpurified reaction

mixture it was noted that peaks at δ_H 2.66 and 4.55 ppm corresponding to C(1)*H* and C(2)*H*, respectively, within **391A** were present. Indeed, chromatographic purification of this complex mixture allowed the isolation of **391A** in 10% yield and >99:1 dr (Scheme 96). The formation of **391A** as a result of the epimerisation of the C(1)-stereocentre corroborated the assignment of the absolute (1*R*,2*S*,7*R*,α*R*)-configuration of **391B** and the (2*R*,3*R*,1′*S*,α*R*)-configuration of **390B**.



Scheme 96 *Reagents and conditions:* (i) Grubbs I catalyst (20 mol%), CH_2Cl_2, 30 °C, 12 h; (ii) K_2CO_3, MeOH, 60 °C, 2 h.

In order to provide an alternative, more efficient route to **391B**, it was envisaged that **391A** might be transformed into **391B** by a kinetic deprotonation/reprotonation pathway to epimerise the C(1)-stereocentre, and this possibility was briefly investigated. Treatment of **391A** with LDA (2.5 equiv) at −78 °C and treatment of the resultant lithium di-anion **411** with 2-pyridone **412** gave returned starting material. In order to evaluate whether deprotonation at C(1) was occurring the reaction was repeated but with the addition of D_2O to effect reprotonation with deuterium; this reaction also returned starting materials. On further analysis of the single crystal X-ray structure of **391A**, it was noted that the C(1)–H bond was co-incident with the plane of the carbonyl group; should this conformation persist in solution then deprotonation may be unachievable in this system (Fig. 46).

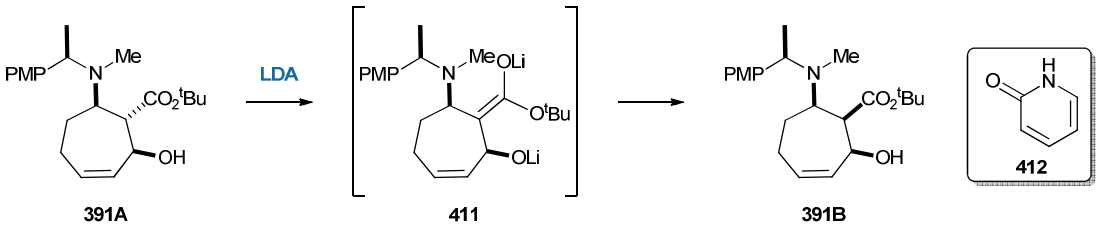
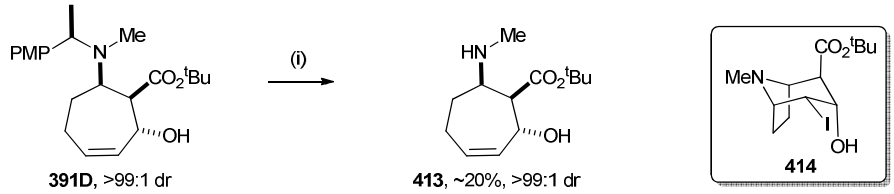


Figure 46 Attempted kinetic deprotonation/reprotonation of **391A**.

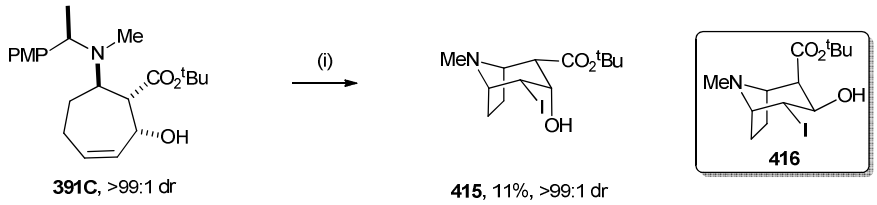
5.8 Transannular iodoaminations of 391B, 391C and 391D

With samples of **391B**, **391C** and **391D** in hand it was decided to subject all three to the iodoamination conditions. Reaction of **391D** with iodine for 12 h gave a complex mixture of products along with remaining starting material, and with no evidence of the desired cyclised product **414** in the complex ^{1}H NMR spectrum of the unpurified reaction mixture. Purification of the mixture by column chromatography, after treatment with base, enabled isolation of an impure sample of *N*-debenzylated aminocycloheptene **413** in ~20% yield (Scheme 97).



Scheme 97 *Reagents and conditions:* (i) I_2, CH_2Cl_2 (EtOH-stabilised), rt, 12 h then K_2CO_3, CH_2Cl_2.

Reaction of **391B** with iodine also produced (following treatment with aqueous base) a complex ^{1}H NMR spectrum of the unpurified reaction mixture, although peaks at δ_H 1.20 and 3.34 ppm indicated the presence of ether **193**. Column chromatography gave an impure sample of a compound that was tentatively assigned, by limited ^{1}H NMR spectroscopic data, as the iodotropane **416**. Unfortunately this compound decomposed before further spectroscopic data could be obtained. Finally, treatment of aminocycloheptene **391C** with iodine resulted in the formation of a complex mixture of products. After basification of the unpurified mixture and column chromatography, iodotropane **415** was isolated in 11% yield as a single diastereoisomer. No other identifiable species were isolated (Scheme 98).



Scheme 98 *Reagents and conditions:* (i) I_2, CH_2Cl_2 (EtOH-stabilised), rt, 12 h then KOH (1.0 M aq), $CHCl_3$.

The relative configuration within **415** was unambiguously established by single crystal X-ray diffraction analysis, and with the determination of a Flack *x* parameter[29] of –0.04(3) for this crystal structure, the absolute (1*R*,2*S*,3*S*,4*R*,5*S*)-configuration within **415** was also assigned, confirming that the C(1)-stereocentre (tropane numbering) formed upon conjugate addition of lithium amide (*R*)-**383** to α,β-unsaturated ester **133** was as expected. This provided further confirmation of the assigned absolute configurations within **391B**-**391D** and within **390B**-**390D** (Fig. 47).

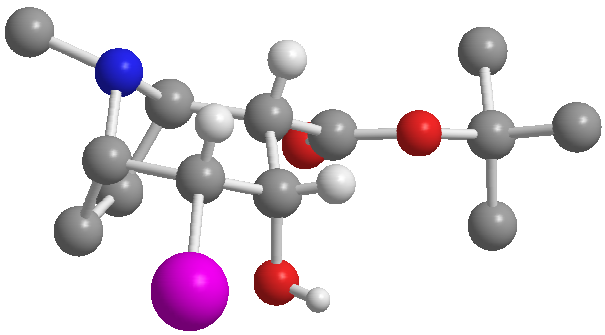


Figure 47 Chem3D representation of the single crystal X-ray structure of (1*R*,2*S*,3*S*,4*R*,5*S*)-**414** (selected H atoms have been omitted for clarity).

The reluctance of **391B**, **391C** and **391D** to undergo a transannular cyclisation is in contrast to the behaviour of **391A** under analogous conditions. This transannular iodoamination reaction is presumed to arise following reversible formation of iodonium ion **417** from **391A**, with subsequent attack of the nitrogen atom. Assuming that the reaction proceeds via a transition state similar to **418**, the configuration at C(1) and C(2) within **391A** is such that their substituents are placed pseudoequatorial, and so all 1,3-diaxial interactions are minimised. Any other stereochemical permutation of **391** involves a change in configuration at C(1) and/or C(2), which consequently results in an increased contribution to the 1,3-diaxial interactions within the corresponding transition state for cyclisation, disfavouring this reaction pathway (Fig. 48).

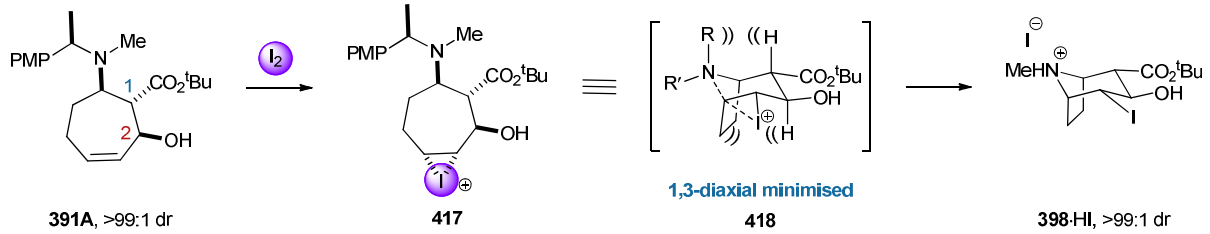


Figure 48 Proposed transition state for the transannular cyclisation of **391A** [R, R′ = Me, CHMePMP].

5.9 Synthesis of (+)-pseudococaine 419

The successful transannular iodoamination of **391A** on treatment with iodine had furnished the corresponding iodotropane **398** in good yield, and attention was now turned to the synthesis of a known alkaloid. (–)-Cocaine **359**, first isolated from the leaves of the *Erythroxylan coca* plant in 1860 by Albert Niemann,[37] can exist as one of four diastereoisomers – naturally occurring cocaine **359** and pseudococaine **419**,[38] both found in the *Erythroxylan coca* plant, and the synthetic compounds allococaine **420**[39] and pseudoallococaine **421**[39] (Fig. 49). Although the tandem conjugate addition/aldol procedure had given access to all four of the possible cocaine diastereoisomer precursors, only the diastereoisomer which corresponded to pseudococaine **419** was cyclised in a synthetically useful yield. And so, total synthesis of pseudococaine **419** was next investigated.

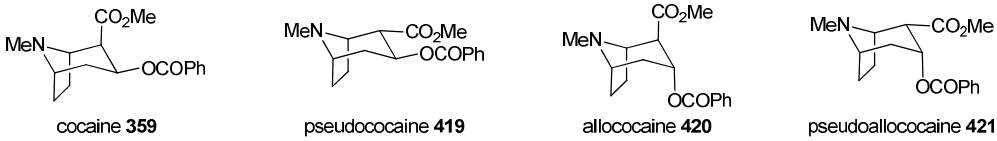
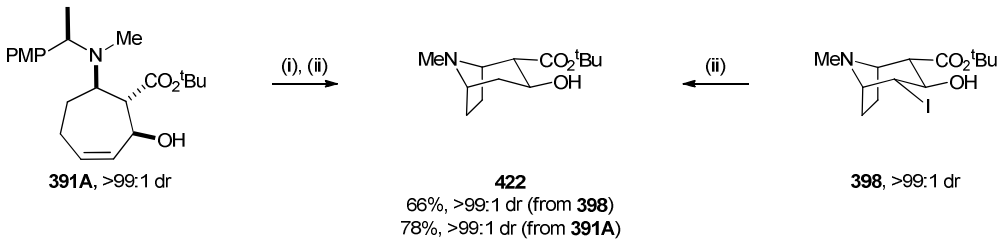


Figure 49 The four diastereoisomers of cocaine: cocaine **359**, pseudococaine **419**, allococaine **420** and pseudoallococaine **421**.

Removal of the iodine from within **398** was achieved using Bu_3SnH and AIBN to give **422** in 61% yield and >99:1 dr (40% overall yield from **391A**).[40] If this reaction was carried out on

the unpurified mixture of **398**·HI and ether **193**, resulting from the iodoamination reaction, **422** was isolated in an improved 78% yield over two steps from **391A**, and as a single diastereoisomer (Scheme 99).



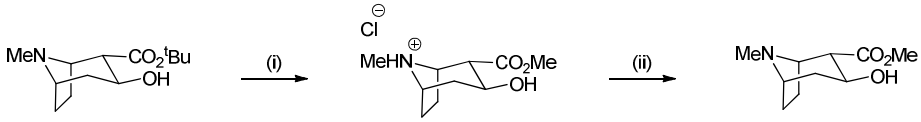
391A, >99:1 dr

422
66%, >99:1 dr (from **398**)
78%, >99:1 dr (from **391A**)

398, >99:1 dr

Scheme 99 *Reagents and conditions:* (i) I_2, CH_2Cl_2 (EtOH-stabilised), rt, 12 h; (ii) Bu_3SnH, AIBN, PhMe, 80 °C, 5 h.

Transesterification of **422** was achieved with $SOCl_2$ in MeOH and led to the isolation of (+)-methyl pseudoecgonine hydrochloride **423**·HCl in quantitative yield, which after treatment with K_2CO_3 in THF gave the known tropane alkaloid (+)-methyl pseudoecgonine **423** in 55% yield. The specific rotation of this synthetic sample of (+)-methyl pseudoecgonine **423** {$[\alpha]_D^{20}$ +17.5 (*c* 0.44 in H_2O)} was in agreement with those reported in the literature {lit.[41] $[\alpha]_D^{20}$ +22.8 (*c* 1.7 in H_2O); lit.[42] $[\alpha]_D^{23}$ +23.1 (*c* 0.1 in H_2O); lit.[9] $[\alpha]_D^{20}$ +19.5 (*c* 0.2 in H_2O)} (Scheme 100). Moreover, the relative configuration within **423** was unambiguously confirmed by single crystal X-ray diffraction analysis with the absolute (1*R*,2*S*,3*R*,5*S*)-configuration being assigned from the known absolute configuration of the precursors **390A**, **391A** and **398**·HI (Fig. 50).



422, >99:1 dr

423·HCl, quant, >99:1 dr

423, 55%, >99:1 dr

Scheme 100 *Reagents and conditions:* (i) $SOCl_2$, MeOH, 60 °C, 5 h; (ii) K_2CO_3, THF, rt, 4 h.

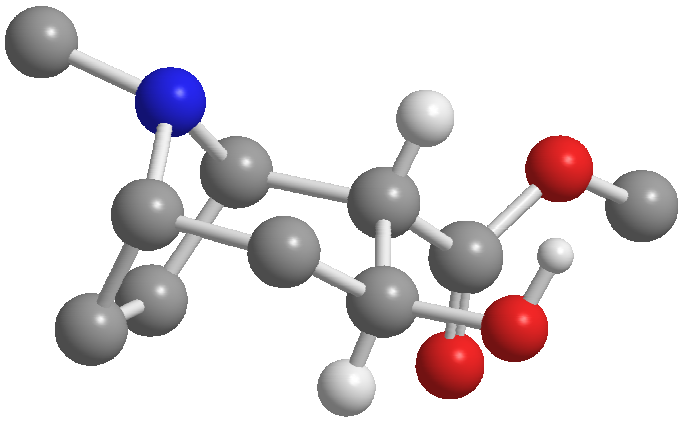
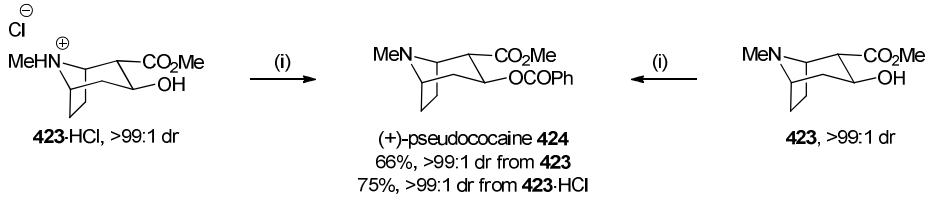


Figure 50 Chem3D representation of the single crystal X-ray structure of (1*R*,2*S*,3*R*,5*S*)-**423** (selected H atoms have been omitted for clarity).

O-Benzoylation of **423** with PhCOCl and Et_3N at rt gave (+)-pseudococaine **419** in 66% yield, as a single diastereoisomer.[43] This yield could be improved by carrying out the benzoylation procedure on **423**·HCl directly, which gave (+)-pseudococaine **419** in 75% yield. This completed a total synthesis of (+)-**419** in 7 steps from commercially available 4-pentenal and in 31% overall yield. Conversion of **419** into the known hydrochloride salt **419**·HCl was achieved in quantitative yield by co-evaporation with 1.25 M HCl in MeOH (Scheme 101).[44]



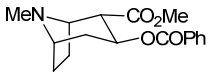
423·HCl, >99:1 dr

(+)-pseudococaine **424**
66%, >99:1 dr from **423**
75%, >99:1 dr from **423**·HCl

423, >99:1 dr

Scheme 101 *Reagents and conditions:* (i) PhCOCl, DMAP, Et_3N, CH_2Cl_2, rt, 12 h.

Limited characterisation data has been reported for the sample of (+)-pseudococaine **419** isolated from the natural source; however comparison of the ^1H and ^{13}C data for this synthetic sample of (+)-pseudococaine **419** showed excellent agreement with data previously reported for a synthetic sample of (+)-pseudococaine **419** by Carroll *et al.* (Tables 11 and 12).[45]



(+)-pseudococaine **419**

^1H data for (+)-pseudococaine **419**		
H	Carroll *et al.*[45] δ_H (250 MHz, $CDCl_3$)	This study δ_H (500 MHz, $CDCl_3$)
C(1)H	3.5 (m)	3.49-3.51 (m)
C(2)H	3.1 (dd, *J* 10.9, 2.9)	3.14 (dd, *J* 10.7, 2.8)
C(3)H	5.5 (dd, *J* 10.5, 6.6)	5.54 (app t, *J* 10.7, 6.6)
$C(4)H_A$	1.8 (m)	1.75-1.81 (m)
$C(4)H_B$	2.1 (m)	2.05-2.14 (m)
C(5)H	3.3 (m)	3.26-3.29 (m)
$C(6)H_A$	-	1.75-1.81 (m)
$C(6)H_B$	-	2.05-2.14 (m)
$C(7)H_A$	-	1.84-1.89 (m)
$C(7)H_B$	-	1.92-1.99 (m)
NMe	2.4 (s)	2.45 (s)
OMe	3.6 (s)	3.66 (s)
Ph	-	7.42 (app t, *J* 7.6) 7.54 (app t, *J* 7.3) 7.99 (app d, *J* 6.9)

Table 11 Comparison of ^1H NMR data of (+)-pseudococaine **419** [^1H NMR data for $C(6)H_2$, $C(7)H_2$ and Ph were not given by Carroll *et al.*] [Chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

^{13}C data for (+)-pseudococaine **419**		
H	Carroll *et al.*[45] δ_C (63 MHz, $CDCl_3$)	This study δ_C (125 MHz, $CDCl_3$)
C(1)	62.4	62.7
C(2)	48.4	48.7
C(3)	67.6	67.9
C(4)	33.6	33.8
C(5)	59.5	59.8
C(6)	26.6	26.9
C(7)	23.9	24.1
NMe	37.4	37.7
OMe	51.6	51.9
CO_2Me	172.0	172.8
COPh	165.2	165.6
Ph	127.9 129.2 130.0 132.5	128.3 129.6 130.3 132.8

Table 12 Comparison of ^{13}C NMR data of (+)-pseudococaine **419** [Chemical shifts (δ_C) are reported in ppm].

The specific rotation and melting point of the synthetic sample of (+)-pseudococaine **419**·HCl {mp 209-211 °C; $[\alpha]_D^{20}$ +43.7 (*c* 0.2 in H_2O)} were also in excellent agreement with data reported in the literature {lit.[45] mp 208-209 °C; lit.46 for *ent*-**419**·HCl mp 210-212 °C; lit.47 $[\alpha]_D^{20}$ +42 (*c* 1.5 in H_2O); lit.[46] for *ent*-**419**·HCl $[\alpha]_D^{24}$ –42.3 (*c* 1.0 in H_2O)}.

5.10 Summary

Conjugate addition of (*R*)-**383** to α,β-unsaturated ester **133** with *in situ* α-allylation was followed by ring-closing metathesis to give aminocycloheptene **389**. Iodine-promoted transannular cyclisation of **389** gave an inseparable 77:23 mixture of regioisomers **395** and **396**. The regioselectivity of the transannular process could be positively influenced by incorporation of an allylic hydroxyl group, which directed the attack of the nitrogen atom onto the distal carbon atom within the intermediate iodonium ion, giving **398**·HI as a single regio- and diastereoisomer. Elaboration of **398**·HI enabled the synthesis of the alkaloid (+)-pseudococaine **419** in 7 steps and 31% yield from commercially available 4-pentenal (Fig. 51).

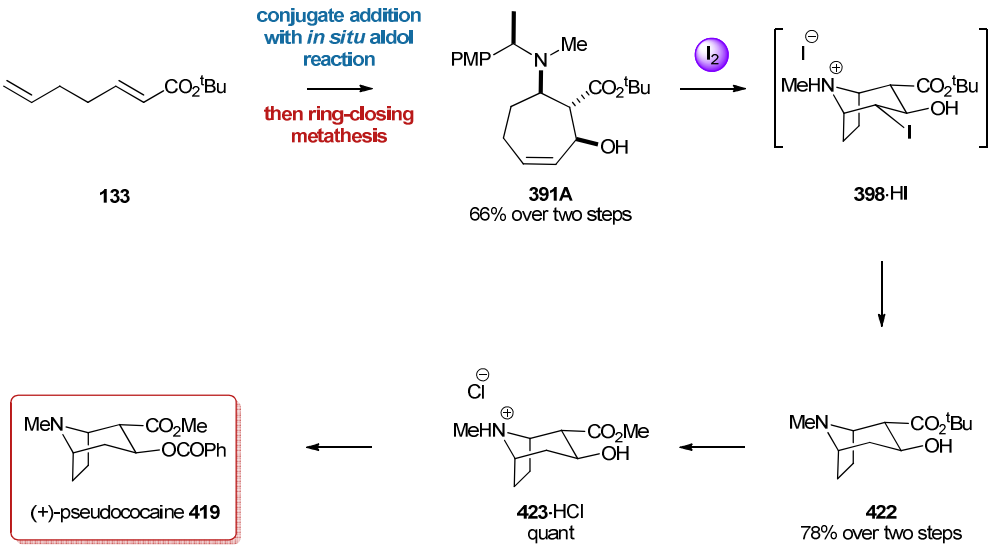


Figure 51 The total asymmetric synthesis of (+)-pseudococaine **419** via transannular iodoamination.

5.11 References and notes

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Future Work

Future work concerning the synthesis of pyrrolidizine alkaloids will commence with an investigation into tuning the diastereoselectivity of the transannular iodoamination approach to access further diastereoisomers of the pyrrolizidine alkaloid family. An investigation into double asymmetric induction upon conjugate addition of the enantiomers of lithium *N*-but-3-enyl-*N*-(α-methylbenzyl)amide **184** to chiral α,β-unsaturated esters **108** containing non-cyclic protecting groups, with *in situ* enolate oxidation, will ultimately allow for the synthesis of further diastereoisomeric hexahydroazocines **427** through exploitation of the 'matching' and 'mismatching' effects in the initial lithium amide conjugate addition. These hexahydroazocine substrates **427** will then be subjected to transannular iodocyclisation, and the diastereoisomeric iodopyrrolizidines **428** isolated from these studies will be elaborated to their corresponding 'hyacinthacine' or 'alexine' diastereoisomers **429**, using the previously developed procedures for either direct reduction of the iodine functionality, or radical mediated displacement, respectively (Fig. 52).

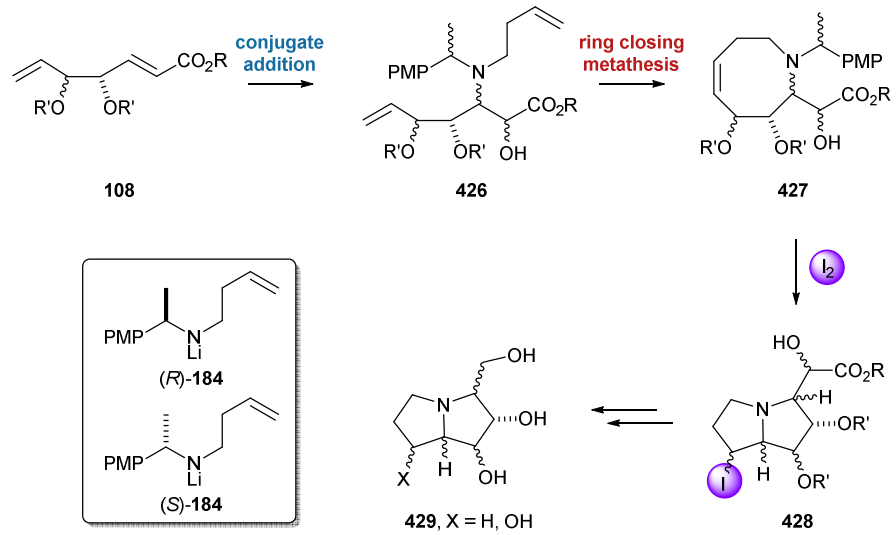


Figure 52 Route to alternate diastereoisomeric 'alexine' and 'hyacinthacine' pyrrolizidine alkaloids **429**.

Further investigation into the use of an iodine-promoted transannular cyclisation in the synthesis of the tropane alkaloids will initially be focussed on probing the selectivity of the aldol reaction. Studies will examine the effect of altering the ester alkoxy group within **112** in both the stepwise and tandem procedures: for example, the methyl and ethyl ester analogues will be investigated so that the diastereoselectivity of the aldol reaction with either acrolein or crotonaldehyde may be directly compared to the results of Yamamoto and Warren. With

greater understanding of the aldol reaction selectivity having been reached, the lithium amide conjugate addition and aldol approach can then be tailored to give access to synthetically useful amounts of diastereoisomers **431B**, **431C** and **431D**, which would subsequently allow further development of the transannular cyclisation procedure in these three systems in order to access diastereoisomeric iodotropanes **433**. For example, the transannular iodocyclisation of the corresponding secondary amines **432B**, **432C** and **432D** will be investigated, as well as the use of alternative electrophiles to induce the reaction. The C(4)-substituted tropanes resulting from these reactions are precursors to allococaine **420**, pseudoallococaine **421**, and cocaine **359** itself (Fig. 53).

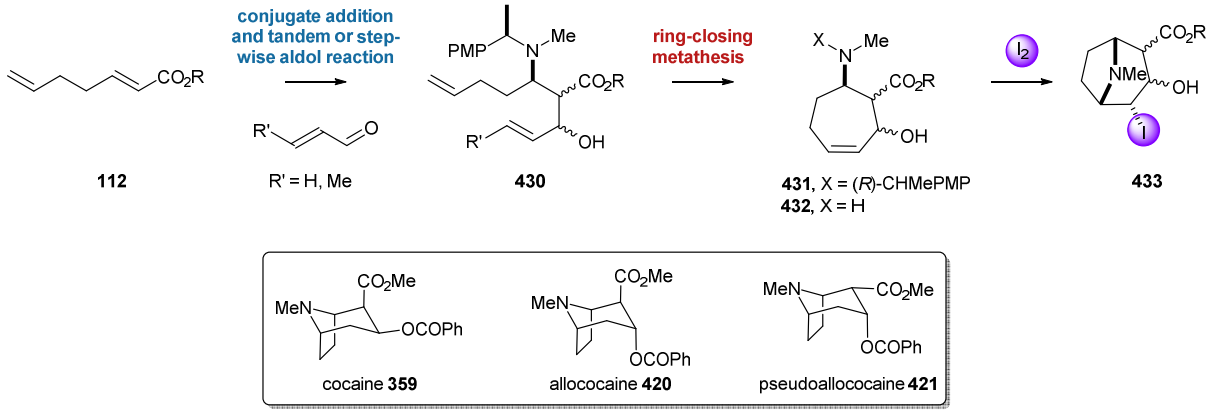


Figure 53 Accessing allococaine **420**, pseudoallococaine **421**, and cocaine **359** via a lithium amide conjugate addition and aldol protocol.

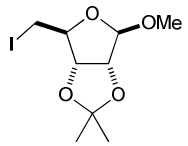
Chapter 6: Experimental

6.1 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 and co-workers.[1] Water was purified by an Elix® UV-10 system. BuLi was titrated against Ph_2CHCO_2H before use. Zn dust was activated by stirring with 1.0 M HCl for 15 mins, then washed twice with H_2O and Et_2O and dried *in vacuo* at 110 °C for 12 h. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ or Na_2SO_4. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine or 1% aq $KMnO_4$. Flash column chromatography was performed on Kieselgel 60 silica. Elemental analyses were recorded by the microanalysis service of London Metropolitan University, U.K. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 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 a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film), a KBr disc (KBr) or on an ATR module (ATR), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. 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. In cases where the methine or methylene groups of carbocyclic rings could not be unambiguously assigned the descriptors CH and CH_2 (respectively) are used in δ_H/δ_C assignments. When the diastereotopic methyl groups of acetonide functionalities could not be unambiguously assigned, the descriptor *Me*CMe was employed. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

6.2 Experimental data for Chapter 2

(2*R*,3*R*,4*S*,5*S*)-2-Methoxy-3,4-*O*-isopropylidene-3,4-dihydroxy-5-(iodomethyl) tetrahydrofuran 153[2]

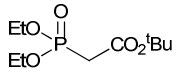


Method A: Conc. HCl (7.0 mL) was added dropwise to a stirred solution of D-ribose **152** (50.0 g, 333 mmol) in acetone/MeOH (v/v 1:1, 560 mL). The reaction mixture was heated at reflux for 1 h, then allowed to cool to rt and neutralised with pyridine until pH ~7 was acheieved. The resultant mixture was diluted with H_2O (500 mL) and Et_2O (500 mL) and the aqueous layer was extracted with EtOAc (2 × 500 mL). The combined organic extracts were washed sequentially with satd aq $CuSO_4$ (2 × 500 mL), H_2O (2 × 500 mL) and brine (2 × 500 mL), then dried and concentrated *in vacuo*. The residue was then dissolved in PhMe/MeCN (v/v 5:1, 840 mL) and I_2 (47.9 g, 189 mmol), imidazole (16.1 g, 236 mmol) and PPh_3 (49.5 g, 189 mmol) were added sequentially to the resultant solution. The reaction mixture was heated at 60 °C for 1 h then allowed to cool to rt and diluted with Et_2O (500 mL). The organic layer was washed sequentially with 10% aq Na_2SO_3 (1.0 L), H_2O (1.0 L) and brine (1.0 L), then dried and concentrated *in vacuo*. The residue was filtered through a short plug of silica gel (eluent 30-40 °C petrol/Et_2O, 19:1) to give **153** as a colourless oil (47.1 g, 45%, >99:1 dr);[2] $[\alpha]_D^{25}$ −64.0 (*c* 1.0 in $CHCl_3$); {lit.3 $[\alpha]_D^{24}$ −68.6 (*c* 2.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 3.17 (1H, app t, *J* 9.9, CH_AH$_B$I), 3.29 (1H, dd, *J* 9.9, 6.1, CH$_A$$H_B$I), 3.38 (3H, s, O*Me*), 4.45 (1H, app dd, *J* 9.9, 5.8, C(5)*H*), 4.63 (1H, app d, *J* 5.8, C(4)*H*), 4.77 (1H, app d, *J* 6.1, C(3)*H*), 5.06 (1H, app s, C(2)*H*).

Method B: Conc. HCl (0.30 mL) was added dropwise to a stirred solution of D-ribose **152** (2.00 g, 13.3 mmol) in acetone/MeOH (v/v 1:1, 28.0 mL). The reaction mixture was heated at reflux for 1 h then allowed to cool to rt and neutralised with solid Na_2CO_3 until pH ~7 was acheived. The resultant mixture was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. The residue was partitioned between EtOAc (25 mL) and H_2O (25 mL) and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic extracts were then dried and concentrated *in vacuo*. The residue was dissolved in

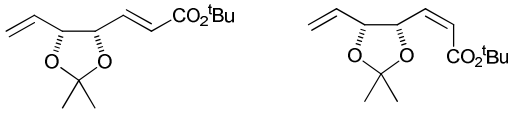
PhMe/MeCN (v/v 5:1, 48 mL) and I_2 (4.10 g, 16.2 mmol), imidazole (1.36 g, 19.9 mmol) and PPh_3 (4.20 g, 16.0 mmol) were added sequentially to the resultant solution. The reaction mixture was heated at 60 °C for 1 h then allowed to cool to rt and diluted with Et_2O (50 mL). The organic layer was washed sequentially with 10% aq $Na_2S_2O_3$ (100 mL), H_2O (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. The residue was filtered through a short plug of silica gel (eluent 30-40 °C petrol/Et_2O, 19:1) to give **153** as a colourless oil (2.72 g, 65%, >99:1 dr).

tert-Butyl (diethylphosphono)acetate 155[4]



A stirred mixture of *tert*-butyl bromoacetate (37.9 mL, 256 mmol) and $P(OEt)_3$ (44.0 mL, 256 mmol) was heated at 50 °C for 12 h then allowed to cool to rt and concentrated *in vacuo* to give **155** as a colourless oil (60.1 g, 94%);[4] δ_H (400 MHz, $CDCl_3$) 1.33 (6H, t, *J* 7.2, $P(OCH_2CH_3)_2$), 1.46 (9H, s, CMe_3), 2.87 (2H, d, *J* 21.5, PCH_2), 4.08-4.19 (4H, m, $P(OCH_2CH_3)_2$).

tert-Butyl (4*S*,5*R*,*E*)-4,5-*O*-isopropylidene-4,5-dihydroxyhepta-2,6-dienoate 140[5] and *tert*-butyl (4*S*,5*R*,*Z*)-4,5-*O*-isopropylidene-4,5-dihydroxyhepta-2,6-dienoate 156[6]

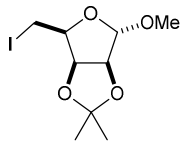


Method A: Activated Zn dust (100 g, 1.53 mol) was added to a stirred solution of **153** (47.0 g, 150 mmol, >99:1 dr) in MeOH (500 mL). The resultant mixture was heated at reflux for 2.5 h then allowed to cool to rt and filtered through Celite® (eluent MeOH). The filtrate was concentrated *in vacuo* at 15 °C, the residue was dissolved in 30-40 °C petrol/Et_2O (v/v 1:1, 250 mL) and the resultant solution was filtered through a short plug of Florisil (eluent 30-40 °C petrol/Et_2O, 3:1). The filtrate was then concentrated *in vacuo*. The residue was dissolved in THF (50 mL) and the resultant solution was added via cannula to a stirred solution of MeMgBr (3.0 M in Et_2O, 75 mL, 225 mmol) and **155** (56.7 g, 225 mmol) in THF (1.0 L) at 0 °C. The reaction mixture was heated at 50 °C for 12 h then cooled to 0 °C before satd aq NH_4Cl (50 mL) was added. The resultant solution was extracted with Et_2O (1.0 L) and the

organic extract was washed with brine (1.0 L), then dried and concentrated *in vacuo* to give (4*S*,5*R*,*E*)-**140** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 25:1) gave (4*S*,5*R*,*E*)-**140** as a yellow oil (12.8 g, 33%, >99:1 dr);[5] $[\alpha]_D^{25}$ −40.1 (*c* 1.0 in $CHCl_3$); {lit.6 $[\alpha]_D^{24}$ −41.3 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 1.56 (3H, s, *Me*CMe), 4.69 (1H, app t, *J* 7.5, C(5)*H*), 4.73-4.76 (1H, m, C(4)*H*), 5.27 (1H, app d, *J* 10.2, C(7)H_A), 5.37 (1H, app d, *J* 17.1, C(7)H_B), 5.67-5.76 (1H, m, C(6)*H*), 5.99 (1H, app dd, *J* 15.5, 1.4, C(2)*H*), 6.68 (1H, dd, *J* 15.5, 5.8, C(3)*H*).

Method B: BuLi (2.5 M in hexanes, 1.66 mL, 4.15 mmol) was added dropwise to a stirred solution of **153** (500 mg, 1.59 mmol, >99:1 dr) and **155** (400 mg, 1.59 mmol) in Et_2O (10 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 2 h then allowed to warm to rt over 2 h before satd aq NH_4Cl (5 mL) was added. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give an 88:12 mixture of (4*S*,5*R*,*E*)-**140** and (4*S*,5*R*,*Z*)-**156**. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 25:1) gave (4*S*,5*R*,*Z*)-**156** as a colourless oil (47 mg, 12%, >99:1 dr); $[\alpha]_D^{20}$ +86.1 (*c* 0.5 in $CHCl_3$); {lit.[6] $[\alpha]_D^{24}$ +85.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 1.55 (3H, s, *Me*CMe), 4.85-4.89 (1H, m, C(5)*H*), 5.15-5.17 (1H, m, C(7)H_A), 5.25 (1H, m, C(7)H_B), 5.63-5.72 (2H, m, C(4)*H*, C(6)*H*), 5.81 (1H, app dd, *J* 11.6, 1.7, C(2)*H*), 6.10 (1H, dd, *J* 11.6, 7.2, C(3)*H*); Further elution gave (4*S*,5*R*,*E*)-**140** as a colourless oil (350 mg, 85%, >99:1 dr); $[\alpha]_D^{25}$ −40.1 (*c* 1.0 in $CHCl_3$).

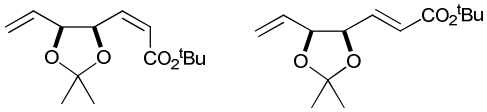
(2*S*,3*S*,4*R*,5*S*)-2- Methoxy-3,4-*O*-isopropylidene-3,4-dihydroxy-5-(iodomethyl) tetrahydrofuran 158



Conc. HCl (0.30 mL) was added dropwise to a stirred solution of D-lyxose **157** (1.00 g, 6.66 mmol) in acetone/MeOH (v/v 1:1, 14 mL). The reaction mixture was heated at reflux for 1 h then allowed to cool to rt and neutralised with solid Na_2CO_3 until pH ~7 was acheieved. The resultant mixture was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. The residue was partitioned between EtOAc (25 mL) and H_2O (25 mL)

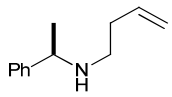
and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organic extracts were then dried and concentrated *in vacuo*. The residue was dissolved in PhMe/MeCN (v/v 5:1, 24 mL) and I_2 (2.02 g, 8.00 mmol), imidazole (680mg, 10.0 mmol) and PPh_3 (2.10 g, 8.00 mmol) were added sequentially to the resultant solution. The reaction mixture was heated at 60 °C for 1 h then allowed to cool to rt and diluted with Et_2O (25 mL). The organic layer was washed sequentially with 10% aq $Na_2S_2O_3$ (30 mL), H_2O (30 mL) and brine (30 mL), then dried and concentrated *in vacuo*. The residue was filtered through a short plug of silica gel (eluent 30-40 °C petrol/Et_2O, 19:1) to give **158** as a colourless oil (1.25 g, 60%, >99:1 dr); $[\alpha]_D^{25}$ +49.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2988, 2850 (C−H); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, *Me*CMe), 1.45 (3H, s, *Me*CMe), 3.28 (1H, dd, *J* 9.6, 6.5, C*H*$_A$CH$_B$I), 3.37-3.33 (1H, m, CH$_A$C*H*$_B$I) overlapping 3.35 (3H, s, O*Me*), 4.19 (1H, td, *J* 7.1, 3.5, C(5)*H*), 4.59 (1H, app d, *J* 5.8, C(4)*H*), 4.75 (1H, dd, *J* 5.8, 3.5, C(3)*H*), 4.92 (1H, app s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 0.8 (*C*H_2I), 25.0 (*Me*CMe), 26.1 (*Me*CMe), 54.7 (O*Me*), 79.4 (*C*(3)), 80.5 (*C*(5)), 85.2 (*C*(4)), 107.2 (*C*(2)), 112.8 (*C*Me$_2$); HRMS (FI$^+$) $C_9H_{15}IO_4^+$ ([M]$^+$) requires 314.0010; found 314.0008.

tert-Butyl (4*R*,5*S*,*Z*)-4,5-*O*-isopropylidene-4,5-dihydroxyhepta-2,6-dienoate 140 and *tert*-butyl (4*R*,5*S*,*E*)-4,5-*O*-isopropylidene-4,5-dihydroxyhepta-2,6-dienoate 156



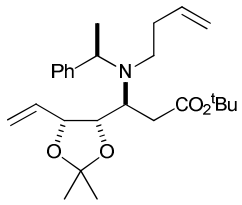
BuLi (2.3 M in hexanes, 5.54 mL, 12.7 mmol) was added dropwise to a stirred solution of **158** (2.00 g, 6.37 mmol, >99:1 dr) and **155** (1.60 g, 6.37 mmol) in Et_2O (200 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h then allowed to warm to rt over 2 h before satd aq NH_4Cl (10 mL) was added. 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 a 96:4 mixture of **140** and **156**. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 30:1) gave (4*R*,5*S*,*Z*)-**156** as a colourless oil (49 mg, 3%, >99:1 dr); $[\alpha]_D^{20}$ −85.3 (*c* 0.5 in $CHCl_3$); {lit.[6] for *ent*-**156** $[\alpha]_D^{24}$ +85.6 (*c* 1.0 in $CHCl_3$)}. Further elution gave (4*R*,5*S*,*E*)-**140** (1.21 g, 75%, >99:1 dr) as a colourless oil; $[\alpha]_D^{25}$ +38.8 (*c* 1.0 in $CHCl_3$); {lit.[6] for *ent*-**140** $[\alpha]_D^{24}$ −41.3 (*c* 0.5 in $CHCl_3$)}.

(*R*)-*N*-But-3-enyl-*N*-(α-methylbenzyl)amine 162[7]



4-Bromobut-1-ene (17.0 mL, 167 mmol) was added to a stirred mixture of (*R*)-α-methylbenzylamine (53.3 mL, 419 mmol, >98% ee) and K_2CO_3 (27.8 g, 201 mmol). The reaction mixture was heated at 50 °C for 12 h then allowed to cool to rt and partitioned between Et_2O (200 mL) and H_2O (200 mL). The aqueous layer was extracted with Et_2O (2 × 200 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **162** as a yellow oil (22.1 g, 75%, >98% ee);8 $[\alpha]_D^{25}$ +40.8 (*c* 1.0 in $CHCl_3$); {lit.9 $[\alpha]_D^{24}$ +41.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.49 (1H, br s, N*H*), 2.20-2.70 (2H, m, C(2)H_2), 2.47-2.63 (2H, m, C(1)H_2), 3.77 (1H, q, *J* 6.8, C(α)*H*), 5.01-5.12 (2H, m, C(4)H_2), 5.70-5.81 (1H, m, C(3)*H*), 7.22-7.36 (5H, m, *Ph*).

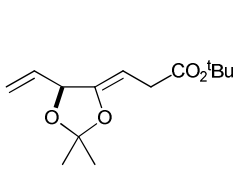
***tert*-Butyl (3*S*,4*S*,5*R*,α*R*)-3-[*N*-but-3′-enyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 163**

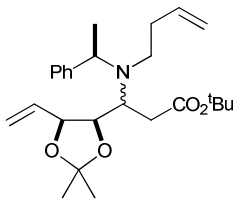


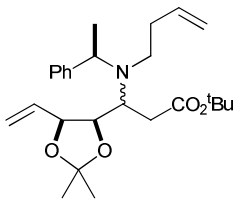
BuLi (2.5 M in hexanes, 0.51 mL, 1.22 mmol) was added dropwise to a stirred solution of **162** (221 mg, 1.26 mmol) in THF (2.5 mL) at −78 °C. After stirring for 30 min at −78 °C a solution of (4*R*,5*S*,*E*)-**140** (200 mg, 0.79 mmol, >99:1 dr) in THF (2.5 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for a further 2 h, before satd aq NH_4Cl (2 mL) was added. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **163** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 20:1) gave **163** as a pale yellow oil (195 mg, 60%, >99:1 dr); $C_{26}H_{39}NO_4$

requires C, 72.7; H, 9.15; N, 3.3%; found C, 72.7; H, 9.1; N, 3.3%; $[\alpha]_D^{25}$ −24.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1729 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.46 (12H, s, C*Me*$_3$, *Me*CMe), 2.04 (2H, app q, *J* 7.6, C(2′)H_2), 2.25 (1H, dd, *J* 15.7, 5.3, C(2)H_A), 2.34 (1H, dd, *J* 15.7, 7.6, C(2)H_B), 2.51-2.70 (2H, m, C(1′)H_2), 3.60-3.67 (1H, m, C(3)*H*), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.27 (1H, dd, *J* 4.0, 6.9, C(4)*H*), 4.60 (1H, app t, *J* 6.9, C(5)*H*), 4.88-4.95 (2H, m, C(4′)H_2), 5.28-5.39 (2H, m, C(7)H_2), 5.60-5.72 (1H, m, C(3′)*H*), 5.88-5.99 (1H, m, C(6)*H*), 7.19-7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.1 (C(α)*Me*), 24.9, 27.4 (C*Me*$_2$), 28.2 (C*Me*$_3$), 34.9 (*C*(2′)), 36.3 (*C*(2)), 46.2 (*C*(1′)), 55.4 (*C*(3)), 58.7 (*C*(α)), 78.6 (*C*(4)), 79.6 (*C*(5)), 79.9 (*C*Me$_3$), 108.1 (*C*Me$_2$), 115.2 (*C*(4′)), 118.9 (*C*(7)), 126.8 (*p-Ph*), 127.6, 128.0 (*o,m-Ph*), 134.5 (*C*(6)), 137.2 (*C*(3′)), 144.6 (*i-Ph*), 171.8 (*C*(1)); *m/z* (ESI^+) 430 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{40}NO_4^+$ ($[M+H]^+$) requires 430.2952; found 430.2948.

tert-Butyl (*S*,*Z*)-4,5-*O*-isopropylidene-4,5-dihydroxyhepta-3,6-dienoate 161, _tert_-butyl (3*R*/*S,4*R*,5*S*,α*R*)-3-[*N*-but-3′-enyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 164 and _tert_-butyl (3*R*/*S**,4*R*,5*S*,α*R*)-3-[*N*-but-3′-enyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 165**





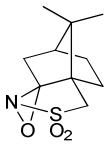


BuLi (2.4 M in hexanes, 0.51 mL, 1.22 mmol) was added dropwise to a stirred solution of **162** (221 mg, 1.26 mmol) in THF (5 mL) at −78 °C. After stirring for 30 min at −78 °C a solution of (4*R*,5*S*,*E*)-**140** (200 mg, 0.79 mmol, >99:1 dr) in THF (5 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for a further 2 h, before satd aq NH_4Cl (2 mL) was added. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a 78:13:9 mixture of (*S*,*Z*)-**161**, **164** and **165**. Purification via flash column

chromatography (eluent 30-40 °C petrol/Et_2O, 30:1) gave (*S*,*Z*)-**161** as a colourless oil (103 mg, 51%, >99:1 dr);10 $[\alpha]_D^{20}$ +31.1 (*c* 1.1 in $CHCl_3$); {lit.[10] for *ent*-**161** $[\alpha]_D^{24}$ −35.8 (*c* 1.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 1.50 (3H, s, *Me*CMe), 2.95-3.09 (2H, m, C(2)H_2), 4.29 (1H, app td, *J* 7.0, 1.7, C(3)*H*), 4.93 (1H, d, *J* 7.5, C(5)*H*), 5.26 (1H, app d, *J* 9.9, C(7)H_A), 5.35 (1H, app d, *J* 17.1, C(7)H_B), 5.72-5.81 (1H, m, C(6)*H*). Further elution gave **164** as a colourless oil (39 mg, 12%, >99:1 dr); $[\alpha]_D^{20}$ +5.0 (*c* 0.69 in $CHCl_3$); ν_{max} (film) 2980, 2933 (C−H), 1730 (C=O), 1642 (C=C); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, s, *Me*CMe), 1.39 (3H, d, *J* 7.0, C(α)*Me*), 1.40 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 2.11 (2H, app q, *J* 7.1, C(2′)H_2), 2.22 (1H, dd, *J* 15.2, 5.6, C(2)H_A), 2.40 (1H, dd, *J* 15.2, 7.3, C(2)H_B), 2.55-2.62 (1H, m, C(1′)H_A), 2.65-2.73 (1H, m, C(1′)H_B), 3.63 (1H, app q, *J* 5.3, C(3)*H*), 3.79 (1H, app t, *J* 5.1, C(4)*H*), 3.91 (1H, q, *J* 7.0, C(α)*H*), 4.31 (1H, app t, *J* 7.1, C(5)*H*), 4.94-4.99 (2H, m, C(4′)H_2), 5.27 (2H, app t, *J* 11.0, C(7)H_2), 5.68-5.79 (1H, m, C(3′)*H*), 5.81-5.91 (1H, m, C(6)*H*), 7.21-7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0, 24.9, 27.4 (C*Me*$_2$, C(α)*Me*), 28.2 (C*Me*$_3$), 34.9 (*C*(2′)), 35.8 (*C*(2)), 46.9 (*C*(1′)), 54.5 (*C*(3)), 59.2 (*C*(α)), 78.9, 79.5 (*C*(4), *C*(5)), 88.2 (*C*Me$_3$), 107.9 (*C*Me$_2$), 115.3 (*C*(4′)), 118.3 (*C*(7)), 127.0 (*p-Ph*), 127.9, 128.1 (*o*,*m-Ph*), 134.6 (*C*(6)), 137.1 (*C*(3′)), 143.8 (*i-Ph*), 171.9 (*C*(1)); *m/z* (ESI^+) 452 ($[M+Na]^+$, 10%); 430 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{40}NO_4^+$ ($[M+H]^+$) requires 430.2952; found 430.2942. Further elution gave **165** as a yellow oil (10 mg, 3%, >99:1 dr); $[\alpha]_D^{20}$ −10.2 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 2979, 2931 (C−H), 1731 (C=O), 1639 (C=C); δ_H (500 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.45 (3H, d, *J* 6.6, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 1.54 (3H, s, *Me*CMe), 1.82-1.89 (1H, m, C(2′)H_A), 1.95-2.02 (1H, m, C(2′)H_B), 2.07 (1H, dd, *J* 14.8, 2.8, C(2)H_A), 2.31 (1H, dd, *J* 14.8, 10.7, C(2)H_B), 2.62-2.73 (2H, m, C(1′)H_2), 3.77 (1H, td, *J* 10.7, 2.8, C(3)*H*), 4.12 (1H, q, *J* 6.6, C(α)*H*), 4.28 (1H, dd, *J* 10.7, 5.7, C(4)*H*), 4.36 (1H, dd, *J* 8.5, 5.7, C(5)*H*), 4.81 (1H, br s, C(4′)H_A), 4.83 (1H, br s, C(4′)H_B), 5.30 (1H, br s, C(7)H_A), 5.33 (1H, br s, C(7)H_B), 5.52-5.60 (1H, m, C(3′)*H*), 5.93-6.00 (1H, m, C(6)*H*), 7.17-7.39 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.1 (C(α)*Me*), 25.4 (*Me*CMe), 28.1 (C*Me*$_3$), 28.3 (*Me*CMe), 34.3 (*C*(2′)), 37.0 (*C*(2)), 47.4 (*C*(1′)), 53.6 (*C*(3)), 59.6 (*C*(α)), 79.1 (*C*(4)), 80.0 (*C*(5)), 80.3 (*C*Me$_3$), 108.6 (*C*Me$_2$), 114.7 (*C*(4′)), 119.2 (*C*(7)), 126.3 (*p-Ph*), 127.5, 127.8 (*o,m-Ph*), 134.3 (*C*(6)), 137.4 (*C*(3′)), 147.5 (*i-Ph*), 170.6 (*C*(1)); *m/z* (ESI^+) 452 ($[M+Na]^+$, 30%);

430 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{40}NO_4^+$ ([M+H]$^+$) requires 430.2952; found 430.2945.

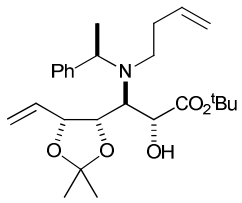
(–)-(10-Camphorsulfonyl)oxaziridine [(–)-CSO] 169[11]



$SOCl_2$ (252 mL, 3.44 mol) was added dropwise to a stirred solution of (1*R*)-(–)-10-camphorsulfonic acid [(–)-CSA] (200 g, 864 mmol) in $CHCl_3$ (1.0 L). The resultant mixture was heated at reflux for 12 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (1.0 L) and added dropwise to stirred 35% aq NH_3 (2.0 L) at 0 °C. The reaction mixture was left to stir at 0 °C for 4 h, then the aqueous layer was extracted with CH_2Cl_2 (2 × 2.0 L). The combined organic extracts were then dried and concentrated *in vacuo*. The residue was dissolved in PhMe (1.2 L) and Amberlyst 15 (wet) ion exchange resin (12 g) was added. A Dean-Stark apparatus was fitted to the flask and the reaction mixture was heated at reflux for 4 h, then allowed to cool to rt and filtered through Celite® (eluent $CHCl_3$). The filtrate was concentrated *in vacuo* to give (+)-CSI as a white solid (166 g); δ_H (400 MHz, $CDCl_3$) 0.82 (3H, s, *Me*CMe), 1.04 (3H, s, *Me*CMe), 1.39-1.49 (1H, m), 1.65-1.75 (1H, m), 1.97-2.07 (2H, m), 2.23 (1H, t, *J* 4.1), 2.29-2.39 (1H, m), 2.68-2.77 (1H, m), 2.94 (1H, d, *J* 13.5, C*H*$_A$H$_B$SO$_2$), 3.16 (1H, d, *J* 13.5 CH$_A$*H*$_B$SO$_2$).

5.0 M aq K_2CO_3 (774 mL) was added dropwise to a stirred solution of (+)-CSI (200 g, 93.7 mmol) and Aliquat 336 (50 mL) in CH_2Cl_2 (1.5 L) at 0 °C at such a rate as to maintain the temperature below 5 °C. Peracetic acid solution (32% in AcOH, 850 mL) was then added in a similar fashion and stirring was continued for 48 h before Na_2SO_3 (100 g) was added. 1.0 M aq NaOH (400 mL) was immediately added and the aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic extracts were washed sequentially with H_2O (1.0 L) and satd aq $NaHCO_3$ (1.0 L), then dried and concentrated *in vacuo*. Purification via recrystallisation (CH_2Cl_2/40-60 °C petrol) gave (–)-**169** as a white solid (203 g, 86% from (–)-CSA);[11] $[\alpha]_D^{25}$ –45.0 (*c* 1.0 in $CHCl_3$); {lit.[11] for *ent*-**169** $[\alpha]_D^{25}$ +44.6 (*c* 2.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, s, *Me*CMe), 1.19 (3H, s, *Me*CMe), 1.48-1.56 (1H, m), 1.79 (1H, d, *J* 15.4), 1.91-2.16 (4H, m), 2.61-2.68 (1H, m), 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 (2*R*,3*S*,4*S*,5*R*,α*R*)-2-hydroxy-3-[*N*-but-3′-enyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 170**

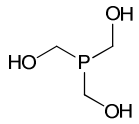


Method A: BuLi (2.5 M in hexanes, 8.46 mL, 21.1 mmol) was added dropwise to a stirred solution of **162** (2.74 g, 21.8 mmol) in THF (25 mL) at −78 °C. After stirring for 30 min at −78 °C a solution of (4*S*,5*R*,*E*)-**140** (3.74 g, 13.6 mmol, >99:1 dr) in THF (25 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for a further 2 h, before (−)-CSO **169** (6.26 g, 27.3 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo* to give a mixture of **163** and **170**.12 Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:1 increased to 30-40 °C petrol/EtOAc, 20:1) gave **163** as a colourless oil (344 mg, 5%, >99:1 dr). Further elution gave **170** as a colourless oil (3.43 g, 56%, >99:1 dr); $C_{26}H_{39}NO_5$ requires C, 70.1; H, 8.8; N, 3.1%; found C, 70.15; H, 8.7; N, 3.1%; $[\alpha]_D^{25}$ −12.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3497 (O−H), 1731 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.43 (3H, d, *J* 6.8, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.97-2.18 (2H, m, C(2′)H_2), 2.63-2.72 (1H, m, C(1′)H_A), 3.05 (1H, d, *J* 7.3, O*H*), 3.07-3.18 (1H, m, C(1′)H_B), 3.59 (1H, app d, *J* 10.1, C(3)*H*), 3.99 (1H, app d, *J* 7.3, C(2)*H*), 4.11 (1H, q, *J* 6.8, C(α)*H*), 4.46 (1H, dd, *J* 10.1, 5.7, C(4)*H*), 4.61 (1H, app t, *J* 5.7, C(5)*H*), 4.93-4.99 (2H, m, C(4′)H_2), 5.23 (1H, app d, *J* 10.4, C(7)H_A), 5.40 (1H, app d, *J* 16.4, C(7)H_B), 5.64-5.76 (1H, m, C(3′)*H*), 5.83-5.93 (1H, m, C(6)*H*), 7.21-7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.2 (C(α)*Me*), 25.6 (*Me*CMe), 28.1 (C*Me*$_3$), 28.2 (*Me*CMe), 35.0 (*C*(2′)), 45.9 (*C*(1′)), 59.2 (*C*(α)), 59.8 (*C*(3)), 72.0 (*C*(2)), 76.2 (*C*(4)), 79.2 (*C*(5)), 82.0 (*C*Me$_3$), 107.9 (*C*Me$_2$), 115.6 (*C*(4′)), 118.5 (*C*(7)), 127.1 (*p-Ph*), 128.1, 128.4 (*o,m-Ph*), 135.3, 137.0 (*C*(6), *C*(3′)), 142.8 (*i-Ph*), 173.1 (*C*(1)); *m/z* (ESI$^+$) 913 ([2M+Na]$^+$, 100%), 446 ([M+H]$^+$, 20%); HRMS (ESI$^+$) $C_{26}H_{39}NNaO_5^+$ ([M+Na]$^+$) requires 468.2720; found 468.2705.

Method B: BuLi (2.4 M in hexanes, 1.27 mL, 3.05 mmol) was added dropwise to a stirred solution of **162** (551 mg, 3.15 mmol) in THF (3 mL) at −78 °C. After stirring for 30 min at

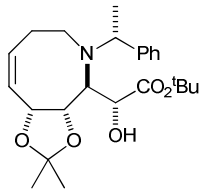
−78 °C a solution of (4*S*,5*R*,*E*)-**140** (500 mg, 1.97 mmol, >99:1 dr) in THF (3 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for a further 2 h, before (+)-CSO **169** (900 mg, 3.93 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo* to give a mixture of **163** and **170**.[12] Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 100:1) gave **163** as a colourless oil (19 mg, 2%, >99:1 dr). Further elution gave **170** as a pale yellow oil (307 mg, 35%, >99:1 dr); $[\alpha]_D^{25}$ −12.3 (*c* 1.0 in $CHCl_3$).

Tris(hydroxymethyl)phosphine 424[13]



Dry tetrakis(hydroxymethyl)phosphonium chloride14 (321 g, 1.68 mmol) was added in one portion to Et_3N (3.0 L) stirring under N_2. The resultant mixture was heated at 60 °C for 1 h then allowed to cool to rt, filtered (eluent Et_3N) and concentrated *in vacuo*. The residue was heated at 90 °C for 12 h *in vacuo*, then allowed to cool to rt to give **424** as a colourless oil (136 g, 65%);[13] δ_H (200 MHz, DMSO-d_6) 3.87 (6H, d, *J* 5.5, $P(CH_2OH)_3$), 4.75 (3H, br s, $P(CH_2OH)_3$).

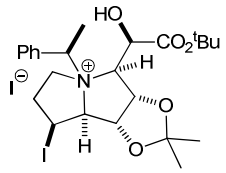
***tert*-Butyl (2*R*,2′*S*,3′*S*,4′*R*,α*R*,*Z*)-2-hydroxy-2-[*N*(1′)-α-methylbenzyl-3′,4′-*O*-isopropylidine-3′,4′-dihydroxy-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate 171**



Grubbs I catalyst (536 mg, 0.65 mmol) was added to a stirred solution of **170** (3.40 g, 8.14 mmol, >99:1 dr) in degassed CH_2Cl_2 (400 mL). The resultant mixture was stirred at rt for 12 h then concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 (100 mL) and **424** (8.06 g, 65.0 mmol), Et3N (2.28 mL, 16.2 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for 12 h, then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **171** as a yellow oil (2.74 g, 86%, >99:1 dr); $[\alpha]_D^{25}$ −28.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3490 (O–H), 1730 (C=O),

1600 (C=C); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.43 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 1.53 (3H, d, *J* 7.1, C(α)*Me*), 2.03-2.22 (2H, m, C(7′)H_2), 2.78 (1H, app dd, *J* 14.7, 10.9, C(8′)H_A), 3.17-3.22 (2H, m, C(8′)H_B, O*H*), 3.78 (1H, app d, *J* 10.4, C(2′)*H*), 4.30 (1H, app d, *J* 5.8, C(2)*H*), 4.66 (1H, dd, *J* 10.4, 5.6, C(3′)*H*), 4.86 (1H, q, *J* 7.1, C(α)*H*), 5.13 (1H, app t, *J* 5.6, C(4′)*H*), 5.65 (1H, dd, *J* 11.1, 5.6, C(5′)*H*), 5.84-5.92 (1H, m, C(6′)*H*), 7.18-7.43 (5H, m, *Ph*); 15 δ_C (100 MHz, $CDCl_3$) 22.1 (C(α)*Me*), 26.4 (*Me*CMe), 28.0 (C*Me*$_3$), 28.2 (*Me*CMe), 32.5 (*C*(7′)), 47.7 (*C*(8′)), 54.7 (*C*(α)), 62.7 (*C*(2′)), 75.1 (*C*(2)), 76.8 (*C*(4′)), 78.7 (*C*(3′)), 82.1 (*C*Me$_3$), 109.8 (*C*Me$_2$), 126.1 (*p-Ph*), 127.8, 128.2 (*o,m-Ph*), 130.4 (*C*(6′)), 133.8 (*C*(5′)), 146.3 (*i-Ph*), 172.7 (*C*(1)); *m/z* (ESI$^+$) 440 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{35}NNaO_5^+$ ([M+Na]$^+$) requires 440.2407; found 440.2409.

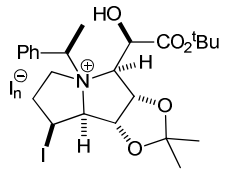
(1*R*,2*S*,3*S*,4*R*,7*S*,7a*S*,1′*R*,α*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-*N*(4)-(α-methylbenzyl)-7-iodooctahydropyrolizinium iodide 178[16]



I_2 (180 mg, 718 mmol) and $NaHCO_3$ (60 mg, 718 mmol) were added sequentially to a stirred solution of **171** (100 mg, 239 mmol, >99:1 dr) in $CHCl_3$ (10 mL) at rt. The resultant mixture was stirred at rt for 12 h before $Na_2S_2O_3$ (excess) was added. After stirring at rt for 1 h the mixture was filtered and concentrated *in vacuo*. Purification via direct crystallisation from 30-40 °C petrol (10 mL) gave **178** as a pale pink solid (103 mg, 70%, >99:1 dr); mp 107-110 °C; $[\alpha]_D^{25}$ −23.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3279 (O–H), 2983, 2936 (C–H), 1745 (C=O); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, s, *Me*CMe), 1.62 (3H, s, *Me*CMe), 1.63 (9H, s, C*Me*$_3$), 2.01 (3H, d, *J* 6.8, C(α)*Me*), 2.39-2.45 (1H, m, C(6)H_A), 3.45-3.48 (1H, m, C(6)H_B), 3.79 (1H, dt, *J* 12.3, 6.4, C(5)H_A), 3.84 (1H, d, *J* 3.5, O*H*), 4.02 (1H, app d, *J* 3.5, C(1′)*H*), 4.24 (1H, td, *J* 12.3, 5.4, C(5)H_B), 4.47 (1H, app d, *J* 6.9, C(3)*H*), 4.80 (1H, app d, *J* 5.6, C(1)*H*), 5.32 (1H, dd, *J* 6.9, 5.6, C(2)*H*), 5.36-5.39 (1H, m, C(7)*H*), 5.52 (1H, app d, *J* 7.3, C(7a)*H*), 6.00 (1H, q, *J* 6.8, C(α)*H*), 7.45-7.48 (2H, m, *Ph*), 7.51-7.58 (1H, m, *Ph*), 7.68-7.69 (2H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) [selected peaks] 16.6 (C(α)*Me*), 25.4, 27.6 (C*Me*$_2$), 28.0 (C*Me*$_3$), 37.5 (*C*(6)), 57.8 (*C*(5)), 68.1 (*C*(1′)), 72.9 (*C*(3)), 74.4 (*C*(α)), 81.4 (*C*(7a)), 86.6 (*C*Me$_3$), 86.4 (*C*(1)), 113.9 (*C*Me$_2$), 129.4, 131.5, 132.5 (*o-*,*m-*,*p-Ph*), 168.5 (*C*(2′));

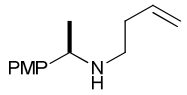
δ_H (400 MHz, CD_2Cl_2) 1.43 (3H, s, *Me*CMe), 1.65 (9H, s, C*Me*$_3$), 1.66 (3H, s, *Me*CMe), 2.02 (3H, d, *J* 6.7, C(α)*Me*), 2.42-2.49 (1H, m, C(6)H_A), 3.34-3.44 (1H, m, C(6)H_B), 3.82 (1H, dt, *J* 12.1, 4.6, C(5)H_A), 4.02 (1H, br s, O*H*), 4.10 (1H, app s, C(1′)*H*), 4.26 (1H, app qd, *J* 10.6, 5.5, C(5)H_B), 4.51 (1H, app d, *J* 6.8, C(3)*H*), 4.89 (1H, app d, *J* 5.3, C(1)*H*), 5.31-5.36 (2H, m, C(2)*H*, C(7)*H*), 5.50 (1H, app d, *J* 7.2, C(7a)*H*), 5.93 (1H, q, *J* 6.7, C(α)*H*), 7.51-7.60 (3H, m, *Ph*), 7.71-7.73 (2H, m, *Ph*); δ_C (100 MHz, CD_2Cl_2) 17.1 (C(α)*Me*), 22.8 (*C*(7)), 25.6, 27.8 (C*Me*$_2$), 28.2 (C*Me*$_3$), 37.7 (*C*(6)), 58.5 (*C*(5)), 68.5 (*C*(1′)), 73.7 (*C*(3)), 74.8 (*C*(α)), 77.6 (*C*(2)), 81.8 (*C*(7a)), 85.7 (*C*(1)), 86.5 (*C*Me$_3$), 114.5 (*C*Me$_2$), 129.9, 131.0, 131.8, 133.0 (*Ph*), 169.0 (*C*(2′)); *m/z* (FI^+) 439 ($[M–C_8H_9]^+$, 100%); HRMS (FI^+) $C_{16}H_{26}INO_5^+$ ($[M–C_8H_9]^+$) requires 439.0850, found 439.0842.

(1*R*,2*S*,3*S*,4*R*,7*S*,7a*S*,1′*R*,α*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-*N*(4)-(α-methylbenzyl)-7-iodooctahydropyrolizinium polyiodide 182



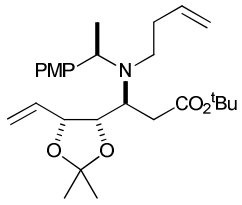
I_2 (36 mg, 0.14 mmol) was added to a stirred solution of **171** (20 mg, 0.05 mmol, >99:1 dr) in $CHCl_3$ (2 mL) at rt. The resultant mixture was stirred at rt for 12 h then concentrated *in vacuo* to give **178** as a dark pink oil (54 mg, >99:1 dr); δ_H (500 MHz, $CDCl_3$) 1.41 (3H, s, *Me*CMe), 1.60 (3H, s, *Me*CMe), 1.62 (9H, s, C*Me*$_3$), 2.08 (3H, d, *J* 6.6, C(α)*Me*), 2.52-2.57 (1H, m, C(6)H_A), 2.88-2.96 (1H, m, C(6)H_B), 3.85-3.89 (1H, m, C(5)H_A), 3.95 (1H, br s, O*H*), 4.19 (1H, app s, C(1′)*H*), 4.37-4.42 (1H, m, C(5)H_B), 4.48-4.49 (1H, m, C(3)*H*), 4.87 (2H, app d, *J* 5.0, C(7)*H*, C(1)*H*), 4.94-4.96 (1H, m, C(7a)*H*), 5.03-5.06 (1H, m, C(α)*H*), 5.33 (1H, app d, *J* 6.0, C(2)*H*), 7.55-7.61 (3H, m, *Ph*), 7.66-7.68 (2H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 20.1 (*C*(7)), 25.8, 27.9 (C*Me*$_2$), 28.2 (C*Me*$_3$), 37.7 (*C*(6)), 58.3 (*C*(5)), 68.2 (*C*(1′)), 75.0 (*C*(3)), 76.9, 77.0 (*C*(2), *C*(α)), 82.1 (*C*(7a)), 85.1 (*C*(1)), 86.9 (*C*Me$_3$), 114.4 (*C*Me$_2$), 130.3 (*m-Ph*), 130.9 (*o-Ph*), 131.6, 132.2 (*p-Ph*, *i-Ph*), 168.3 (*C*(2′)).

(*R*)-*N*-But-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amine 183



4-Bromobut-1-ene (13.4 mL, 132 mmol) was added to a stirred mixture of (*R*)-*N*-(α-methyl-*p*-methoxybenzyl)amine (50.0 g, 330 mmol, >99% ee) and K_2CO_3 (21.9 g, 158 mmol). The reaction mixture was heated at 50 °C for 12 h then allowed to cool to rt and partitioned between Et_2O (200 mL) and H_2O (200 mL). The aqueous layer was extracted with Et_2O (2 × 200 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 2:1) gave **183** as a yellow oil (19.8 g, 73%, >99% ee);17 $[\alpha]_D^{25}$ +39.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3324 (N−H), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.5, C(α)*Me*), 2.23 (2H, app q, *J* 6.1, C(2)H_2), 2.47-2.59 (2H, m, C(1)H_2), 3.73 (1H, q, *J* 6.5, C(α)*H*), 3.81 (3H, s, O*Me*), 5.00-5.10 (2H, m, C(4)H_2), 5.69-5.80 (1H, m, C(3)*H*), 6.87 (2H, d, *J* 8.5, *Ar*), 7.23 (2H, d, *J* 8.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 24.3 (C(α)*Me*), 34.3 (*C*(2)), 46.7 (*C*(1)), 55.2 (O*Me*), 57.5 (*C*(α)), 113.7 (*Ar*), 116.3 (*C*(4)), 127.5 (*Ar*), 136.6 (*C*(3)), 137.8, 158.5 (*Ar*); *m/z* (ESI^+) 206 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{20}NO^+$ ($[M+H]^+$) requires 206.1539; found 206.1539.

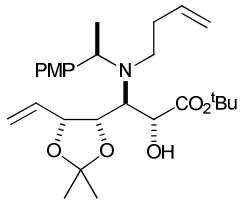
***tert*-Butyl (3*S*,4*S*,5*R*,α*R*)-3-[*N*-but-3′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 185**



BuLi (2.5 M in hexanes, 0.61 mL, 1.21 mmol) was added dropwise to a stirred solution of **183** (258 mg, 1.26 mmol) in THF (2.5 mL) at −78 °C. After stirring for 30 min at −78 °C a solution of (4*S*,5*R*,*E*)-**140** (200 mg, 0.79 mmol, >99:1 dr) in THF (2.5 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for a further 2 h, before satd aq NH_4Cl (2 mL) was added. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq

$NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **185** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 10:1) gave **185** as a yellow oil (239 mg, 66%, >99:1 dr); $C_{27}H_{41}NO_5$ requires C, 70.6; H, 9.0; N, 3.05; found C, 70.6; H, 8.9; N, 3.0; $[\alpha]_D^{25}$ −19.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2979, 2935 (C−H), 1728 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.36 (3H, d, *J* 6.7, C(α)*Me*), 1.44 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 2.03 (2H, q, *J* 7.1, C(2′)H_2), 2.23 (1H, dd, *J* 15.7, 5.6, C(2)H_A), 2.31 (1H, dd, *J* 15.7, 7.3, C(2)H_B), 2.49-2.56 (1H, m, C(1′)H_A), 2.59-2.66 (1H, m, C(1′)H_B), 3.61-3.65 (1H, m, C(3)*H*), 3.79 (3H, s, O*Me*), 3.97 (1H, q, *J* 6.7, C(α)*H*), 4.23-4.26 (1H, m, C(4)*H*), 4.59 (1H, app t, *J* 7.1, C(5)*H*), 4.89-4.93 (2H, m, C(4′)H_2), 5.30 (1H, app d, *J* 10.4, C(7)H_A), 5.36 (1H, app d, *J* 17.2, C(7)H_B), 5.61-5.71 (1H, m, C(3′)*H*), 5.90-5.98 (1H, m, C(6)*H*), 6.81 (2H, d, *J* 8.6, *Ar*), 7.24 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.1, 25.0 (C*Me*$_2$), 27.4 (C(α)*Me*), 28.1 (C*Me*$_3$), 34.8 (*C*(2′)), 36.2 (*C*(2)), 46.1 (*C*(1′)), 55.2 (*C*(3), O*Me*), 57.9 (*C*(α)), 78.7 (*C*(4)), 79.6 (*C*(5)), 79.8 (*C*Me$_3$), 108.0 (*C*Me$_2$), 113.2 (*Ar*), 115.2 (*C*(4′)), 118.8 (*C*(7)), 128.9 (*Ar*), 134.5 (*C*(6)), 136.7 (*Ar*), 137.1 (*C*(3′)), 158.4 (*Ar*), 171.8 (*C*(1)); *m/z* (ESI^+) 460 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{42}NO_5^+$ ($[M+H]^+$) requires 460.3057; found 460.3058.

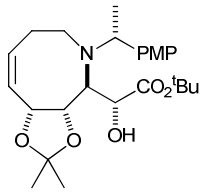
tert-Butyl (2*R*,3*S*,4*S*,5*R*,α*R*)-2-hydroxy-3-[*N*-but-3′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 186



BuLi (2.5 M in hexanes, 12.9 mL, 28.3 mmol) was added dropwise to a stirred solution of **183** (6.00 g, 29.2 mmol) in THF (30 mL) at −78 °C. After stirring for 30 min at −78 °C a solution of (4*S*,5*R*,*E*)-**140** (4.65 g, 18.3 mmol, >99:1 dr) in THF (25 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for a further 2 h, before addition of (−)-CSO **169** (8.38 g, 37.6 mmol). The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo* to give a mixture of **185** and **186**.18 Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:1) gave **185** as a colourless oil (670 mg, 8%, >99:1 dr). Further elution gave **186** as a yellow oil (5.61 g, 50%, >99:1 dr);

$C_{27}H_{41}NO_6$ requires C, 68.2; H, 8.7; N, 2.9%; found C, 68.3; H, 8.8; N, 2.8%; $[\alpha]_D^{25}$ −15.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3498 (O−H), 2980, 2934 (C−H), 1734 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.40 (3H, d, *J* 7.2, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.97-2.17 (2H, m, C(2′)H_2), 2.61-2.68 (1H, m, C(1′)H_A), 3.03 (1H, d, *J* 7.2, O*H*), 3.06-3.14 (1H, m, C(1′)H_B), 3.58 (1H, app d, *J* 10.0, C(3)*H*), 3.79 (3H, s, O*Me*), 3.97 (1H, app d, *J* 7.2, C(2)*H*), 4.08 (1H, q, *J* 7.2, C(α)*H*), 4.45 (1H, dd, *J* 10.0, 5.8, C(4)*H*), 4.60 (1H, app t, *J* 5.8, C(5)*H*), 4.93-4.99 (2H, m, C(4′)H_2), 5.24 (1H, app d, *J* 10.1, C(7)H_A), 5.35 (1H, app d, *J* 17.2, C(7)H_B), 5.65-5.75 (1H, m, C(3′)*H*), 5.86-5.95 (1H, m, C(6)*H*), 6.82 (2H, d, *J* 8.5, *Ar*), 7.28 (2H, d, *J* 8.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.3, 25.6 (C*Me*$_2$), 28.1 (C*Me*$_3$), 28.2 (C(α)*Me*), 34.9 (*C*(2′)), 45.8 (*C*(1′)), 55.2 (O*Me*), 58.4 (*C*(α)), 59.6 (*C*(3)), 72.0 (*C*(2)), 76.1 (*C*(4)), 79.2 (*C*(5)), 81.9 (*C*Me$_3$), 107.8 (*C*Me$_2$), 113.3 (*Ar*), 115.5 (*C*(7)), 118.4 (*C*(4′)), 129.3, 134.8 (*Ar*), 135.3, 137.1 (*C*(6), (*C*(3′)), 158.6 (*Ar*), 173.1 (*C*(1)); *m/z* (FI^+) 475 ($[M]^+$, 100%); HRMS (FI^+) $C_{27}H_{41}NO_6^+$ ($[M]^+$) requires 475.2928; found 475.2931.

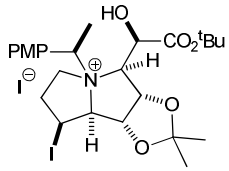
tert-Butyl (2*R*,2′*S*,3′*S*,4′*R*,α*R*,*Z*)-2-hydroxy-2-[*N*(1′)-(α-methyl-*p*-methoxybenzyl)-3′,4′-*O*-isopropylidine-3′,4′-dihydroxy-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate 187



Grubbs I catalyst (844 mg, 0.12 mmol) was added to a stirred solution of **186** (6.10 g, 12.8 mmol, >99:1 dr) in CH_2Cl_2 (1.0 L). The resultant mixture was stirred at rt for 12 h then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (200 mL) and **424** (1.49 g, 12.0 mmol), Et_3N (3.57 mL, 16.2 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for 12 h, then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 2:1) gave **187** as a pale yellow oil (4.18 g, 73%, >99:1 dr); $C_{25}H_{37}NO_6$ requires C, 67.1; H, 8.3; N, 3.1%; found C, 67.1; H, 8.2; N, 3.1%; $[\alpha]_D^{25}$ −10.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2980, 2934 (C−H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.50 (3H, d, *J* 7.1, C(α)*Me*), 2.03-2.20 (2H, m, C(7′)H_2), 2.73 (1H, app dd, *J* 14.2, 10.6, C(8′)H_A),

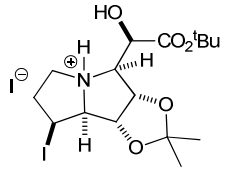
3.14 (1H, br s, C(8′)H_B), 3.18 (1H, d, *J* 5.7, O*H*), 3.76 (1H, app d, *J* 10.4, C(2′)*H*), 3.80 (3H, s, O*Me*), 4.30 (1H, app d, *J* 5.7, C(2)*H*), 4.65 (1H, dd, *J* 10.4, 5.7, C(3′)*H*), 4.79 (1H, q, *J* 7.1, C(α)*H*), 5.11 (1H, app t, *J* 5.7, C(4′)*H*), 5.64 (1H, dd, *J* 11.0, 5.7, C(5′)*H*), 5.87 (1H, app q, *J* 11.0, C(6′)*H*), 6.86 (2H, d, *J* 8.6, *Ar*), 7.32 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.1, 26.3 (C*Me*$_2$), 28.1 (C*Me*$_3$), 28.2 (C(α)*Me*), 32.4 (*C*(7′)), 47.5 (*C*(8′)), 54.0 (*C*(α)), 55.2 (O*Me*), 62.7 (*C*(2′)), 75.1 (*C*(2)), 76.8 (*C*(4′)), 78.7 (*C*(3′)), 82.1 (*C*Me$_3$), 109.8 (*C*Me$_2$), 113.5, 127.8 (*Ar*), 130.4, 133.7 (*C*(5′), *C*(6′)), 138.3, 157.9 (*Ar*), 172.6 (*C*(1)); *m/z* (FI$^+$) 447 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{25}H_{37}NO_6^+$ ([M]$^+$) requires 447.2615; found 447.2614.

(1*R*,2*S*,3*S*,4*R*,7*S*,7a*S*,1′*R*,α*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-*N*(4)-(α-methyl-*p*-methoxybenzyl)-7-iodooctahydropyrolizinium iodide 188



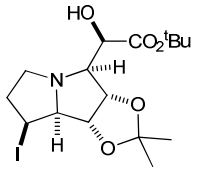
I_2 (34 mg, 0.13 mmol) was added to a solution of **187** (20 mg, 0.04 mmol, >99:1 dr) in $CDCl_3$ (0.6 mL) at rt. The reaction mixture was left for 5 min at rt and then analysed by NMR spectroscopy which revealed the presence of **188** in >99:1 dr; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 1.62 (9H, s, C*Me*$_3$), 2.01 (3H, d, *J* 6.6, C(α)*Me*), 2.43-2.48 (1H, m, C(6)H_A), 3.15-3.26 (1H, m, C(6)H_B), 3.79-3.84 (2H, m, C(5)H_A, C(1′)*H*), 3.86 (3H, s, O*Me*), 4.23-4.30 (1H, m, C(5)H_B), 4.44 (1H, app d, *J* 6.6, C(3)*H*), 4.82 (1H, app d, *J* 5.3, C(1)*H*), 5.08-5.14 (1H, m, C(7)*H*), 5.17-5.20 (1H, m, C(7a)*H*), 5.30 (1H, dd, *J* 5.3, 6.6, C(2)*H*), 5.43-5.51 (1H, m, C(α)*H*), 6.98 (2H, d, *J* 8.6, *Ar*), 7.61 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 17.0 (C(α)*Me*), 21.8 (*C*(7)), 25.5, 27.7 (C*Me*$_2$), 28.1 (C*Me*$_3$), 37.5 (*C*(6)), 55.3, 55.7 (*C*(1′), O*Me*), 57.8 (*C*(5)), 73.4 (*C*(3)), 75.9 (*C*(α)), 75.9 (*C*(2)), 81.4 (*C*(7a)), 85.3 (*C*(1)), 86.4 (*C*Me$_3$), 113.9 (*C*Me$_2$), 114.0, 114.9 (*Ar*), 123.0, 161.7 (*Ar*), 168.4 (*C*(2′).

(1*R*,2*S*,3*S*,4*S*,7*S*,7a*S*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-iodooctahydropyrolizinium iodide 189·HI[16]



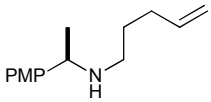
I_2 (4.25 g, 16.8 mmol) and $NaHCO_3$ (1.41 g, 16.8 mmol) were added sequentially to a stirred solution of **187** (2.50 g, 5.59 mmol, >99:1 dr) in CH_2Cl_2 (250 mL) at rt. The reaction mixture was stirred at rt for 12 h before $Na_2S_2O_3$ (excess) was added. After stirring at rt for 1 h the reaction mixture was filtered and concentrated *in vacuo* to give a pale brown solid. Purification via direct crystallisation from 30-40 °C petrol gave **189**·HI as a pale brown solid (2.49 g, 79%, >99:1 dr); $C_{16}H_{27}I_2NO_5$ requires C, 33.9; H, 4.8; N, 2.5%; found C, 33.6; H, 4.6; N, 2.4%; mp 164-167 °C (30-40 °C petrol); $[\alpha]_D^{25}$ –4.8 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2981, 2925 (C−H), 1727 (C=O); δ_H (500 MHz, $CDCl_3$) 1.35 (3H, s, *Me*CMe), 1.54 (9H, s, C*Me*$_3$), 1.58 (3H, s, *Me*CMe), 2.42-2.48 (1H, m, C(6)H_A), 2.71-2.78 (1H, m, C(6)H_B), 3.46-4.45 (5H, m, C(5)H_2, C(7a)*H*, C(1′)*H*, O*H*),19 4.55 (1H, br s, C(3)*H*), 4.63-4.67 (1H, m, C(7)*H*), 4.72 (1H, br s, C*H*), 5.06 (1H, app t, *J* 6.6, C*H*), 12.12 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) [selected peaks] 14.0 (*C*(7)), 22.3, 25.5 (C*Me*$_2$), 27.9 (C*Me*$_3$), 115.0 (*C*Me$_2$), 169.4 (*C*(2′));20 *m/z* (ESI$^+$) 462 ([M+Na]$^+$, 97%), 440 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{26}INNaO_5^+$ ([M+Na]$^+$) requires 462.0748; found 462.0748. Concentration of the mother liquors gave α-methyl-*p*-methoxybenzyl ethyl ether **193** as a brown oil (493 mg, 95%, 3% ee);21 $[\alpha]_D^{25}$ +10.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2974, 2930 (C−H); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.1, CH_2CH_3), 1.43 (3H, d, *J* 6.5, C(α)*Me*), 3.34 (2H, q, *J* 7.1, CH_2CH_3), 3.80 (3H, s, O*Me*), 4.37 (1H, q, *J* 6.5, C(α)*H*), 6.88 (2H, d, *J* 8.5, *Ar*), 7.24 (2H, d, *J* 8.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 11.5 (CH_2CH_3), 24.2 (C(α)*Me*), 55.2 (O*Me*), 64.8 (CH_2CH_3), 77.2 (*C*(α)), 113.7, 127.4, 136.3, 158.9 (*Ar*); *m/z* (FI$^+$) 180 ([M+H]$^+$, 100%); HRMS (FI$^+$) $C_{11}H_{16}O_2^+$ ([M]$^+$) requires 180.1145; found 180.1158.

(1*R*,2*S*,3*S*,7*S*,7a*S*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-iodohexahydro-1*H*-pyrrolizine 189



189·HI (500 mg, 0.88 mmol, >99:1 dr) was dissolved in $CHCl_3$/^{i}PrOH (v/v 3:1, 4 mL). The resultant solution was washed with 2.0 M aq NaOH (2 × 2 mL), then dried and concentrated *in vacuo* to give **189** as a pink oil which darkened on standing (385 mg, quant); $[\alpha]_D^{25}$ +23.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2979, 2933 (C−H), 1728 (C=O); δ_H (500 MHz, $CDCl_3$) 1.31 (3H, s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 1.53 (9H, s, C*Me*$_3$), 2.53-2.63 (3H, m, C(3)*H*, C(5)H_A, C(6)H_A), 2.78-2.87 (1H, m, C(6)H_B), 3.15-3.21 (1H, m, C(5)H_B), 3.23-3.32 (2H, m, C(1′)*H*, O*H*), 4.33-4.36 (2H, m, 2 × C*H*), 4.48-4.47 (1H, m, C(7)*H*), 4.90 (1H, dd, *J* 6.8, 4.8, C*H*); δ_C (125 MHz, $CDCl_3$) 24.4 (*C*(7)), 25.3, 27.3 (C*Me*$_2$), 28.0 (C*Me*$_3$), 40.0 (*C*(6)), 45.7 (*C*(5)), 68.6 (*C*(1′)), 69.8 (*C*H), 76.0 (*C*(3)), 77.2 (*C*Me$_3$), 83.4 (*C*H), 83.6 (*C*H), 113.9 (*C*Me$_2$), 171.3 (*C*(2′); *m/z* (ESI$^+$) 440 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{27}INO_5^+$ ([M+H]$^+$) requires 440.0928; found 440.0933.

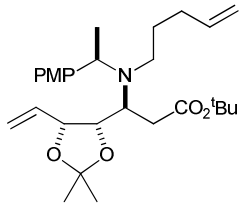
(*R*)-*N*-Pent-4-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amine 205



5-Brompent-1-ene (15.7 mL, 132 mmol) was added to a stirred mixture of (*R*)-*N*-(α-methyl-*p*-methoxybenzyl)amine (50.0 g, 330 mmol, >99% ee) and K_2CO_3 (21.9 g, 158 mmol). The resultant mixture was heated at 50 °C for 12 h then cooled to rt and partitioned between Et_2O (200 mL) and H_2O (200 mL). The aqueous layer was extracted with Et_2O (2 × 200 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 5:1:0.1) gave **205** as a yellow oil (24.0 g, 83%, >99% ee);22 $[\alpha]_D^{25}$ +53.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3325 (N−H), 2959, 2929 (C−H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.6, C(α)*Me*), 1.46 (1H, br s, N*H*), 1.51-1.60 (2H, m, C(2)H_2), 2.03-2.09 (2H, m, C(3)H_2), 2.40-2.56 (2H, m, C(1)H_2), 3.72 (1H, q, *J* 6.6, C(α)*H*), 3.80 (3H, s, O*Me*), 4.93 (1H, dd, *J* 17.2, 1.2, C(5)H_A), 4.99 (1H, dd, *J* 10.1, 1.2, C(5)H_B), 5.74-5.84 (1H, m, C(4)*H*), 6.87 (2H, d, *J* 8.6, *Ar*), 7.23 (2H, d, *J* 8.6, *Ar*);

δ_C (100 MHz, $CDCl_3$) 24.3 (C(α)*Me*), 29.4 (*C*(2)), 31.6 (*C*(3)), 47.2 (*C*(1)), 55.2 (O*Me*), 57.6 (*C*(α)), 113.7 (*Ar*), 114.5 (*C*(5)), 127.5, 138.0 (*Ar*), 138.5 (*C*(4)), 158.5 (*Ar*); *m/z* (ESI^+) 220 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{22}NO^+$ ($[M+H]^+$) requires 220.1696; found 220.1696.

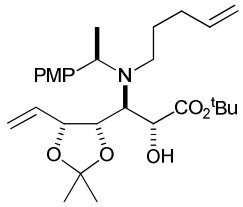
tert-Butyl (3*S*,4*S*,5*R*,α*R*)-3-[*N*-pent-4′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 208



BuLi (2.5 M in hexanes, 1.22 mL, 3.05 mmol) was added dropwise to a stirred solution of **205** (690 mg, 3.14 mmol) in THF (3 mL) at −78 °C. After stirring at −78 °C for 30 min a solution of (4*S*,5*R*,*E*)-**140** (500 mg, 1.97 mmol, >99:1 dr) in THF (2 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for a further 2 h, before satd aq NH_4Cl (3 mL) was added. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (15 mL) and 10% aq citric acid solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (25 mL), H_2O (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give **208** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 10:1) gave **208** as a colourless oil (472 mg, 51%, >99:1 dr); $[\alpha]_D^{25}$ −13.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2979, 2934 (C−H), 1730 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 1.44-1.47 (14H, m, C*Me*$_3$, *Me*CMe, C(2′)H_2), 1.89 (2H, app quintet, *J* 6.8, C(3′)H_2), 2.20 (1H, dd, *J* 15.7, 5.6, C(2)H_A), 2.30 (1H, dd, *J* 15.7, 7.1, C(2)H_B), 2.43-2.57 (2H, m, C(1′)H_2), 3.59-3.66 (1H, m, C(3)*H*), 3.79 (3H, s, O*Me*), 3.96 (1H, q, *J* 6.8, C(α)*H*), 4.25 (1H, dd, *J* 6.1, 4.5, C(4)*H*), 4.59 (1H, app t, *J* 4.5, C(5)*H*), 4.88-4.95 (2H, m, C(5′)H_2), 5.29-5.88 (2H, m, C(7)H_2), 5.65-5.76 (1H, m, C(4′)*H*), 5.90-6.00 (1H, m, C(6)*H*), 6.81 (2H, d, *J* 8.6, *Ar*), 7.24 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.0 (*Me*CMe), 25.0 (C(α)*Me*), 27.4 (*Me*CMe), 28.1 (C*Me*$_3$), 29.1, 31.3 (*C*(2′), *C*(3′)), 36.1 (*C*(2)), 45.6 (*C*(1′)), 55.0 (*C*(3)), 55.2 (O*Me*), 57.6 (*C*(α)), 78.7, 79.7 (*C*(4), *C*(5)), 79.8 (*C*Me$_3$), 108.0 (*C*Me$_2$), 113.2 (*Ar*), 114.2 (*C*(5′)), 118.8 (*C*(7)), 128.9 (*Ar*),

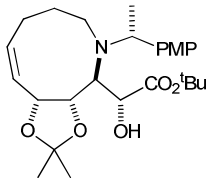
134.6, 138.8 (*C*(6), *C*(4′)), 136.7, 158.3 (*Ar*), 171.8 (*C*(1)); *m/z* (ESI$^+$) 474 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{44}NO_5^+$ ([M+H]$^+$) requires 474.3214; found 474.3202.

tert-Butyl (2*R*,3*S*,4*S*,5*R*,α*R*)-2-hydroxy-3-[*N*-pent-4′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 209



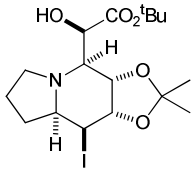
BuLi (2.5 M in hexanes, 2.44 mL, 6.09 mmol) was added dropwise to a stirred solution of **205** (1.38 g, 6.29 mmol) in THF (5 mL) at −78 °C. After stirring at −78 °C for 30 min a solution of (4*S*,5*R*,*E*)-**140** (1.00 g, 3.93 mmol, >99:1 dr) in THF (5 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for a further 2 h, before (−)-CSO **169** (1.80 g, 7.86 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo* to give a mixture of **208** and **209**.23 Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:1 increased to 30-40 °C petrol/EtOAc, 25:1) gave **208** as a colourless oil (279 mg, 15%, >99:1 dr). Further elution gave **209** as a colourless oil (677 mg, 35%, >99:1 dr); $[\alpha]_D^{25}$ −12.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3499 (O−H), 2980, 2933 (C−H), 1730 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.47-1.49 (2H, m, C(2′)H_2), 1.49 (9H, s, CMe_3), 1.90-2.05 (2H, m, C(3′)H_2), 2.53-2.60 (1H, m, C(1′)H_A), 2.98-3.06 (2H, m, C(1′)H_B, O*H*), 3.60 (1H, app d, *J* 10.0, C(3)*H*), 3.79 (3H, s, O*Me*), 3.94 (1H, app d, *J* 6.7, C(2)*H*), 4.05 (1H, q, *J* 6.8, C(α)*H*), 4.45 (1H, dd, *J* 10.0, 5.7, C(4)*H*), 4.59 (1H, app t, *J* 5.7, C(5)*H*), 4.93 (1H, app d, *J* 9.1, C(5′)H_A), 4.98 (1H, app d, *J* 17.2, C(5′)H_B), 5.24 (1H, app d, *J* 11.1, C(7)H_A), 5.36 (1H, app d, *J* 17.2, C(7)H_B), 5.72-5.82 (1H, m, C(4′)*H*), 5.86-5.95 (1H, m, C(6)*H*), 6.82 (2H, d, *J* 8.6, *Ar*), 7.26 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.6, 25.6 (CMe_2), 28.1 (CMe_3), 28.2 (C(α)*Me*), 29.5, 31.4 (*C*(2′), *C*(3′)), 45.6 (*C*(1′)), 55.2 (O*Me*), 58.3 (*C*(α)), 59.4 (*C*(3)), 71.8 (*C*(2)), 76.1 (*C*(4)), 79.2 (*C*(5)), 81.9 (*C*Me$_3$), 107.8 (*C*Me$_2$), 113.2 (*Ar*), 114.4 (*C*(5′)), 118.4 (*C*(7)), 129.4, 134.7 (*Ar*), 135.3, 138.8 (*C*(6), *C*(4′)), 158.6 (*Ar*), 173.1 (*C*(1)); *m/z* (ESI)$^+$ 512 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{44}NO_6^+$ ([M+H]$^+$) requires 490.3163; found 490.3168.

tert-Butyl (2*R*,2′*S*,3′*S*,4′*R*,α*R*,*Z*)-2-hydroxy-2-[*N*(1′)-(α-methyl-*p*-methoxybenzyl)-3′,4′-*O*-isopropylidine-3′,4′-dihydroxy-2′,3′,4′,7′,8′,9′-hexahydro-1*H*-azonin-2′-yl]ethanoate 210



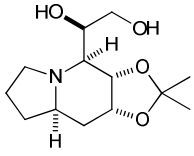
Grubbs I catalyst (129 mg, 0.16 mmol) was added to a stirred solution of **209** (385 mg, 0.79 mmol, >99:1 dr) in CH_2Cl_2 (40 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and **424** (1.95 g, 16.0 mmol), Et_3N (0.22 mL, 1.57 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for 12 h, then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **210** as a pale yellow oil (264 mg, 73%, >99:1 dr); $[\alpha]_D^{25}$ +18.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2980, 2933 (C–H), 1730 (C=O), 1650 (C=C); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.48 (3H, d, *J* 7.6, C(α)*Me*), 1.64 (1H, br s, C(8′)H_A), 1.74-1.82 (1H, m, C(8′)H_B), 1.96-2.00 (1H, m, C(7′)H_A), 2.24-2.33 (1H, m, C(9′)H_A), 2.51-2.61 (1H, m, C(7′)H_B), 2.94-3.00 (1H, m, C(9′)H_B), 3.27 (1H, d, *J* 6.6, O*H*), 3.38 (1H, app d, *J* 10.5, C(2′)*H*), 3.81 (3H, s, O*Me*), 4.30 (1H, app d, *J* 6.6, C(2)*H*), 4.59 (1H, dd, *J* 10.5, 6.6, C(3′)*H*), 4.79 (1H, q, *J* 7.6, C(α)*H*), 5.23 (1H, app t, *J* 6.6, C(4′)*H*), 5.43 (1H, dd, *J* 11.1, 6.6, C(5′)*H*), 5.59 (1H, dt, *J* 11.1, 5.8, C(6′)*H*), 6.87 (2H, d, *J* 8.5, *Ar*), 7.43 (2H, d, *J* 8.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.9 (*Me*CMe), 24.0 (*C*H_2), 26.0 (*Me*CMe), 28.0 (C*Me*$_3$), 28.4 (C(α)*Me*), 29.7 (*C*H_2), 50.1 (*C*(9′)), 53.6 (*C*(α)), 55.2 (O*Me*), 69.2 (*C*(2′)), 73.6 (*C*(2)), 76.0 (*C*(4′)), 76.6 (*C*(3′)), 82.0 (*C*Me$_3$), 109.1 (*C*Me$_2$), 113.3, 129.4 (*Ar*), 130.7, 132.3 (*C*(5′), *C*(6′)), 134.7, 158.3 (*Ar*), 173.0 (*C*(1)); *m/z* $(ESI)^+$ 484 ($[M+Na]^+$, 100%), 462 ($[M+H]^+$, 35%); HRMS (ESI^+) $C_{26}H_{39}NNaO_6^+$ ($[M+Na]^+$) requires 484.2670; found 484.2664.

(5*S*,6*S*,7*S*,8*S*,8a*R*,1′*R*)-6,7-*O*-Isopropylidene-6,7-dihydroxy-5-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-8- iodohexahydro-1*H*-pyrrolizine 212



I_2 (4.95 g, 19.5 mmol) and $NaHCO_3$ (1.64 g, 19.5 mmol) were added sequentially to a stirred solution of **210** (3.0 g, 6.5 mmol, >99:1 dr) in CH_2Cl_2 (300 mL). The reaction mixture was stirred at rt for 12 h before $Na_2S_2O_3$ (excess) was added. After stirring at rt for 1 h the reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (150 mL) and the resultant solution was washed with 2.0 M aq NaOH (2 × 150 mL). The combined aqueous layers were extracted with $CHCl_3$ (2 × 150 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 2:1) gave **212** as a brown oil (1.70 g, 58%, >99:1 dr); $[\alpha]_D^{25}$ −6.5 (*c* 0.76 in MeOH); ν_{max} (film) 3251 (O−H), 2981, 2935 (C−H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 1.52 (9H, s, C*Me*$_3$), 1.54-1.61 (1H, m, C(1)H_A), 1.65-1.71 (1H, m, C(8a)*H*), 1,72-1.81 (3H, m, C(1)H_B, C(2)H_2), 2.34 (1H, app q, *J* 7.1, C(3)H_A), 2.69 (1H, app d, *J* 7.3, C(5)*H*), 3.15 (1H, br s, O*H*), 3.18-3.23 (1H, m, C(3)H_B), 4.32 (1H, br s, C(1′)*H*), 4.63 (1H, br s, C(8)*H*), 4.68-4.73 (2H, m, C(6)*H*, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 21.9 (*C*(8)), 26.8 (*Me*CMe), 28.0 (C*Me*$_3$), 28.5 (*Me*CMe), 31.4 (*C*(2)), 35.7 (*C*(1)), 51.5 (*C*(3)), 60.4 (*C*(8a)), 69.5, 70.1, 70.5, 79.5 (*C*(5), *C*(6), *C*(7), *C*(1′)), 82.9 (*C*Me$_3$), 110.1 (*C*Me$_2$), 171.9 (*C*(2′)); *m/z* (ESI)$^+$ 929 ([2M+Na]$^+$, 100%), 476 ([M+Na]$^+$, 70%), 454 ([M+H]$^+$, 70%); HRMS (ESI$^+$) $C_{17}H_{29}INO_5^+$ ([M+H]$^+$) requires 454.1085; found 454.1068.

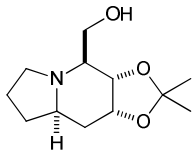
(5*S*,6*S*,7*R*,8a*R*,1′*R*)-6,7-*O*-Isopropylidene-6,7-dihydroxy-5-(1′,2′-dihydroxyethyl) octahydro-1*H*-indolizine 213



$LiAlH_4$ (1.0 M in THF, 10.2 mL, 10.2 mmol) was added to a stirred solution of **212** (1.16 g, 2.56 mmol, >99:1 dr) in THF (100 mL) at −78 °C. The resultant mixture was allowed to

warm to rt over 12 h before 2.0 M aq NaOH (10 mL) was added. The resultant mixture was left to stir for 1 h, then filtered through Celite® (eluent EtOAc), dried and concentrated in *vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 10:1) gave **213** as a colourless oil (273 mg, 41%, >99:1 dr); $[\alpha]_D^{25}$ −31.3 (*c* 0.08 in $CHCl_3$); ν_{max} (film) 3386 (O−H), 2981, 2927 (C−H); δ_H (500 MHz, MeOH-d_4) [selected peaks] 1.37 (3H, s, *Me*CMe), 1.51 (3H, s, *Me*CMe), 1.60-1.69 (1H, m, C(1)H_A), 1.90-2.11 (3H, m, C(2)H_2, C(8)H_A), 2.16-2.22 (1H, m, C(1)H_B), 2.43 (1H, app d, *J* 15.1, C(8)H_B), 2.94 (1H, br s, C(3)H_A), 3.56-3.60 (1H, m, C(3)H_B), 3.68-3.69 (2H, m, C(2′)H_2), 4.08-4.11 (1H, m, C(1′)*H*), 4.42-4.45 (1H, m, C(6)*H*), 4.48 (1H, br s, C(7)*H*); δ_C (125 MHz, MeOH-d_4) [selected peaks] 21.7 (*C*(2)), 26.4, 28.3 (C*Me*$_2$), 29.7, 30.6 (*C*(1), *C*(8)), 52.3 (*C*(3)), 64.8 (*C*(2′)), 71.3, 71.8 (*C*(6), *C*(1′)), 73.8 (*C*(7)), 110.6 (*C*Me$_2$); *m/z* (ESI)$^+$ 258 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{24}NO_4^+$ ([M+H]$^+$) requires 258.1700; found 258.1700.

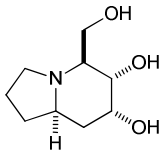
(5*S*,6*S*,7*R*,8a*R*)-6,7-*O*-Isopropylidene-6,7-dihydroxy-5-(hydroxymethyl)octahydro-1*H*-indolizine 214



$NaIO_4$ (831 mg, 1.94 mmol) was added to a solution of **213** (50 mg, 0.19 mmol, >99:1 dr) in MeOH/H_2O (v/v 5:1, 3 mL). The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (147 mg, 1.94 mmol) was then added to the filtrate and the resultant mixture was allowed to stir at rt for 12 h before satd aq NH_4Cl (0.5 mL) was added. The resultant mixture was filtered through Celite® (eluent EtOAc/MeOH, 3:1) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 10:1 increased to CH_2Cl_2/MeOH, 5:1) gave **214** as a light brown oil (17 mg, 40%, >99:1 dr); $[\alpha]_D^{25}$ −41.3 (*c* 0.87 in MeOH); δ_H (500 MHz, MeOH-d_4) 1.33-1.43 (1H, m, C(1)H_A) overlapping 1.36 (3H, s, *Me*CMe), 1.47 (3H, s, *Me*CMe), 1.65-1.72 (1H, m, C(8)H_A), 1.80-1.07 (2H, m, C(2)H_2), 1.91-1.99 (1H, m, C(1)H_B), 2.15-2.19 (1H, m, C(5)*H*), 2.21-2.30 (2H, m, C(3)H_A, C(8)H_B), 2.40-2.47 (1H, m, C(8a)*H*), 3.25-3.30 (1H, m, C(3)H_B), 3.68 (1H, dd, *J* 12.8, 3.8, C(1′)H_A), 3.85 (1H, dd, *J* 12.8, 2.5, C(1′)H_B), 4.03 (1H, dd, *J* 9.1, 4.7, C(6)*H*), 4.37-4.40 (1H, m, C(7)*H*); δ_C (125 MHz, $CDCl_3$) 22.5 (*C*(2)), 26.5, 28.55

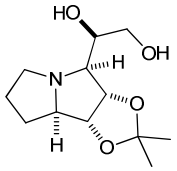
(C*Me*$_2$), 30.6 (*C*(1)), 32.6 (*C*(8)), 52.4 (*C*(3)), 60.5 (*C*(8a)), 61.4 (*C*(1′)), 68.6 (*C*(5)) 74.4 (*C*(6), *C*(7)), 109.8 (*C*Me$_2$); *m/z* (ESI)$^+$ 250 ([M+Na]$^+$, 20%), 228 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_3^+$ ([M+H]$^+$) requires 228.1594; found 228.1589.

(5*S*,6*S*,7*R*,8a*R*)-6,7-Dihydroxy-5-(hydroxymethyl)hexahydro-1*H*-indolizine 215



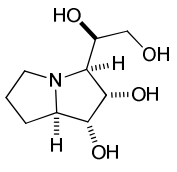
$NaIO_4$ (1.66 g, 7.77 mmol) was added to a solution of **214** (200 mg, 0.78 mmol, >99:1 dr) in MeOH/H_2O (v/v 5:1, 3 mL). The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (294 mg, 7.77 mmol) was then added to the filtrate and the resultant mixture was allowed to stir at rt for 12 h before satd aq NH_4Cl (1 mL) was added. The resultant mixture was filtered through Celite® (eluent EtOAc/MeOH, 3:1) and concentrated *in vacuo*. The residue was then dissolved in 3.0 M aq HCl/MeOH (v/v 2:1, 5 mL) and the resultant solution was heated at reflux for 2 h, then allowed to cool to rt and concentrated *in vacuo*. Purification on DOWEX 1X8-200 (OH^- form) ion exchange resin gave **215** as a colourless oil (124 mg, 85%, >99:1 dr); $[\alpha]_D^{25}$ −14.8 (*c* 0.93 in MeOH); δ_H (400 MHz, MeOH-d_4) 1.28-1.40 (1H, m, C(1)H_A), 1.44-1.51 (1H, m, C(8)H_A), 1.76-1.86 (3H, m, C(1)H_B, C(2)H_2), 1.97 (1H, app dt, *J* 13.9, 3.0, C(8)H_B), 2.15-2.24 (1H, m, C(3)H_A), 2.35 (1H, dt, *J* 9.9, 3.3, C(5)*H*), 2.49-2.57 (1H, m, C(8a)*H*), 3.21-3.27 (1H, m, C(3)H_B), 3.61 (1H, dd, *J* 9.9, 3.0, C(6)*H*), 3.84 (2H, app dd, *J* 3.3, 1.8, C(1′)H_2), 3.99 (1H, app q, *J* 3.0, C(7)*H*); δ_C (100 MHz, MeOH-d_4) 21.5 (*C*(2)), 29.4 (*C*(1)), 35.5 (*C*(8)), 51.0 (*C*(3)), 58.0 (*C*(8a)), 60.8 (*C*(1′)), 64.3 (*C*(5)), 68.4 (*C*(7)), 70.1 (*C*(6)); *m/z* (ESI)$^+$ 210 ([M+Na]$^+$, 25%), 188 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO_3^+$ ([M+H]$^+$) requires 188.1281; found 188.1279.

(1*R*,2*S*,3*S*,7a*R*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′,2′-dihydroxyethyl) hexahydro-1*H*-pyrrolizine 217



$LiAlH_4$ (1.0 M in THF, 7.06 mL, 7.06 mmol) was added to a stirred solution of **189**·HI (1.00 g, 1.77 mmol, >99:1 dr) in THF (50 mL) at −78 °C. The resultant mixture was allowed to warm to rt over 12 h before 2.0 M aq NaOH (2 mL) was added. The resultant mixture was left to stir at rt for a further 1 h, then filtered through Celite® (eluent EtOAc), dried and concentrated in *vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 2:1) gave **217** as a pale yellow oil (376 mg, 87%, >99:1 dr); $[\alpha]_D^{25}$ −25.9 (*c* 1.1 in MeOH); ν_{max} (film) 3384 (O−H), 2937 (C−H); δ_H (400 MHz, MeOH-d_4) 1.32 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 1.74-1.84 (2H, m, C(6)H_A, C(7)H_A), 1.91-2.0 (1H, m, C(6)H_B), 2.10-2.20 (1H, m, C(7)H_B), 2.79-2.85 (2H, m, C(5)H_2), 3.12 (1H, dd, *J* 6.7, 5.1, C(3)*H*), 3.41-3.46 (1H, m, C(7a)*H*), 3.56 (1H, dd, *J* 11.3, 7.1, C(2′)H_A), 3.66 (1H, dd, *J* 11.3, 4.8, C(2′)H_B), 3.90-3.95 (1H, m, C(1′)*H*), 4.45 (1H, dd, *J* 6.7, 3.8, C(1)*H*), 4.94 (1H, app t, *J* 6.7, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 24.5 (*Me*CMe), 25.7 (*C*(6)), 26.8 (*Me*CMe), 28.3 (*C*(7)), 48.3 (*C*(5)), 64.9 (*C*(2′)), 68.4 (*C*(3)), 70.4 (*C*(7a)), 70.8 (*C*(1′)), 81.6 (*C*(2)), 86.6 (*C*(1)), 113.9 (CMe_2); *m/z* (ESI^+) 509 ($[2M+Na]^+$, 100%), 266 ($[M+Na]^+$, 80%), 244 ($[M+H]^+$, 85%); HRMS (ESI^+) $C_{12}H_{22}NO_4^+$ ($[M+H]^+$) requires 244.1543; found 244.1543.

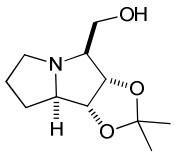
(1*R*,2*S*,3*S*,7a*R*,1′*R*)-1,2-Dihydroxy-3-(1′,2′-dihydroxyethyl)hexahydro-1H-pyrrolizidine 219



3.0 M aq HCl (0.5 mL) was added to a stirred solution of **217** (35 mg, 0.14 mmol, >99:1 dr) in MeOH (1 mL). The reaction mixture was heated at reflux for 2 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in H_2O (1 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **219** as a colourless oil (23 mg, 79%, >99:1 dr); $[\alpha]_D^{25}$ −5.5 (*c* 0.3 in MeOH); δ_H (500 MHz, MeOH-d_4) 1.54-1.61 (1H, m,

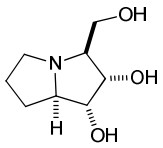
C(7)H_A), 1.69-1.79 (1H, m, C(6)H_A), 1.90-1.97 (1H, m, C(6)H_B), 2.12-2.19 (1H, m, C(7)H_B), 2.83-2.87 (1H, m, C(5)H_A), 2.98 (1H, td, *J* 9.8, 6.0, C(5)H_B), 3.13 (1H, dd, *J* 8.2, 3.8, C(3)*H*), 3.37-3.41 (1H, m, C(7a)*H*), 3.64 (1H, dd, *J* 11.4, 6.6, C(2′)H_A), 3.72 (1H, dd, *J* 11.4, 4.4, C(2′)H_B), 3.80 (1H, dd, *J* 5.5, 3.2, C(1)*H*), 4.01-4.05 (1H, m, C(1′)*H*), 4.26 (1H, dd, *J* 8.2, 5.5, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 27.4 (*C*(6)), 30.6 (*C*(7)), 49.9 (*C*(5)), 66.2, 66.4 (*C*(3)), *C*(2′)), 71.7 (*C*(7a)), 72.0 (*C*(2), *C*(1′)), 77.0 (*C*(1)); *m/z* (ESI^+) 204 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{18}NO_4^+$ ($[M+H]^+$) requires 204.1230; found 204.1227.

(1*R*,2*S*,3*S*,7a*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxymethyl)hexahydro-1*H*-pyrrolizine 218



$NaIO_4$ (695 mg, 3.25 mmol) was added to a stirred solution of **217** (79 mg, 0.32 mmol, >99:1 dr) in MeOH/H_2O (v/v 5:1, 3 mL). The reaction mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (123 mg, 3.25 mmol) was then added to the filtrate and the resultant mixture was allowed to stir at rt for 12 h before satd aq NH_4Cl (0.5 mL) was added. The resultant mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 20:1) gave **218** as a yellow oil (61 mg, 88%, >99:1 dr); $[\alpha]_D^{25}$ −45.0 (*c* 0.1 in MeOH); ν_{max} (film) 3388 (O−H), 2917 (C−H); δ_H (400 MHz, MeOH-d_4) 1.36 (3H, s, *Me*CMe), 1.57 (3H, s, *Me*CMe), 1.19-2.13 (2H, m, C(6)H_A, C(7)H_A), 2.20-2.28 (1H, m, C(6)H_B), 2.37-2.45 (1H, m, C(7)H_B), 3.39-3.46 (1H, m, C(5)H_A), 3.50-3.55 (1H, m, C(5)H_B), 3.82-4.01 (3H, m, C(3)*H*, C(1′)H_2), 4.26-4.31 (1H, m, C(7a)*H*), 4.73 (1H, dd, *J* 5.6, 2.3, C(1)*H*), 4.85-4.91 (1H, m, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 24.5 (*Me*CMe), 25.6 (*C*(6)), 26.8 (*Me*CMe)), 28.3 (*C*(7)), 49.2 (*C*(5)), 57.4 (*C*(1′)), 69.2 (*C*(3)), 72.4 (*C*(7a)), 80.6 (*C*(2)), 83.3 (*C*(1)), 114.2 (*C*Me_2); *m/z* (ESI^+) 214 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{11}H_{20}NO_3^+$ ($[M+H]^+$) requires 214.1438; found 214.1437.

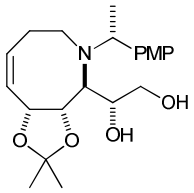
(1*R*,2*S*,3*S*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizidine [(–)-7a-*epi*-hyacinthacine A1] 216[24]



3.0 M aq HCl (1 mL) was added to a stirred solution of **218** (17 mg, 0.08 mmol, >99:1 dr) in MeOH (2 mL). The resultant mixture was heated at reflux for 2 h then allowed to cool to rt and concentrated *in vacuo*. The residue was diluted with H_2O (2 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **216** as a colourless oil (11 mg, 83%, >99:1 dr); $[\alpha]_D^{25}$ –45.9 (*c* 0.2 in H_2O); {lit.[24d] $[\alpha]_D^{22}$ –45.3 (*c* 1.5 in H_2O); lit.[24b] for *ent*-**416** $[\alpha]_D^{27}$ +47.0 (*c* 0.65 in H_2O); lit.[24c] for *ent*-**416** $[\alpha]_D^{30}$ +56.5 (*c* 0.21 in H_2O)}; δ_H (500 MHz, MeOH-d_4) 1.50-1.58 (1H, m, C(7)H_A), 1.69-1.70 (1H, m, C(6)H_A), 1.89-1.95 (1H, m, C(6)H_B), 2.16-2.22 (1H, m, C(7)H_B), 2.86 (1H, td, *J* 10.1, 6.0, C(5)H_A), 2.97-3.01 (1H, m, C(5)H_B), 3.29 (1H, td, *J* 8.8, 4.1, C(3)*H*), 3.47 (1H, td, *J* 8.2, 2.3, C(7a)*H*), 3.81 (1H, dd, *J* 5.3, 2.3, C(1)*H*), 3.84-3.91 (2H, m, C(1′)H_2), 3.93 (1H, dd, *J* 8.8, 5.3, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 27.3 (*C*(6)), 30.9 (*C*(7)), 46.5 (*C*(5)), 60.9 (*C*(1′)), 66.9 (*C*(3)), 71.7 (*C*(7a)), 72.4 (*C*(2)), 77.0 (*C*(1)); *m*/*z* $(ESI)^+$ 174 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_3^+$ ($[M+H]^+$) requires 174.1125; found 174.1129.

6.3 Experimental data for Chapter 3

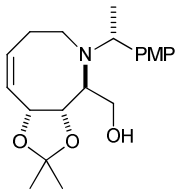
(2*S*,3*S*,4*R*,1′*R*,α*R*,*Z*)-*N*(1)-(α-methyl-*p*-methoxybenzyl)-2-(1′,2′-dihydroxyethyl)-3,4-*O*-isopropylidine-3,4-dihydroxy-1,2,3,4,7,8-hexahydroazocine 226



$LiAlH_4$ (1.0 M in THF, 0.52 mL, 0.52 mmol) was added to a stirred solution of **187** (118 mg, 0.26 mmol) in THF (10 mL) at −78 °C. The resultant mixture was allowed to warm to rt over 12 h before 2.0 M aq NaOH (1 mL) was added. The resultant mixture was stirred at rt for 1 h then filtered through Celite® (eluent EtOAc), dried and concentrated in *vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 20:1) gave **226** as a white oil (91 mg, 89%, >99:1 dr); $[\alpha]_D^{25}$ +44.9 (*c* 0.2 in MeOH); ν_{max} (film) 3356 (O–H), 2933 (C–H), 1609

(C=C); δ_H (400 MHz, $CDCl_3$) 1.46 (3H, s, *Me*CMe), 1.49 (3H, d, *J* 6.8, C(α)Me), 1.53 (3H, s, *Me*CMe), 1.66 (1H, br s, O*H*), 2.01-2.08 (1H, m, C(7)H_A), 2.21-2.29 (1H, m, C(7)H_B), 2.33 (1H, br s, O*H*), 2.77 (1H, app dd, *J* 14.9, 11.1, C(8)H_A), 3.29-3.35 (2H, m, C(2)*H*, C(8)H_B), 3.49-3.54 (2H, m, C(2′)H_2), 3.80 (3H, s, O*Me*), 3.80-3.84 (1H, m, C(1′)*H*), 4.33 (1H, q, *J* 6.8, C(α)*H*), 4.63 (1H, dd, *J* 10.4, 5.3, C(3)*H*), 5.24-5.27 (1H, m, C(4)*H*), 5.59-5.64 (1H, m, C(5)*H*), 5.89-5.96 (1H, m, C(6)*H*), 6.85 (2H, d, *J* 8.6, *Ar*), 7.20 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 23.0 (C(α)*Me*), 26.7, 28.1 (CMe_2), 31.1 (*C*(7)), 48.4 (*C*(8)), 55.0 (*C*(α)), 55.2 (O*Me*), 61.2 (*C*(2)), 64.8 (*C*(2′)), 73.9 (*C*(1′)), 77.8 (*C*(4)), 80.8 (*C*(3)), 110.2 (*C*Me_2), 113.7, 127.9 (*Ar*), 131.2 (*C*(6)), 132.7 (*C*(5)), 137.7, 158.2 (*Ar*); *m/z* (ESI^+) 777 ($[2M+Na]^+$, 100%), 400 ($[M+Na]^+$, 30%); HRMS (ESI^+) $C_{21}H_{31}NNaO_5^+$ ($[M+Na]^+$) requires 400.2094; found 400.2094.

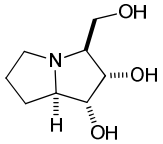
(2*S*,3*S*,4*R*,α*R*,*Z*)-*N*(1′)-(α-methyl-*p*-methoxybenzyl)-2-(hydroxymethyl)-3,4-*O*-isopropylidine-3,4-dihydroxy-1′,2′,3′,4′,7′,8′-hexahydroazocine 227



$NaIO_4$ (2.63 g, 12.3 mmol) was added to a solution of **226** (464 mg, 1.23 mmol) in MeOH (10 mL). The resultant mixture was stirred at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (465 mg, 12.3 mmol) was then added to the filtrate and the reaction mixture was allowed to stir at rt for 4 h before satd aq NH_4Cl (1 mL) was added. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography gave **227** as a colourless oil (66 mg, 15%, >99:1 dr); $[\alpha]_D^{25}$ +2.81 (*c* 0.96 in MeOH); ν_{max} (film) 3463 (O−H), 2970, 2937 (C−H), 1609 (C=C); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 1.50 (3H, d, *J* 6.8, C(α)*Me*), 2.03-2.09 (1H, m, C(7)H_A), 2.22-2.30 (1H, m, C(7)H_B), 2.36 (1H, br s, O*H*), 2.73 (1H, app dd, *J* 14.4, 11.4, C(8)H_A), 3.31-3.45 (3H, m, C(1′)H_A, C(2)*H*, C(8)H_B), 3.65 (1H, dd, *J* 10.9, 5.1, C(1′)H_B), 3.80 (3H, s, O*Me*), 4.24 (1H, q, *J* 6.8, C(α)*H*), 4.34 (1H, dd, *J* 10.1, 5.6,

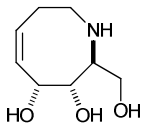
C(3)*H*), 5.15-5.18 (1H, m, C(4)*H*), 5.64 (1H, dd, *J* 11.1, 5.8, C(5)*H*), 5.83-5.91 (1H, m, C(6)*H*), 6.87 (2H, d, *J* 8.7, *Ar*), 7.25 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.2 (C(α)*Me*), 26.4, 28.0 (C*Me*$_2$), 30.6 (*C*(7)), 48.9 (*C*(8)), 53.5 (*C*(α)), 55.2 (O*Me*), 62.0 (*C*(1′)), 62.1 (*C*(2)), 77.0 (*C*(4)), 80.9 (*C*(3)), 109.2 (*C*Me$_2$), 113.9, 127.6 (*Ar*), 130.6 (*C*(6)), 133.4 (*C*(5)), 137.9, 158.4 (*Ar*); *m/z* (ESI$^+$) 717 ([2M+Na]$^+$, 100%), 370 ([M+Na]$^+$, 80%), 348 ([M+H]$^+$, 30%); HRMS (ESI$^+$) $C_{20}H_{29}NNaO_4^+$ ([M+Na]$^+$) requires 370.1989; found 370.1983.

(1*R*,2*S*,3*S*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizidine [(–)-7a-*epi*-hyacinthacine A1] 216[24d]



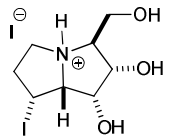
I_2 (77 mg, 0.30 mmol) was added to a stirred solution of **227** (35 mg, 0.10 mmol, >99:1 dr) in CH_2Cl_2 (3 mL). The resultant mixture was left to stir at rt for 12 h then concentrated *in vacuo*. The residue was dissolved in degassed MeOH (3 mL) and 10% Pd/C (18 mg, 50% w/w) and Et_3N (0.03 mL, 0.20 mmol) were added. The reaction mixture was stirred at rt under 1 atm H_2 for 18 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in MeOH (2 mL) and co-evaporated with 6.0 M aq HCl (2 × 2 mL), then dissolved in H_2O (2 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **216** (13 mg, 75%, >99:1 dr) as a colourless oil; $[\alpha]_D^{20}$ −39.5 (*c* 0.3 in H_2O); δ_H (500 MHz, D_2O) 1.39-1.47 (1H, m, C(7)H_A), 1.53-1.62 (1H, m, C(6)H_A), 1.78-1.84 (1H, m, C(6)H_B), 2.07-2.13 (1H, m, C(7)H_B), 2.64 (1H, td, *J* 10.4, 5.7, C(5)H_A), 2.82-2.85 (1H, m, C(5)H_B), 3.14 (1H, dt, 6.3, 9.5, C(3)*H*), 3.31 (1H, td, 7.9, 2.2, C(7a)*H*), 3.79 (2H, d, *J* 6.3, C(1′)H_2), 3.82 (1H, dd, *J* 5.0, 2.2, C(1)*H*), 3.92 (1H, dd, *J* 9.5, 5.0, C(2)*H*); δ_C (125 MHz, D_2O) 25.7 (*C*(6)), 29.3 (*C*(7)), 47.2 (*C*(5)), 59.4 (*C*(1′), 64.4 (*C*(3)), 69.5 (*C*(7a)), 70.8 (*C*(2)), 75.4 (*C*(1)); δ_H (500 MHz, D_2O [TSP]) 1.49-1.57 (1H, m, C(7)H_A), 1.63-1.73 (1H, m, C(6)H_A), 1.89-1.94 (1H, m, C(6)H_B), 2.17-2.23 (1H, m, C(7)H_B), 2.76 (1H, td, *J* 10.4, 5.7, C(5)H_A), 2.94-2.97 (1H, m, C(5)H_B), 3.25 (1H, app dd, 9.5, 6.6, C(3)*H*), 3.43 (1H, app dd, 8.2, 2.3, C(7a)*H*), 3.89 (2H, d, *J* 6.6, C(1′)H_2), 3.82 (1H, dd, *J* 5.0, 2.3, C(1)*H*), 3.92 (1H, dd, *J* 9.5, 5.0, C(2)*H*); δ_C (125 MHz, D_2O [TSP]) 28.6 (*C*(6)), 32.2 (*C*(7)), 50.1 (*C*(5)), 62.3 (*C*(1′), 67.3 (*C*(3)), 72.6 (*C*(7a)), 73.8 (*C*(2)), 78.2 (*C*(1)).

(2*S*,3*S*,4*R*,*Z*)-2-(hydroxymethyl)-3,4-dihydroxy-1,2,3,4,7,8-hexahydroazocine 230[16]



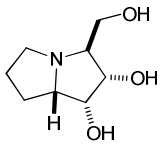
3.0 M aq HCl (0.5 mL) was added to a stirred solution of **227** (53 mg, 0.15 mmol, >99:1 dr) in MeOH (1 mL). The reaction mixture was heated at reflux for 2 h then concentrated *in vacuo*. The residue was dissolved in H_2O (1.5 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **230** as a white solid (18 mg, 69%, >99:1 dr); mp 194-198 °C; $[\alpha]_D^{20}$ −8.1 (*c* 0.27 in H_2O); δ_H (500 MHz, D_2O) 2.09-2.22 (2H, m, C(7)H_2), 2.35-2.39 (1H, m, C(2)*H*), 2.46-2.52 (1H, m, C(8)H_A), 3.02 (1H, ddd, *J* 13.2, 4.4, 3.2, C(8)H_B), 3.38 (1H, dd, *J* 11.5, 7.9, C(1′)H_A), 3.54 (1H, dd, *J* 9.5, 3.2, C(3)*H*), 3.78 (1H, dd, *J* 11.5, 3.2, C(1′)H_B), 4.79 (1H, app ddd, *J* 8.2, 3.2, 1.3, C(4)*H*), 5.54-5.58 (1H, m, C*H*), 5.89-5.95 (1H, m, C*H*); δ_C (125 MHz, D_2O) 29.4, (*C*(7)), 50.4 (*C*(8)), 63.5 (*C*(1′)), 64.2, (*C*(2)), 69.2 (*C*(4)), 75.9 (*C*(3)), 131.2, 131.3 (*C*(5), *C*(6)); *m/z* (ESI^+) 196 ($[M+Na]^+$, 100%), 174 ($[M+H]^+$, 75%); HRMS (ESI^+) $C_8H_{15}NNaO_3^+$ ($[M+Na]^+$) requires 196.0944; found 196.0950.

(1*R*,2*S*,3*S*,4*R*,7*R*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)-7-iodohexahydropyrrolizidinium iodide 232·HI



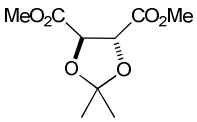
I_2 (21 mg, 0.08 mmol) was added to a stirred solution of **230** (14 mg, 0.08 mmol) in MeOH (1.5 mL). The resultant mixture was stirred at rt for 12 h then concentrated *in vacuo* to give **232**·HI as a brown oil (35 mg, quant, >99:1 dr); δ_H (500 MHz, MeOH-d_4) 2.44-2.49 (1H, m, C(6)H_A), 2.76-2.85 (1H, m, C(6)H_B), 3.44-3.48 (1H, m, C(5)H_A), 3.54 (1H, td, *J* 12.0, 6.9, C(5)H_B), 3.63-3.67 (1H, m, C(3)*H*), 3.85 (1H, dd, *J* 12.1, 5.0, C(1′)H_A), 4.01 (1H, dd, *J* 12.1, 2.8, C(1′)H_B), 4.18 (1H, dd, *J* 10.4, 3.3, C(2)*H*), 4.26-4.32 (2H, m, C(7)*H*, C(7a)*H*), 4.41 (1H, app t, *J* 2.8, C(1)*H*); δ_C (125 MHz, MeOH-d_4) 9.3 (*C*(7)), 36.8 (*C*(6)), 57.5 (*C*(5)), 58.5 (*C*(1′)), 71.8 (*C*(7a)), 73.3 (*C*(2)), 74.7, 74.8 (*C*(1), *C*(3)); *m/z* (ESI^+) 322 ($[M+Na]^+$, 10%), 300 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{15}INO_3^+$ ($[M+H]^+$) requires 300.0091; found 300.0086.

(1*R*,2*S*,3*S*,7a*S*)-1,2-Dihydroxy-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizidine [(−)-hyacinthacine A1] 120[25]



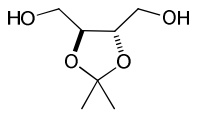
10% Pd/C (17 mg, 50% w/w) was added to a solution of **232**·HI (35 mg, 0.08 mmol, >99:1 dr) and Et_3N (0.08 mL, 0.58 mmol) in degassed MeOH (2 mL). The resultant mixture was stirred at rt under 1 atm H_2 for 18 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The resultant residue was dissolved in HCl (1.25 M in MeOH, 2 mL). The resultant solution was stirred at rt for 5 min then concentrated *in vacuo*. This co-evaporation process was then repeated and the residue dissolved in H_2O (2 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **120** as a colourless oil (13 mg, 94%, >99:1 dr); $[\alpha]_D^{20}$ −34.1 (*c* 0.4 in H_2O); $[\alpha]_D^{20}$ −32.0 (*c* 0.64 in MeOH); {lit.[25] for *ent*-**120** $[\alpha]_D^{20}$ +38.2 (*c* 0.23 in H_2O); lit.[26] for *ent*-**120** $[\alpha]_D^{25}$ +33.5 (*c* 0.2 in MeOH); lit.[27] for *ent*-**120** $[\alpha]_D^{22}$ +43.5 (*c* 0.23 in H_2O); lit.[28] for *ent*-**120** $[\alpha]_D^{20}$ +45.0 (*c* 0.23 in H_2O)}; δ_H (500 MHz, MeOH-d_4) 1.66-1.72 (1H, m, C(7)H_A), 1.75-1.82 (1H, m, C(6)H_A), 1.92-1.99 (1H, m, C(6)H_B), 2.06-2.13 (1H, m, C(7)H_B), 2.63-2.68 (1H, m, C(5)H_A), 2.75-2.79 (1H, m, C(3)*H*), 3.05-3.09 (1H, m, C(5)H_B), 3.46 (1H, td, *J* 7.6, 3.8, C(7a)*H*), 3.60 (1H, dd, *J* 11.0, 6.6, C(1′)H_A), 3.81 (1H, dd, *J* 11.0, 3.5, C(1′)H_B), 3.87-3.90 (2H, m, C(1)*H*, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 25.2 (*C*(7)), 28.1 (*C*(6)), 56.8 (*C*(5)), 64.7 (*C*(1′)), 66.9 (*C*(7a)), 71.1 (*C*(3)), 72.9 (*C*(1)), 76.8 (*C*(2)); *m/z* (ESI^+) 196 ($[M+Na]^+$, 15%), 174 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_3^+$ ($[M+H]^+$) requires 174.1125; found 174.1123.

Dimethyl (*R*,*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 242



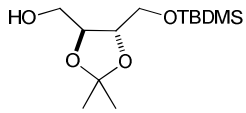
DMP (12.0 mL, 96.9 mmol) and TsOH (128 mg, 0.65 mmol) were added to a solution of dimethyl L-tartrate (11.5 g, 64.6 mmol) in PhMe (75 mL). The reaction mixture was fitted with a Dean-Stark apparatus and heated at reflux for 16 h, then allowed to cool to rt before satd aq $NaHCO_3$ (50 mL) was added. The resultant mixture was stirred at rt for 15 min then the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with H_2O (40 mL) and brine (40 mL), then dried and concentrated *in vacuo* to give **242** as a yellow oil (13.5 g, 96%, >99:1 dr);[29] $[\alpha]_D^{24}$ −56.1 (*c* 1.0 in MeOH); {lit.[30] $[\alpha]_D^{24}$ −49.1 (*c* 1.0 in MeOH)}; δ_H (400 MHz, $CDCl_3$) 1.50 (6H, s, C*Me*$_2$), 3.83 (6H, s, CO_2*Me*), 4.82 (2H, s, C(4)*H*, C(5)*H*).

(*S*,*S*)-2,2-Dimethyl-4,5-bis(hydroxymethyl)-1,3-dioxolane 243



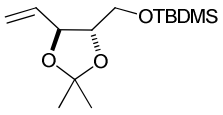
$LiAlH_4$ (1.0 M in THF, 100 mL, 100 mmol) was added dropwise to a stirred solution of **242** (10.0 g, 45.8 mmol, >99:1 dr) in THF (160 mL) at 0 °C. The reaction mixture was heated at reflux for 16 h then allowed to cool to rt before 10% aq NaOH (150 mL), H_2O (70 mL) and EtOAc (150 mL) were added sequentially. The resultant mixture was stirred at rt for 1 h then filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give **243** as a pale yellow oil (7.00 g, 94%, >99:1 dr);[31] δ_H (400 MHz, $CDCl_3$) 1.44 (6H, s, C*Me*$_2$), 2.52 (2H, br s, O*H*), 3.67-3.74 (2H, m, 2 × C*H*$_A$H$_B$OH), 3.81-3.87 (2H, m, 2 × CH$_A$*H*$_B$OH), 4.02-4.05 (2H, m, C(4)*H*, C(5)*H*).

(*S*,*S*)-2,2-Dimethyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-5-(hydroxymethyl)-1,3-dioxolane 244



A solution of **243** (10.7 g, 66.0 mmol, >99:1 dr) in THF (50 mL) was added dropwise to a stirred slurry of NaH (60% dispersion in mineral oil, 2.61 g, 66.0 mmol) in THF (50 mL) at 0 °C. The reaction mixture was allowed to warm to for 45 min before TBDMSCl (9.84 g, 66.0 mmol) was added. The resultant mixture was stirred at rt for 16 h then diluted with Et_2O (50 mL) and satd aq $NaHCO_3$ (2 × 50 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 5:1) gave **244** as a pale yellow oil (15.3 g, 83%, >99:1 dr);[32] $[\alpha]_D^{24}$ +14.5 (*c* 1.0 in $CHCl_3$); {lit.[33] $[\alpha]_D^{24}$ +15.3 (*c* 7.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, Si*Me*$_2$), 0.91 (9H, s, SiC*Me*$_3$), 1.41 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 2.38 (1H, dd, *J* 8.3, 4.4, O*H*), 3.64-3.81 (3H, m, C*H*$_2$OH, C*H*$_A$H$_B$OSi), 3.86-3.92 (2H, m, C*H*, CH$_A$*H*$_B$OSi), 4.00 (1H, dt, *J* 7.5, 4.6, C*H*).

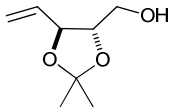
(*S*,*S*)-2,2-Dimethyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-5-(hydroxymethyl)-1,3-dioxolane 246



DMSO (14.8 mL, 208 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (8.92 mL, 104 mmol) in CH_2Cl_2 (100 mL) at −78 °C. The reaction mixture was left to stir for 15 min before a solution of **244** (14.4 g, 51.9 mmol, >99:1 dr) in CH_2Cl_2 (50 mL) was added. The resultant mixture was stirred at −78 °C for 1 h, then Et_3N (43.4 mL, 312 mmol) was added and the reaction mixture was allowed to warm to rt over 30 min. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and the resultant solution washed sequentially with H_2O (100 mL) and brine (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts dried and concentrated *in vacuo*. The residue was dissolved in THF (50 mL) and the resultant solution was added dropwise to a solution of $[MePh_3P]^+[I]^-$

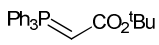
(63.3 g, 156 mmol) and KO^{t}Bu (17.5 g, 156 mmol) in THF (100 mL) that had been stirring at rt for 2 h. The resultant mixture was stirred at rt for 1 h before H_2O (100 mL) was added. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were washed sequentially with H_2O (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. The residue was passed through a plug of silica (eluent 30-40 °C petrol/EtOAc, 50:1) to give **246** as a colourless oil (13.0 g, 92%, >99:1 dr); $[\alpha]_D^{20}$ −6.1 (*c* 0.2 in $CHCl_3$); {lit.[34] for *ent*-**246** $[\alpha]_D^{25}$ +5.5 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.07 (3H, s, *Me*SiMe), 0.08 (3H, s, *Me*SiMe), 0.90 (9H, s, SiC*Me*$_3$), 1.43 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 3.74-3.78 (3H, m, C*H*$_2$OSi, C*H*), 4.32-4.37 (1H, m, C*H*), 5.24 (1H, app dt, *J* 10.2, 1.4, CH=C*H*$_A$H$_B$), 5.37 (1H, app dt, *J* 17.2, 1.4, CH=CH$_A$*H*$_B$), 5.82-5.91 (1H, m, C*H*=CH$_2$).

(*S*,*S*)-2,2-Dimethyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-5-vinyl-1,3-dioxolane 247



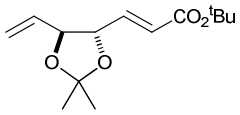
TBAF (1.0 M in THF, 57.3 mL, 57.3 mmol) was added to a stirred solution of **246** (13.0 g, 47.7 mmol, >99:1 dr) in THF (500 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 2.5 h before satd aq NH_4Cl (15 mL) was added. The resultant mixture was partitioned between Et_2O (200 mL) and H_2O (300 mL) and the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with brine (500 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography gave **247** as a colourless oil (5.57 g, 74%, >99:1 dr); $[\alpha]_D^{20}$ −3.6 (*c* 1.1 in $CHCl_3$); {lit.[35] $[\alpha]_D^{18}$ −3.1 (*c* 0.51 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.45 (6H, s, C*Me*$_2$), 1.99 (1H, br s, O*H*), 3.58-3.64 (1H, m, C*H*$_A$H$_B$OH), 3.79-3.87 (2H, m, CH$_A$*H*$_B$OH, C*H*), 4.33 (1H, app t, *J* 7.5, C*H*), 5.28 (1H, app dt, *J* 10.2, 1.0, CH=C*H*$_A$H$_B$), 5.40 (1H, app dt, *J* 17.1, 1.0, CH=CH$_A$*H*$_B$), 5.80-5.89 (1H, m, C*H*=CH$_2$).

tert-Butyl (triphenylphosphoranylidene)acetate 248[36]



tert-Butyl bromoacetate (50.0 g, 256 mmol) was added to a stirred solution of PPh_3 (74.9 g, 256 mmol) in EtOAc (500 mL) at rt. After 12 h the white precipitate was collected by filtration and washed with EtOAc (500 mL). The solid residue was dissolved in CH_2Cl_2 (800 mL) and the resultant solution was washed with 2.0 M aq NaOH (800 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 800 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **248** as a white solid (96.4 g, quant); mp 147-150 °C; lit.[36] mp 148 °C; δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 2.78 (1H, br s, PC*H*), 7.2-8.1 (15H, m, *Ph*).

tert-Butyl (*S*,*S*,*E*)-4,5-*O*-isopropylidene-4,5-dihydroxyhepta-2,6-dienoate 233



Method A: BuLi (2.5 M in hexanes, 0.83 mL, 2.07 mmol) was added to a stirred solution of **158** (500 mg, 1.59 mmol, >99:1 dr) in Et_2O (10 mL) at −78 °C. The resultant mixture was left to stir at −78 °C for 2 h before satd aq NH_4Cl (2 mL) was added. The aqueous layer was extracted with Et_2O (2 × 5 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was dissolved in MeCN/MeOH (v/v 10:1, 20 mL) then K_2CO_3 (1.09 g, 7.96 mmol), LiCl (452 mg, 10.7 mmol), **155** (0.45 mL, 1.91 mmol) and $^iPr_2NEt$ (0.30 mL, 1.75 mmol) were added. The reaction mixture was stirred at rt for 12 h before H_2O (10 mL) and Et_2O (10 mL) were added. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give an 88:12 mixture of (*S*,*S*,*E*)-**233** and (4*R*,5*S*,*E*)-**140**. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 25:1) gave (*S*,*S*,*E*)-**233** as a colourless oil (125 mg, 31%, >99:1 dr); $[\alpha]_D^{25}$ +7.1 (*c* 0.4 in $CHCl_3$); {lit.[6] for *ent*-**233** $[\alpha]_D^{27}$ −7.0 (*c* 0.74 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.46 (3H, s, *Me*CMe), 1.47 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 4.14 (1H, app t, *J* 7.7, C(5)*H*), 4.21-4.25 (1H, m, C(4)*H*), 5.31 (1H, app d, *J* 9.6, C(7)H_A), 5.41 (1H, app d, *J* 17.1, C(7)H_B), 5.78-5.88 (1H, m, C(6)*H*), 6.04 (1H, app dd, *J* 15.7, 1.5, C(2)*H*), 6.76 (1H, dd, *J* 15.7, 5.5, C(3)*H*).

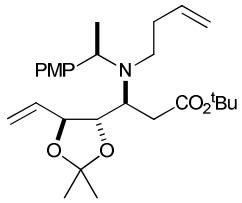
Method B: BuLi (2.5 M in hexanes, 0.83 mL, 2.07 mmol) was added to a stirred solution of **158** (500 mg, 1.59 mmol, >99:1 dr) in Et_2O (10 mL) at −78 °C. The resultant mixture was left to stir at −78 °C for 2 h before satd aq NH_4Cl (2 mL) was added. The aqueous layer was extracted with Et_2O (2 × 5 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was dissolved in MeOH (3 mL) then K_2CO_3 (220 mg, 5.57 mmol) was added. The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). The filtrate was diluted with MeCN (20 mL) and LiCl (452 mg, 10.7 mmol), **155** (0.45 mL, 1.91 mmol) and $^{i}Pr_2NEt$ (0.30 mL, 1.75 mmol) were added. The reaction mixture was stirred at rt for 12 h before H_2O (10 mL) and Et_2O (10 mL) were added. The aqueous layer was extracted with Et_2O (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 92:8 mixture of (*S*,*S*,*E*)-**233** and (4*R*,5*S*,*E*)-**140**. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 25:1) gave (*S*,*S*,*E*)-**233** as a colourless oil (162 mg, 40%, >99:1 dr).

Method C: BuLi (2.5 M in hexanes, 33.1 mL, 82.8 mmol) was added to a stirred solution of **158** (20.0 g, 63.7 mmol, >99:1 dr) in Et_2O (400 mL) at −78 °C. The resultant mixture was left to stir at −78 °C for 2 h before satd aq NH_4Cl (10 mL) was added. The aqueous layer was extracted with Et_2O (2 × 200 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was dissolved in MeOH (120 mL) then K_2CO_3 (30.8 g, 223 mmol) was added. The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). The filtrate was diluted with MeCN (500 mL) and LiCl (18.1 g, 427 mol), **155** (17.9 mL, 76.4 mol) and $^{i}Pr_2NEt$ (12.2 mL, 70.0 mmol) were added. The reaction mixture was stirred at rt for 12 h before H_2O (200 mL) and Et_2O (250 mL) were added. The aqueous layer was extracted with Et_2O (2 × 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, 25:1) gave (*S*,*S*,*E*)-**233** as a colourless oil (2.91 g, 18%, >99:1 dr).

Method D: DMSO (3.25 mL, 45.7 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (3.63 mL, 42.3 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The resultant mixture was left to stir at −78 °C for 15 min before **247** (5.57 g, 35.2 mmol, >99:1 dr) in CH_2Cl_2 (50 mL) was added. The reaction was stirred for 1 h at −78 °C then Et_3N (9.82 mL, 70.4 mmol) was added and the reaction mixture was allowed to warm to rt over 30 min. After this time **248** (13.3 g,

35.2 mmol) was added and the resultant mixture was left to stir for 12 h at rt then concentrated *in vacuo* to give (*S*,*S*,*E*)-**233** in 98:2 dr. Purification via flash coloumn chromatography (eluent 30-40 °C petrol/Et_2O, 25:1) gave (*S*,*S*,*E*)-**233** as a colourless oil (5.64 g, 63%, >99:1 dr).

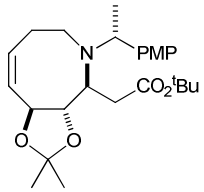
***tert*-Butyl (3*S*,4*S*,5S,α*R*)-3-[*N*-but-3′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 249**



BuLi (2.5 M in hexanes, 0.47 mL, 1.18 mmol) was added dropwise to a stirred solution of (*R*)-**183** (258 mg, 1.26 mmol) in THF (5 mL) at −78 °C. After stirring at −78 °C for 30 min a solution of **233** (200 mg, 0.79 mmol) in THF (5 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir for 2 h, before satd aq NH_4Cl (2 mL) was added. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **249** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 10:1) gave **249** as a yellow oil (230 mg, 65%, >99:1 dr); $[\alpha]_D^{25}$ −23.6 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 2979, 2933, 2835 (C–H), 1726 (C=O), 1640, 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, app d, *J* 7.3, C(α)*Me*, C*Me*$_2$), 1.44 (9H, s, C*Me*$_3$), 2.10-2.17 (2H, m, C(2′)*H*$_2$), 2.20 (1H, dd, *J* 15.7, 5.8, C(2)*H*$_A$), 2.31 (1H, dd, *J* 15.7, 6.3, C(2)*H*$_B$), 2.48-2.61 (2H, m, C(1′)*H*$_2$), 3.54 (1H, app q, *J* 5.8, C(3)*H*), 3.79 (3H, s, O*Me*), 3.84 (1H, dd, *J* 8.3, 4.3, C(4)*H*), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.09 (1H, app t, *J* 7.8, C(5)*H*), 4.91-5.00 (2H, m, C(4′)*H*$_2$), 5.24 (1H, app d, *J* 10.6, C(7)*H*$_A$), 5.39 (1H, app d, *J* 17.2, C(7)*H*$_B$), 5.64-5.75 (1H, m, C(3′)*H*), 5.83-5.93 (1H, m, C(6)*H*), 6.82 (2H, d, *J* 8.7, *Ar*), 7.25 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 27.0 (*Me*CMe), 28.1 (*Me*CMe, C*Me*$_3$), 34.3, 34.5 (*C*(2), *C*(2′)), 46.3 (*C*(1′)), 55.2 (*C*(3), O*Me*), 57.0 (*C*(α)), 80.0 (*C*Me$_3$), 81.0 (*C*(5)), 82.1 (*C*(4)), 109.0 (*C*Me$_2$), 113.3 (*Ar*), 115.2 (*C*(4′)), 118.0 (*C*(7)), 128.8

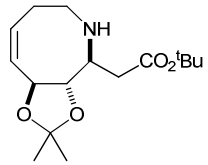
(*Ar*), 136.1 (*C*(6)), 136.2 (*Ar*), 137.0 (*C*(3′), 158.4 (*Ar*), 172.0 (*C*(1)); *m/z* (ESI)$^+$ 482 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{42}NO_5^+$ ([M+H]$^+$) requires 460.3057; found 460.3041.

***tert*-Butyl (2′*S*,3′*S*,4′*S*,α*R*,*Z*)-2-[*N*(1′)-(α-methyl-*p*-methoxybenzyl)-3′,4′-*O*-isopropylidine-3′,4′-dihydroxy-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate 279**



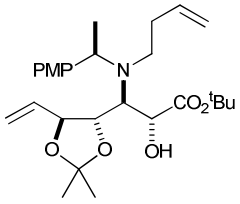
Grubbs I catalyst (16 mg, 0.02 mmol) was added to a stirred solution of **249** (90 mg, 0.21 mmol, >99:1 dr) in CH_2Cl_2 (9 mL) at 30 °C. The reaction mixture was stirred at 30 °C for 12 h then concentrated *in vacuo*. The resultant residue was then dissolved in CH_2Cl2 (5 mL) and **424** (248 mg, 2.00 mmol), Et_3N (0.06 mL, 0.42 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for 12 h, then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **279** as a pale yellow oil (57 mg, 67%, >99:1 dr); $[\alpha]_D^{25}$ +18.6 (*c* 0.29 in $CHCl_3$); ν_{max} (film) 2979, 2933, 2835 (C−H), 1726 (C=O), 1611 (C=C); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 2.18 (2H, br q, *J* 6.1, C(7′)H_2), 2.29 (1H, dd, *J* 14.0, 8.1, C(2)H_A), 2.42 (1H, dd, *J* 14.0, 5.2, C(2)H_B), 2.63-2.70 (1H, m, C(8′)H_A), 2.89 (1H, dt, *J* 13.9, 5.3, C(8′)H_B), 3.29 (1H, td, *J* 8.1, 5.2, C(2′)*H*), 3.78 (3H, s, O*Me*), 3.85-3.91 (2H, m, C(3′)*H*, C(α)*H*), 4.60-4.65 (1H, m, C(4′)*H*), 5.62-5.70 (1H, m, C(6′)*H*), 5.81-5.86 (1H, m, C(5′)*H*), 6.84 (2H, d, *J* 8.6, *Ar*), 7.23 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.8, 26.5, 27.0 (C*Me*$_2$, C(α)*Me*), 28.0 (C*Me*$_3$), 29.9 (*C*(7′)), 36.1 (*C*(2)), 45.4 (*C*(8′)), 55.2 (O*Me*), 58.9 (*C*(2′)), 59.8 (*C*(α)), 78.9 (*C*(4′)), 80.0 (*C*Me$_3$), 84.0 (*C*(3′)), 108.2 (*C*Me$_2$), 113.7 (*Ar*), 127.9 (*C*(6′)), 128.3 (*Ar*), 130.7 (C(5′)), 137.5, 158.4 (*Ar*), 171.5 (*C*(1)); *m/z* (ESI)$^+$ 885 ([2M+Na]$^+$, 100%), 454 ([M+Na]$^+$, 90%); HRMS (ESI$^+$) $C_{25}H_{37}NNaO_5^+$ ([M+Na]$^+$) requires 454.2564; found 454.2551.

tert-Butyl (*S*,*S*,*S*,*Z*)-3′,4′-*O*-isopropylidine-3′,4′-dihydroxy-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate 280



I_2 (158 g, 0.62 mmol) and $NaHCO_3$ (58 mg, 0.69 mmol) were added sequentially to a stirred solution of **279** (100 mg, 0.23 mmol, >99:1 dr) in CH_2Cl_2 (10 mL). The reaction was stirred at rt for 12 h before $Na_2S_2O_3$ (excess) was added. After stirring for 1 h the reaction mixture was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **280** as a colourless oil (50 mg, 72%, >99:1 dr); $[\alpha]_D^{25}$ −1.59 (*c* 0.4 in MeOH); ν_{max} (film) 2981, 2931, 2864 (C−H), 1726 (C=O), 1646 (C=C); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, *Me*CMe), 1.40 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 2.05-2.13 (1H, m, C(7′)H_A), 2.19 (1H, dd, *J* 15.3, 9.9, C(2)H_A), 2.32-2.44 (1H, m, C(7′)H_B), 2.70 (1H, dd, *J* 15.3, 3.5, C(2)H_B), 2.71-2.79 (1H, m, C(8′)H_A), 2.95-3.04 (2H, m, C(2′)*H*, C(8′)H_B), 3.20 (1H, app t, *J* 9.4, C(3′)*H*), 4.51 (1H, br t, *J* 7.1, C(4′)*H*), 5.55-5.63 (1H, m, C(6′)*H*), 5.88 (1H, app ddd, *J* 10.9, 5.7, 1.3, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 26.9, 27.0 (C*Me*$_2$), 28.2 (C*Me*$_3$), 29.0 (*C*(7′)), 41.8 (*C*(2)), 46.6 (*C*(8′)), 54.6 (*C*(2′)), 78.4 (*C*(4′)), 80.3 (*C*Me$_3$), 83.6 (*C*(3′)), 108.5 (*C*Me$_2$), 127.5 (*C*(6′)), 130.2 (*C*(5′)), 171.6 (*C*(1)); *m/z* (ESI)$^+$ 298 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{28}NO_4^+$ ([M+H]$^+$) requires 298.2013; found 298.2004.

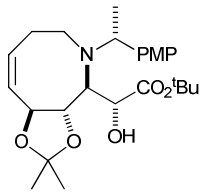
tert-Butyl (2*R*,3*S*,4*S*,5*S*,α*R*)-2-hydroxy-3-[*N*-but-3′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 250



BuLi (2.3 M in hexanes, 8.35 mL, 19.4 mmol) was added dropwise to a stirred solution of (*R*)-**183** (4.12 g, 20.0 mmol) in THF (10 mL) at −78 °C. After stirring at −78 °C for 30 min a solution of **233** (3.19 g, 12.5 mmol, >99:1 dr) in THF (5 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir for 2 h, before (−)-CSO **169** (5.75 g, 25.0 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h then

concentrated *in vacuo* to give a mixture of **249** and **250**.[18] Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 30:1) gave **249** as a colourless oil (520 mg, 9%, >99:1 dr). Further elution gave **250** as a yellow oil (3.47 g, 58%, >99:1 dr); $[\alpha]_D^{25}$ −57.8 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3491 (O–H), 2980, 2934, 2836 (C–H), 1726 (C=O), 1640, 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 2.21-2.31 (1H, m, C(2′)H_A), 2.33-2.42 (1H, m, C(2′)H_B), 2.60-2.67 (1H, m, C(1′)H_A), 2.98-3.06 (1H, m, C(1′)H_B) overlapping 3.04 (1H, d, *J* 6.2, O*H*), 3.50 (1H, app d, *J* 9.4, C(3)*H*), 3.74 (1H, app d, *J* 6.2, C(2)*H*), 3.80 (3H, s, O*Me*), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.06 (1H, app t, *J* 9.4, C(4)*H*), 4.22 (1H, app t, *J* 7.8, C(5)*H*), 4.98-5.01 (1H, m, C(4′)H_A), 5.07-5.09 (1H, m, C(4′)H_B), 5.21-5.24 (1H, m, C(7)H_A), 5.40-5.45 (1H, m, C(7)H_B), 5.74-5.85 (1H, m, C(3′)*H*), 5.98-6.06 (1H, m, C(6)*H*), 6.83 (2H, d, *J* 8.4, *Ar*), 7.26 (2H, d, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 26.7, 27.1 (C*Me*$_2$), 28.1 (C*Me*$_3$), 33.6 (*C*(2′)), 46.5 (*C*(1′)), 55.2 (O*Me*), 57.4 (*C*(α)), 61.9 (*C*(3)), 70.4 (*C*(2)), 78.1 (*C*(4)), 81.4 (*C*(5)), 82.2 (*C*Me$_3$), 108.4 (*C*Me$_2$), 113.4 (*Ar*), 115.4 (*C*(4′)), 116.3 (*C*(7)), 129.2, 134.4 (*Ar*), 136.9, 137.3 (*C*(6), *C*(3′)), 158.7 (*Ar*), 173.3 (*C*(1)); *m/z* (ESI^+) 498 ($[M+Na]^+$, 95%), 476 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{41}NNaO_6^+$ ($[M+Na]^+$) requires 498.2826; found 498.2824.

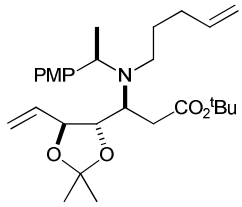
tert-Butyl (2*R*,2′*S*,3′*S*,4′*S*,α*R*,*Z*)-2-hydroxy-2-[*N*(1′)-(α-methyl-*p*-methoxybenzyl)-3′,4′-*O*-isopropylidine-3′,4′-dihydroxy-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate 251[16]



Grubbs I catalyst (625 mg, 0.76 mmol) was added to a stirred solution of **250** (3.40 g, 7.15 mmol, >99:1 dr) in CH_2Cl_2 (300 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and **424** (17.7 g, 143 mmol), Et_3N (2.0 mL, 14.3 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for 12 h, then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **251** as a yellow crystalline solid (2.91 g, 91%, >99:1 dr); mp 60-63 °C; $[\alpha]_D^{25}$ +17.9 (*c* 1.6 in $CHCl_3$);

ν_{max} (ATR) 3482 (O−H), 2980, 2934, 2836 (C−H), 1723 (C=O), 1611 (C=C); δ_H (400 MHz, $CDCl_3$) 1.11 (3H, s, *Me*CMe), 1.29 (3H, s, *Me*CMe), 1.35 (9H, s, C*Me*$_3$), 1.40 (3H, d, *J* 6.7, C(α)*Me*), 2.02-2.12 (1H, m, C(7′)H_A), 2.34-2.45 (1H, m, C(7′)H_B), 2.83-2.91 (1H, m, C(8′)H_A), 3.11-3.16 (1H, m, C(8′)H_B), 3.17 (1H, app d, *J* 8.8, C(2′)*H*), 3.21 (1H, d, *J* 4.6, O*H*), 3.77 (3H, s, O*Me*), 3.94 (1H, q, *J* 6.7, C(α)*H*), 4.27-4.33 (2H, m, C(2)*H*, C(3′)*H*), 4.66-4.70 (1H, m, C(4′)*H*), 5.65-5.73 (1H, m, C(6′)*H*), 5.79-5.84 (1H, m, C(5′)*H*), 6.84 (2H, d, *J* 8.7, *Ar*), 7.25 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.3 (C(α)*Me*), 26.1, 27.0 (C*Me*$_2$), 27.9 (C*Me*$_3$), 30.5 (*C*(7′)), 46.5 (*C*(8′)), 55.2 (O*Me*), 61.3 (*C*(α)), 63.3 (*C*(2′)), 68.6, 78.0, 78.4 (*C*(2), *C*(3′), *C*(4′)), 82.3 (*C*Me$_3$), 108.1 (*C*Me$_2$), 113.8 (*Ar*), 128.5, 128.6 (*C*(6′), *Ar*), 130.6 (*C*(5′)), 137.1, 158.5 (*Ar*), 173.6 (*C*(1)); *m/z* (ESI$^+$) 917 ([2M+Na]$^+$, 100%), 470 ([M+Na]$^+$, 65%), 448 ([M+H]$^+$, 90%); HRMS (ESI$^+$) $C_{25}H_{37}NNaO_6^+$ ([M+Na]$^+$) requires 470.2513; found 470.2500.

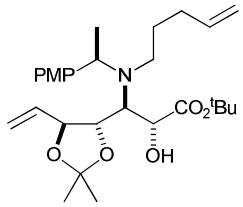
tert-Butyl (3*S*,4*S*,5*S*,α*R*)-3-[*N*-pent-4′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 252



BuLi (2.3 M in hexanes, 0.40 mL, 0.91 mmol) was added dropwise to a stirred solution of (*R*)-**205** (199 mg, 0.94 mmol) in THF (2.5 mL) at −78 °C. After stirring at −78 °C for 30 min a solution of **233** (150 mg, 0.59 mmol, >99:1 dr) in THF (2.5 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for 2 h, before satd aq NH_4Cl (2 mL) was added. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **252** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:1) gave **252** as a yellow oil (155 mg, 55%, >99:1 dr); $[\alpha]_D^{25}$ −20.0 (*c* 0.73 in $CHCl_3$); ν_{max} (ATR) 2979, 2933 (C−H), 1726 (C=O), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, *Me*CMe), 1.39

(3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.46-1.52 (2H, m, C(2′)H_2), 1.89-1.96 (2H, m, C(3′)H_2), 2.18 (1H, dd, *J* 15.8, 5.6, C(2)H_A), 2.29 (1H, dd, *J* 15.8, 6.6, C(2)H_B), 2.46 (2H, app t, *J* 7.3, C(1′)H_2), 3.51-3.56 (1H, m, C(3)*H*), 3.79 (3H, s, O*Me*), 3.83 (1H, dd, *J* 8.3, 4.3, C(4)*H*), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.09 (1H, app t, *J* 7.6, C(5)*H*), 4.89-4.97 (2H, m, C(5′)H_2), 5.22-5.25 (1H, m, C(7)H_A), 5.27-5.42 (1H, m, C(7)H_B), 5.69-5.79 (1H, m, C(4′)*H*), 5.84-5.92 (1H, m, C(6)*H*), 6.82 (2H, d, *J* 8.6, *Ar*), 7.25 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.2 (C(α)*Me*), 27.0 (*Me*CMe), 28.1 (*Me*CMe, C*Me*$_3$), 28.6 (*C*(2′)), 31.5 (*C*(3′)), 34.5 (*C*(2)), 46.0 (*C*(1′)), 55.1, 55.2 (*C*(3), O*Me*), 56.7 (*C*(α)), 79.9 (*C*Me$_3$), 81.0 (*C*(5)), 82.1 (*C*(4)), 109.0 (*C*Me$_2$), 113.2 (*Ar*), 114.3 (*C*(5′), 117.9 (*C*(7)), 128.9 (*Ar*), 136.2 (*C*(6)), 136.2 (*Ar*), 138.8 (*C*(4′)), 158.3 (*Ar*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 496 ([M+Na]$^+$, 45%), 474 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{44}NO_5^+$ ([M+H]$^+$) requires 474.3214; found 474.3214.

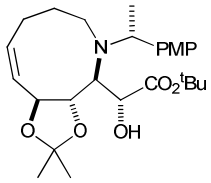
tert-Butyl (2*R*,3*S*,4*S*,5*S*,α*R*)-2-hydroxy-3-[*N*-pent-4′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-*O*-isopropylidene-4,5-dihydroxyhept-6-enoate 253



BuLi (2.3 M in hexanes, 1.32 mL, 3.05 mmol) was added dropwise to a stirred solution of (*R*)-**205** (665 mg, 3.15 mmol) in THF (1.5 mL) at −78 °C. After stirring at −78 °C for 30 min a solution of **233** (500 mg, 1.97 mmol) in THF (1.5 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir at −78 °C for 2 h, before (−)-CSO **169** (902 mg, 3.93 mmol) waas added. The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo* to give a mixture of **252** and **253**.[23] Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 40:1) gave **252** as a colourless oil (40 mg, 4%, >99:1 dr). Further elution gave **253** as a yellow oil (290 mg, 30%, >99:1 dr); $[\alpha]_D^{25}$ −57.5 (*c* 0.76 in $CHCl_3$); ν_{max} (ATR) 3489 (O−H), 2980, 2934 (C−H), 1726 (C=O), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.54-1.61 (1H, m, C(2′)H_A), 1.67-1.76 (1H, m, C(2′)H_B), 2.02 (2H, app q, *J* 7.1, C(3′)H_2), 2.52-2.59 (1H, m, C(1′)H_A), 2.93 (1H, ddd, *J* 16.4, 11.1, 5.6,

C(1′)H_B), 3.03 (1H, br d, *J* 5.8, O*H*), 3.50 (1H, app d, *J* 9.4, C(3)*H*), 3.72 (1H, br d, *J* 4.8, C(2)*H*), 3.79 (3H, s, O*Me*), 3.97 (1H, q, *J* 6.8, C(α)*H*), 4.04 (1H, app t, *J* 9.4, C(4)*H*), 4.21 (1H, app t *J* 7.6, C(5)*H*), 4.95-5.06 (2H, m, C(5′)H_2), 5.21 (1H, app d, *J* 10.6, C(7)H_A), 5.42 (1H, app d, *J* 15.9, C(7)H_B), 5.79-5.89 (1H, m, C(4′)*H*), 5.96-6.05 (1H, m, C(6)*H*), 6.82 (2H, d, *J* 8.6, *Ar*), 7.25 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 26.1, 27.1 (CMe_2), 28.1 (CMe_3), 28.4 (*C*(2′)), 31.9 (*C*(3′)), 46.5 (*C*(1′)), 55.2 (O*Me*), 57.4 (*C*(α)), 61.8 (*C*(3)), 70.4 (*C*(2)), 78.1 (*C*(4)), 81.4 (*C*(5)), 82.1 (*C*Me_3)), 108.4 (*C*Me_2), 113.4 (*Ar*), 114.5 (*C*(5′)), 116.2 (*C*(7)), 129.2, 134.5 (*Ar*), 137.3 (*C*(6)), 138.7 (*C*(4′)), 158.7 (*Ar*), 173.3 (*C*(1)); *m/z* (ESI$^+$) 512 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{43}NNaO_6^+$ ([M+Na]$^+$) requires 512.2983; found 512.2982.

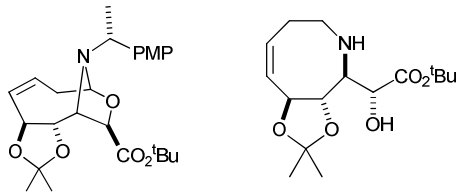
tert-Butyl (2*R*,2′*S*,3′*S*,4′*S*,α*R*,*Z*)-2-hydroxy-2-[*N*(1′)-(α-methyl-*p*-methoxybenzyl)-3′,4′-*O*-isopropylidine-3′,4′-dihydroxy-2′,3′,4′,7′,8′,9′-hexahydro-1*H*-azonin-2′-yl]ethanoate 254



Grubbs I catalyst (97 mg, 0.12 mmol) was added to a stirred solution of **253** (290 mg, 0.59 mmol, >99:1 dr) in degassed CH_2Cl_2 (30 mL). The resultant mixture was stirred at 30 °C for 12 h then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and **424** (1.46 g, 11.8 mmol), Et_3N (0.17 mL, 1.18 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for 12 h then filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **254** as a pale yellow oil (191 mg, 70%, >99:1 dr); $[\alpha]_D^{25}$ −50.8 (*c* 0.85 in $CHCl_3$); ν_{max} (ATR) 3488 (O−H), 2980, 2933, 2861 (C−H), 1722 (C=O), 1609 (C=C); δ_H (400 MHz, $CDCl_3$) 1.16-1.20 (1H, m, C(8′)H_A) overlapping 1.19 (3H, s, *Me*CMe), 1.33 (3H, s, *Me*CMe), 1.47 (9H, s, CMe_3), 1.54 (3H, d, *J* 6.9, C(α)*Me*), 1.84-1.99 (2H, m, C(7′)H_A, C(8′)H_B), 2.69-2.78 (3H, m, C(7′)H_B, C(9′)H_2), 3.05 (1H, d, *J* 4.3, O*H*), 3.39 (1H, app d, *J* 8.1, C(2′)*H*) 3.79 (3H, s, O*Me*), 3.83 (1H, app d, *J* 4.3, C(2)*H*), 3.95 (1H, q, *J* 6.9, C(α)*H*), 4.10 (1H, app t, *J* 7.7, C(3′)*H*), 5.13 (1H, app t, *J* 7.7, C(4′)*H*), 5.45 (1H, td, *J* 11.0 , 6.1, C(6′)*H*), 5.59 (1H, dd, *J* 11.0, 7.7, C(5′)*H*), 6.85 (2H, d, *J* 8.6, *Ar*), 7.28 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*),

23.4, 24.2 (*C*(7′), *C*(8′)), 25.9, 26.9 (C*Me*$_2$), 28.0 (C*Me*$_3$), 43.0 (*C*(9′)), 55.2 (O*Me*), 56.4 (*C*(α)), 62.6 (*C*(2′)), 69.3 (*C*(2)), 74.4 (*C*(4′)), 77.4 (*C*(3′)), 82.3 (*C*Me$_3$), 109.1 (*C*Me$_2$), 113.6, 128.9 (*Ar*), 129.1 (*C*(6′)), 132.5 (*C*(5′)), 135.2, 158.7 (*Ar*), 173.7 (*C*(1)); *m/z* (ESI$^+$) 945 ([2M+Na]$^+$, 70%), 484 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{39}NNaO_6^+$ ([M+Na]$^+$) requires 484.2670; found 484.2669.

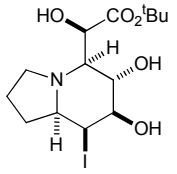
(1*R*,2*S*,3*S*,7*S*,9*R*,α*R*,*Z*)-2,3-*O*-Isopropylidene-2,3-dihydroxy-9-(*tert*-butoxycarbonyl)-*N*(10)-(α-methyl-*p*-methoxybenzyl)-8-oxa-10-azabicyclo[5.2.1]dec-4-ene 256 and *tert*-butyl(2*R*,2′*S*,3′*S*,4′*S*,*Z*)-2-hydroxy-3′,4′-*O*-isopropylidine-3′,4′-dihydroxy-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate 255



I_2 (340 mg, 1.34 mmol) and $NaHCO_3$ (113 mg, 1.34 mmol) were added sequentially to a stirred solution of **251** (200 mg, 0.45 mmol, >99:1 dr) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at rt for 12 h before $Na_2S_2O_3$ (excess) was added. After stirring for 1 h the reaction mixture was filtered and concentrated *in vacuo* to give a 9:62:29 mixture of **257**, **255** and **256**. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **256** as a colourless oil (48 mg, 24%, >99:1 dr); $[\alpha]_D^{25}$ −26.0 (*c* 0.52 in $CHCl_3$); ν_{max} (ATR) 2980, 2932 (C−H), 1731 (C=O), 1611 (C=C); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.43-1.45 (12H, m, C*Me*$_3$, C(α)*Me*), 2.26-2.31 (1H, m, C(6)H_A), 2.64-2.71 (1H, m, C(6)H_B), 3.44 (1H, dd, *J* 8.6, 1.15, C(2)*H*), 3.69 (1H, dd, 6.3, 1.15, C(1)*H*), 3.81 (3H, s, O*Me*), 3.95 (1H, q, *J* 6.6, C(α)*H*), 3.99 (1H, d, *J* 6.3, C(9)*H*), 4.81-4.85 (1H, m, C(3)*H*), 5.10 (1H, d, *J* 4.3, C(7)*H*), 5.59-5.65 (1H, m, C(5)*H*), 5.77-5.82 (1H, m, C(4)*H*), 6.87 (2H, d, *J* 8.6, *Ar*), 7.28 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.5 (C(α)*Me*), 27.0, 27.1 (C*Me*$_2$), 28.0 (C*Me*$_3$), 34.8 (*C*(6)), 55.2 (O*Me*), 61.3, 61.6 (*C*(1), *C*(α)), 77.5, 77.8 (*C*(9), *C*(3)), 81.5 (*C*(2)), 82.0 (*C*Me$_3$), 94.5 (*C*(7)), 108.1 (*C*Me$_2$), 113.9 (*Ar*), 125.4 (*C*(5)), 128.8 (*Ar*), 129.6 (*C*(4)), 134.9, 159.0 (*Ar*), 168.0 (*C*O$_2^t$Bu); *m/z* (ESI$^+$) 913 ([2M+Na]$^+$, 100%), 446 ([M+H]$^+$, 80%); HRMS (ESI$^+$) $C_{25}H_{36}NO_6^+$ ([M+H]$^+$) requires 446.2573; found 446.2542. Further elution gave **255** as a colourless oil (57 mg, 40%, >99:1 dr);

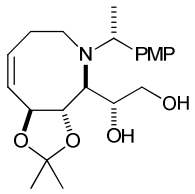
$[\alpha]_D^{25}$ −1.65 (*c* 1.03 in $CHCl_3$); ν_{max} (ATR) 3493 (O–H), 2982, 2933, 2867 (C–H), 1727 (C=O), 1611 (C=C); δ_H (400 MHz, $CDCl_3$) 1.40 (6H, s, C*Me*$_2$), 1.48 (C*Me*$_3$), 2.03-2.09 (1H, m, C(7′)H_A), 2.29-2.40 (1H, m, C(7′)H_B), 2.79 (1H, ddd, *J* 14.4, 12.6, 4.6, C(8′)H_A), 2.85 (1H, dd, *J* 9.8, 3.5, C(2′)*H*), 2.93-2.98 (1H, m, C(8′)H_B), 3.38 (1H, app t, *J* 9.8, C(3′)*H*), 4.19 (1H, app d, *J* 3.5, C(2)*H*), 4.49 (1H, br t, *J* 7.3, C(4′)*H*), 5.55-5.62 (1H, m, C(6′)*H*), 5.86-5.90 (1H, m, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 26.9, 27.0 (C*Me*$_2$), 28.1 (C*Me*$_3$), 28.7 (*C*(7′)), 46.8 (*C*(8′)), 59.9 (*C*(2′)), 72.8 (*C*(2)), 78.5 (*C*(4′)), 81.2 (*C*(3′)), 81.9 (*C*Me$_3$), 109.1 (*C*Me$_2$), 127.4 (*C*(6′)), 130.4 (*C*(5′)), 171.7 (*C*(1)); *m/z* (ESI^+) 649 ($[2M+Na]^+$, 100%), 336 ($[M+Na]^+$, 85%), 314 ($[M+H]^+$, 90%); HRMS (ESI^+) $C_{16}H_{27}NNaO_5^+$ ($[M+Na]^+$) requires 336.1781; found 336.1787.

(5*R*,6*S*,7*R*,8*S*,8a*S*,1′*R*)-6,7-Dihydroxy-5-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-8-iodohexahydro-1*H*-pyrrolizine 265



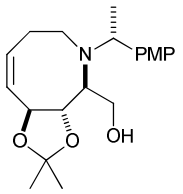
I_2 (82 mg, 0.32 mmol) and $NaHCO_3$ (27 mg, 0.32 mmol) were added sequentially to a stirred solution of **254** (50 mg, 0.11 mmol, >99:1 dr) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at rt for 12 h before $Na_2S_2O_3$ (excess) was added. After stirring for 1 h the resultant mixture was filtered and concentrated *in vacuo*. Purification gave **265** as a brown oil (5 mg, 12%, >99:1 dr); $[\alpha]_D^{25}$ −26.3 (*c* 0.10 in $CHCl_3$); ν_{max} (ATR) 3488 (O–H), 2981, 2930 (C–H), 1729 (C=O); δ_H (500 MHz, MeOH-d_4) 1.52 (9H, s, C*Me*$_3$), 2.18-2.33 (3H, m, C(1)H_A, C(2)H_2), 2.66-2.74 (1H, m, C(1)H_B), 3.54-3.60 (2H, m, C(3)H_A, C(5)*H*), 3.73 (1H, app t, *J* 10.4, C(6)*H*), 3.83 (1H, dd, *J* 10.4, 8.8, C(7)*H*), 4.01-4.05 (1H, m, C(3)H_B), 4.18 (1H, dd, *J* 10.7, 5.7, C(8)*H*), 4.19 (1H, m, C(8a)*H*), 4.53 (1H, m, C(1′)*H*); δ_C (125 MHz, MeOH-d_4) 19.8 (*C*(2)), 24.1 (*C*(8)), 26.8 (*C*(1)), 28.2 (C*Me*$_3$), 54.4 (*C*(3)), 64.15 (*C*(5)), 67.5 (*C*(1′)), 69.0 (*C*(6)), 69.8 (*C*(8a)), 73.4 (*C*(7)), 83.9 (*C*Me$_3$), 171.15 (*C*(2′)); *m/z* (ESI^+) 436 ($[M+Na]^+$, 100%), 414 ($[M+H]^+$, 95%); HRMS (ESI^+) $C_{14}H_{24}INNaO_5^+$ ($[M+Na]^+$) requires 436.0591; found 436.0587.

(2*S*,3*S*,4*S*,1′*R*,α*R*,*Z*)-*N*(1)-(α-methyl-*p*-methoxybenzyl)-2-(dihydroxyethyl)-3,4-*O*-isopropylidine-3,4-dihydroxy-1,2,3,4,7,8-hexahydroazocine 266



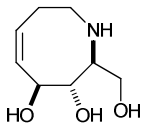
$LiAlH_4$ (1.0 M in THF, 11.4 mL, 11.4 mmol) was added to a stirred solution of **251** (2.56 g, 5.72 mmol, >99:1 dr) in THF (100 mL) at −78 °C. The reaction mixture was allowed to warm to rt over 12 h before 2.0 M aq NaOH (10 mL) was added. The resultant mixture was stirred for 1 h then filtered through Celite® (eluent EtOAc), dried and concentrated in *vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 10:1 increased to 2:1) gave **266** as a pale brown oil (1.65 g, 77%, >99:1 dr); $[\alpha]_D^{25}$ +53.3 (*c* 0.29 in $CHCl_3$); ν_{max} (ATR) 3425 (O−H), 2982, 2934, 2836 (C−H), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, s, *Me*CMe), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 1.31 (3H, s, *Me*CMe), 2.08-2.18 (1H, m, C(7)H_A), 2.32-2.42 (1H, m, C(7)H_B), 2.71 (1H, dd, *J* 8.6, 3.0, C(2)*H*), 2.81-3.05 (2H, m, 2 × O*H*) overlapping 2.87-2.91 (1H, m, C(8)H_A), 3.05-3.13 (1H, m, C(8)H_B), 3.39 (1H, dd, *J* 11.6, 3.5, C(2′)H_A), 3.51 (1H, dd, *J* 11.6, 4.3, C(2′)H_B), 3.80 (3H, s, O*Me*), 3.92 (1H, q, *J* 6.8, C(α)*H*), 3.94-3.98 (1H, m, C(1′)*H*), 4.28 (1H, app t, *J* 8.6, C(3)*H*), 4.68-4.72 (1H, m, C(4)*H*), 5.69-5.76 (1H, m, C(6)*H*), 5.80-5.86 (1H, m, C(5)*H*), 6.85 (2H, d, *J* 8.7, *Ar*), 7.19 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.5 (C(α)*Me*), 26.4, 27.0 (CMe_2), 29.9 (*C*(7)), 46.3 (*C*(8)), 55.3 (O*Me*), 60.9 (*C*(α)), 63.0 (*C*(2)), 65.1 (*C*(2′)), 69.7 (*C*(1′)), 79.1, 79.2 (*C*(3), *C*(4)), 108.6 (*C*Me_2), 113.9, 128.3 (*Ar*), 128.7 (*C*(6)), 129.9 (*C*(5)), 137.4, 158.6 (*Ar*); *m/z* (ESI$^+$) 400 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{31}NNaO_5^+$ ([M+Na]$^+$) requires 400.2094; found 400.2082.

(2*S*,3*S*,4*S*,α*R*,*Z*)-*N*(1)-(α-methyl-*p*-methoxybenzyl)-2-(hydroxymethyl)-3,4-*O*-isopropylidine-3,4-dihydroxy-1,2,3,4,7,8-hexahydroazocine 267



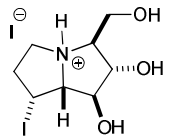
$NaIO_4$ (9.41 g, 44.0 mmol) was added to a solution of **266** (1.66 g, 4.40 mmol, >99:1 dr) in MeOH/H_2O (v/v 5:1, 40 mL). The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (1.66 g, 44.0 mmol) was then added to the filtrate and the reaction mixture was allowed to stir at rt for 12 h before satd aq NH_4Cl (2 mL) was added. The resultant mixture was filtered through Celite® (eluent $CHCl_3$/MeOH, 3:1) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **267** as a yellow oil (877 mg, 57%, >99:1 dr); $[\alpha]_D^{25}$ +38.7 (*c* 0.38 in $CHCl_3$); ν_{max} (ATR) 3469 (O−H), 2980, 2933 (C−H), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.39 (3H, s, *Me*CMe), 2.05-2.24 (3H, m, C(7)H_2, O*H*), 2.88-3.01 (3H, m, C(2)*H*, C(8)H_2), 3.65 (1H, dd, *J* 11.1, 6.3, C(1′)H_A), 3.72 (1H, dd, *J* 11.1, 6.6, C(1′)H_B), 3.77 (3H, s, O*Me*), 3.84 (1H, app t, *J* 8.6, C(3)*H*), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.61-4.66 (1H, m, C(4)*H*), 5.64-5.71 (1H, m, C(6)*H*), 5.84 (1H, dd, *J* 11.6, 3.8, C(5)*H*), 6.84 (2H, d, *J* 8.6, *Ar*), 7.22 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.4 (C(α)*Me*), 26.6, 27.0 (CMe_2), 29.9 (*C*(7)), 46.0 (*C*(8)), 55.2 (O*Me*), 58.9 (*C*(α)), 61.8, 62.0 (*C*(2), *C*(1′)), 79.1 (*C*(4)), 82.3 (*C*(3)), 108.8 (*C*Me_2), 113.9, 127.8 (*Ar*), 128.5 (*C*(6)), 130.3 (*C*(5)), 138.2, 158.4 (*Ar*); *m/z* (ESI$^+$) 717 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{29}NNaO_4^+$ ([M+Na]$^+$) requires 370.1989; found 370.1983.

(*S*,*S*,*S*,*Z*)-2-(hydroxymethyl)-3,4-dihydroxy-1,2,3,4,7,8-hexahydroazocine 268



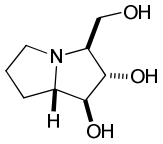
3.0 M aq HCl (2 mL) was added to a stirred solution of **267** (656 mg, 1.89 mmol) in MeOH (6 mL). The reaction mixture was heated at reflux for 2 h then concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **268** as a colourless oil (229 mg, 70%, >99:1 dr); $[\alpha]_D^{25}$ −1.23 (*c* 1.06 in MeOH); ν_{max} (ATR) 3340 (O−H), 2939 (C−H), 1648 (C=C); δ_H (500 MHz, MeOH-d_4) 2.13-2.18 (1H, m, C(7)H_A), 2.26-2.35 (1H, m, C(7)H_B), 2.42-2.47 (1H, m, C(2)*H*), 2.64 (1H, ddd, *J* 13.6, 12.3, 4.7, C(8)H_A), 2.82 (1H, ddd, *J* 13.6, 6.0, 1.9, C(8)H_B), 3.13 (1H, app t, *J* 9.5, C(3)*H*), 3.41 (1H, dd, *J* 10.6, 7.3, C(1′)H_A), 3.81 (1H, dd, *J* 10.6, 4.7, C(1′)H_B), 4.16-4.19 (1H, m, C(4)*H*), 5.51-5.57 (1H, m, C(6)*H*), 5.74-5.77 (1H, m, C(5)*H*); δ_C (125 MHz, MeOH-d_4) 28.8 (*C*(7)), 46.1 (*C*(8)), 61.4 (*C*(2)), 65.5 (*C*(1′)), 74.0 (*C*(4)), 76.2 (*C*(3)), 127.0 (*C*(6)), 136.0 (*C*(5)); *m/z* (ESI^+) 196 ($[M+Na]^+$, 30%), 174 ($[M+H]^+$, 55%); HRMS (ESI^+) $C_8H_{15}NNaO_3^+$ ($[M+Na]^+$) requires 196.0944; found 196.0945.

(1*S*,2*S*,3*S*,4*R*,7*R*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)-7-iodohexahydropyrrolizidinium iodide 270·HI



I_2 (74 mg, 0.29 mmol) was added to a stirred solution of **268** (50 mg, 0.29 mmol, >99:1 dr) in MeOH (5 mL). The resultant mixture was stirred at rt for 12 h then concentrated *in vacuo* to give **270**·HI as a brown oil (124 mg, quant, >99:1 dr); δ_H (400 MHz, MeOH-d_4) 2.52-2.61 (1H, m, C(6)H_A), 2.64-2.74 (1H, m, C(6)H_B), 3.39-3.43 (1H, m, C(3)*H*), 3.50-3.61 (2H, m, C(5)H_2), 3.68 (1H, app t, *J* 7.3, C(7a)*H*), 3.87 (1H, dd, *J* 12.4, 4.55, C(1′)H_A), 3.97 (1H, dd, *J* 12.4, 3.0, C(1′)H_B), 4.06 (1H, dd, *J* 10.1, 7.3, C(2)*H*), 4.19 (1H, app t, *J* 7.3, C(1)*H*), 4.73 (1H, app q, *J* 5.8, C(7)*H*); δ_C (100 MHz, MeOH-d_4) 19.0 (*C*(7)), 37.5 (*C*(6)), 54.1 (*C*(5)), 56.5 (*C*(1′)), 71.0, 71.1 (*C*(3), *C*(7a)), 75.0 (*C*(2)), 81.1 (*C*(1)); *m/z* (ESI^+) 300 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{15}INO_3^+$ ($[M+H]^+$) requires 300.0091; found 300.0087.

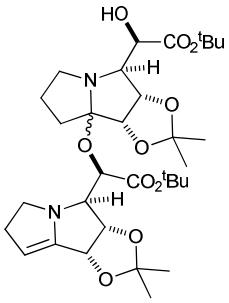
(*S*,*S*,*S*,*S*)-1,2-Dihydroxy-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizidine [(−)-hyacinthacine A2] 222[25]



10% Pd/C (43 mg, 50% w/w) was added to a solution of **270**·HI (86 mg, 0.20 mmol) and Et_3N (0.08 mL, 0.58 mmol) in degassed MeOH (2 mL). The resultant mixture was stirred at rt under 1 atm H_2 for 18 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was then dissolved in MeOH (2 mL) and co-evaporated with 6.0 M aq HCl (2 × 2 mL), then purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **222** as a colourless oil (33 mg, 95%, >99:1 dr); $[\alpha]_D^{25}$ −11.2 (*c* 0.83 in MeOH); $[\alpha]_D^{25}$ −11.0 (*c* 0.43 in H_2O); {lit.[37] $[\alpha]_D^{20}$ −11.0 (*c* 1.0 in MeOH); lit.[25] for *ent*-**222** $[\alpha]_D^{25}$ +20.1 (*c* 0.44 in H_2O); lit.[38] for *ent*-**222** $[\alpha]_D^{20}$ +11.2 (*c* 0.52 in H_2O); lit.[39] for *ent*-**222** $[\alpha]_D^{20}$ +10.6 (*c* 1.64 in H_2O)}; δ_H (400 MHz, MeOH-d_4); 1.71-1.80 (2H, m, C(6)H_A, C(7)H_A), 1.81-1.88 (1H, m, C(6)H_B), 1.92-1.99 (1H, m, C(7)H_B), 2.58-2.62 (1H, m, C(3)*H*), 2.76-2.82 (1H, m, C(5)H_A), 2.90-2.96 (1H, m, C(5)H_B), 3.15-3.20 (1H, m, C(7a)*H*), 3.56-3.61 (2H, m, C(1)*H*, C(1′)H_A), 3.71-3.77 (2H, m, C(2)*H*, C(1′)H_B); δ_C (100 MHz, MeOH-d_4) 24.8 (*C*(6)), 30.6 (*C*(7)), 55.2 (*C*(5)), 63.4 (*C*(1′)), 67.5 (*C*(7a)), 70.9 (*C*(3)), 77.9 (*C*(2)), 81.6 (*C*(1)); δ_H (500 MHz, D_2O) 1.61-1.70 (2H, m, C(6)H_A, C(7)H_A), 1.73-1.80 (1H, m, C(6)H_B), 1.81-1.88 (1H, m, C(7)H_B), 2.59-2.62 (1H, m, C(3)*H*), 2.62-2.67 (1H, m, C(5)H_A), 2.77-2.82 (1H, m, C(5)H_B), 3.05 (1H, app td, *J* 7.6, 4.4, C(7a)*H*), 3.54 (1H, dd, *J* 11.7, 6.6, C(1′)H_A), 3.63-3.70 (3H, m, C(1)*H*, C(2)*H*, C(1′)H_B); δ_C (125 MHz, D_2O) 24.5 (*C*(6)), 29.8 (*C*(7)), 54.8 (*C*(5)), 63.1 (*C*(1′)), 66.0 (*C*(7a)), 69.1 (*C*(3)), 77.2 (*C*(2)), 80.2 (*C*(1)); δ_H (500 MHz, D_2O [TSP]) 1.73-1.81 (2H, m, C(6)H_A, C(7)H_A), 1.84-1.91 (1H, m, C(6)H_B), 1.93-1.99 (1H, m, C(7)H_B), 2.71-2.74 (1H, m, C(3)*H*), 2.75-2.79 (1H, m, C(5)H_A), 2.89-2.94 (1H, m, C(5)H_B), 3.17 (1H, app td, *J* 7.9, 4.7, C(7a)*H*), 3.65 (1H, dd, *J* 12.0, 6.6, C(1′)H_A), 3.72-3.81 (3H, m, C(1)*H*, C(2)*H*, C(1′)H_B); δ_C (125 MHz, D_2O [TSP]) 27.4 (*C*(6)), 32.6 (*C*(7)), 57.7 (*C*(5)), 65.7 (*C*(1′)), 69.0 (*C*(7a)), 72.1 (*C*(3)), 80.0 (*C*(2)), 83.0 (*C*(1)); *m/z* (ESI$^+$) 174 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_3^+$ ($[M+H]^+$) requires 174.1125; found 174.1131.

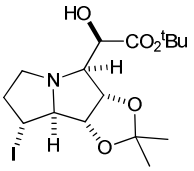
6.4 Experimental data for Chapter 4

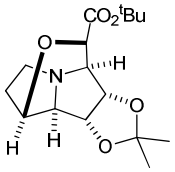
(1*R*,2*S*,3*R*,1′*R*,1″*S*,2″*S*,3″*S*,7a″*R*/*S,1‴*R*,*Z*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-{1′-[1″,2″-*O*-isopropylidene-1″,2″-dihydroxy-3″-(1‴-hydroxy-2‴-*tert*-butoxy-2‴-oxoethyl)hexahydro-1*H*-pyrrolizin-7a″-yl-oxy]-2′-*tert*-butoxy-2′-oxoethyl}-2,3,5,6-tetrahydro-1*H*-pyrrolizine 295**



DBU (0.79 mL, 5.29 mmol) was added to a stirred solution of **189**·HI (300 mg, 0.53 mmol, >99:1 dr) in PhMe (5 mL). The reaction mixture was heated at 60 °C for 12 h then allowed to cool to rt before 1.0 M aq HCl (2 mL) and EtOAc (5 mL) were added. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with $NaHCO_3$ (5 mL) and brine (5 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 10:1) gave **295** as a white solid (98 mg, 60%, >99:1 dr; $[\alpha]_D^{25}$ +30.0 (*c* 0.66 in $CHCl_3$); ν_{max} (ATR) 3445 (O–H), 2979, 2935, 2871 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.30 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 1.45-1.51 (1H, m, C(7″)H_A) overlapping 1.46 (12H, s, *Me*CMe, CMe_3) and 1.47 (9H, s, CMe_3), 1.83-1.90 (2H, m, C(6″)H_2), 1.96-2.02 (2H, m, C(6)H_2), 2.55-2.52 (1H, m, C(7″)H_B), 3.00-3.07 (2H, m, C(5)H_A, O*H*), 3.17-3.21 (2H, m, C(5″)H_2), 3.33-3.37 (1H, m, C(5)H_B), 3.47 (1H, br s, C*H*), 3.77-3.80 (1H, m, C*H*), 4.20-4.26 (3H, m, 2 × C*H*, C(7)*H*), 4.67-4.70 (2H, m, 2 × C*H*), 4.82 (1H, d, *J* 5.3, C*H*), 4.88 (1H, d, *J* 4.8, C*H*); δ_C (100 MHz, $CDCl_3$) 23.8, 24.2 (2 × *Me*CMe), 25.8 (*C*(6″)), 26.1, 26.6 (2 × *Me*CMe), 28.0, 28.1 (2 × CMe_3), 29.7 (*C*(6)), 32.8 (*C*(7″)), 54.3 (*C*(5)), 55.7 (*C*(5″)), 67.7, 73.3, 73.4, 77.9, 78.0 (5 × *C*H), 81.3 (*C*Me_3), 82.4 (*C*H), 82.9 (*C*Me_3), 83.8, 84.2, 85.5 (3 × *C*H), 109.5 (2 × *C*Me_2), 111.4, 111.5 (*C*(7a), *C*(7a″)), 168.4, 171.1 (2 × *C*$O_2{}^t$Bu); *m/z* (ESI^+) 623 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{50}N_2NaO_{10}^+$ ($[M+Na]^+$) requires 645.3358; found 645.3377.

(1*R*,2*S*,3*S*,7*R*,7a*S*,1′*R*)-1,2-*O*-Isopropylidene-1,2 dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-iodohexahydro-1*H*-pyrrolizine 311[16] **and (5*R*,6*S*,7*R*,7a*R*)-6,7-*O*-isopropylidene-6,7-dihydroxy-8-(*tert*-butoxycarbonyl)-1*H*-1,5-(epoxymethano)pyrrolizine 312**

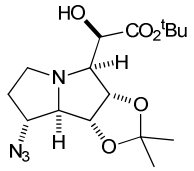




KI (73 mg, 0.44 mmol) was added to a stirred solution of **189**·HI (250 mg, 0.44 mmol) in DMF (5 mL). The resultant mixture was heated at 50 °C for 12 h then allowed to cool to rt and diluted with EtOAc (10 mL). The resultant mixture was washed sequentially with satd aq $Na_2S_2O_3$ (10 mL) and satd aq $NaHCO_3$ (10 mL), then the combined aqueous layers were extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (5 × 15 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 5:1:0.05) gave **311** as a pale brown solid (96 mg, 49%, >99:1 dr); mp 73-75 °C; $[\alpha]_D^{25}$ +31.8 (*c* 0.80 in $CHCl_3$); ν_{max} (ATR) 3468 (O−H), 2980, 2933, 2876 (C−H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 1.52 (3H, s, *Me*CMe), 2.14-2.27 (1H, m, C(6)H_A), 2.50-2.60 (1H, m, C(6)H_B), 2.87-2.94 (1H, m, C(5)H_A), 2.97-3.03 (1H, m, C(5)H_B), 3.08-3.25 (1H, m, O*H*), 3.64 (1H, br s, C(3)*H*), 3.68-3.73 (1H, m, C(7a)*H*), 3.90 (1H, app q, *J* 9.1, C(7)*H*), 4.30-4.35 (2H, m, C(1)*H*, C(1′)*H*), 4.49-4.52 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (*C*(7)), 25.3, 27.4 (C*Me*$_2$), 27.9 (C*Me*$_3$), 40.1 (*C*(6)), 46.1 (*C*(5)), 67.25 (*C*(1′)), 68.5 (*C*(3)), 81.1 (*C*(1)), 82.3 (*C*(2)), 82.6 (*C*(7a)), 83.8 (*C*Me$_3$), 112.2 (*C*Me$_2$), 173.0 (*C*(2′)); *m/z* (ESI)$^+$ 462 ([M+Na]$^+$, 20%), 440 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{27}INO_5^+$ ([M+H]$^+$) requires 440.0928; found 440.0911. Further elution gave **189** as a pale brown oil (30 mg, 12%, >99:1 dr). Further elution (eluent MeOH) gave **312** as a yellow oil (63 mg, 36%, >99:1 dr); $[\alpha]_D^{25}$ +27.5 (*c* 0.68 in MeOH); ν_{max} (film) 2978, 2933 (C−H), 1744 (C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 1.53 (3H, s, *Me*CMe), 1.91-1.99 (1H, m, C(2)H_A), 2.07-2.14 (1H, m, C(2)H_B), 3.00 (1H, d, *J* 2.0, C*H*), 3.16-3.28 (2H, m, C(3)H_2), 3.40 (1H, d, *J* 2.5, C*H*), 4.28-4.31 (2H, m, C(1)*H*, C(8)*H*), 4.45 (1H, app d, *J* 6.1, C*H*), 4.94 (1H, app d, *J* 6.1, C*H*); δ_C (100 MHz, $CDCl_3$) 24.3, 25.9 (C*Me*$_2$), 28.0 (C*Me*$_3$), 31.9 (*C*(2)), 47.1 (*C*(3)), 66.0, 72.1 (*C*(5), *C*(7a)), 69.8, 76.8 (*C*(1), *C*(8)), 78.3, 80.3 (*C*(6), *C*(7)),

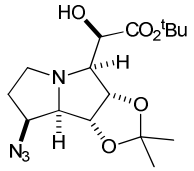
82.5 (*C*Me$_3$), 111.4 (*C*Me$_2$), 168.7 (*C*(1′)); *m/z* (ESI)$^+$ 645 ([2M+Na]$^+$, 100%), 334 ([M+Na]$^+$, 90%), 312 ([M+H]$^+$, 90%); HRMS (ESI$^+$) $C_{16}H_{26}NO_5^+$ ([M+H]$^+$) requires 312.1805; found 312.1799.

(1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-azidohexahydro-1*H*-pyrrolizine 320



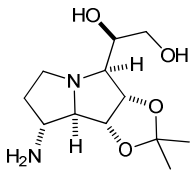
NaN_3 (429 mg, 6.59 mmol) was added to a stirred solution of **189** (1.45 g, 3.30 mmol, >99:1 dr) in DMF (30 mL). The resultant mixture was stirred at 50 °C for 12 h then allowed to cool to rt and partitioned between Et_2O (20 mL) and brine (20 mL). The organic layer was washed with brine (4 × 20 mL) then dried and concentrated *in vacuo* to give **320** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 3:1) gave **320** as a pale yellow oil (754 mg, 71%, >99:1 dr);[40] $[\alpha]_D^{25}$ +15.3 (*c* 0.9 in MeOH); ν_{max} (film) 2980, 2896 (C−H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.51 (9H, s, C*Me*$_3$), 1.52 (3H, s, *Me*CMe), 1.86-1.96 (1H, m, C(6)*H*$_A$), 2.29-2.39 (1H, m, C(6)*H*$_B$), 2.89-2.96 (1H, m, C(5)*H*$_A$), 2.99-3.06 (1H, m, C(5)*H*$_B$), 3.13 (1H, br s, O*H*), 3.25 (1H, dd, *J* 6.8, 3.8, C(7a)*H*), 3.46-3.48 (1H, m, C(3)*H*), 3.81 (1H, app q, *J* 7.6, C(7)*H*), 4.35 (1H, br s, C(1′)*H*), 4.43 (1H, dd, *J* 6.3, 3.8, C(1)*H*), 4.62 (1H, dd, *J* 6.3, 3.5, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 25.3, 27.4 (C*Me*$_2$), 28.0 (C*Me*$_3$), 33.2 (*C*(6)), 45.8 (*C*(5)), 62.7 (*C*(7)), 68.2 (*C*(1′)), 68.5 (*C*(3)), 77.0 (*C*(7a)), 81.8 (*C*(1)), 82.3 (*C*(2)), 83.8 (*C*Me$_3$), 113.1 (*C*Me$_2$), 172.8 (*C*(2′)); *m/z* (ESI)$^+$ 731 ([2M+Na]$^+$, 100%), 377 ([M+Na]$^+$, 100%), 355 ([M+H]$^+$, 90%); HRMS (ESI$^+$) $C_{16}H_{27}N_4O_5^+$ ([M+H]$^+$) requires 355.1976; found 355.1961.

(1*R*,2*S*,3*S*,7*S*,7a*R*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-azidohexahydro-1*H*-pyrrolizine 321



NaN_3 (19 mg, 0.30 mmol) was added to a stirred solution of **311** (65 mg, 0.15 mmol, >99:1 dr) in DMF (2 mL). The resultant mixture was stirred at 50 °C for 12 h then allowed to cool to rt and partitioned between Et_2O (10 mL) and brine (10 mL). The organic layer was washed with brine (5 × 10 mL) then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 10:1) gave a 90:10 mixture of **321** and **294** as a pale yellow oil (12 mg);[40] Data for **321**: δ_H (500 MHz, $CDCl_3$) 1.31 (3H, s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 1.51 (9H, s, C*Me*$_3$), 2.14-2.20 (1H, m, C(6)H_A), 2.32-2.39 (1H, m, C(6)H_B), 2.56 (1H, br s, C(5)H_A), 3.05-3.09 (1H, m, C(5)H_B), 3.18 (2H, br s, C(3)*H*, C(7a)*H*), 4.01-4.03 (1H, m, C(7)*H*), 4.35 (1H, app d, *J* 1.9, C(1′)*H*), 4.57 (1H, dd, *J* 6.8, 5.4, C(1)*H*), 4.85 (1H, dd, *J* 6.8, 4.7, C(2)*H*); δ_C (125 MHz, $CDCl_3$) [selected peaks] 25.2, 27.4 (C*Me*$_2$), 28.0 (C*Me*$_3$), 33.9 (*C*(6)), 45.1 (*C*(5)), 58.3 (*C*(7a)), 69.3 (*C*(1′)), 76.1 (*C*(1)), 82.2 (*C*(2)), 113.6 (*C*Me$_2$), 171.6 (*C*(2′)). Further elution (eluent 100% acetone) gave **312** as a yellow oil (20 mg, 44%, >99:1 dr).

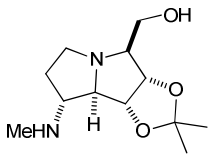
(1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′,2′-dihydroxyethyl)-7-aminohexahydro-1*H*-pyrrolizine 322



$LiAlH_4$ (1.0 M in THF, 8.50 mL, 8.50 mmol) was added to a stirred solution of **320** (754 mg, 2.12 mmol, >99:1 dr) in THF (75 mL) at −78 °C. The reaction mixture was allowed to warm to rt over 12 h before 2.0 M aq NaOH (5 mL) was added. The resultant mixture was left to stir at rt for 1 h then filtered through Celite® (eluent EtOAc), dried and concentrated in *vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 5:4:1) gave **322** as a brown oil (358 mg, 65%, >99:1 dr); $[\alpha]_D^{25}$ −17.4 (*c* 0.3 in MeOH); ν_{max} (film) 3341, 3287 (O−H), 2982, 2934 (C−H), 1602 (N−H); δ_H (500 MHz, MeOH-d_4) [selected peaks] 1.34 (3H,

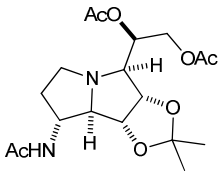
s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 1.56-1.64 (1H, m, C(6)H_A), 2.23-2.29 (1H, m, C(6)H_B), 2.85-2.95 (2H, m, C(5)H_2), 3.10 (1H, dd, *J* 6.0, 4.1, C(3)*H*), 3.12 (1H, dd, *J* 5.4, 3.5, C(7a)*H*), 3.57 (1H, dd, *J* 11.2, 6.9, C(2′)H_A), 3.64 (1H, dd, *J* 11.2, 5.0, C(2′)H_B), 3.90-3.94 (1H, m, C(1′)*H*), 4.56 (1H, dd, *J* 6.6, 3.5, C(1)*H*); δ_C (125 MHz, MeOH-d_4) [selected peaks] 25.5, 27.8 (C*Me*$_2$) 36.4 (*C*(6)), 56.2 (*C*(7)), 65.9 (*C*(2′)), 69.2 (*C*(3)), 71.2 (*C*(1′)), 79.3 (*C*(7a)), 85.6 (*C*(2)), 85.4 (*C*(1)), 114.6 (*C*Me$_2$); *m/z* (ESI)$^+$ 259 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{23}N_2O_4^+$ ([M+H]$^+$) requires 259.1652; found 259.1653.

(1*R*,2*S*,3*S*,7*R*,7a*R*)- 1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(hydroxymethyl)-7-(*N*-methylamino)hexahydro-1*H*-pyrrolizine 323



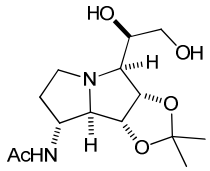
$NaIO_4$ (720 mg, 3.37 mmol) was added to a solution of **322** (87 mg, 0.34 mmol, >99:1 dr) in MeOH/H_2O (v/v 5:1, 3 mL). The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (127 mg, 3.37 mmol) was then added to the filtrate and the reaction mixture was allowed to stir at rt for 12 h before satd aq NH_4Cl (3 mL) was added. The resultant mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 2:1 increased to $CHCl_3$/MeOH/NH_4OH, 5:4:1) gave an impure sample of **323** as a pale brown oil (15 mg, 20%, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 1.57-1.66 (1H, m, C(6)H_A), 2.19-2.29 (1H, m, C(6)H_B), 2.45 (3H, s, N*Me*), 2.79-2.85 (1H, m, C(5)H_A), 2.87-2.91 (1H, m, C(5)H_B), 3.06-3.14 (1H, m, C(7a)*H*), 3.16-3.19 (1H, m, C(3)*H*), 3.27-3.32 (1H, m, C(7)*H*), 3.74-3.82 (2H, m, C(1′)H_2), 4.56-4.63 (2H, m, C(1)*H*, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 25.6, 27.8 (C*Me*$_2$), 34.1 (*C*(6)), 34.6 (N*Me*), 47.3 (*C*(5)), 61.2 (*C*(7)), 64.6 (*C*(1′)), 69.8 (*C*(7a)), 77.0 (*C*(3)), 84.3, 85.8 (*C*(1), *C*(2)), 114.6 (*C*Me$_2$); *m/z* (ESI)$^+$ 265 ([M+Na]$^+$, 60%), 243 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{23}N_2O_3^+$ ([M+H]$^+$) requires 243.1703; found 243.1704.

(1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′,2′-diacetylethyl)-7-acetamidohexahydro-1*H*-pyrrolizine 325



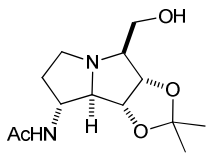
Ac_2O (0.18 mL, 1.94 mmol) and DMAP (5 mg, cat.) were added sequentially to a stirred solution of **322** (100 mg, 0.39 mmol, >99:1 dr) in pyridine (5 mL). The reaction mixture was left to stir at rt for 12 h then H_2O (5 mL) was added. The resultant mixture was diluted with EtOAc (5 mL) and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed sequentially with satd aq $CuSO_4$ (5 mL), H_2O (5 mL) and brine (5 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 10:1) gave **325** as a yellow oil (101 mg, 67%, >99:1 dr); $[\alpha]_D^{20}$ −7.6 (*c* 0.2 in MeOH); ν_{max} (film) 2986, 2937 (C−H), 1741, 1655 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.48 (3H, s, *Me*CMe), 1.61-1.70 (1H, m, C(6)H_A), 1.97 (3H, s, CO*Me*), 2.05 (3H, s, CO*Me*), 2.11 (3H, s, CO*Me*), 2.29-2.36 (1H, m, C(6)H_B), 2.67 (1H, app q, *J* 8.5, C(5)H_A), 2.85-2.89 (1H, m, C(5)H_B), 3.06 (1H, app t, *J* 6.6, C(3)*H*), 3.13 (1H, br t, *J* 4.1, C(7a)*H*), 4.10 (1H, dd, *J* 12.3, 7.6, C(2′)H_A), 4.29-4.35 (1H, m, C(7)*H*), 4.43 (1H, dd, *J* 12.3, 3.2, C(2′)H_B), 4.53 (1H, dd, *J* 6.6, 4.1, C(1)*H*), 4.73 (1H, app t, *J* 6.6, C(2)*H*), 5.39-5.43 (1H, m, C(1′)*H*), 5.94 (1H, br d, *J* 7.3, N*H*); δ_C (100 MHz, $CDCl_3$) 20.7, 21.0, 23.2 (3 × CO*Me*), 25.1, 27.4 (CMe_2), 33.6 (*C*(6)), 46.5 (*C*(5)), 52.2 (*C*(7)), 64.0 (*C*(2′)), 66.6 (*C*(3)), 69.5 (*C*(1′)), 76.2 (*C*(7a)), 82.0 (*C*(2)), 83.6 (*C*(1)), 114.3 (*C*Me$_2$), 169.9, 170.4, 170.7 (*C*OMe); *m/z* (ESI)$^+$ 407 ([M+Na]$^+$, 100%), 385 ([M+H]$^+$, 90%); HRMS (ESI$^+$) $C_{18}H_{29}N_2O_7^+$ ([M+H]$^+$) requires 385.1969; found 385.1963.

(1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′,2′-dihydroxyethyl)-7-acetamidohexahydro-1*H*-pyrrolizine 326



KOH (50 mg, cat.) was added to a stirred solution of **325** (80 mg, 0.21 mmol, >99:1 dr) in MeOH/H_2O (v/v 1:1, 5 mL). The resultant mixture was stirred at rt for 2 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 5:1) gave **326** as a yellow oil (39 mg, 62%, >99:1 dr); $[\alpha]_D^{25}$ +16.1 (*c* 0.29 in MeOH); ν_{max} (film) 3341 (O−H), 2927 (C−H), 1638 (C=O); δ_H (400 MHz, MeOH-d_4) 1.34 (3H, s, *Me*CMe), 1.51 (3H, s, *Me*CMe), 1.75-1.83 (1H, m, C(6)H_A), 1.98 (3H, s, NCO*Me*), 2.30-2.37 (1H, m, C(6)H_B), 3.08-3.12 (1H, m, C(5)H_A), 3.15-3.20 (1H, m, C(5)H_B), 3.31-3.33 (1H, m, C(3)*H*), 3.42 (1H, dd, *J* 6.0, 2.8, C(7a)*H*), 3.58-3.64 (2H, m, C(2′)H_2), 3.98 (1H, td, *J* 6.3, 3.2, C(1′)*H*), 4.35 (1H, app q, *J* 7.9, C(7)*H*), 4.73 (1H, dd, *J* 6.2, 2.8, C(1)*H*), 5.00 (1H, app t, *J* 6.2, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 22.5 (NCO*Me*), 25.5, 27.7 (C*Me*$_2$), 33.3 (*C*(6)), 48.3 (*C*(5)), 54.0 (*C*(7)), 65.4 (*C*(2′)), 69.0 (*C*(3)), 70.3 (*C*(1′)), 77.4 (*C*(7a)), 81.7 (*C*(2)), 84.9 (*C*(1)), 114.5 (*C*Me$_2$), 173.3 (N*C*OMe); *m/z* (ESI)$^+$ 623 ([2M+Na]$^+$, 100%), 323 ([M+Na]$^+$, 65%), 301 ([M+H]$^+$, 50%); HRMS (ESI$^+$) $C_{14}H_{25}N_2O_5^+$ ([M+H]$^+$) requires 301.1758; found 301.1748.

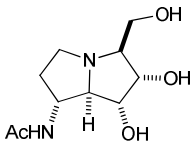
(1*R*,2*S*,3*S*,7*R*,7a*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(hydroxymethyl)-7-acetamidohexahydro-1*H*-pyrrolizidine 327



$NaIO_4$ (192 mg, 0.90 mmol) was added to a solution of **326** (27 mg, 0.09 mmol) in MeOH/H_2O (v/v 2:1, 3 mL). The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (34 mg, 0.90 mmol) was then added to the filtrate and the resultant mixture was allowed to stir at rt for 12 h then satd aq NH_4Cl (0.5 mL) was added. The resultant mixture was filtered through Celite® (eluent EtOAc/MeOH, 3:1) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography

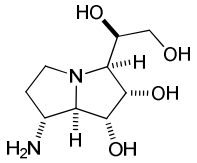
(eluent CH_2Cl_2/MeOH, 5:1 increased to CH_2Cl_2/MeOH, 2:1) gave **327** as a dark brown oil (21 mg, 85%, >99:1 dr); δ_H (500 MHz, MeOH-d_4) [selected peaks] 1.37 (3H, s, *Me*CMe), 1.56 (3H, s, *Me*CMe), 2.02 (3H, s, NCO*Me*), 2.04-2.12 (1H, m, C(6)H_A), 2.48 (1H, app quint d, *J* 6.6, 3.2, C(6)H_B), 3.56 (1H, td, *J* 11.0, 6.6, C(5)H_A), 3.61-3.65 (1H, m, C(5)H_B), 3.83-3.86 (1H, m, C(3)*H*), 3.93 (1H, dd, *J* 12.9, 6.6, C(1′)H_A), 3.99-4.02 (2H, m, C(7a)*H*, C(1′)H_B), 4.59 (1H, app q, *J* 7.6, C(7)*H*); δ_C (125 MHz, MeOH-d_4) 22.6 (NCO*Me*), 25.6, 27.7 (CMe_2), 31.9 (*C*(6)), 48.3 (*C*(5)), 53.5 (*C*(7)), 58.2 (*C*(1′)), 70.5 (*C*(3)), 77.6 (*C*(7a)), 82.3, 83.5 (*C*(1), *C*(2)), 114.9 (*C*Me_2), 173.9 (N*C*OMe); *m/z* $(ESI)^+$ 293 ($[M+Na]^+$, 40%), 271 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{23}N_2O_4^+$ ($[M+H]^+$) requires 271.1652; found 271.1651.

(1*R*,2*S*,3*S*,7*R*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)-7-acetamidohexahydro-1*H*-pyrrolizidine 328



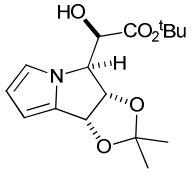
3.0 M aq HCl (2 mL) was added to a stirred solution of **327** (20 mg, 0.07 mmol, >99:1 dr) in MeOH (2 mL). The resultant mixture was heated at reflux for 2 h and then concentrated *in vacuo*. The residue was diluted with H_2O (2 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **328** as a colourless oil (11 mg); δ_H (500 MHz, MeOH-d_4) 1.68-1.76 (1H, m, C(6)H_A), 1.98 (3H, s, NCO*Me*), 2.10-2.16 (1H, m, C(6)H_B), 2.94-3.00 (2H, m, C(5)H_2), 3.09-3.11 (1H, m, C(7a)*H*), 3.16-3.20 (1H, m, C(3)*H*), 3.82-3.88 (2H, m, C(1′)H_2), 3.92 (1H, dd, *J* 8.8, 5.2, C(2)*H*), 4.02-4.06 (2H, m, C(1)*H*, C(7)*H*); δ_C (125 MHz, MeOH-d_4) 22.6 (NCO*Me*), 33.4 (*C*(6)), 47.0 (*C*(5)), 49.3 (*C*(3)), 54.7 (*C*(7)), 60.7 (*C*(1′)), 66.6 (*C*(7a)), 72.7 (*C*(2)), 75.9 (*C*(1)), 173.4 (N*C*OMe); *m/z* $(ESI)^+$ 253 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{18}N_2NaO_4^+$ ($[M+Na]^+$) requires 253.1159; found 253.1165.

(1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-1,2-Dihydroxy-3-(1′,2′-dihydroxyethyl)-7-aminohexahydro-1*H*-pyrrolizine 329



3.0 M aq HCl (2 mL) was added to a stirred solution of **322** (50 mg, 0.19 mmol, >99:1 dr) in MeOH (2 mL). The resultant mixture was heated at reflux for 2 h then allowed to cool to rt and concentrated *in vacuo*. The residue was diluted with H_2O (2 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **329** as a colourless oil (32 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ −22.3 (*c* 0.5 in MeOH); δ_H (400 MHz, MeOH-d_4) 1.54-1.65 (1H, m, C(5)H_A), 2.08-2.15 (1H, m, C(5)H_B), 2.84-2.89 (1H, m, C(6)H_A), 2.96-2.99 (1H, m, C(7a)*H*), 3.02-3.08 (3H, m, C(3)*H*, C(6)H_B, C(7)*H*), 3.62 (1H, dd, *J* 11.4, 6.6, C(2′)H_A), 3.69 (1H, dd, *J* 11.4, 4.3, C(2′)H_B), 3.92-3.95 (1H, m, C(1)*H*), 3.99-4.03 (1H, m, C(1′)*H*), 4.21 (1H, dd, *J* 8.3, 5.3, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 35.6 (*C*(5)), 46.8 (*C*(6)), 56.0, 64.7 (*C*(3), *C*(7)), 65.4 (*C*(2′)), 70.5 (*C*(1′)), 71.2 (*C*(2)), 74.5 (*C*(1)), 77.8 (*C*(7a)); *m/z* $(ESI)^+$ 219 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{19}N_2O_4^+$ ($[M+H]^+$) requires 219.1339; found 219.1337.

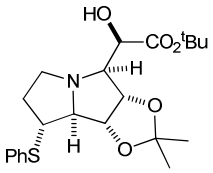
(1*R*,2*S*,3*S*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine 294



KOAc (350 mg, 1.76 mmol) was added to a stirred solution of **311** (100 mg, 0.18 mmol) in DMF (7 mL). The resultant mixture was stirred at 85 °C for 21 h then allowed to cool to rt. EtOAc (5 mL), $Na_2S_2O_3$ (5 mL) and satd aq $NaHCO_3$ (5 mL) were added sequentially and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with H_2O (5 x 5 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent, 30-40 °C petrol/EtOAc, 2:1) gave **294** as a yellow oil (3 mg, 5%, >99:1 dr); $[\alpha]_D^{25}$ +16.8 (*c* 0.1 in MeOH); ν_{max} (film) 3436 (O–H), 2979, 2926, 2853 (C−H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 3.17 (1H, d, *J* 3.5, O*H*), 4.46-4.48 (1H, m, C(1′)*H*), 4.61 (1H, br t, *J* 1.8,

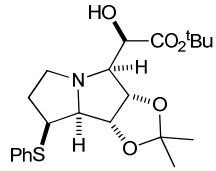
C(3)*H*), 5.13 (1H, dd, *J* 6.0, 1.8, C(2)*H*), 5.50 (1H, d, *J* 6.0, C(1)*H*), 6.10 (1H, d, *J* 3.2, C(7)*H*), 6.29 (1H, app t, *J* 3.2, C(6)*H*), 6.68-6.69 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 26.0, 26.9 (C*Me*$_2$), 27.8 (C*Me*$_3$), 67.0 (*C*(3)), 72.0 (*C*(1′)), 75.9 (*C*(1)), 84.5 (*C*(2)), 84.7 (*C*Me$_3$), 102.1 (*C*(7)), 112.2 (*C*Me$_2$), 113.9 (*C*(5)), 114.2 (*C*(6)), 135.3 (*C*(7a), 170.6 (*C*(2′)); *m/z* (ESI)$^+$ 641 ([2M+Na]$^+$, 95%), 332 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{23}NNaO_5^+$ ([M+Na]$^+$) requires 332.1468; found 332.1460. Further elution gave a complex mixture of products containing **295**. Further elution (eluent MeOH) gave **312** as a brown oil (36 mg, 65%, >99:1 dr).

(1*R*,2*S*,3*S*,7*R*,7a*S*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-(phenylthio)hexahydro-1*H*-pyrrolizine 341



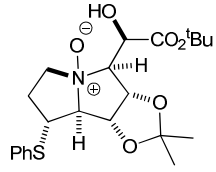
PhSH (0.18 mL, 1.77 mmol) and K_2CO_3 (244 mg, 1.77 mmol) were added to a stirred solution of **189**·HI (200 mg, 0.35 mmol) in THF (6 mL). The reaction mixture was left to stir at rt for 28 h then poured onto H_2O (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 10:1 increased to 30-40 °C petrol/EtOAc, 2:1) gave **341** as a yellow oil (101 mg, 67%, >99:1 dr);[41] $[\alpha]_D^{25}$ +32.6 (*c* 0.29 in $CHCl_3$); ν_{max} (film) 3367 (O–H), 2979, 2293, (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, s, *Me*CMe), 1.49 (12H, s, *Me*CMe, C*Me*$_3$), 1.84-1.94 (1H, m, C(6)H_A), 2.37-2.46 (1H, m, C(6)H_B), 2.88 (1H, td, *J* 8.3, 3.8, C(5)H_A), 2.95-3.02 (1H, m, C(5)H_B), 3.21 (1H, br s, O*H*), 3.33 (1H, dd, *J* 8.1, 3.3, C(7a)*H*), 3.40 (1H, app q, *J* 8.1, C(7)*H*), 3.46-3.48 (1H, m, C(3)*H*), 4.35-3.39 (2H, m, C(1)*H*, C(1′)*H*), 4.63 (1H, dd, *J* 6.3, 4.3, C(2)*H*), 7.18-7.45 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.1, 27.5 (C*Me*$_2$), 28.0 (C*Me*$_3$), 35.7 (*C*(6)), 46.6 (*C*(5)), 47.7 (*C*(7)), 68.2, 68.5 (*C*(3), *C*(1′)), 77.3 (*C*(7a)), 81.8 (*C*(2)), 82.7 (*C*(1)), 83.5 (*C*Me$_3$), 112.8 (*C*Me$_2$), 126.8 (*p-Ph*), 128.8, 131.7 (*o*,*m-Ph*), 135.0 (*i-Ph*), 172.9 (*C*(2′)); *m/z* (ESI$^+$) 865 ([2M+Na]$^+$, 100%), 444 ([M+Na]$^+$, 40%), 422 ([M+H]$^+$, 90%); HRMS (ESI$^+$) $C_{22}H_{32}NO_5S^+$ ([M+H]$^+$) requires 422.1996; found 422.1976.

(1*R*,2*S*,3*S*,7*S*,7a*S*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-(phenylthio)hexahydro-1*H*-pyrrolizine 342



PhSH (0.04 mL, 0.34 mmol) and K_2CO_3 (47 mg, 0.34 mmol) were added to a stirred solution of **311** (30 mg, 0.07 mmol) in THF (3 mL). The resultant mixture was stirred at rt for 7 days then poured onto H_2O (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave an impure sample of **342** as a yellow oil (2 mg, 4%, >99:1 dr); δ_H (500 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.51 (3H, s, *Me*CMe), 1.53 (9H, s, C*Me*$_3$), 2.03-2.09 (1H, m, C(6)H_A), 2.44-2.49 (1H, m, C(5)H_A), 2.51-2.58 (1H, m, C(6)H_B), 3.03-3.07 (1H, m, C(5)H_B), 3.13 (1H, app br s, C(3)*H*), 3.24-3.23 (1H, m, O*H*), 3.30 (1H, br t, C(7a)*H*), 3.72-3.75 (1H, m, C(7)*H*), 4.35 (1H, br s, C(1′)), 4.61 (1H, app t, *J* 6.0, C(1)*H*), 4.87 (1H, dd, *J* 5.0, 7.3, C(2)*H*), 7.16-7.20 (1H, m, *Ph*), 7.28-7.31 (2H, m, *Ph*), 7.34-7.36 (2H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 25.2, 27.4 (C*Me*$_2$), 28.0 (C*Me*$_3$), 36.1 (*C*(6)), 44.1 (*C*(7)), 45.8 (*C*(5)), 64.0 (*C*(3)), 69.8 (*C*(1′)), 76.2 (*C*(7a)), 77.7 (*C*(1)), 82.9 (*C*(2)), 83.2 (*C*Me$_3$), 113.8 (*C*Me$_2$), 125.9 (*p-Ph*), 127.5, 128.9 (*o,m-Ph*), 129.0 (*i-Ph*), 171.8 (*C*(2′)); *m/z* (ESI$^+$) 865 ([2M+Na]$^+$, 100%), 843 ([2M+H]$^+$, 40%), 444 ([M+Na]$^+$, 10%), 422 ([M+H]$^+$, 30%); HRMS (ESI$^+$) $C_{22}H_{32}NO_5S^+$ ([M+H]$^+$) requires 422.1996; found 422.1995. Further elution (eluent EtOAc) gave **312** as a yellow oil (7 mg, 34%, >99:1 dr).

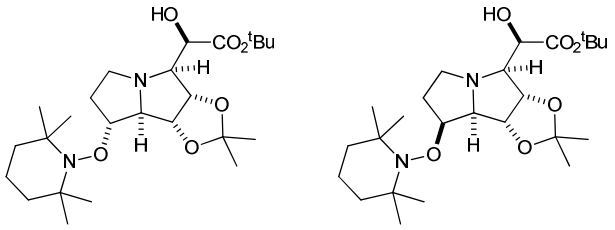
(1*R*,2*S*,3*S*,4*R*,7*R*,7a*S*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-4(*N*)-7-(phenylthio)hexahydro-1*H*-pyrrolizine *N*(4)-oxide 343[16]



A solution of *m*-CPBA (96 mg, 0.43 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of **341** (165 mg, 0.39 mmol, >99:1 dr) in CH_2Cl_2 (3 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min then diluted with CH_2Cl_2 (10 mL). The resultant

mixture was washed sequentially with satd aq $Na_2S_2O_3$ (10 mL), $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **343** as a white solid (109 mg, 64%, >99:1 dr); mp 150-155 °C; $[\alpha]_D^{20}$ +55.3 (*c* 0.23 in MeOH); δ_H (500 MHz, $CDCl_3$) 1.26 (3H, s, *Me*CMe), 1.50 (9H, s, C*Me*$_3$), 1.53 (3H, s, *Me*CMe), 2.47 (1H, app quintet, *J* 6.6, C(6)H_A), 2.77-2.86 (1H, m, C(6)H_B), 3.41 (1H, td, *J* 12.6, 5.4, C(5)H_A), 3.55-3.65 (2H, m, C(5)H_B, C*H*), 4.16 (1H, dd, *J* 8.6, C*H*), 4.25-4.32 (2H, m, 2 × C*H*), 4.82 (1H, dd, *J* 8.2, 5.9, C*H*), 4.95-4.97 (1H, m, C*H*), 7.29-7.56 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 25.3, 27.4 (C*Me*$_2$), 28.0 (C*Me*$_3$), 32.6 (*C*(6)), 48.3, 65.0 (*C*H), 65.6 (*C*(5)), 74.1, 81.7, 81.8 (*C*H), 84.6 (*C*Me$_3$), 92.0 (*C*H), 114.9 (*C*Me$_2$), 124.8 (*p-Ph*), 127.9, 129.2 (*o,m-Ph*), 132.2 (*i-Ph*), 171.0 (*C*(2′)); *m/z* (ESI$^+$) 438 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{32}NO_6S^+$ ([M+H]$^+$) requires 438.1945; found 438.1941.

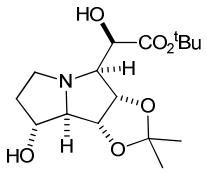
(1*R*,2*S*,3*S*,7*R*,7a*S*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexahydro-1*H*-pyrrolizine 351 and (1*R*,2*S*,3*S*,7*S*,7a*S*,1′*R*)-1,2-*O*-isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexahydro-1*H*-pyrrolizine 350



Bu_3SnH (0.15 mL, 0.53 mmol) was added in three portions to a stirred solution of **189**·HI (100 mg, 0.18 mmol, >99:1 dr) and TEMPO (140 mg, 0.88 mmol) in PhMe (5 mL) at 70 °C. The reaction mixture was heated at 70 °C for 1.5 h then cooled to rt and concentrated *in vacuo* to give an 75:25 mixture of **351** and **350**. Purification via flash column chromatography (10% KI in silica,42 eluent 30-40 °C petrol/acetone, 50:1 increased to 10:1) gave **351** as a yellow oil (57 mg, 69%, >99:1 dr);[43] $[\alpha]_D^{20}$ −6.3 (*c* 2.4 in $CHCl_3$); ν_{max} (ATR) 3484 (O−H), 2977, 2833, 2871 (C−H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.07 (3H, s, *Me*CMe), 1.09 (3H, s, *Me*CMe), 1.16 (3H, s, *Me*CMe), 1.22-1.27 (1H, m, CH_B) overlapping 1.22 (3H, s, *Me*CMe) and 1.26 (3H, s, *Me*CMe), 1.28-1.34 (1H, m, CH_B), 1.40-1.47 (4H, m, 2 × CH_2) 1.47 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 1.88-1.97 (1H, m, C(6)H_A), 2.26-2.33 (1H, m, C(6)H_B), 2.67

(1H, td, *J* 10.1, 6.3, C(5)H_A), 2.92-2.95 (1H, m, C(5)H_B), 3.22 (1H, d, *J* 4.3, O*H*), 3.40 (1H, app d, *J* 5.8, C(3)*H*), 3.55-3.58 (1H, m, C(7a)*H*), 4.36 (1H, td, *J* 7.6, 4.3, C(7)*H*), 4.41-4.43 (1H, m, C(1′)*H*), 4.54 (1H, dd, *J* 6.8, 3.5, C(1)*H*), 4.73 (1H, app t, *J* 6.8, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 17.2 (*C*H_2), 20.2 (2 × *Me*CMe), 25.4 (*Me*CMe), 27.7 (*Me*CMe), 27.9 (C*Me*$_3$), 34.2, 34.3 (*Me*CMe), 34.8 (*C*(6)), 40.2 (2 × *C*H_2), 47.7 (*C*(5)), 59.4, 59.8 (*C*Me_2), 68.8 (*C*(3), *C*(1′)), 75.6 (*C*(7a)), 78.9 (*C*(2)), 83.4 (*C*Me_3), 85.4 (*C*(1)), 89.7 (*C*(7)), 113.5 (*C*Me_2), 172.9 (*C*(2′)); *m/z* (ESI$^+$) 469 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{45}N_2O_6^+$ ([M+H]$^+$) requires 469.3272; found 469.3275. Further elution gave an impure sample of **350** as a brown oil (16 mg, 19%, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.16 (6H, s, 2 × *Me*CMe), 1.24-1.33 (2H, m, C*H*$_2$) overlapping 1.26 (6H, s, 2 × *Me*CMe) and 1.32 (3H, s, *Me*CMe), 1.43-1.49 (4H, m, 2 × C*H*$_2$), 1.49 (3H, s, *Me*CMe), 1.50 (9H, s, C*Me*$_3$), 2.08 (2H, app q, *J* 7.1, C(6)H_2), 2.63-2.69 (1H, m, C(5)H_A), 3.00-3.06 (1H, m, C(5)H_B), 3.27 (1H, d, *J* 3.8, O*H*), 3.38 (1H, dd, *J* 6.1, 1.5, C(3)*H*), 3.53-3.58 (1H, m, C(7a)*H*), 4.39-4.42 (1H, m, C(1′)*H*), 4.56 (1H, app q, *J* 6.1, C(7)*H*), 4.76 (1H, app t, *J* 6.6, C(2)*H*), 4.91 (1H, dd, *J* 6.8, 4.3, C(1)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 17.2 (*C*H_2), 25.4, 27.7 (C*Me*$_2$), 28.0 (C*Me*$_3$), 29.7 (C*H*$_2$), 33.2 (*C*(6)), 40.4 (*C*H_2), 45.5 (*C*(5)), 69.1 (*C*(3), *C*(1′)), 73.3 (*C*(7a)), 78.8 (*C*(1)), 80.1 (*C*(2)), 83.1 (*C*Me_3), 83.6 (*C*(7)), 113.4 (*C*Me_2), 172.5 (*C*(2′)); *m/z* (ESI$^+$) 469 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{45}N_2O_6^+$ ([M+H]$^+$) requires 469.3272; found 469.3263.

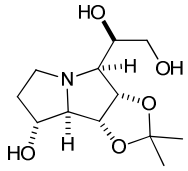
(1*R*,2*S*,3*S*,7*R*,7a*S*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-(hydroxy)hexahydro-1*H*-pyrrolizine 352



Activated Zn dust (1.12 g, 17.1 mmol) was added to a stirred solution of **351** (200 mg, 0.43 mmol, >99:1 dr) in AcOH/THF/H_2O (v/v 3:1:1, 35 mL). The reaction mixture was heated at 70 °C for 2 h then cooled to rt and filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo*. The resultant residue was redissolved in EtOAc (20 mL) and filtered through Celite® (eluent EtOAc). Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 2:1) gave **352** as a yellow oil (86 mg, 61%, >99:1 dr);[43] $[\alpha]_D^{20}$ +3.4 (*c* 1.3 in MeOH); ν_{max} (ATR) 3313 (O–H), 2981 (C–H), 1732 (C=O);

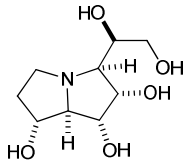
δ_H (300 MHz, MeOH-d_4) 1.30 (3H, s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 1.51 (9H, s, C*Me*$_3$), 1.68-1.79 (1H, m, C(6)H_A), 2.17-2.26 (1H, m, C(6)H_B), 2.90-2.97 (1H, m, C(5)H_A), 3.03-3.11 (1H, m, C(5)H_B), 3.27 (1H, dd, *J* 5.1, 3.1, C(7a)*H*), 3.47-3.49 (1H, m, C(3)*H*), 4.19 (1H, app q, *J* 6.9, C(7)*H*), 4.39 (1H, d, *J* 2.1, C(1′)*H*), 4.54 (1H, dd, *J* 6.3, 3.1, C(1)*H*), 4.77-4.81 (1H, m, C(2)*H*); δ_C (75 MHz, MeOH-d_4) 25.6, 27.9 (C*Me*$_2$), 28.3 (C*Me*$_3$), 36.4 (*C*(6)), 47.1 (*C*(5)), 69.6 (*C*(1′)), 70.1 (*C*(3)), 75.4 (*C*(7)), 79.7 (*C*(7a)), 82.4 (*C*(2)), 83.5 (*C*Me$_3$), 84.2 (*C*(1)), 114.0 (*C*Me$_2$), 173.7 (*C*(2′)); *m/z* (ESI$^+$) 330 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{28}NO_6^+$ ([M+H]$^+$) requires 330.1911; found 330.1907.

(1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-1,2-*O*-Isopropylidene-1,2-dihydroxy-3-(1′,2′-dihydroxyethyl)-7-(hydroxy)hexahydro-1*H*-pyrrolizidine 353



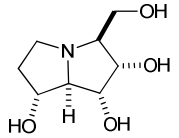
$LiAlH_4$ (1.0 M in THF, 0.91 mL, 0.91 mmol) was added to a stirred solution of **352** (75 mg, 0.23 mmol, >99:1 dr) in THF (5 mL) at −78 °C. The resultant mixture was allowed to warm to rt over 12 h before 2.0 M aq NaOH (1 mL) was added. The resultant mixture was left to stir at rt for a further 1 h, then filtered through Celite® (eluent EtOAc), dried and concentrated in *vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/Et_3N, 10:1:0.1) gave **353** as a pale yellow oil (27 mg, 46%, >99:1 dr); $[\alpha]_D^{20}$ −19.1 (*c* 1.1 in MeOH); ν_{max} (ATR) 3367 (O−H), 2983, 2933 (C−H); δ_H (300 MHz, MeOH-d_4) 1.22 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.57-1.68 (1H, m, C(6)H_A), 2.05-2.15 (1H, m, C(6)H_B), 2.79-2.84 (2H, m, C(5)H_2), 2.96-3.00 (1H, m, C(3)*H*), 3.17 (1H, app t, *J* 3.8, C(7a)*H*), 3.39-3.54 (2H, m, C(2′)H_2), 3.76-3.82 (1H, m, C(1′)*H*), 4.13-4.18 (1H, m, C(7)*H*), 4.42 (1H, dd, *J* 6.6, 3.8, C(1)*H*), 4.73-4.77 (1H, m, C(2)*H*); δ_C (75 MHz, MeOH-d_4) 25.5, 27.8 (C*Me*$_2$), 36.0 (*C*(6)), 47.6 (*C*(5)), 65.9 (*C*(2′)), 69.4 (*C*(3)), 71.3 (*C*(1′)), 75.5 (*C*(7)), 79.2 (*C*(7a)), 82.3 (*C*(2)), 85.1 (*C*(1)); *m/z* (ESI$^+$) 282 ([M+Na]$^+$, 30%), 260 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_5^+$ ([M+H]$^+$) requires 260.1492; found 260.1489.

(1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-1,2-Dihydroxy-3-(1′,2′-dihydroxyethyl)-7-(hydroxy)hexahydro-1*H*-pyrrolizidine 354



3.0 M aq HCl (0.5 mL) was added to a stirred solution of **353** (7 mg, 0.03 mmol, >99:1 dr) in MeOH (1 mL). The reaction mixture was heated at reflux for 2 h then concentrated *in vacuo*. The residue was dissolved in H_2O (0.5 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **354** as a colourless oil (5 mg, 84%, >99:1 dr); $[\alpha]_D^{20}$ –22.0 (*c* 0.3 in MeOH); δ_H (500 MHz, MeOH-d_4) 1.71-1.78 (1H, m, C(6)H_A), 2.07-2.13 (1H, m, C(6)H_B), 2.92 (1H, ddd, *J* 10.4, 6.9, 3.5, C(5)H_A), 3.06-3.11 (2H, m, C(3)*H*, C(5)H_B), 3.17 (1H, dd, *J* 5.4, 3.0, C(7a)*H*), 3.63 (1H, dd, *J* 11.4, 6.6, C(2′)H_A), 3.69 (1H, dd, *J* 11.4, 6.6, C(2′)H_B), 3.91 (1H, dd, *J* 5.6, 3.0, C(1)*H*), 4.00-4.07 (2H, m, C(7)*H*, C(1′)*H*), 4.17 (1H, dd, *J* 8.5, 5.6, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 35.7 (*C*(6)), 47.0 (*C*(5)), 66.1 (*C*(3)), 66.5 (*C*(2′)), 71.4 (*C*(1′)), 71.9 (*C*(2)), 75.3 (*C*(1)), 75.9 (*C*(7)), 78.4 (*C*(7a)); *m/z* (ESI^+) 220 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{18}NO_5^+$ ($[M+H]^+$) requires 220.1179; found 220.1188.

(1*R*,2*S*,3*S*,7*R*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)-7-(hydroxy)hexahydro-1*H*-pyrrolizidine [(–)-1-*epi*-alexine] 356[44]

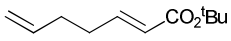


$NaIO_4$ (165 mg, 0.77 mmol) was added to a solution of **353** (19 mg, 0.08 mmol) in MeOH/H_2O (v/v 2:1, 1.5 mL). The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (29 mg, 0.77 mmol) was then added to the filtrate and the resultant mixture was allowed to stir at rt for 12 h before satd aq NH_4Cl (0.5 mL) was added. The resultant mixture was filtered through Celite® (eluent EtOAc/MeOH, 3:1) and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 10:1) gave **355**. 3.0 M aq HCl (0.5 mL) was added to a stirred solution of **355** in MeOH (1 mL). The reaction mixture was heated at reflux for 2 h then concentrated *in vacuo*. The residue was dissolved in H_2O (0.5 mL) and purified on DOWEX 1X8-200 (OH^- form) ion

exchange resin, and then on DOWEX 50WX8 (H^+ form) to give **356** as a colourless oil (4 mg, 29%, >99:1 dr); $[\alpha]_D^{20}$ −48 (*c* 0.03 in H_2O); $[\alpha]_D^{20}$ −60 (*c* 0.03 in MeOH); {lit.[27] $[\alpha]_D^{20}$ −51.0 (*c* 0.51 in H_2O); lit.[44a] for *ent*-**356** $[\alpha]_D$ +59.7 (*c* 0.58 in H_2O); lit.[44b] for *ent*-**356** $[\alpha]_D^{25}$ +53.4 (*c* 0.43 in H_2O)}; δ_H (500 MHz, D_2O) 1.62-1.70 (1H, m, C(6)H_A), 2.02-2.07 (1H, m, C(6)H_B), 2.80 (1H, td, *J* 10.5, 5.8, C(5)H_A), 2.88-2.91 (1H, m, C(5)H_B), 3.07-3.12 (2H, m, C(3)*H*, C(7a)*H*), 3.76 (1H, s, C(1′)H_A), 3.78 (1H, d, *J* 1.9, C(1′)H_B), 3.85 (1H, dd, *J* 9.8, 5.2, C(2)*H*), 3.96 (1H, dd, *J* 5.2, 2.2, C(1)*H*), 4.02-4.06 (1H, m, C(7)*H*); δ_C (125 MHz, D_2O) 33.4 (*C*(6)), 44.7 (*C*(5)), 58.9 (*C*(1′)), 64.4 (*C*(3)), 70.9 (*C*(2)), 73.6 (*C*(1)), 74.2 (*C*(7)), 75.7 (*C*(7a); δ_H (500 MHz, D_2O [TSP]) 1.71-1.78 (1H, m, C(6)H_A), 2.09-2.16 (1H, m, C(6)H_B), 2.85 (1H, td, *J* 10.4, 5.7, C(5)H_A), 2.96 (1H, ddd, *J* 10.1, 6.9, 3.2, C(5)H_B), 3.13 (1H, dd, J 5.7, 2.4, C(7a)*H*), 3.15-3.18 (1H, m, C(3)*H*), 3.86 (1H, d, *J* 1.6, C(1′)H_A), 3.87 (1H, d, *J* 4.1, C(1′)H_B), 3.93 (1H, dd, *J* 9.5, 5.4, C(2)*H*), 4.05 (1H, dd, *J* 5.4, 2.4, C(1)*H*), 4.12 (1H, ddd, *J* 8.2, 6.3, 6.0, C(7)*H*); δ_C (125 MHz, D_2O [TSP]) 36.4 (*C*(6)), 47.5 (*C*(5)), 62.0 (*C*(1′)), 67.3 (*C*(3)), 73.9 (*C*(2)), 76.7 (*C*(1)), 77.2 (*C*(7)), 78.5 (*C*(7a); *m/z* (ESI^+) 190 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_4^+$ ($[M+H]^+$) requires 190.1074; found 190.1076.

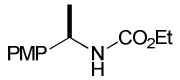
6.5 Experimental data for Chapter 5

tert-Butyl (*E*)-hepta-2,6-dienoate 133[45]



248 (49.2 g, 131 mmol) was added to a stirred mixture of 4-pentenal (10.0 g, 119 mmol) in CH_2Cl_2 (500 mL) and the reaction mixture was left to stir for 48 h at rt then concentrated *in vacuo* to give **133** in 97:3 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 100:1) gave **133** as a colourless oil (17.5 g, 81%, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, CMe_3), 2.18-2.32 (4H, m, C(4)H_2, C(5)H_2), 4.99-5.09 (2H, m, C(7)H_2), 5.74-5.87 (2H, m, C(2)*H*, C(6)*H*), 6.86 (1H, dt, *J* 15.4, 6.5, C(3)*H*).

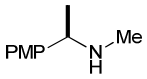
Ethyl (*R*)-*N*-(α-methyl-*p*-methoxybenzyl)carbamate 425



A solution of ethyl chloroformate (31.5 mL, 0.33 mmol) in Et_2O (250 mL) at 0 °C was added to a stirred solution of (*R*)-*N*-(α-methyl-*p*-methoxybenzyl)amine (50.0 g, 0.33 mmol) and

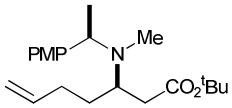
Et_3N (55.0 mL, 0.40 mmol) in Et_2O (250 mL) at 0 °C and the resultant mixture was left to warm to rt over 2 h. After this time the reaction mixture was washed sequentially with 1.0 M aq HCl (250 mL), satd aq $NaHCO_3$ (250 mL) and brine (250 mL), then filtered through Celite®, dried and concentrated *in vacuo* to give **425** as a white solid (64.5 g, 87%); mp 67-70 °C; $[\alpha]_D^{20}$ +79.3 (*c* 0.29 in CH_2Cl_2); ν_{max} (ATR) 3356 (N–H), 2976, 2933 (C–H), 1686 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1, CH_2CH_3), 1.46 (3H, d, *J* 6.8, C(α)*Me*), 3.80 (3H, s, O*Me*), 4.04-4.06 (2H, m, CH_2CH_3), 4.75-4.84 (1H, m, C(α)*H*), 4.93 (1H, br s, N*H*), 6.87 (2H, d, *J* 8.6, *Ar*), 7.24 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_2CH_3), 22.4 (C(α)*Me*), 49.9 (*C*(α)), 55.3 (O*Me*), 60.7 (CH_2CH_3), 113.9, 127.1, 135.8, 155.8 (*Ar*), 158.7 (CO_2Et); *m/z* (ESI)$^+$ 246 ($[M+H]^+$, 100%), 278 ($[M+Na]^+$, 25%); HRMS (ESI^+) $C_{12}H_{17}NNaO_3^+$ ($[M+Na]^+$) requires 246.1101, found 246.1098.

(*R*)-*N*-Methyl-*N*-(α-methyl-*p*-methoxybenzyl)amine 382[46]



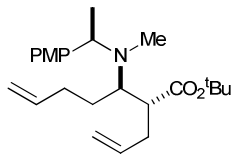
A solution of **425** (5.00 g, 22.4 mmol) in THF (50 mL) at 0 °C was added to a stirred solution of $LiAlH_4$ (1.69 g, 44.8 mmol) in THF (100 mL) at 0 °C. The resultant mixture was heated at 60 °C for 24 h then allowed to cool to rt and satd aq Na_2SO_4 (15 mL) was added. The resultant slurry was filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. The resultant residue was dissolved in CH_2Cl_2 (100 mL) and washed with 1.0 M aq HCl (100 mL). The aqueous layer was separated and 35% aq NH_4OH (~50 mL) was added until the solution was pH~13. The resultant aqueous solution was then extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **382** as a colourless oil (3.54 g, 96%, >99% ee);[47] δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.5, C(α)*Me*), 1.39-1.55 (1H, br s, N*H*), 2.30 (3H, s, N*Me*), 3.60 (1H, q, *J* 6.5, C(α)*H*), 3.81 (3H, s, O*Me*), 6.88 (2H, d, *J* 8.5, *Ar*), 7.23 (2H, d, *J* 8.5, *Ar*).

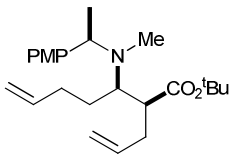
tert-Butyl (*R*,*R*)-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] hept-6-enoate 385



BuLi (2.2 M in hexanes, 4.31 mL, 9.39 mmol) was added dropwise via syringe to a stirred solution of **382** (1.63 g, 8.94 mmol) in THF (10 mL) at −78 °C. After stirring for 30 min a solution of **133** (1.63 g, 9.84 mmol, >99:1 dr) in THF (10 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir for a further 2 h, before addition of satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (25 mL) and 10% aq citric acid solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (25 mL), H_2O (25 mL) and brine (25 mL), then dried and concentrated *in vacuo* to give **385** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave **385** as a yellow oil (2.29 g, 74%, >99:1 dr); $[\alpha]_D^{20}$ −3.2 (*c* 1.32 in $CHCl_3$); ν_{max} (ATR) 2975, 2932 (C−H), 1725 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.26-1.36 (1H, m, C(4)H_A) overlapping 1.32 (3H, d, *J* 6.7, C(α)*Me*), 1.42 (9H, s, CMe_3), 1.51-1.58 (1H, m, C(4)H_B), 1.88-1.98 (1H, m, C(5)H_A), 2.05-2.13 (1H, m, C(5)H_B) overlapping 2.08 (1H, dd, *J* 13.7, 8.3, C(2)H_A) and 2.12 (3H, s, N*Me*), 2.38 (1H, dd, *J* 13.7, 5.6, C(2)H_B), 3.12-3.19 (1H, m, C(3)*H*), 3.56 (1H, q, *J* 6.7, C(α)*H*), 3.79 (3H, s, O*Me*), 4.89-4.99 (2H, m, C(7)H_2), 5.70-5.80 (1H, m, C(6)*H*), 6.83 (2H, d, *J* 8.7, *Ar*), 7.23 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.8 (C(α)*Me*), 28.1 (CMe_3), 30.4, 30.8 (*C*(4), *C*(5)), 31.8 (N*Me*), 36.5 (*C*(2)), 55.2 (O*Me*), 55.5 (*C*(3)), 61.2 (*C*(α)), 79.9 (*C*Me_3), 113.5 (*Ar*), 114.2 (*C*(7)), 128.4, 138.0 (*Ar*), 138.8 (*C*(6)), 158.4 (*Ar*), 172.4 (*C*(1)); *m/z* (ESI)$^+$ 348 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{34}NO_3^+$ ([M+H]$^+$) requires 348.2533, found 348.2529.

tert-Butyl (*R*,*R*,*R*)-2-[1′-allyl]-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-hept-6-enoate 386 and _tert_-butyl (2*S*,3*R*,α*R*)-2-[1′-allyl]-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-hept-6-enoate 387



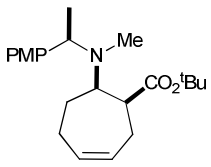


Method A: BuLi (2.1 M in hexanes, 0.80 mL, 1.70 mmol) was added dropwise via syringe to a stirred solution of **382** (290 mg, 1.76 mmol) in THF (3 mL) at −78 °C. After stirring for 30 min a solution of **133** (200 mg, 1.10 mmol, >99:1 dr) in THF (3 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir for a further 2 h, before the addition of freshly distilled allyl bromide (0.47 mL, 5.49 mmol). The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (5 mL) and 10% aq citric acid solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 20:1 increased to 10:1) gave **386** as a colourless oil (102 mg, 24%, >99:1 dr); $[\alpha]_D^{25}$ +22.8 (*c* 0.22 in $CHCl_3$); ν_{max} (ATR) 2975, 2934 (C−H), 1725 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31-1.41 (1H, m, C(4)H_A) overlapping 1.35 (3H, d, *J* 6.6, C(α)*Me*), 1.45 (9H, s, CMe_3), 1.64-1.73 (1H, m, C(4)H_B), 1.95-2.04 (1H, m, C(5)H_A), 2.11 (3H, s, N*Me*), 2.12-2.19 (1H, m, C(5)H_B, 2.25-2.31 (1H, m, C(1′)H_A), 2.43-2.53 (2H, m, C(2)*H*, C(1′)H_B), 3.03 (1H, td, *J* 8.0, 4.5, C(3)*H*), 3.73 (1H, q, *J* 6.6, C(α)*H*), 3.80 (3H, s, O*Me*), 4.92-5.08 (4H, m, C(7)H_2, C(3′)H_2), 5.70-5.83 (2H, m, C(6)*H*, C(2′)*H*), 6.85 (2H, d, *J* 8.6, *Ar*), 7.22 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.5 (C(α)*Me*), 28.1 (CMe_3), 28.6 (*C*(4)), 31.8 (*C*(5)), 32.6 (N*Me*), 36.0 (*C*(1′)), 49.3 (*C*(2)), 55..2 (O*Me*), 59.0 (*C*(3)), 61.9 (*C*(α)), 80.3 (*C*Me$_3$), 113.6 (*Ar*), 114.1, 116.1 (*C*(7), *C*(3′)), 128.2 (*Ar*), 136.3, 138.9 (*C*(6), *C*(2′)), 138.7, 158.4 (*Ar*), 174.5 (*C*(1)); *m/z* (ESI)$^+$ 388 ([M+H], 100%), 410 ([M+Na], 75%); HRMS (ESI$^+$) $C_{24}H_{38}NO_3^+$ ([M+H]$^+$) requires 388.2846, found 388.2844. Further elution gave an 38:62 mixture of **386** and **387** (115 mg, 27%); *m/z* (ESI)$^+$ 797 ([2M+Na], 100%), 410 ([M+Na]$^+$, 80%); HRMS (ESI$^+$) $C_{24}H_{37}NNaO_3^+$ ([M+H]$^+$) requires 410.2666, found 410.2667. Data for **387**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.34 (3H, d, *J* 6.7, C(α)*Me*), 1.46 (9H, s, CMe_3),

2.10 (3H, s, N*Me*), 3.12 (1H, app q, *J* 6.6, C(3)*H*), 3.63 (1H, q, *J* 6.7, C(α)*H*), 3.78 (3H, s, O*Me*), 4.92-5.11 (4H, m, C(7)H_2, C(3′)H_2), 5.70-5.83 (2H, m, C(6)*H*, C(2′)*H*), 6.81 (2H, d, *J* 8.6, *Ar*), 7.21 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 22.1 (C(α)*Me*), 28.1 (CMe_3), 56.9 (*C*(3)), 62.9 (*C*(α)), 80.4 (*C*Me_3), 113.3 (*Ar*), 114.4, 116.3 (*C*(7), *C*(3′)), 128.4 (*Ar*), 135.7, 135.9 (*C*(6), *C*(2′)), 138.6, 158.3 (*Ar*), 174.1 (*C*(1)). Further elution gave **385** as a colourless oil (76 mg, 20%, >99:1 dr).

Method B: BuLi (2.3 M in hexanes, 3.81 mL, 8.93 mmol) was added dropwise via syringe to a stirred solution of **382** (1.52 g, 9.22 mmol) in THF (20 mL) at −78 °C. After stirring for 30 min a solution of **133** (1.05 g, 5.76 mmol, >99:1 dr) in THF (20 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir for a further 2 h, before the addition of freshly distilled allyl bromide (2.50 mL, 28.8 mmol). The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (20 mL) and 10% aq citric acid solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 20:1 increased to 10:1) gave a 68:32 mixture of **386** and **387** (1.42 g, 64%). Further elution gave **385** as a colourless oil (118 mg, 5%, >99:1 dr).

tert-Butyl (1*S*,7*R*,*αR*)-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] cyclohept-3-ene-1-carboxylate 388

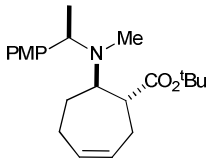


Method A: Grubbs I catalyst (42 mg, 0.05 mmol) was added to a stirred solution of **386** (100 mg, 0.26 mmol, >99:1 dr) in degassed CH_2Cl_2 (10 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and **424** (633 mg, 5.10 mmol), Et_3N (0.07 mL, 0.52 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for a further 12 h, then filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 20:1) gave **388** as a yellow oil (79 mg, 85%,

>99:1 dr); $[\alpha]_D^{25}$ +18.9 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 2972, 2931 (C–H), 1727 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.6, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.52-1.55 (1H, m, C(6)*H*$_A$), 1.96-2.03 (1H, m, C(5)*H*$_A$), 2.05-2.11 (1H, m, C(6)*H*$_B$), 2.17 (3H, s, N*Me*), 2.20-2.27 (2H, m, C(2)*H*$_A$, C(5)*H*$_B$), 2.54-2.62 (1H, m, C(2)*H*$_B$), 2.96 (1H, ddd, *J* 10.1, 5.8, 2.3, C(1)*H*), 3.42 (1H, app quintet, *J* 6.1, C(7)*H*), 3.73 (1H, q, *J* 6.6, C(α)*H*), 3.80 (3H, s, O*Me*), 5.58-5.64 (1H, m, C(3)*H*), 5.67-5.74 (1H, m, C(4)*H*), 6.83 (2H, d, *J* 8.7, *Ar*), 7.24 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 24.0 (*C*(6)), 26.0 (*C*(5)), 27.6 (*C*(2)), 28.3 (C*Me*$_3$), 33.5 (N*Me*), 48.3 (*C*(1)), 55.2 (O*Me*), 61.0 (*C*(α)), 61.5 (*C*(7)), 79.6 (*C*Me$_3$), 113.4, 128.4 (*Ar*), 128.9 (*C*(3)), 131.4 (*C*(4)), 137.7, 158.2 (*Ar*), 173.7 (*C*O_2^tBu); *m/z* $(ESI)^+$ 360 ([M+H], 100%); HRMS (ESI^+) $C_{22}H_{34}NO_3^+$ ($[M+H]^+$) requires 360.2533, found 360.2535.

Method B: Grubbs I catalyst (595 mg, 0.72 mmol) was added to a stirred solution of a 68:32 mixture of **386** and **387** (1.40 g, 3.61 mmol) in degassed CH_2Cl_2 (140 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and **424** (8.97 g, 72.2 mmol), Et_3N (1.0 mL, 7.22 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for a further 12 h, then filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 20:1) gave a 61:39 mixture of **388** and **389** as a yellow oil (1.00 g, 77%, >99:1 dr); *m/z* $(ESI)^+$ 360 ([M+H], 100%); HRMS (ESI^+) $C_{22}H_{34}NO_3^+$ ($[M+H]^+$) requires 360.2533, found 360.2532. Further elution gave **388** as a yellow oil (50 mg, 4%, >99:1 dr).

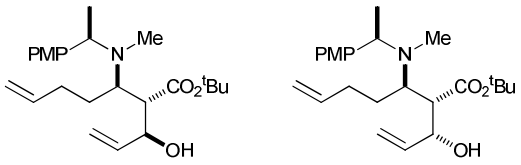
tert-Butyl (*R*,*R*,*R*)-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] cyclohept-3-ene-1-carboxylate 389



KO^{t}Bu (20 mg, cat.) was added to a stirred solution of an 61:39 mixture of **388** and **389** (744 mg, 2.07 mmol) in ^{t}BuOH (70 mL). The reaction mixture was left to stir at 80 °C for 3 h before the addition of satd aq NH_4Cl (10 mL). The resultant mixture was diluted with Et_2O (50 mL) and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography

(eluent 30-40 °C petrol/acetone, 20:1) gave **389** as a pale yellow oil (513 mg, 69%, >99:1 dr); $[\alpha]_D^{25}$ 18.1 (*c* 0.97 in $CHCl_3$); ν_{max} (ATR) 2972, 2931 (C–H), 1725 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 1.22 (1H, app q, *J* 11.9, C(6)H_A), 1.32 (3H, d, *J* 6.7, C(α)*Me*), 1.50 (9H, s, CMe_3), 1.65-1.74 (1H, m, C(6)H_B), 1.91-2.00 (1H, m, C(5)H_A) overlapping 2.00 (3H, s, N*Me*), 2.14-2.23 (1H, m, C(5)H_B), 2.24-2.39 (2H, m, C(2)H_2), 2.41 (1H, td, *J* 9.85, 2.8, C(7)*H*), 3.34 (1H, td, *J* 10.6, 2.8, C(1)*H*), 3.55 (1H, q, *J* 6.7, C(α)*H*), 3.78 (3H, s, O*Me*), 5.73-5.79 (1H, m, C(3)*H*), 5.85-5.91 (1H, m, C(4)*H*), 6.80 (2H, d, *J* 8.6, *Ar*), 7.21 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.0 (C(α)*Me*), 23.7 (*C*(6)), 25.1 (*C*(5)), 28.2 (CMe_3), 29.5 (*C*(2)), 33.0 (N*Me*), 49.4 (*C*(7)), 55.1 (O*Me*), 61.6 (*C*(α)), 63.6 (*C*(1)), 79.3 (*C*Me_3), 113.3, 128.3 (*Ar*), 129.3 (*C*(3)), 133.6 (*C*(4)), 138.6, 158.3 (*Ar*), 174.6 (*C*$O_2{}^t$Bu); *m/z* $(ESI)^+$ 360 ([M+H], 100%); HRMS (ESI^+) $C_{22}H_{34}NO_3^+$ ($[M+H]^+$) requires 360.2533, found 360.2531.

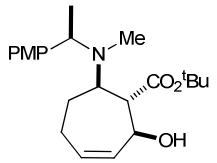
***tert*-Butyl (2*S*,3*R*,α*R*,1′*S*)-2-(1′-hydroxyprop-2′-en-1′-yl)-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] hept-6-enoate 390A**[16] **and *tert*-butyl (2*S*,3*R*,α*R*,1′*R*)-2-(1′-hydroxyprop-2′-en-1′-yl)-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] hept-6-enoate 390C**



BuLi (1.9 M in hexanes, 0.69 mL, 1.15 mmol) was added dropwise via syringe to a stirred solution of **382** (200 mg, 1.20 mmol) in THF (1 mL) at −78 °C. After stirring for 30 min a solution of **133** (200 mg, 1.10 mmol, >99:1 dr) in THF (1.2 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir for a further 2 h, before addition of acrolein (0.15 mL, 2.19 mmol). The resultant mixture was allowed to warm to rt over 2 h then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (5 mL) and 10% aq citric acid solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 77:6:13:4 mixture of **390A**, **390B**, **390C** and **390D**. Purification via flash column chromatography gave **390A** as a pale yellow solid (261 mg, 59%, >99:1 dr); mp 79-83 °C; $[\alpha]_D^{25}$ +7.6 (*c* 1.9 in $CHCl_3$); ν_{max} (ATR) 3482 (O–H), 2976, 2933 (C–H), 1700 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$)

1.36 (3H, d, *J* 6.7, C(α)*Me*), 1.46 (9H, s, C*Me*$_3$), 1.56-1.71 (2H, m, C(4)*H*$_2$), 2.08 (3H, s, N*Me*), 2.11-2.25 (2H, m, C(5)*H*$_2$), 2.60 (1H, dd, *J* 9.6, 2.5, C(2)*H*), 3.61-3.67 (1H, m, C(3)*H*) overlapping 3.64 (1H, q, *J* 6.7, C(α)*H*), 3.79 (3H, s, O*Me*), 4.27 (1H, br s, C(1′)*H*), 4.38 (1H, br s, O*H*), 4.94-4.98 (1H, m, C(7)*H*$_A$), 5.00-5.05 (1H, m, C(7)*H*$_B$), 5.16 (1H, dt, 10.6, 1,5, C(3′)*H*$_A$), 5.37 (1H, dt, *J* 17.2, 1.5, C(3′)*H*$_B$), 5.73-5.83 (1H, m, C(6)*H*), 5.86-5.94 (1H, m, C(2′)*H*), 6.81 (2H, d, *J* 8.7, *Ar*), 7.19 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(α)*Me*), 27.2 (*C*(4)), 28.3 (C*Me*$_3$), 32.1 (*C*(5)), 32.7 (N*Me*), 54.6 (*C*(2)), 55.2 (O*Me*), 57.2, 62.7 (*C*(3), *C*(α)), 71.1 (*C*(1′)), 81.3 (*C*Me$_3$), 113.4 (*Ar*), 114.6 (*C*(7), *C*(3′)), 128.5, 137.8 (*Ar*), 138.6, 139.1 (*C*(6), *C*(2′)), 158.5 (*Ar*), 173.3 (*C*(1)); *m/z* (ESI)$^+$ 829 ([2M+Na]$^+$, 100%), 426 ([M+Na]$^+$, 20%), 404 ([M+H]$^+$, 40%); HRMS (ESI$^+$) $C_{24}H_{38}NO_4^+$ ([M+H]$^+$) requires 404.2795; found 404.2786. Further elution gave **390D** as an impure fraction (14 mg). Further elution gave **390C** as a pale yellow oil (31 mg, 7%, >99:1 dr); $[\alpha]_D^{20}$ +29.8 (*c* 1.45 in $CHCl_3$); ν_{max} (ATR) 3400 (O−H), 2856, 2931, 2975 (C−H), 1723 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.36-1.42 (1H, m, C(4)*H*$_A$) overlapping 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.46 (9H, s, C*Me*$_3$), 1.75-1.84 (1H, m, C(4)*H*$_B$), 1.91-2.00 (1H, m, C(5)*H*$_A$), 2.07-2.16 (1H, m, C(5)*H*$_B$), 2.19 (3H, s, N*Me*), 2.65 (1H, app t, *J* 5.3, C(2)*H*), 3.42-3.46 (1H, m, C(3)*H*), 3.80 (3H, s, O*Me*), 3.81 (1H, q, *J* 6.8, C(α)*H*), 4.66-4.69 (1H, m, C(1′)*H*), 4.95-4.99 (1H, m, C(7)*H*$_2$), 5.23 (1H, dt, *J* 10.4, 1.5, C(3′)*H*$_A$), 5.48 (1H, dt, *J* 16.9, 1.5, C(3′)*H*$_B$), 5.64-5.75 (1H, m, C(6)*H*), 5.95 (1H, ddd, *J* 16.9, 10.4, 4.8, C(2′)*H*), 6.85 (2H, d, *J* 8.6, *Ar*), 7.19 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 25.2 (*C*(4)), 28.1 (C*Me*$_3$), 31.5 (*C*(5)), 32.7 (N*Me*), 50.6 (*C*(2)), 55.2 (O*Me*), 58.9 (*C*(3)), 61.9 (*C*(α)), 72.4 (*C*(1′)), 80.9 (*C*Me$_3$), 113.7 (*Ar*), 115.2 (*C*(7)), 115.5 (*C*(3′)), 128.7 (*Ar*), 137.9 (*C*(6)), 140.0 (*C*(2′)), 158.8 (*Ar*), 171.9 (*C*(1)); *m/z* (ESI)$^+$ 829 ([2M+Na]$^+$, 100%), 426 ([M+Na]$^+$, 15%), 404 ([M+H]$^+$, 75%); HRMS (ESI$^+$) $C_{24}H_{38}NO_4^+$ ([M+H]$^+$) requires 404.2795; found 404.2780.

tert-Butyl (1*S*,2*S*,7*R*,α*R*)-2-hydroxy-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] cyclohept-3-ene-1-carboxylate 391A[16]

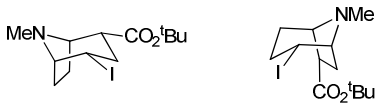


Method A: Grubbs I catalyst (526 mg, 0.64 mmol) was added to a stirred solution of **390A** (1.20 g, 3.20 mmol, >99:1 dr) in degassed CH_2Cl_2 (120 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (70mL) and **424** (7.94 g, 64.0 mmol), Et_3N (0.89 mL, 6.40 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for a further 12 h, then filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 10:1) gave **391A** as a white solid (1.05 g, 95%, >99:1 dr); mp 97-103 °C; $[\alpha]_D^{25}$ +29.4 (*c* 1.19 in $CHCl_3$); ν_{max} (ATR) 3440 (O–H), 2972, 2932 (C–H), 1708 (C=O), 1654 (C=C); δ_H (400 MHz, $CDCl_3$) 1.13-1.23 (1H, m, C(6)H_A), 1.30 (3H, d, *J* 6.7, C(α)*Me*), 1.51 (9H, s, CMe_3), 1.62-1.67 (1H, m, C(6)H_B), 1.80-1.88 (1H, m, C(5)H_A), 1.97 (N*Me*), 2.13-2.20 (1H, m, C(5)H_B), 2.66 (1H, app t, *J* 10.6, C(1)*H*), 2.76-2.87 (1H, br s, O*H*), 3.35 (1H, td, *J* 10.6, 2.8, C(7)*H*), 3.52 (1H, q, *J* 6.7, C(α)*H*), 3.77 (3H, s, O*Me*), 4.51-4.58 (1H, m, C(2)*H*), 5.71-5.81 (2H, m, C(3)*H*, C(4)*H*), 6.79 (2H, d, *J* 8.6, *Ar*), 7.19 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(α)*Me*), 23.3 (*C*(6)), 25.1 (*C*(5)), 28.3 (CMe_3), 33.1 (N*Me*), 55.2 (O*Me*), 57.9 (*C*(1)), 60.9 (*C*(7)), 61.6 (*C*(α)), 71.2 (*C*(2)), 80.3 (*C*Me_3), 113.3, 128.4, 137.0 (*Ar*), 129.6, 138.2 (*C*(3), *C*(4)), 158.3 (*Ar*), 173.1 (*C*O_2^{t}Bu); *m/z* (ESI)$^+$ 376 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{34}NO_4^+$ ([M+H]$^+$) requires 376.2482; found 376.2486.

Method B: BuLi (2.3 M in hexanes, 8.62 mL, 19.8 mmol) was added dropwise via syringe to a stirred solution of **382** (3.43 g, 20.8 mmol) in THF (25 mL) at −78 °C. After stirring for 30 min a solution of **133** (3.44 g, 18.9 mmol, >99:1 dr) in THF (25 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir for a further 2 h, before addition of acrolein (2.52 mL, 37.7 mmol). The resultant mixture was allowed to warm to rt over 2 h then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (50 mL), H_2O

(50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. The resulting residue was dissolved in degassed CH_2Cl_2 (600 mL) and heated to 30 °C then Grubbs I catalyst (2.60 g, 3.16 mmol) was added. The resultant mixture was stirred at 30 °C for 12 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (150 mL) and **424** (39.2 g, 316 mmol), EtN (5.27 mL, 37.8 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for a further 12 h, then filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 30:1) gave **391A** as a white solid (4.68 g, 66%, >99:1 dr).

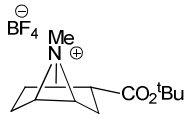
tert-Butyl (1*R*,2*R*,4*R*,5*S*)-4-iodo-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate 395 and *tert*-butyl (1*R*,2*R*,5*R*,6*S*)-2-iodo-8-methyl-8-azabicyclo[3.2.1]octane-6-carboxylate 396



I_2 (203 mg, 0.80 mmol) was added to a stirred solution of **389** (100 mg, 0.27 mmol, >99:1 dr) in CH_2Cl_2 (10 mL) at rt. The reaction mixture was allowed to stir at rt for 12 h before the addition of $Na_2S_2O_3$ (excess). After stirring for 15 min the mixture was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 10:1 increased to 2:1) gave a 77:23 mixture of **395** and **396** as a brown oil (56 mg, 57%); Data for **395**: ν_{max} (ATR) 2970, 2879, 2797 (C−H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, CMe_3), 1.59-1.65 (1H, m, C(7)H_A), 1.96-2.01 (2H, m, C(6)H_2), 2.03-2.07 (1H, m, C(7)H_B), 2.10-2.17 (1H, m, C(3)H_A), 2.29-2.32 (1H, m, C(3)H_B), 2.36 (3H, s, N*Me*), 2.77 (1H, ddd, *J* 12.4, 5.1, 3.0, C(2)*H*), 3.37 (1H, br s, C(5)*H*), 3.51 (1H, br s, C(1)*H*), 4.42 (1H, ddd, *J* 12.4, 5.3, 2.8, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 23.5, 23.7 (*C*(6), *C*(7)), 28.0 (CMe_3), 30.9 (*C*(4)), 32.2 (*C*(3)), 39.5 (N*Me*), 47.7 (*C*(2)), 62.1 (*C*(1)), 68.5 (*C*(5)), 80.8 (*C*Me$_3$), 171.2 (*C*O$_2$^{t}Bu); *m/z* (FI+) 351 ([M+H], 100%); HRMS (FI$^+$) $C_{13}H_{22}INO_2^+$ ([M]$^+$) requires 351.0695; found 351.0695; Data for **396**: δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 1.50-1.56 (1H, m, C(4)H_A), 1.79-1.88 (1H, m, C(4)H_B), 1.96-2.09 (3H, m, C(3)H_2, C(7)H_A), 2.23 (1H, app dd, *J* 13.4, 6.3, C(7)H_B), 2.34 (3H, s, N*Me*), 2.56 (1H, app dd, *J* 14.4, 6.1, C(6)*H*), 3.33 (1H, app dd, *J* 11.9, 6.3, C(1)*H*), 3.42 (1H, br s, C(5)*H*), 4.51 (1H, ddd, *J* 11.9, 5.6, 2.5, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 25.4

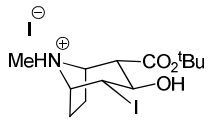
(*C*(7)), 28.1 (C*Me*$_3$), 30.0, 30.1 (*C*(3), *C*(4)), 32.9 (*C*(2)), 40.2 (N*Me*), 45.6 (*C*(6)), 63.1 (*C*(5)), 69.0 (*C*(1)), 80.7 (*C*Me$_3$), 172.2 (*C*O$_2$^{t}Bu).

(1*S*,2a*S*,2b*S*,4a*S*,5*R*)-1-*tert*-Butoxy-*N*(5)-methyloctahydroazirino[2,1,3-*cd*]pyrrolizin-5-ium tetraflouroborate 397



$AgBF_4$ (37 mg, 0.18 mmol) was added to a stirred solution of a 77:23 mixture of **395** and **396** (55 mg, 0.16 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was left to stir at rt for 2 h then filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo* to give **397** (47 mg, quant, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.82-1.87 (1H, m, C(3)*H*$_A$), 1.92-1.99 (1H, m, C(4)*H*$_A$), 2.17-2.23 (1H, m, C(2)*H*$_A$), 2.62-2.81 (3H, m, C(2)*H*$_B$, C(3)*H*$_B$, C(4)*H*$_B$), 3.35 (3H, s, N*Me*), 3.92-4.05 (3H, m, C(1)*H*, C(2a)*H*, C(4a)*H*), 4.30 (1H, app t, C(2b)*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (*C*(4)), 23.4 (*C*(2)), 27.9 (C*Me*$_3$), 31.9 (*C*(3)), 43.0 (N*Me*), 52.4, 60.3, 62.3 (*C*(1), *C*(2a), *C*(4a)), 72.9 (*C*(2b)), 82.8 (*C*Me$_3$), 167.6 (*C*O$_2$^{t}Bu); *m/z* (ESI)$^+$ 224 ([M+H], 100%); HRMS (ESI$^+$) $C_{13}H_{22}NO_2^+$ ([M+H]$^+$) requires 224.1645, found 224.1641.

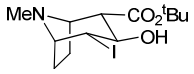
(1*R*,2*S*,3*R*,4*R*,5*S*)-3-hydroxy-4-iodo-*N*(8)-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate hydroiodide 398·HI[16]



I_2 (203 mg, 0.80 mmol) was added to a stirred solution of **391A** (100 mg, 0.27 mmol, >99:1 dr) in CH_2Cl_2 (10 mL) at rt. The reaction mixture was allowed to stir at rt for 12 h before the addition of $Na_2S_2O_3$ (excess). After stirring for 15 min the mixture was filtered and concentrated *in vacuo*. Purification via direct crystallisation from CH_2Cl_2/Et_2O gave **398**·HI as a white solid (95 mg, 72%, >99:1 dr); mp 147-150 °C; $[\alpha]_D^{20}$ −5.7 (*c* 0.44 in MeOH); ν_{max} (ATR) 3364 (O−H), 2836, 2714, 2579 (C−H), 1724 (C=O); δ_H (500 MHz, D_2O) 1.40 (9H, s, C*Me*$_3$), 2.10-2.15 (1H, m, C*H*$_A$), 2.22-2.36 (2H, m, C*H*$_A$, C*H*$_B$), 2.43-2.48 (1H, m, C*H*$_B$), 2.80 (3H, s, N*Me*), 2.91 (1H, app d, *J* 9.1, C(2)*H*), 4.17-4.27 (4H, m, C(1)*H*, C(3)*H*,

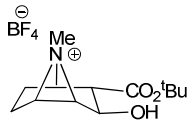
C(4)*H*, C(5)*H*); δ_C (125 MHz, D_2O) 21.5, 22.5 (*C*(6), *C*(7)), 27.4 (C*Me*$_3$), 30.2 (*C*(4)), 38.9 (N*Me*), 53.2 (*C*(2)), 64.9, 69.0, 69.4 (*C*(1), *C*(3), *C*(5)), 85.2 (*C*Me$_3$), 168.2 (*C*O$_2^t$Bu); HRMS (FI$^+$) $C_{13}H_{22}INO_3^+$ ([M]$^+$) requires 367.0644; found 367.0637.

tert-Butyl (1*R*,2*S*,3*R*,4*R*,5*S*)-3-hydroxy-4-iodo-*N*(8)-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate 398



I_2 (203 mg, 0.80 mmol) was added to a stirred solution of **398**·HI (100 mg, 0.27 mmol, >99:1 dr) in CH_2Cl_2 (10 mL) at rt. The resultant mixture was allowed to stir at rt for 12 h then $Na_2S_2O_3$ (excess) was added. After stirring for 15 min the reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in THF (5 mL) and K_2CO_3 (74 mg, 0.53 mmol) was added. The resultant mixture was left to stir for 4 h at rt then filtered through Celite® (eluent THF) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 100:1 increased to 2:1) gave **398** as a yellow oil (90 mg, 92%, >99:1 dr); $[\alpha]_D^{25}$ −7.3 (*c* 0.85 in $CHCl_3$); ν_{max} (ATR) 3127 (O−H), 2973 (C−H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 1.59-1.65 (1H, m, C(7)H_A), 1.91-2.03 (2H, m, C(6)H_A, C(7)H_B), 2.06-2.14 (1H, m, C(6)H_B), 2.45 (3H, s, N*Me*), 2.82 (1H, dd, *J* 9.6, 3.8, C(2)*H*), 3.49-3.51 (1H, m, C(5)*H*), 3.53-3.55 (1H, m, C(1)*H*), 4.08 (1H, app t, *J* 9.9, C(3)*H*), 4.32 (1H, dd, *J* 9.9, 2.3, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 24.8 (*C*(6), *C*(7)), 28.1 (C*Me*$_3$), 37.1 (N*Me*), 39.3 (*C*(4)), 52.9 (*C*(2)), 62.1 (*C*(5)), 67.8 (*C*(1)), 71.2 (*C*(3)), 81.8 (*C*Me$_3$), 171.3 (*C*O$_2^t$Bu); HRMS (FI$^+$) $C_{13}H_{22}INO_3^+$ ([M]$^+$) requires 367.0644; found 367.0651.

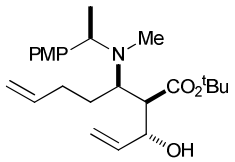
(1*S*,2*R*,2a*S*,2b*S*,4a*S*,5*R*)-1-*tert*-Butoxy-2-hydroxy-*N*(5)-methyloctahydroazirino[2,1,3-*cd*]pyrrolizin-5-ium tetrafluoroborate 399



$AgBF_4$ (49 mg, 0.25 mmol) was added to a stirred solution of **398** (75mg, 0.20 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) at rt. The resultant mixture was left to stir for 2 h then filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo* to give **399** as a brown oil

(66 mg, quant, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, C*Me*$_3$), 1.78-1.99 (2H, m, C(3)*H*$_A$, C(4)*H*$_A$), 2.59-2.72 (2H, m, C(3)*H*$_B$, C(4)*H*$_B$), 3.38 (3H, s, N*Me*), 3.81 (1H, app t, *J* 7.9, C(1)*H*), 3.88 (1H, app d, *J* 8.2, C(2a)*H*), 3.97-4.01 (1H, m, C(2b)*H*), 4.31 (1H, br s, O*H*), 4.40 (1H, app t, C(4a)*H*), 4.70 (1H, app d, *J* 7.3, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 22.2, 32.3 (*C*(3), *C*(4)), 27.9 (C*Me*$_3$), 43.2 (N*Me*), 60.5 (*C*(2b)), 60.8 (*C*(1)), 64.9 (*C*(2a)), 69.7 (*C*(2)), 71.6 (*C*(4a)), 83.2 (*C*Me$_3$), 166.8 (*C*O$_2$^{t}Bu); *m/z* (ESI)$^+$ 240 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{22}NO_3^+$ ([M]$^+$) requires 240.1594; found 240.1597.

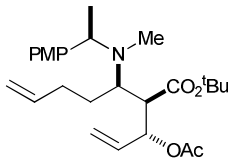
tert-Butyl (*R*,*R*,*R*,*R*)-2-(1′-hydroxyprop-2′-en-1′-yl)-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] hept-6-enoate 390D



BuLi (2.4 M in hexanes, 7.62 mL, 18.4 mmol) was added to a stirred solution of ^{i}Pr$_2$NH (2.61 mL, 18.6 mmol) in THF (10 mL) at 0 °C. After stirring for 30 min a solution of **385** (1.85 g, 5.32 mmol, >99:1 dr) in THF (12 mL) at 0 °C was added dropwise via cannula. The reaction mixture was left to stir at 0 °C for a further 2 h then cooled to −78 °C and acrolein (1.42 mL, 21.3 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h then satd aq NH_4Cl (5 mL) and EtOAc (20 mL) were added. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with brine (30 mL), then dried and concentrated *in vacuo* to give a 12:42:17:29 mixture of **390A**, **390B**, **390C** and **390D**. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 40:1) gave **390A** as a pale yellow solid (238 mg, 11%, >99:1 dr). Further elution gave **390D** as a pale yellow oil (460 mg, 21%, >99:1 dr); $[\alpha]_D^{20}$ +38.7 (*c* 1.75 in $CHCl_3$); ν_{max} (ATR) 3498 (O–H), 2976, 2933, 2836 (C−H), 1722 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.26-1.37 (1H, m, C(4)*H*$_A$), 1.42 (3H, d, *J* 6.6, C(α)*Me*), 1.45 (9H, s, C*Me*$_3$), 1.60-1.71 (1H, m, C(4)*H*$_B$), 2.00-2.13 (2H, m, C(5)*H*$_2$) overlapping 2.08 (3H, s, N*Me*), 2.71 (1H, dd, *J* 9.9, 2.0, C(2)*H*), 3.56-3.62 (1H, m, C(3)*H*), 3.72 (1H, q, *J* 6.6, C(α)*H*), 3.79 (3H, s, O*Me*), 4.54 (1H, br s, C(1′)*H*), 4.92-5.00 (2H, m, C(7)*H*$_2$), 5.21 (1H, app d, *J* 11.1, C(3′)*H*$_A$), 5.24 (1H, app d, *J* 17.7, C(3′)*H*$_B$), 5.69-5.79 (1H, m, C(6)*H*), 5.98-6.06 (1H, m, C(2′)*H*), 6.84 (2H, d, *J* 8.3, *Ar*), 7.21 (2H, d, *J* 8.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(α)*Me*), 28.1 (C*Me*$_3$), 28.7 (*C*(4)),

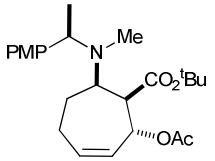
31.9 (*C*(5)), 32.7 (N*Me*), 53.1 (*C*(2)), 55.2 (O*Me*), 56.3 (*C*(3)), 62.6 (*C*(α)), 71.1 (*C*(1′)), 81.5 (*C*Me$_3$), 113.7 (*Ar*), 114.4, 114.9 (*C*(7), *C*(3′)), 128.2, 137.9 (*Ar*), 138.5 (*C*(6)), 139.0 (*C*(2′)), 158.5 (*Ar*), 173.2 (*C*(1)); *m/z* (ESI)$^+$ 829 ([2M+Na]$^+$, 100%), 426 ([M+Na]$^+$, 65%), 404 ([M+H]$^+$, 70%); HRMS (ESI$^+$) $C_{24}H_{38}NO_4^+$ ([M+H]$^+$) requires 404.2795; found 404.2780. Further elution gave an inseparable 72:28 mixture of **390B** and **390C** (999 mg, 46%).

tert-Butyl (*R*,*R*,*R*,*R*)-2-[1′-acetoxyprop-2′-en-1′-yl]-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] hept-6-enoate 409D



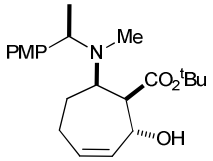
Ac_2O (0.61 mL, 6.49 mmol) and DMAP (2 mg, cat.) were added sequentially to a stirred solution of **390D** (524 mg, 1.30 mmol, >99:1 dr) in pyridine (10 mL) at rt and the resultant mixture was left to stir at rt for 12 h. H_2O (5 mL) was then added and the reaction mixture was diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with satd aq $CuSO_4$ (15 mL), H_2O (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 20:1) gave **409D** as a colourless oil (465 mg, 80%, >99:1 dr); $[\alpha]_D^{20}$ +32.0 (*c* 1.28 in $CHCl_3$); ν_{max} (ATR) 2976, 2934, 2836 (C−H), 1743, 1725 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.6, C(α)*Me*), 1.37-1.45 (1H, m, C(4)H_A), 1.45 (9H, s, C*Me*$_3$), 1.70-1.79 (1H, m, C(4)H_B), 1.91-2.00 (1H, m, C(5)H_A), 2.05 (3H, s, OCO*Me*), 2.14 (3H, s, N*Me*), 2.14-2.24 (1H, m, C(5)H_B), 2.78 (1H, app t, *J* 6.3, C(2)*H*), 3.07-3.12 (1H, m, C(3)*H*), 3.69 (1H, q, *J* 6.6, C(α)*H*), 3.78 (3H, s, O*Me*), 4.92 (1H, d, *J* 9.4, C(7)H_A), 4.98 (1H, d, *J* 17.2, C(7)H_B), 5.03 (1H, d, *J* 9.4, C(3′)H_A), 5.15 (1H, d, *J* 15.9, C(3′)H_B), 5.46-5.55 (2H, m, C(1′)*H*, C(2′)*H*), 5.70-5.80 (1H, m, C(6)*H*), 6.83 (2H, d, *J* 8.2, *Ar*), 7.20 (2H, d, *J* 8.2, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.1 (OCO*Me*), 22.6 (C(α)*Me*), 27.7 (*C*(4)), 28.0 (C*Me*$_3$), 31.6 (*C*(5)), 32.6 (N*Me*), 51.5 (*C*(2)), 55.2 (O*Me*), 56.1 (*C*(3)), 61.7 (*C*(α)), 74.1 (*C*(1′)), 80.8 (*C*Me$_3$), 113.6 (*Ar*), 114.3 (*C*(7)), 118.2 (*C*(3′)), 128.3 (*Ar*), 134.4 (*C*(2′)), 138.1 (*Ar*), 138.8 (*C*(6)), 158.5 (*Ar*), 169.7 (O*C*OMe), 171.5 (*C*(1)); *m/z* (ESI)$^+$ 913 ([2M+Na]$^+$, 80%), 468 ([M+Na]$^+$, 100%), 446 ([M+H]$^+$, 75%); HRMS (ESI$^+$) $C_{26}H_{39}NNaO_5^+$ ([M+Na]$^+$) requires 468.2720; found 468.2709.

tert-Butyl (*R*,*R*,*R*,*R*)-2-acetoxy-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] cyclohept-3-ene-1-carboxylate 410D



Grubbs I catalyst (172 mg, 0.21 mmol) was added to a stirred solution of **409D** (465 mg, 1.04 mmol, >99:1 dr) in degassed CH_2Cl_2 (50 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (25 mL) and **424** (2.61 g, 21.0 mmol), Et_3N (0.29 mL, 2.08 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for a further 12 h, then filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 10:1) gave **410D** as a colourless oil (351 mg, 80%, >99:1 dr); $[\alpha]_D^{20}$ −8.30 (*c* 1.12 in $CHCl_3$); ν_{max} (ATR) 2971, 2934, 2795 (C−H), 1725 (C=O), 1700 (C=C); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.6, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 1.54-1.63 (1H, m, C(6)H_A), 1.96 (3H, s, OCO*Me*), 1.98-2.10 (2H, m, C(5)H_A, C(6)H_B), 2.18-2.30 (1H, m, C(5)H_B) overlapping 2.23 (3H, s, N*Me*), 3.13 (1H, dd, *J* 9.7, 6.8, C(1)*H*), 3.40 (1H, m, C(7)*H*), 3.71 (1H, q, *J* 6.6, C(α)*H*), 3.78 (3H, s, O*Me*), 5.34-5.38 (1H, m, C(3)*H*), 5.69-5.74 (1H, m, C(4)*H*), 5.84 (1H, app d, *J* 9.7, C(2)*H*), 6.81 (2H, d, *J* 8.3, *Ar*), 7.23 (2H, d, *J* 8.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.7 (*C*(α)*Me*), 21.0 (OCO*Me*), 24.2 (*C*(6)), 26.2 (*C*(5)), 28.1 (C*Me*$_3$), 34.1 (N*Me*), 53.5 (*C*(1)), 55.2 (O*Me*), 57.9 (*C*(7)), 61.6 (*C*(α)), 71.3 (*C*(2)), 80.2 (*C*Me$_3$), 113.4, 128.4 (*Ar*), 129.0 (*C*(3)), 132.0 (*C*(4)), 137.1, 158.3 (*Ar*), 169.8 (O*C*OMe), 171.1 (*C*O_2^{t}Bu); *m/z* (ESI)$^+$ 440 ([M+Na]$^+$, 85%), 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{36}NO_5^+$ ([M+H]$^+$) requires 418.2588; found 418.2579.

tert-Butyl (*R*,*R*,*R*,*R*)-2-hydroxy-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] cyclohept-3-ene-1-carboxylate 391D

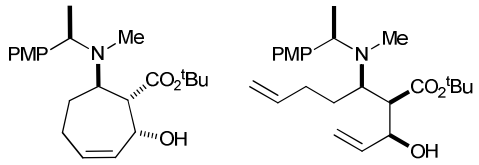


Method A: K_2CO_3 (18 mg, 0.13 mmol) was added to a stirred solution of **410D** (50 mg, 0.12 mmol, >99:1 dr) in MeOH (1 mL) and the resultant mixture was left at rt to stir for 2 h. The reaction mixture was then concentrated *in vacuo* and the resultant residue was partitioned between CH_2Cl_2 (5 mL) and satd aq NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo* to give a 47:53 mixture of **391C** and **391D**. Purification via flash column chromatography (eluent PhMe/acetone, 40:1) gave **391C** as a colourless oil (6 mg, 14%, >99:1 dr). Further elution gave a 47:53 mixture of **391C** and **391D** (10 mg, 22%). Further elution gave **391D** as a yellow oil (8 mg, 17%, >99:1 dr); $[\alpha]_D^{20}$ –40.7 (*c* 0.67 in $CHCl_3$); ν_{max} (ATR) 3515 (O−H), 2973, 2933 (C−H), 1709 (C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.42-1.47 (1H, m, C(6)H_A), 1.53 (9H, s, CMe_3), 1.76-1.86 (1H, m, C(6)H_B), 1.97-2.05 (1H, m, C(5)H_A), 2.12-2.16 (1H, m, C(5)H_B), 2.19 (3H, s, N*Me*), 3.11 (1H, dd, *J* 10.2, 7.6, C(1)*H*), 3.51 (1H, s, O*H*), 3.57-3.63 (1H, m, C(7)*H*), 3.68 (1H, q, *J* 6.8, C(α)*H*), 3.77 (3H, s, O*Me*), 4.95 (1H, app d, *J* 10.2, C(2)*H*), 5.22-5.55 (1H, m, C(3)*H*), 5.64-5.69 (1H, m, C(4)*H*), 6.81 (2H, d, *J* 8.6, *Ar*), 7.20 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 23.1, 25.6 (*C*(5), *C*(6)), 28.4 (CMe_3), 33.4 (N*Me*), 55.1 (O*Me*), 57.8 (*C*(1)), 58.9 (*C*(7)), 61.9 (*C*(α)), 67.7 (*C*(2)), 80.9 (*C*Me$_3$), 113.4, 128.4 (*Ar*), 130.0 (*C*(4)), 133.6 (*C*(3)), 137.0, 158.4 (*Ar*), 173.3 (*C*O$_2$^{t}Bu); *m/z* (ESI)$^+$ 773 ([2M+Na]$^+$, 65%), 398 ([M+Na]$^+$, 40%), 376 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{34}NO_4^+$ ([M+H]$^+$) requires 376.2482; found 376.2475.

Method B: KOH (10 mg, cat.) was added to a stirred solution of **410D** (350 mg, 0.84 mmol, >99:1 dr) in MeOH/CH_2Cl_2 (v/v 30:1, 18 mL) and the resultant mixture was left to stir at rt for 2 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and the resultant solution was washed with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and 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/acetone, 15:1) gave **391D** as a yellow oil (209 mg, 66%, >99:1 dr).

tert-Butyl (1*S*,2*R*,7*R*,α*R*)-2-hydroxy-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] cyclohept-3-ene-1-carboxylate 391C and _tert_-butyl (2*R*,3*R*,1′*S*,α*R*)-2-(1′-hydroxyprop-2′-en-1′-yl)-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] hept-6-enoate 390B

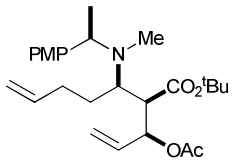


Method A: Grubbs I catalyst (12 mg, 0.01 mmol) was added to a stirred solution of **390C** (30 mg, 0.07 mmol, >99:1 dr) in degassed CH_2Cl_2 (3 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (5 mL) and **424** (124 mg, 1.00 mmol), Et_3N (0.02 mL, 0.14 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for a further 12 h, then filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 10:1) gave **391C** as a yellow oil (27 mg, 97%, >99:1 dr); $[\alpha]_D^{20}$ −12.7 (*c* 0.4 in MeOH); ν_{max} (ATR) 3493 (O–H), 2971, 2931, 2836 (C–H), 1725 (C=O), 1611 (C=C); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.7, C(α)*Me*), 1.44-1.56 (1H, m, C(6)H_A) overlapping 1.48 (9H, s, CMe_3), 1.69-1.76 (1H, m, C(6)H_B), 2.07 (3H, s, N*Me*), 2.11-2.23 (2H, m, C(5)H_2), 2.79 (1H, dd, *J* 9.3, 1.4, C(1)*H*), 3.57 (1H, q, *J* 6.7, C(α)*H*), 3.67 (1H, d, *J* 3.8, O*H*), 3.79 (3H, s, O*Me*), 3.91 (1H, td, *J* 9.3, 3.4, C(7)*H*), 4.53-4.57 (1H, m, C(2)*H*), 5.78 (1H, app ddd, *J* 11.3, 6.0, 1.7, C(3)*H*), 5.86-5.92 (1H, m, C(4)*H*), 6.81 (2H, d, *J* 8.5, *Ar*), 7.20 (2H, d, *J* 8.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.4 (C(α)*Me*), 25.2, 25.5 (*C*(5), *C*(6)), 28.2 (CMe_3), 33.0 (N*Me*), 53.8 (*C*(1)), 55.2 (O*Me*), 56.5 (*C*(7)), 61.7 (*C*(α)), 67.6 (*C*(2)), 81.1 (*C*Me_3), 113.4, 128.3 (*Ar*), 130.9 (*C*(3)), 134.7 (*C*(4)), 138.0, 158.4 (*Ar*), 175.2 (*C*O_2^{t}Bu); *m/z* (ESI)$^+$ 773 ([2M+Na]$^+$, 95%), 398 ([M+Na]$^+$, 100%), 376 ([M+H]$^+$, 70%); HRMS (ESI$^+$) $C_{22}H_{34}NO_4^+$ ([M+H]$^+$) requires 376.2482, found 376.2476.

Method B: Grubbs I catalyst (400 mg, 0.50 mmol) was added to a stirred solution of a 72:28 mixture of **390B** and **390C** (999 mg, 2.48 mmol) in degassed CH_2Cl_2 (90 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and **424** (6.20 g, 50.0 mmol), Et_3N

(0.69 mL, 4.96 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for a further 12 h, then filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent PhMe/acetone, 40:1) gave **390B** as a colourless oil (247 mg, 25%, >99:1 dr); $[\alpha]_D^{20}$ +26.5 (*c* 0.71 in $CHCl_3$); ν_{max} (ATR) 2975, 2933, 2837 (C–H), 1719 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.32-1.39 (1H, m, C(4)H_A), 1.43 (9H, s, CMe_3), 1.53 (3H, d, *J* 6.6, C(α)*Me*), 1.71-1.80 (1H, m C(4)H_B), 2.01 (3H, s, N*Me*), 2.18 (2H, app q, *J* 7.6, C(5)H_2), 2.45 (1H, app t, *J* 9.9, C(2)*H*), 3.69-3.76 (2H, m, C(3)*H*, C(α)*H*), 3.79 (3H, s, O*Me*), 4.46 (1H, dd, *J* 8.6, 7.3, C(1′)*H*), 4.99-5.07 (2H, m, C(7)H_2), 5.14-5.17 (1H, m, C(3′)H_A), 5.30-5.36 (1H, m, C(3′)H_B), 5.71-5.84 (2H, m, C(6)*H*, C(2′)*H*), 6.85 (2H, d, *J* 8.4, *Ar*), 7.20 (2H, d, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.6 (C(α)*Me*), 28.0, 28.2 (*C*(4), CMe_3), 32.5 (*C*(5)), 33.4 (N*Me*), 54.1 (*C*(2)), 55.2 (O*Me*), 60.2, 62.5 (*C*(3), *C*(α)), 76.9 (*C*(1′)), 81.3 (*C*Me_3), 114.1 (*Ar*), 115.1 (*C*(7)), 116.9 (*C*(3′)), 128.2, 136.1 (*Ar*), 137.7, 137.9 (*C*(6), *C*(2′)), 158.9 (*Ar*), 171.4 (*C*(1)); *m/z* $(ESI)^+$ 426 ($[M+Na]^+$, 40%), 404 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{38}NO_4^+$ ($[M+H]^+$) requires 404.2795; found 404.2786. Further elution gave **390C** (253 mg, 27%, >99:1 dr).

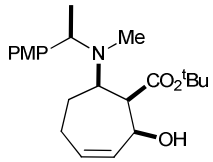
***tert*-Butyl (2*R*,3*R*,1′*S*,α*R*)-2-[1′-acetoxyprop-2′-en-1′-yl]-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] hept-6-enoate 409B**



Ac_2O (0.29 mL, 3.09 mmol) and DMAP (1 mg, cat.) were added sequentially to a stirred solution of **390B** (250 mg, 0.62 mmol, >99:1 dr) in pyridine (5 mL) at rt and the resultant mixture was left to stir at rt for 12 h. H_2O (3 mL) was then added and the reaction mixture was diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with satd aq $CuSO_4$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 20:1) gave **409B** as pale yellow oil (234 mg, 79%, >99:1 dr); $[\alpha]_D^{20}$ +8.59 (*c* 1.96 in $CHCl_3$); ν_{max} (ATR) 2976, 2935, 2836 (C–H), 1725, 1681 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.6, C(α)*Me*), 1.35-1.43 (1H, m, C(4)H_A), 1.45 (9H, s, CMe_3), 1.61-1.71 (1H, m, C(4)H_B), 1.90-1.99 (1H, m, C(5)H_A)

overlapping 1.96 (3H, s, OCO*Me*), 2.05-2.14 (1H, m, C(5)H_B) overlapping 2.14 (3H, s, N*Me*), 3.01 (1H, app t, *J* 6.6, C(2)*H*), 3.14 (1H, app q, *J* 5.3, C(3)*H*), 3.64 (1H, q, *J* 6.6, C(α)*H*), 3.78 (3H, s, O*Me*), 4.88-4.97 (2H, m, C(7)H_2), 5.24-5.30 (2H, m, C(3′)H_2), 5.49 (1H, app t, *J* 6.6, C(1′)*H*), 5.67-5.77 (1H, m, C(6)*H*), 6.02-6.11 (1H, m, C(2′)*H*), 6.83 (2H, d, *J* 7.7, *Ar*), 7.22 (2H, d, *J* 7.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.1 (OCO*Me*), 22.4 (C(α)*Me*), 27.6 (*C*(4)), 28.0 (C*Me*$_3$), 31.7 (*C*(5)), 32.7 (N*Me*), 51.1 (*C*(2)), 55.2 (O*Me*), 56.4 (*C*(3)), 61.8 (*C*(α)), 74.3 (*C*(1′)), 80.9 (*C*Me$_3$), 113.6 (*Ar*), 114.3 (*C*(7)), 118.6 (*C*(3′)), 128.2 (*Ar*), 133.1 (*C*(2′)), 138.3 (*Ar*), 138.8 (*C*(6)), 158.4 (*Ar*), 169.8 (O*C*OMe), 171.4 (*C*(1)); *m/z* (ESI)$^+$ 468 ([M+Na]$^+$, 100%), 446 ([M+H]$^+$, 80%); HRMS (ESI$^+$) $C_{26}H_{40}NO_5^+$ ([M+H]$^+$) requires 446.2901; found 446.2898.

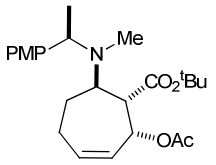
tert-Butyl (1*R*,2*R*,7*S*,α*R*)-2-hydroxy-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] cyclohept-3-ene-1-carboxylate 391B



Grubbs I catalyst (86 mg, 0.11 mmol) was added to a stirred solution of **409B** (234 mg, 0.53 mmol, >99:1 dr) in degassed CH_2Cl_2 (25 mL) at 30 °C and the resultant mixture was stirred at 30 °C for 12 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in MeOH/CH_2Cl_2 (v/v 30:1, 9 mL) and KOH (10 mg, cat.) was added. The resultant mixture was left to stir at rt for 2 h, then diluted with CH_2Cl2 (5 mL) and the resultant mixture was washed with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine (25 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 15:1) gave **391B** as a brown oil (92 mg, 47%, >99:1 dr); $[\alpha]_D^{20}$ +133 (*c* 0.32 in MeOH); ν_{max} (ATR) 3458 (O–H), 2974, 2933, 2836 (C–H), 1721 (C=O), 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.8, C(α)*Me*), 1.45-1.51 (1H, m, C(5)H_A) overlapping 1.48 (9H, s, C*Me*$_3$), 1.73-1.81 (1H, m, C(5)H_B), 2.16-2.26 (2H, m, C(6)H_2), 2.30 (3H, s, N*Me*), 2.85-2.90 (1H, m, C(7)*H*), 3.01 (1H, app s, C(1)*H*), 3.80 (3H, s O*Me*), 3.85 (1H, q, *J* 6.8, C(α)*H*), 4.15 (1H, br s, C(2)*H*), 5.54-5.58 (1H, m, C(3)*H*), 5.71-5.77 (1H, m, C(4)*H*), 6.85 (2H, d, *J* 8.6, *Ar*), 7.27 (2H, d, *J* 8.6, *Ar*);

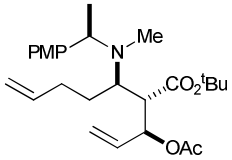
δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 26.2, 26.6 (*C*(5), *C*(6)), 28.1 (C*Me*$_3$), 33.9 (N*Me*), 51.7 (*C*(1)), 55.2 (O*Me*), 60.4 (*C*(α)), 62.7 (*C*(7)), 71.3 (*C*(2)), 81.2 (*C*Me$_3$), 113.6, 113.8 (*Ar*), 128.3 (*C*(4)), 129.4 (*C*(3)), 134.9, 158.4 (*Ar*), 172.1 (*C*O$_2$^{t}Bu); *m/z* (ESI)$^+$ 398 ([M+Na]$^+$, 10%), 376 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{34}NO_4^+$ ([M+H]$^+$) requires 376.2482; found 376.2470.

***tert*-Butyl (1*S*,2*R*,7*R*,α*R*)-2-acetoxy-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] cyclohept-3-ene-1-carboxylate 410C**



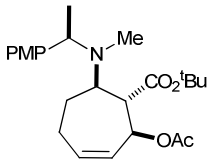
Ac_2O (0.02 mL, 0.18 mmol) and DMAP (1 mg, cat.) were added sequentially to a solution of **391C** (23.0 g, 0.06 mmol, >99:1 dr) in pyridine (1 mL) at rt and the resultant mixture was left to stir at rt for 12 h. H_2O (1 mL) was then added and the reaction mixture was diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with satd aq $CuSO_4$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 15:1) gave **410C** as a yellow oil (15 mg, 61%, >99:1 dr); $[\alpha]_D^{20}$ −14.6 (*c* 0.47 in $CHCl_3$); ν_{max} (ATR) 2973, 2932, 2791 (C–H), 1734 (C=O), 1611 (C=C); δ_H (500 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.6 C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 1.60-1.67 (2H, m, C(6)*H*$_2$), 2.06 (3H, s, N*Me*), 2.10 (3H, s, OCO*Me*), 2.14-2.30 (2H, m, C(5)*H*$_2$), 3.05 (1H, dd, *J* 9.8, 4.1, C(1)*H*), 3.58 (1H, q, *J* 6.6, C(α)*H*), 3.76-3.81 (1H, m, C(7)*H*) overlapping 3.79 (3H, s, O*Me*), 5.61 (1H, dd, *J* 11.0, 5.4, C(3)*H*), 5.73-5.77 (2H, m, C(2)*H*, C(4)*H*), 6.81 (2H, d *J* 8.5, *Ar*), 7.20 (2H, d, *J* 8.5, *Ar*); δ_C (125 MHz, $CDCl_3$) 21.1 (OCO*Me*), 21.6 (C(α)*Me*), 23.5 (*C*(6)), 26.5 (*C*(5)), 28.1 (C*Me*$_3$), 32.7 (N*Me*), 52.5 (*C*(1)), 55.2 (O*Me*), 57.4 (*C*(7)), 61.6 (*C*(α)), 69.4 (*C*(2)), 80.1 (*C*Me$_3$), 113.4 (*Ar*), 127.9 (*C*(3)), 128.1 (*Ar*), 132.4 (*C*(4)), 138.0, 158.3 (*Ar*), 170.1, 171.9 (*C*O$_2$^{t}Bu, O*C*OMe); *m/z* (ESI)$^+$ 440 ([M+Na], 60%), 418 ([M+H], 100%); HRMS (ESI$^+$) $C_{24}H_{36}NO_5^+$ ([M+H]$^+$) requires 418.2588; found 418.2573.

tert-Butyl (2*S*,3*R*,1′*S*,α*R*)-2-[1′-acetoxyprop-2′-en-1′-yl]-3-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] hept-6-enoate 409A



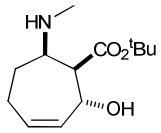
Ac_2O (0.11 mL, 1.12 mmol) and DMAP (2 mg, cat.) were added sequentially to a stirred solution of **390A** (227 mg, 0.56 mmol, >99:1 dr) in pyridine (5 mL) at rt and the resultant mixture was left to stir at rt for 12 h. H_2O (2 mL) was then added and the reaction mixture was diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with satd aq $CuSO_4$ (15 mL), H_2O (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 20:1) gave **409A** as a colourless oil (153 mg, 61%, >99:1 dr); $[\alpha]_D^{20}$ +5.7 (*c* 0.57 in $CHCl_3$); ν_{max} (ATR) 2975, 2935 (C–H), 1741 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.23-1.36 (1H, m, C(4)H_A) overlapping 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.37-1.54 (2H, m, C(4)H_B, C(5)H_A) overlapping 1.44 (9H, s, CMe_3), 1.99-2.14 (1H, m, C(5)H_B) overlapping 2.05 (3H, s, OCO*Me*) and 2.09 (3H, s, N*Me*), 2.72 (1H, app t, *J* 7.1, C(2)*H*), 3.28 (1H, app t, *J* 6.8, C(3)*H*), 3.66 (1H, q, *J* 6.8, C(α)*H*), 3.78 (3H, s, O*Me*), 4.88-5.00 (2H, m, C(7)H_2), 5.26-5.39 (2H, m, C(3′)H_2), 5.61 (1H, app t, *J* 7.1, C(1′)*H*), 5.65-5.75 (1H, m, C(6)*H*), 5.80-5.89 (1H, m, C(2′)*H*), 6.81 (2H, d, *J* 8.6, *Ar*), 7.18 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.1, 21.2 (C(α)*Me*, OCO*Me*), 26.8 (*C*(4)), 28.1 (CMe_3), 31.6 (*C*(5)), 32.3 (N*Me*), 53.7 (*C*(2)), 55.2 (O*Me*), 57.4 (*C*(3)), 62.7 (*C*(α)), 73.6 (*C*(1′)), 80.5 (*C*Me_3), 113.4 (*Ar*), 114.7 (*C*(7)), 118.5 (*C*(3′)), 128.4 (*Ar*), 134.8 (*C*(2′)), 137.3 (*Ar*), 138.3 (*C*(6)), 158.4 (*Ar*), 169.7 (O*C*OMe), 170.9 (*C*(1)); *m/z* $(ESI)^+$ 468 ([M+Na], 40%), 445 ([M+H], 100%); HRMS (ESI^+) $C_{26}H_{40}NO_5^+$ ($[M+H]^+$) requires 446.2901; found 446.2897.

tert-Butyl (1*S*,2*S*,7*R*,α*R*)-2-acetoxy-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino] cyclohept-3-ene-1-carboxylate 410A[16]



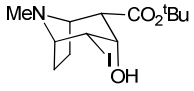
Ac_2O (1.93 mL, 20.5 mmol) and DMAP (cat.) were added sequentially to a stirred solution of **409A** (1.54 g, 4.10 mmol, >99:1 dr) in pyridine (5 mL) at rt and the resultant mixture was left to stir at rt for 12 h. H_2O (5 mL) was then added and the reaction mixture was diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with satd aq $CuSO_4$ (15 mL), H_2O (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 15:1) gave **410A** as a white solid (1.34 g, 78%, >99:1 dr); mp 105-109 °C; $[\alpha]_D^{25}$ +2.90 (*c* 1.55 in $CHCl_3$); ν_{max} (ATR) 2973, 2933, 2837 (C–H), 1740 (C=O), 1657 (C=C); δ_H (400 MHz, $CDCl_3$) 1.13-1.24 (1H, m, C(6)H_A), 1.25 (3H, d, *J* 6.6, C(α)*Me*), 1.44 (9H, s, CMe_3), 1.59-1.66 (1H, m, C(6)H_B), 1.86-1.97 (1H, m, C(5)H_A) overlapping 1.95 (3H, s, N*Me*), 1.99 (3H, s, OCO*Me*), 2.13 (1H, app quintet, *J* 7.1, C(5)H_B), 2.74 (1H, app t, *J* 10.9, C(1)*H*), 3.36 (1H, td, *J* 10.6, 2.3, C(7)*H*), 3.50 (1H, q, *J* 6.6, C(α)*H*), 3.71 (3H, s, O*Me*), 5.40-5.44 (1H, m, C(3)*H*), 5.51-5.56 (1H, m, C(2)*H*), 5.74-5.81 (1H, m, C(4)*H*), 6.74 (2H, d, *J* 8.6, *Ar*), 7.14 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.0, 21.9 (C(α)*Me*, OCO*Me*), 23.5, 25.0 (*C*(5), *C*(6)), 28.2 (CMe_3), 32.8 (N*Me*), 54.6 (*C*(1)), 55.0 (O*Me*), 61.0 (*C*(7)), 61.6 (*C*(α)), 73.4 (*C*(2)), 79.9 (*C*Me$_3$), 113.4, 128.3 (*Ar*), 131.0 (*C*(4)), 133.2 (*C*(3)), 137.8, 158.4 (*Ar*), 169.5, 170.8 (*C*O$_2$^{t}Bu, O*C*OMe); *m/z* (ESI)$^+$ 440 ([M+Na]$^+$, 70%), 418 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{36}NO_5^+$ ([M+H]$^+$) requires 418.2588; found 418.2574.

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-7-[*N*-methyl] cyclohept-3-ene-1-carboxylate 413



I_2 (172 mg, 0.68 mmol) was added to a stirred solution of **391D** (85 mg, 0.23 mmol, >99:1 dr) in CH_2Cl_2 (8 mL) at rt. The resultant mixture was allowed to stir at rt for 12 h then $Na_2S_2O_3$ (excess) was added. After stirring for 15 min the reaction mixture was filtered and concentrated *in vacuo*. The residue was filtered through K_2CO_3 (eluent CH_2Cl_2) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 10:1 increased to 100% acetone) gave **391D** as a yellow oil (26 mg, 31%, >99:1 dr). Further elution gave **413** as an impure dark green oil (7 mg, 20%, >99:1 dr); δ_H (500 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 1.80-1.88 (1H, m, C(6)*H*$_A$), 2.25-2.31 (1H, m, C(5)*H*$_A$), 2.33-2.37 (1H, m, C(6)*H*$_B$), 2.42-2.47 (1H, m, C(5)*H*$_B$), 2.76 (1H, br s, O*H*), 2.85 (3H, s, N*Me*), 3.87-3.90 (1H, m, C(1)*H*), 4.08 (1H, dt, *J* 11.7, 3.2, C(7)*H*), 4.86-4.91 (1H, m, C(2)*H*), 5.96-6.04 (2H, m, C(3)*H*, C(4)*H*); δ_C (125 MHz, $CDCl_3$) 23.5 (*C*(5)), 26.3 (*C*(6)), 28.0 (C*Me*$_3$), 31.6 (N*Me*), 47.8 (*C*(1)), 59.2 (*C*(7)), 64.9 (*C*(2)), 84.6 (*C*Me$_3$), 131.7, 134.5 (*C*(3), *C*(4)), 171.4 (*C*O$_2$^{t}Bu); *m/z* (ESI)$^+$ 242 ([M+H], 100%); HRMS (ESI$^+$) $C_{13}H_{24}NO_3^+$ ([M+H]$^+$) requires 242.1751; found 242.1751.

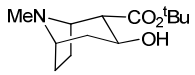
tert-Butyl (1*R*,2*S*,3*S*,4*R*,5*S*)-3-hydroxy-4-iodo-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate 415[16]



I_2 (365 mg, 1.44 mmol) was added to a stirred solution of **391C** (180 mg, 0.48 mmol, >99:1 dr) in CH_2Cl_2 (15 mL) at rt. The resultant mixture was allowed to stir at rt for 12 h then $Na_2S_2O_3$ (excess) was added. After stirring for 15 min the reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in THF (5 mL) and K_2CO_3 (74 mg, 0.53 mmol) was added. The resultant mixture was left to stir for 1 h at rt then filtered through Celite® (eluent THF) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 10:1 increased to 2:1) gave **415** as a brown solid (19 mg, 11%, >99:1 dr); mp 105-109 (dec.); δ_H (500 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$),

1.86-1.96 (1H, m, C(6)H_A), 1.97-2.05 (1H, m, C(6)H_B), 2.27-2.34 (1H, m, C(7)H_A), 2.40-2.48 (1H, m, C(7)H_B) overlapping 2.42 (3H, s, N*Me*), 3.08 (1H, app d, *J* 2.5, C(2)*H*), 3.42 (1H, br s, C(5)*H*), 3.56 (1H, br s, C(1)), 4.23 (1H, app q, *J* 3.8, C(3)*H*), 4.71 (1H, br s, C(4)*H*); δ_C (125 MHz, $CDCl_3$) [selected peaks] 23.4, 23.8 (*C*(6), *C*(7)), 28.1 (C*Me*$_3$), 39.6 (N*Me*), 66.6 (*C*(5)), 68.1 (*C*(3)), 81.8 (*C*Me$_3$), 170.6 (*C*O_2^{t}Bu); *m/z* (FI)$^+$ 367 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{22}INO_3^+$ ([M]$^+$) requires 367.0639; found 367.0635.

tert-Butyl (1*R*,2*S*,3*S*,5*S*)-3-hydroxy-*N*(8)-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate 422

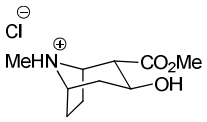


*Method A (from **391A**):* I_2 (608 mg, 2.40 mmol) was added to a stirred solution of **391A** (300 mg, 0.80 mmol, >99:1 dr) in CH_2Cl_2 (30 mL) at rt. The resultant mixture was allowed to stir at rt for 12 h then $Na_2S_2O_3$ (excess) was added. After stirring for 15 min the reaction mixture was filtered and concentrated *in vacuo*. The resultant residue was dissolved in PhMe/MeOH (v/v 5:1, 10 mL) and then AIBN (131 mg, 0.80 mmol) and Bu_3SnH (0.43 mL, 1.60 mmol) were added. The reaction mixture was heated at reflux for 5 h then allowed to cool to rt and concentrated *in vacuo*. Purification via flash column chromatography (10% KI in silica,[42] eluent 30-40 °C petrol/acetone, 100:1 increased to 100% acetone) gave **422** as a yellow oil (150 mg, 78%, >99:1 dr);[48] $[\alpha]_D^{20}$ +34.2 (*c* 0.95 in $CHCl_3$); ν_{max} (ATR) 3136 (O−H), 2973, 2883, 2800 (C−H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 1.48-1.53 (2H, m, C(6)H_A, C(7)H_A), 1.66-1.72 (1H, m, C(4)H_A), 1.77 (1H, ddd, *J* 12.6, 6.6, 3.0, C(4)H_B), 1.85-1.93 (1H, m, C(7)H_A), 1.96-2.03 (1H, m, C(6)H_B), 2.36 (3H, s, N*Me*), 2.58 (1H, dd, *J* 10.2, 3.0, C(2)*H*), 3.00 (1H, br s, O*H*), 3.17-3.21 (1H, m, C(5)*H*), 3.40 (1H, app dd, *J* 6.6, 2.5, C(1)*H*), 4.04 (1H, td, *J* 10.2, 6.6, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 24.8 (*C*(7)), 27.0 (*C*(6)), 28.1 (C*Me*$_3$), 36.0 (*C*(4)), 37.8 (N*Me*), 52.5 (*C*(2)), 60.0 (*C*(5)), 61.9 (*C*(1)), 64.5 (*C*(3)), 81.3 (*C*Me$_3$), 173.3 (*C*O_2^{t}Bu); *m/z* (ESI)$^+$ 505 ([2M+Na]$^+$, 100%), 483 ([2M+H]$^+$, 35%), 264 ([M+Na]$^+$, 75%), 242 ([M+H]$^+$, 90%); HRMS (ESI$^+$) $C_{13}H_{24}NO_3^+$ ([M+H]$^+$) requires 242.1751; found 242.1751.

*Method B (from **398**):* AIBN (128 mg, 0.78 mL) and Bu_3SnH (0.42 mL, 1.56 mmol) were added to a solution of **398** (287 mg, 0.78 mmol, >99:1 dr) in PhMe/MeOH (v/v 5:1, 1.2 mL).

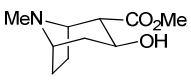
The reaction mixture was then heated at reflux for 5 h, then allowed to cool to rt and concentrated *in vacuo*. Purification via flash column chromatography (10% KF in silica,[42] eluent 30-40 °C petrol/acetone, 100:1 increased to 100% acetone) gave **422** as a yellow oil (124 mg, 66%, >99:1 dr).

Methyl (1*R*,2*S*,3*S*,5*S*)-3-hydroxy-*N*(8)-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate hydrochloride [(+)-methyl pseudoecgonine·HCl] 423·HCl[49]



$SOCl_2$ (0.09 mL, 1.24 mmol) was added to a stirred solution of **422** (150 mg, 0.62 mmol, >99:1 dr) in MeOH (3 mL) and the resultant mixture was heated at 50 °C for 5 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo* to give **423**·HCl as a pale brown solid (177 mg, quant, >99:1 dr); mp 205-208 °C; lit.[49] mp 209.5 °C; $[\alpha]_D^{20}$ +21.2 (*c* 0.1 in H_2O); {lit.[49] $[\alpha]_D^{20}$ +23.4 (*c* 2.2 in H_2O)}; ν_{max} (ATR) 3374 (O–H), 2949, 2883, 2805 (C−H), 1729 (C=O); δ_H (500 MHz, D_2O) 1.78-1.83 (1H, m, C(4)H_A), 1.95-2.00 (1H, m, C(6)H_A), 2.04-2.11 (1H, m, C(7)H_A), 2.13-2.29 (3H, m, C(4)H_B, C(6)H_B, C(7)H_B), 2.74 (3H, s, N*Me*), 2.92 (1H, dd, *J* 10.6, 2.5, C(2)*H*), 3.69 (3H, s, O*Me*), 3.90-3.92 (1H, m, C(5)*H*), 4.08-4.09 (1H, m, C(1)*H*), 4.28 (1H, td, *J* 10.6, 6.3, C(3)*H*); δ_C (125 MHz, D_2O) 21.5 (*C*(7)), 23.8 (*C*(6)), 36.9 (*C*(4)), 38.3 (N*Me*), 52.1 (*C*(2)), 53.0 (O*Me*), 61.7 (*C*(3)), 63.8, 64.0 (*C*(1), *C*(5)), 171.3 (*C*O_2Me); *m/z* (ESI)$^+$ 200 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{18}NO_3^+$ ($[M+H]^+$) requires 200.1281; found 200.1281.

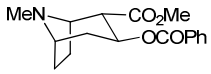
Methyl (1*R*,2*S*,3*S*,5*S*)-3-hydroxy-*N*(8)-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate [(+)-methyl pseudoecgonine] 423[16,50]



$SOCl_2$ (0.12 mL, 1.66 mmol) was added to a stirred solution of **422** (200 mg, 0.83 mmol, >99:1 dr) in MeOH (5 mL) and the resultant mixture was heated at 50 °C for 5 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in THF/MeOH (v/v 10:1, 6 mL) and K_2CO_3 (230 mg, 1.66 mmol) was added. The resultant mixture was left to stir for 4 h at rt before being filtered through Celite® (eluent CH_2Cl_2) and

concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/acetone, 10:1 increased to 100% acetone) gave **423** as a white solid (90 mg, 55%, >99:1 dr); mp 111-113 °C; lit.[49] mp 114-116 °C; $[\alpha]_D^{20}$ +17.5 (*c* 0.44 in H_2O); {lit.[49] $[\alpha]_D^{20}$ +22.8 (*c* 1.7 in H_2O)}; δ_H (400 MHz, $CDCl_3$) 1.50-1.57 (2H, m, C(6)H_A, C(7)H_A), 1.68-1.74 (1H, m, C(4)H_A), 1.80 (1H, ddd, *J* 12.9, 6.6, 3.0, C(4)H_B), 1.84-1.94 (1H, m, C(7)H_B), 1.96-2.06 (1H, m, C(6)H_B), 2.37 (3H, s, N*Me*), 2.85-2.95 (1H, br s, O*H*) overlapping 2.71 (1H, dd, *J* 10.1, 2.8, C(2)*H*), 3.19-3.24 (1H, m, C(5)*H*), 3.45 (1H, app dd, *J* 6.8, 2.8, C(1)*H*), 3.72 (3H, s, O*Me*), 4.11 (1H, td, *J* 10.1, 6.6, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 24.9, 27.1 (*C*(6), *C*(7)), 36.1 (*C*(4)), 37.7 (N*Me*), 51.9, 51.8 (*C*(2), O*Me*), 60.0 (*C*(5)), 61.8 (*C*(1)), 64.3 (*C*(3)), 174.3 (*C*O_2Me).

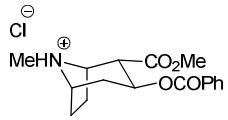
Methyl (1*R*,2*S*,3*S*,5*S*)-3-benzoyloxy-*N*(8)-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate [(+)-pseudococaine] 419[51]



*Method A (from **423**):* PhCOCl (0.05 mL, 0.46 mmol) was added to a stirred solution of **423** (61 mg, 0.31 mmol, >99:1 dr), Et_3N (0.21 mL, 1.53 mmol) and DMAP (2 mg, cat.) in CH_2Cl_2 (3 mL) and the resultant mixture was left to stir at rt for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and washed sequentially with 2.0 M aq NaOH (2 × 4 mL), H_2O (2 × 4 mL) and brine (4 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/Et_3N, 100:1:0.1) gave **419** as a colourless oil (61 mg, 66%, >99:1 dr);[52] $[\alpha]_D^{20}$ +24.3 (*c* 0.54 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.75-1.81 (2H, m, C(4)H_A, C(6)H_A), 1.84-1.89 (1H, m, C(7)H_A), 1.92-1.99 (1H, m, C(7)H_B), 2.05-2.14 (2H, m, C(4)H_B, C(6)H_B), 2.45 (3H, s, N*Me*), 3.14 (1H, dd, *J* 10.7, 2.8, C(2)*H*), 3.26-3.29 (1H, m, C(5)*H*), 3.49-3.51 (1H, m, C(1)*H*), 3.66 (3H, s, O*Me*), 5.54 (1H, td, *J* 10.7, 6.6, C(3)*H*), 7.42 (2H, app t, *J* 7.6, *Ph*), 7.54 (1H, app t, *J* 7.3, *Ph*), 7.99 (2H, app d, *J* 6.9, *Ph*); δ_C (125 MHz, $CDCl_3$) 24.1 (*C*(7)), 26.9 *C*(6)), 33.8 (*C*(4), 37.7 (N*Me*), 48.7 (*C*(2)), 51.9 (O*Me*), 59.8 (*C*(5)), 62.7 (*C*(1)), 67.9 (*C*(3)), 128.3, 129.6, 130.3, 132.8 (*Ph*), 165.6 (O*C*OPh), 172.8 (*C*O_2Me); *m/z* $(ESI)^+$ 629 ([2M+Na], 45%), 326 ([M+Na], 40%), 304 ([M+H], 100%); HRMS (ESI^+) $C_{17}H_{22}NO_4^+$ $([M+H]^+)$ requires 304.1543; found 304.1539.

*Method B (from **423**·HCl):* PhCOCl (0.02 mL, 0.16 mmol) was added to a stirred solution of **423**·HCl (25 mg, 0.11 mmol, >99:1 dr), Et_3N (0.07 mL, 0.53 mmol) and DMAP (2 mg, cat.) in CH_2Cl_2 (2 mL) and the resultant mixture was left to stir at rt for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (2 mL) and washed sequentially with 2.0 M aq NaOH (2 × 4 mL), H_2O (2 × 4 mL) and brine (4 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/Et_3N, 100:1:0.1) gave **419** as a colourless oil (24 mg, 75%, >99:1 dr).

Methyl (1*R*,2*S*,3*S*,5*S*)-3-benzoyloxy-*N*(8)-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate hydrochloride [(+)-pseudococaine·HCl] 419·HCl[51]



A solution of **419** (24 mg, 0.08 mmol, >99:1 dr) in 1.25 M HCl in MeOH (2 mL) was stirred at rt for 5 min then concentrated *in vacuo*. This co-evaporation process was then repeated to give **419**·HCl as a white solid (27 mg, quant, >99:1 dr); mp 209-211 °C; {lit.[49] mp 209.5 °C; lit.53 for *ent*-**419**·HCl mp 210-212 °C}; $[\alpha]_D^{20}$ +43.7 (*c* 0.2 in H_2O); {lit.[54] $[\alpha]_D^{20}$ +42 (*c* 1.5 in H_2O); lit.[53] for *ent*-**419**·HCl $[\alpha]_D^{24}$ –42.3 (*c* 1.0 in H_2O)}; δ_H (500 MHz, MeOH-d_4) 2.18-2.24 (2H, m, C(4)H_A, C(6)H_A), 2.30-2.40 (2H, m, C(7)H_2), 2.41-2.48 (1H, m, C(6)H_B), 2.52 (1H, ddd, *J* 13.9, 6.4, 2.8, C(4)H_A), 2.93 (3H, s, N*Me*), 3.58 (1H, dd, *J* 10.9, 2.5, C(2)*H*), 3.70 (3H, s, O*Me*), 4.07-4.10 (1H, m, C(5)*H*), 4.29-4.31 (1H, m, C(1)*H*), 5.65 (1H, td, *J* 10.9, 6.4, C(3)*H*), 7.49-7.52 (2H, m, *Ph*), 7.63-7.67 (1H, m, *Ph*), 8.00-8.02 (2H, m, *Ph*); δ_C (125 MHz, MeOH-d_4) 23.1 (*C*(7)), 25.4 (*C*(6)), 35.3 (*C*(4)), 38.9 (N*Me*), 49.5 (*C*(2)), 53.3 (O*Me*), 64.7 (*C*(5)), 65.3 (*C*(1)), 66.5 (*C*(3)), 129.7, 130.66, 130.73, 134.7 (*Ph*), 166.9, 170.5 (O*C*OPh, *C*O_2Me).

6.6 References and notes

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[14] 80% Aqueous tetrakis(hydroxymethyl)phosphonium chloride solution (Aldrich) was evaporated to dryness. Dry tetrakis(hydroxymethyl)phosphonium chloride is very hygroscopic and was therefore used immediately.
[15] Upon addition of D_2O to the sample, the resonance at δ_H 3.17-3.22 ppm collapsed to: δ_H 3.19 (1H, ddd, *J* 14.7, 4.8, 2.1, C(8′)H_B); the remainder of the spectrum was unchanged with the exception of δ_H 3.78 (1H, dd, *J* 10.4, 1.4, C(2′)*H*) and 4.30 (1H, d, *J* 1.4, C(2)*H*).
[16] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.
[17] (*R*)-**183** was assessed to be >99% *ee* by 400MHz ^{1}H NMR spectroscopic analysis of a sample of the amine and (*S*)-*O*-acetylmandelic acid in $CDCl_3$, and comparison with that of a racemic sample.
[18] The exact ratio of products could not be determined due to the presence of (−)-CSO **169**, (+)-CSI and excess **183** in the ^{1}H NMR spectrum of the unpurified reaction mixture.
[19] Upon addition of D_2O to the sample, the resonance at δ_H 3.46-4.45 (5H, m, C(5)H_2, C(7a)*H*, C(1′)*H*, O*H*) collapsed to: 3.46-4.15 (4H, m, C(5)H_2, C(7a)*H*, C(1′)*H*)
[20] The ^{1}H and ^{13}C NMR spectra of **26** both showed substantial peak broadening.
[21] Ether **193** was assessed to be 3% ee by Chiral GC (β-cyclodextrin column (0.22 mm x 30 m, thickness 0.25 μm), using He as a carrier gas (flow = 1.0 mL/min, injector T = 220 °C; detector: FID, T = 250 °C); 140 °C tR = 12.7 min, tS = 13.4 min).This value was determined by Dr. Carole Bataille, Chemistry Research Laboratory, University of Oxford, U.K.
[22] (*R*)-**205** was assessed to be >99% *ee* by 400MHz ^{1}H NMR spectroscopic analysis of a sample of the amine and (*S*)-*O*-acetylmandelic acid in $CDCl_3$, and comparison with that of a racemic sample.
[23] The exact ratio of products could not be determined due to the presence of (−)-CSO **169**, (+)-CSI and excess **205** in the ^{1}H NMR spectrum of the unpurified reaction mixture.
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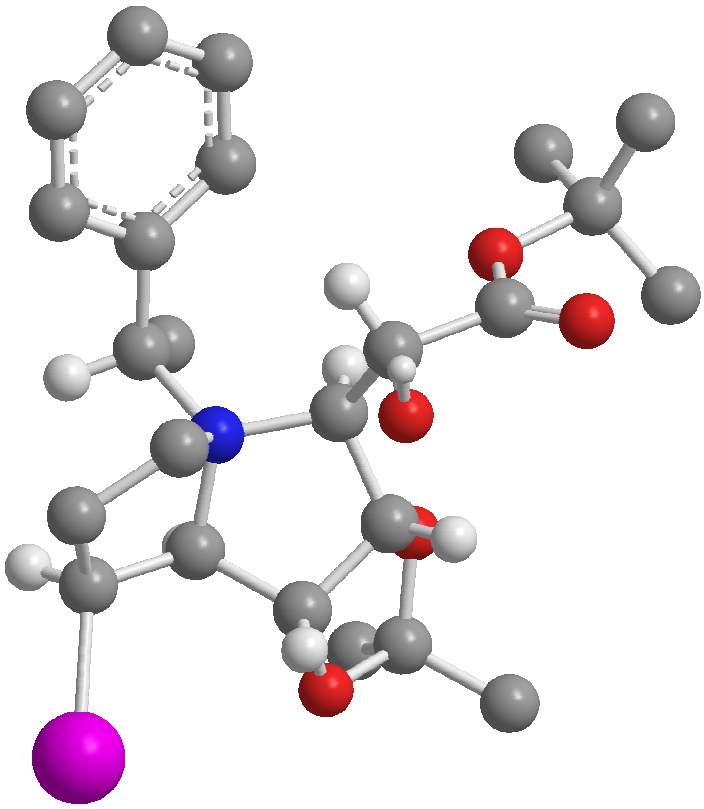
X-Ray crystal structure data for (1*R*,2*S*,3*S*,4*R*,7*S*,7a*S*,1′*R*,α*R*)-178

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 178

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **178** [$C_{24}H_{35}I_2NO_5$]: M = 671.35, triclinic, space group $P\ 1$, a = 8.3429(2) Å, b = 8.7613(3) Å, c = 9.7629(3) Å, α = 96.9997(19)º, β = 101.3959(18)º, γ = 96.5153(14)º, V = 687.36(4) Å^3, Z = 1, μ = 2.32 mm^{-1}, colourless plate, crystal dimensions = 0.07 × 0.09 × 0.11 mm^3. A total of 5243 unique reflections were measured for $5 < \theta < 27$ and 5242 reflections were used in the refinement. The final parameters were wR_2 = 0.056 and R_1 = 0.026 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, UK.

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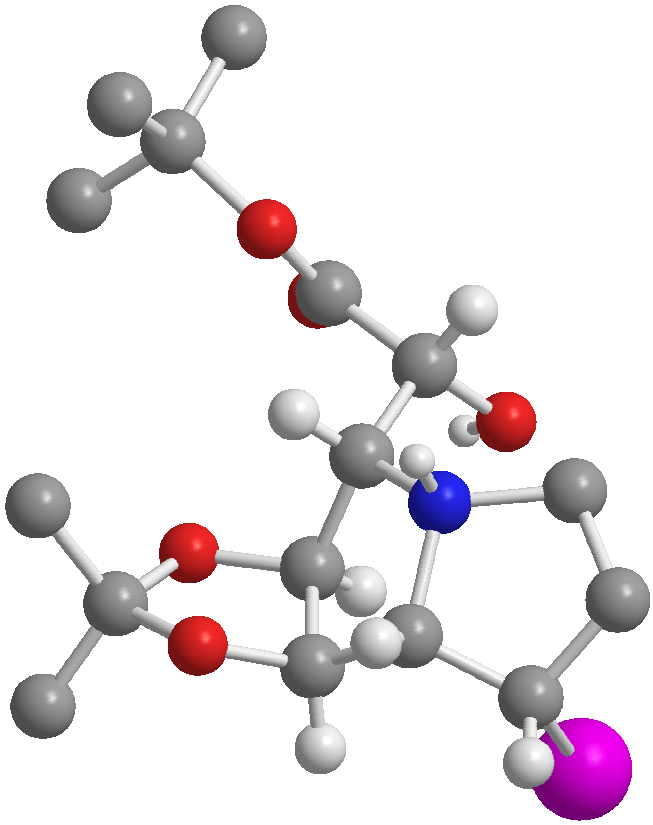
[1] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, C. K. Prout and D. J. Watkin, CRYSTALS, 2001, Issue 11, Chemical Crystallography Laboratory, University of Oxford, UK.

X-Ray crystal structure data for (1*R*,2*S*,3*S*,4*S*,7*S*,7a*S*,1′*R*)-189·HI

(Some H atoms omitted for clarity)



X-ray crystal structure determination for 189·HI

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **189·HI** [$C_{16}H_{27}I_2NO_5$]: M = 567.20, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 11.4404(3) Å, b = 12.2759(3) Å, c = 14.3996(4) Å, V = 2022.30(9) Å^3, Z = 4, μ = 3.13 mm^{-1}, colourless block, crystal dimensions = 0.02 × 0.02 × 0.05 mm^3. A total of 4587 unique reflections were measured for $5 < \theta < 27$ and 4587 reflections were used in the refinement. The final parameters were wR_2 = 0.090 and R_1 = 0.044 [I>–3.0$\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, UK.

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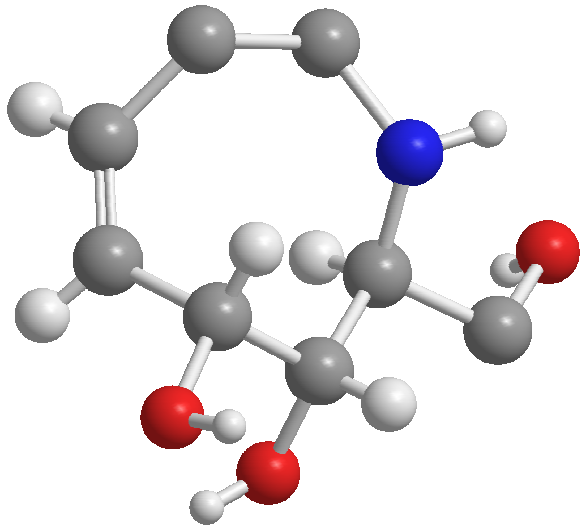
[1] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, C. K. Prout and D. J. Watkin, CRYSTALS, 2001, Issue 11, Chemical Crystallography Laboratory, University of Oxford, UK.

X-Ray crystal structure data for (2*S*,3*S*,4*R*)-230

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 230

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 **230** [$C_8H_{15}NO_3$]: M = 173.21, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.9174(2) Å, b = 9.4363(3) Å, c = 14.0634(4) Å, V = 917.99(5) Å^3, Z = 4, μ = 0.790 mm^{-1}, colourless plate, crystal dimensions = 0.03 × 0.13 × 0.20 mm^3. A total of 2686 unique reflections were measured for $6 < \theta < 76$ and 2676 reflections were used in the refinement. The final parameters were wR_2 = 0.086 and R_1 = 0.038 [I>0.0$\sigma(I)$], with Flack enantiopole = 0.1(2).[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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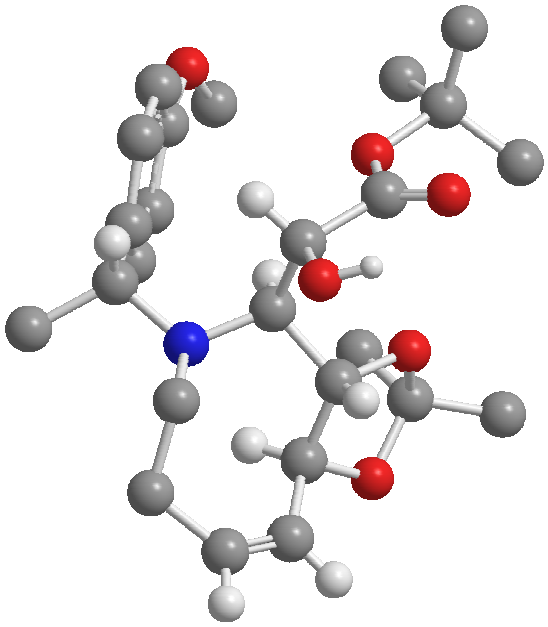
[2] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[3] Flack, H. D.; Bernardelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (2*R*,2′*S*,3′*S*,4′*S*,α*R*)-251

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 251

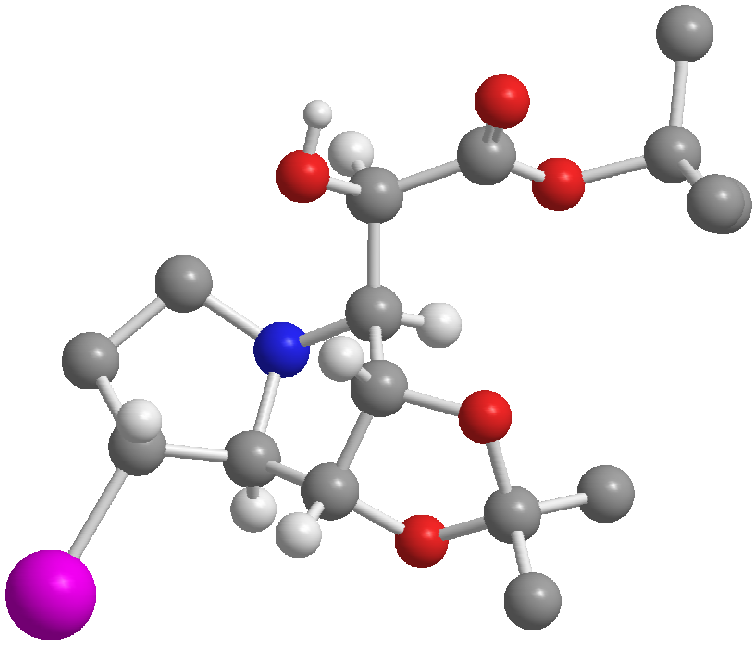
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **251** [$C_{25}H_{37}NO_6$]: M = 447.57, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 9.0523(1) Å, b = 11.9795(2) Å, c = 22.5183(4) Å, V = 2441.93(7) Å^3, Z = 4, μ = 0.086 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.29 × 0.34 mm^3. A total of 3145 unique reflections were measured for $5 < \theta < 27$ and 2332 reflections were used in the refinement. The final parameters were wR_2 = 0.068 and R_1 = 0.032 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[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 (1*R*,2*S*,3*S*,4*S*,7*R*,7a*S*,1′*R*)-311

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 311

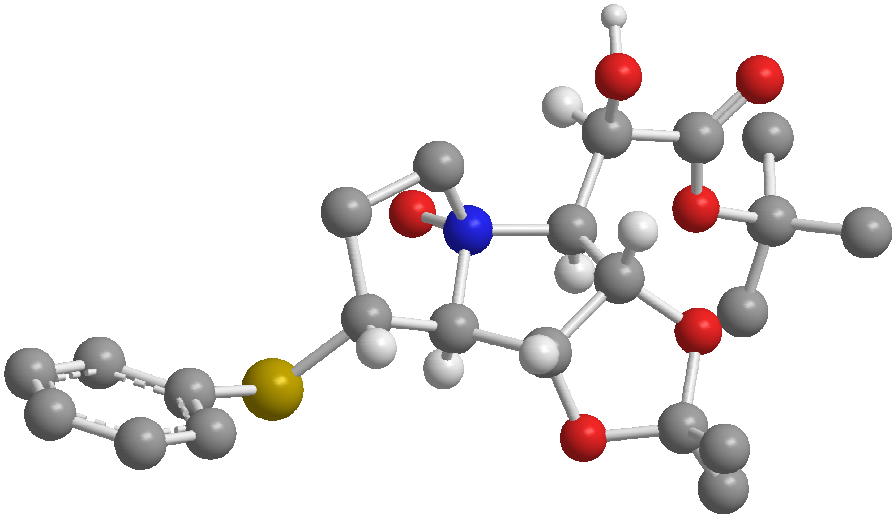
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **311** [$C_{16}H_{26}INO_5$]: M = 1317.87, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 10.8625 (1) Å, b = 21.4681(2) Å, c = 24.6803(2) Å, V = 5755.38(9) Å^3, Z = 12, μ = 1.691 mm^{-1}, colourless block, crystal dimensions = 0.11 × 0.14 × 0.15 mm^3. A total of 12985 unique reflections were measured for $5 < \theta < 27$ and 12985 reflections were used in the refinement. The final parameters were wR_2 = 0.069 and R_1 = 0.036 [$I > -3.0\sigma(I)$], with Flack enantiopole = −0.020(11).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
[2] Flack, H. D.; Bernardelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*R*,2*S*,3*S*,4*R*,7*R*,7a*R*,1′*R*)-343

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 343

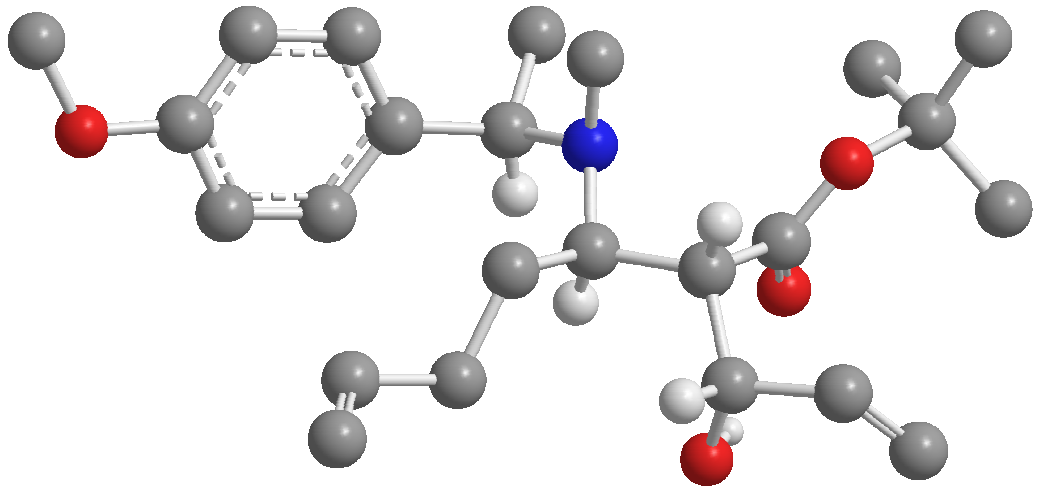
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **343** [$C_{22}H_{31}NO_6S$]: M = 437.56, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.82959(6) Å, b = 16.03625(14) Å, c = 23.7167(2) Å, V = 2217.15(4) Å^3, Z = 4, μ = 1.617 mm^{-1}, colourless block, crystal dimensions = 0.07 × 0.10 × 0.13 mm^3. A total of 21671 unique reflections were measured for $3 < \theta < 77$ and 17475 reflections were used in the refinement. The final parameters were wR_2 = 0.123 and R_1 = 0.050 [I>−3.0σ(I)], with Flack enantiopole = −0.005(13).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
[2] Flack, H. D.; Bernardelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (2*S*,3*R*,1′*S*,α*R*)-390A

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 390A

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 **390A** [$C_{24}H_{37}NO_4$]: M = 403.56, triclinic, space group $P\ 1$, a = 5.6229(3) Å, b = 8.7918(4) Å, c = 12.5901(6) Å, α = 81.487(4)°, β = 82.616(4)°, γ = 76.535(4)°, V = 595.75(5) Å^3, Z = 1, μ = 0.599 mm^{-1}, colourless block, crystal dimensions = 0.11 × 0.17 × 0.25 mm^3. A total of 8922 unique reflections were measured for 4 < θ < 76 and 7575 reflections were used in the refinement. The final parameters were wR_2 = 0.164 and R_1 = 0.063 [I>xx$\sigma(I)$], with Flack enantiopole = –0.2(2).[2]

X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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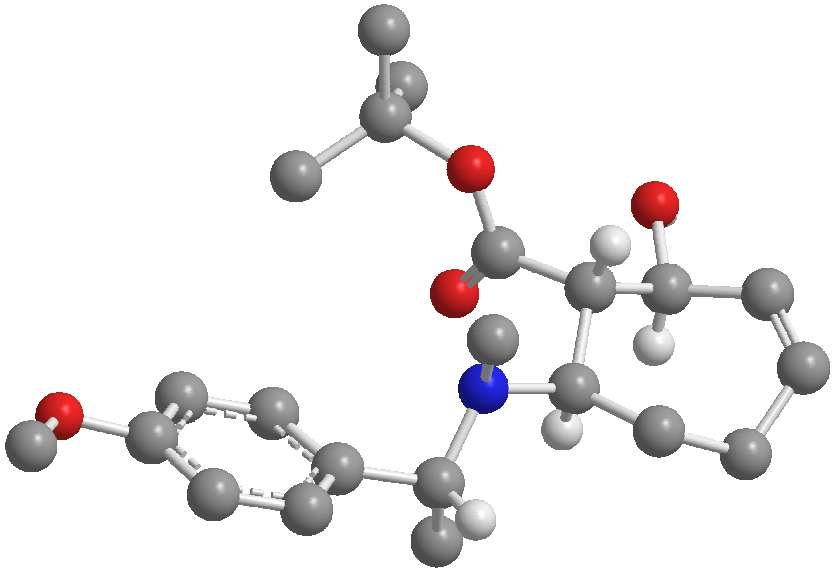
[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[2] Flack, H. D.; Bernardelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*S*,2*S*,7*R*,α*R*)-391A

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 391A

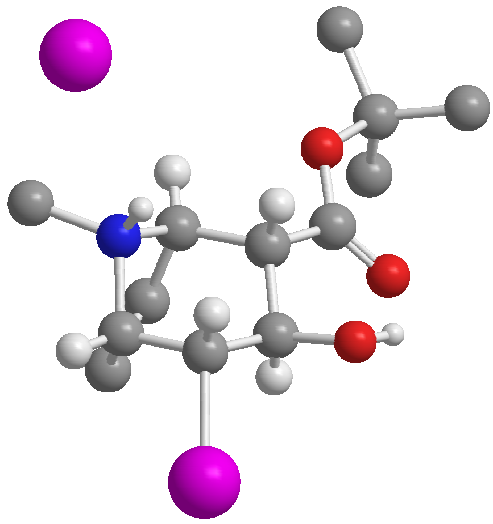
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **391A** [$C_{22}H_{33}NO_4$]: M = 751.02, monoclinic, space group $P\ 2_1$, a = 10.5891(2) Å, b = 10.1907(2) Å, c = 20.7473(4) Å, β = 103.0723(8)°, V = 2180.83(7) Å^3, Z = 4, μ = 0.078 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.24 × 0.27 mm^3. A total of 5228 unique reflections were measured for $5 < \theta < 27$ and 4301 reflections were used in the refinement. The final parameters were wR_2 = 0.101 and R_1 = 0.057 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[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 (1*R*,2*S*,3*R*,4*R*,5*S*)-398·HI

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 398·HI

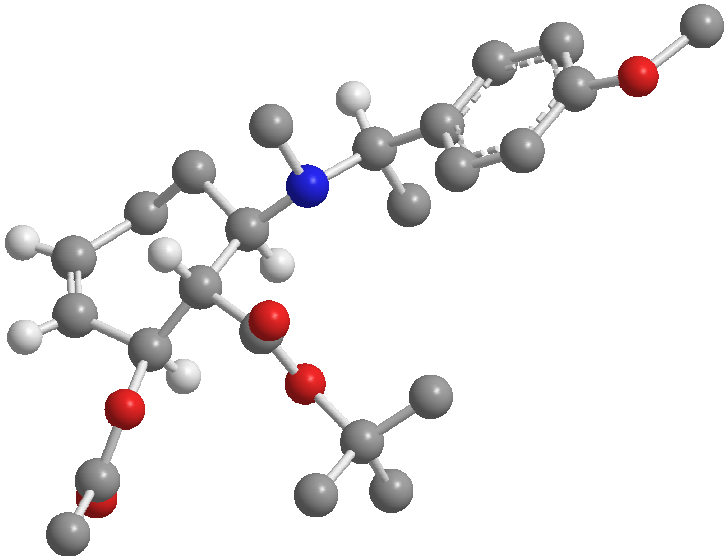
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **398**·HI [$C_{13}H_{23}I_2NO_3$]: M = 495.14, monoclinic, space group $P\ 2_1$, a = 11.7106(5) Å, b = 7.0979(4) Å, c = 11.9661(7) Å, β = 116.827(2)°, V = 887.58(8) Å^3, Z = 2, μ = 3.547 mm^{-1}, colourless prism, crystal dimensions = 0.04 × 0.06 × 0.22 mm^3. A total of 3940 unique reflections were measured for $5 < \theta < 27$ and 3940 reflections were used in the refinement. The final parameters were wR_2 = 0.101 and R_1 = 0.082 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[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 (1*S*,2*S*,7*R*,α*R*)-410A

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 410A

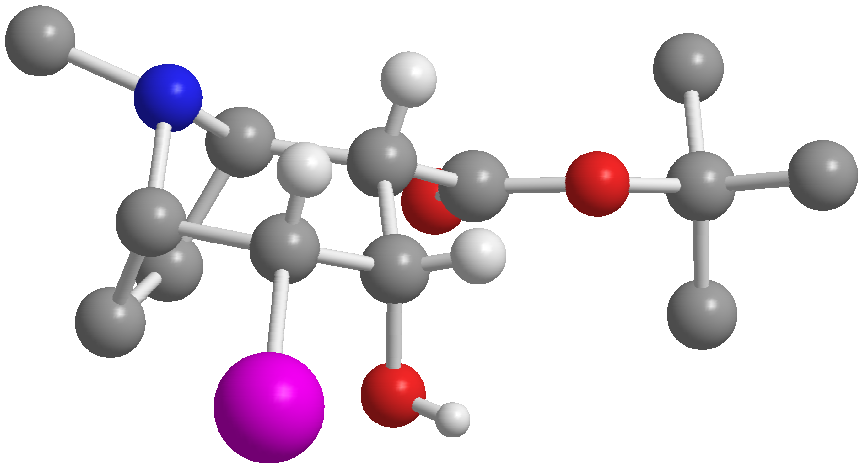
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **410A** [$C_{24}H_{35}NO_5$]: M = 417.55, monoclinic, space group $P\ 2_1$,a = 9.2366(2) Å, b = 13.0553(4) Å, c = 10.8521(3) Å, β = 114.5663(14)°, V = 1190.16(6) Å^3, Z = 2, μ = 0.081 mm^{-1}, colourless block, crystal dimensions = 0.16 × 0.31 × 0.36 mm^3. A total of 2810 unique reflections were measured for 5 < θ < 27 and 2233 reflections were used in the refinement. The final parameters were wR_2 = 0.087 and R_1 = 0.045 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[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 (1*R*,2*S*,3*S*,4*R*,5*S*)-414

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 414

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 **414** [$C_{13}H_{22}INO_3$]: M = 367.23, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 10.5822(4) Å, b = 11.4387(6) Å, c = 12.8091(8) Å, V = 1550.51(13) Å^3, Z = 4, μ = 16.244 mm^{-1}, colourless block, crystal dimensions = 0.05 × 0.05 × 0.05 mm^3. A total of 3217 unique reflections were measured for $5 < \theta < 27$ and 1357 reflections were used in the refinement. The final parameters were wR_2 = 0.06 and R_1 = 0.050 [I>3.0$\sigma(I)$], with Flack enantiopole = −0.04(3).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

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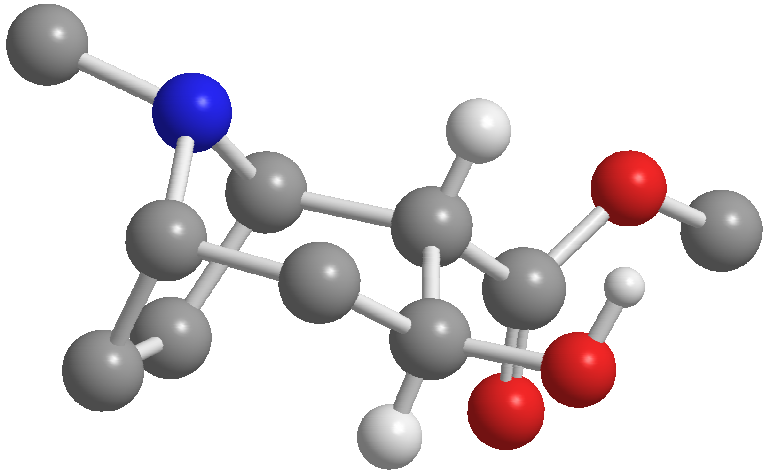
[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

[2] Flack, H. D.; Bernardelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*R*,2*S*,3*R*,5*S*)-423

(selected H atoms are omitted for clarity)



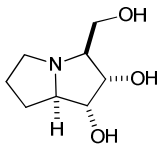
X-ray crystal structure determination for 423

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

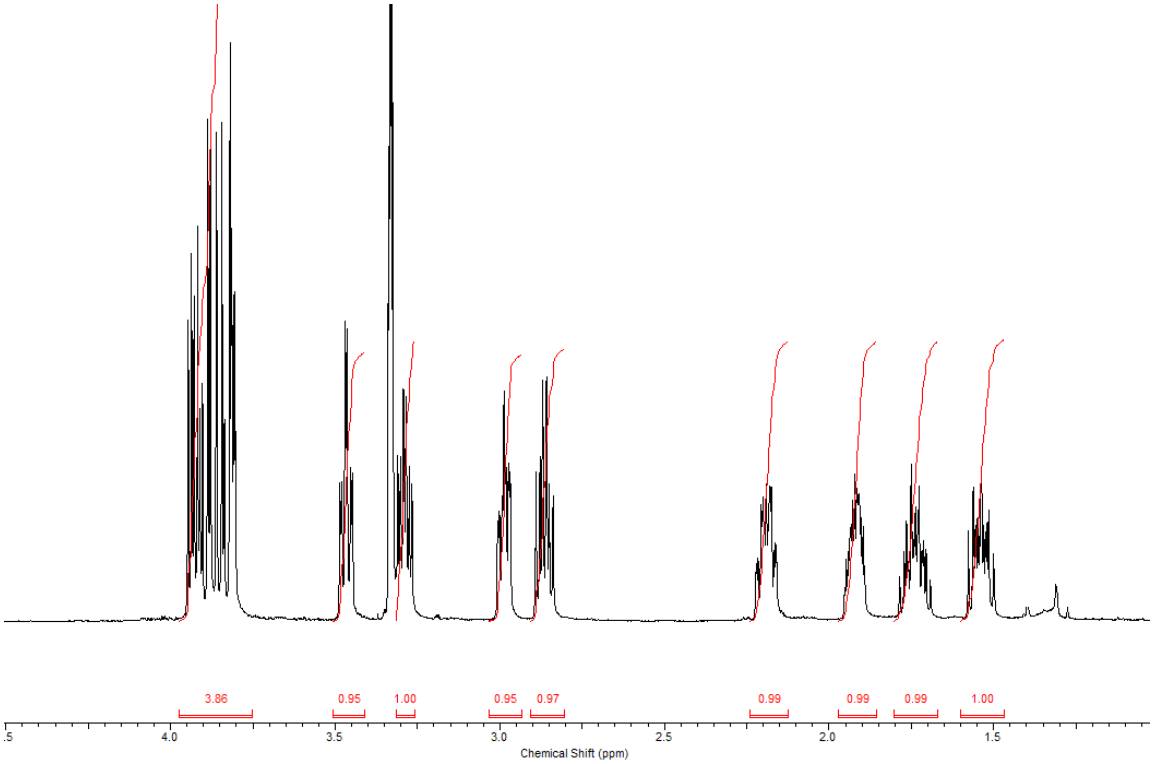
X-ray crystal structure data for **423** [$C_{10}H_{17}NO_3$]: M = 199.25, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.3402(2) Å, b = 8.2496(3) Å, c = 18.8623(6) Å, V = 986.58(6) Å^3, Z = 4, μ = 0.098 mm^{-1}, colourless block, crystal dimensions = 0.11 × 0.13 × 0.25 mm^3. A total of 1323 unique reflections were measured for $5 < \theta < 27$ and 1323 reflections were used in the refinement. The final parameters were wR_2 = 0.105 and R_1 = 0.048 [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

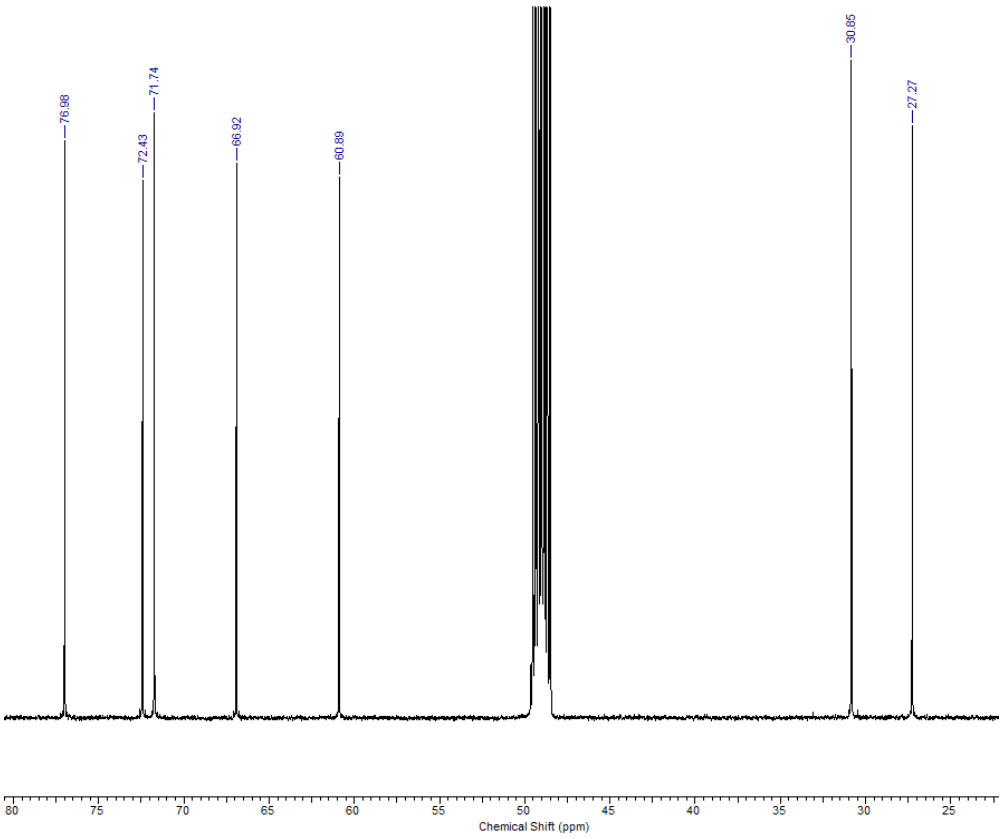
(1*R*,2*S*,3*S*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizidine [(–)-7a-*epi*-hyacinthacine A1] 216



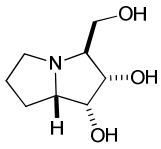
(500 MHz, ^{1}H, MeOH-d_4)



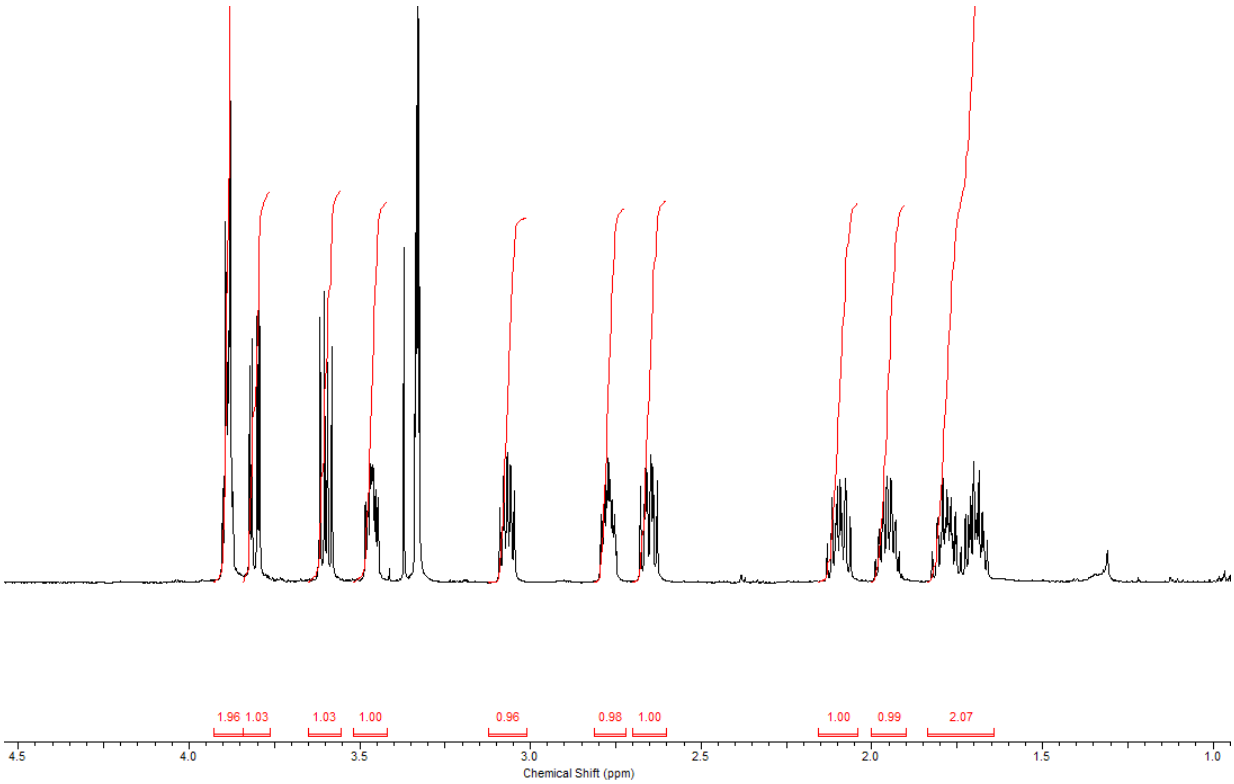
(125 MHz, ^{13}C, MeOH-d_4)



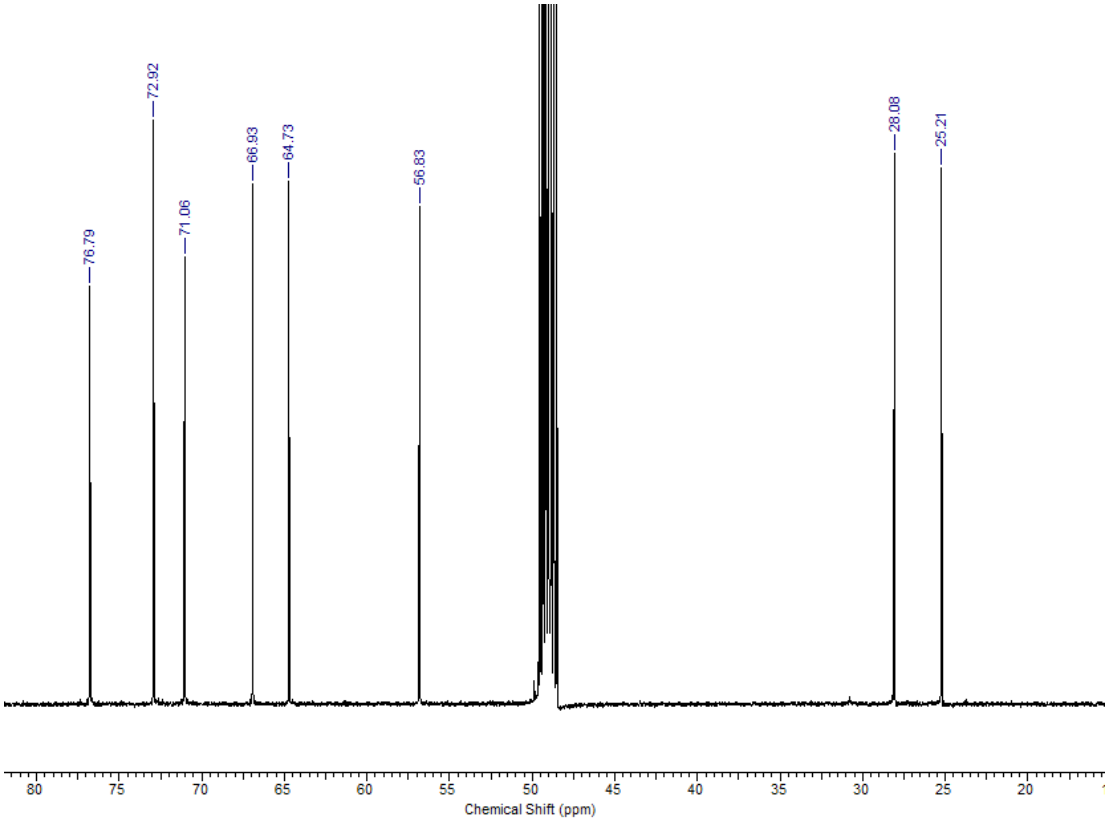
(1*R*,2*S*,3*S*,7a*S*)-1,2-Dihydroxy-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizidine [(−)-hyacinthacine A1] 120



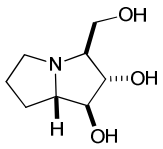
(500 MHz, ^{1}H, MeOH-d_4)



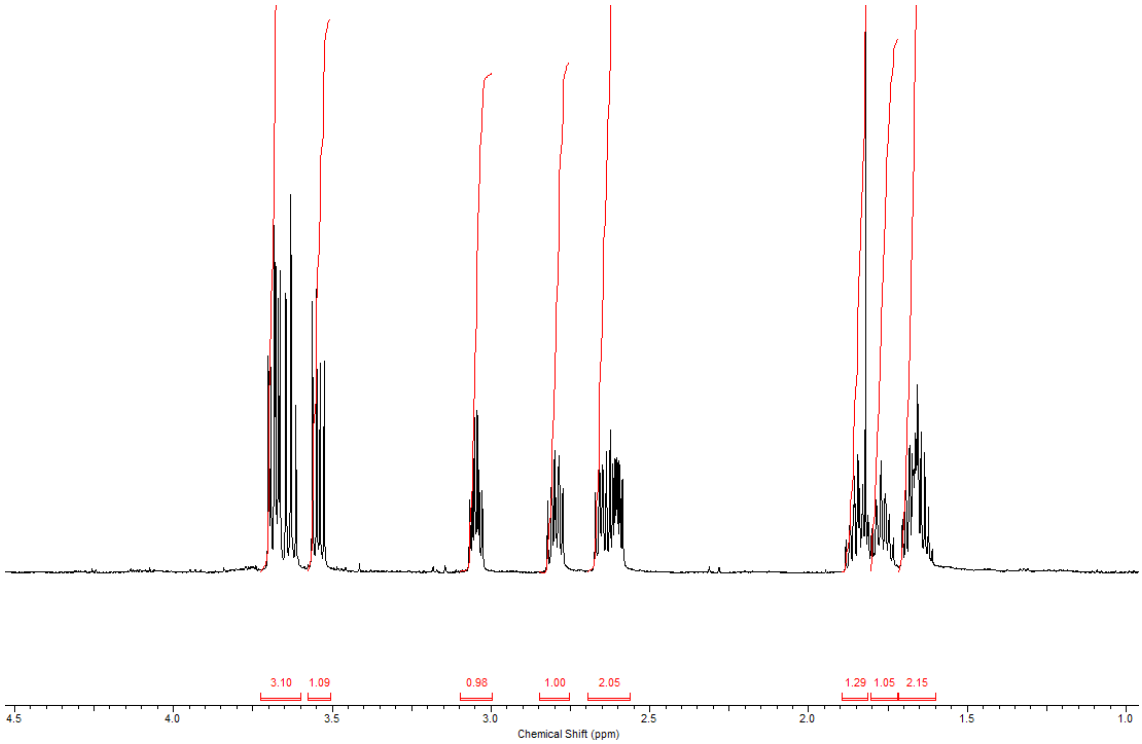
(125 MHz, ^{13}C, MeOH-d_4)



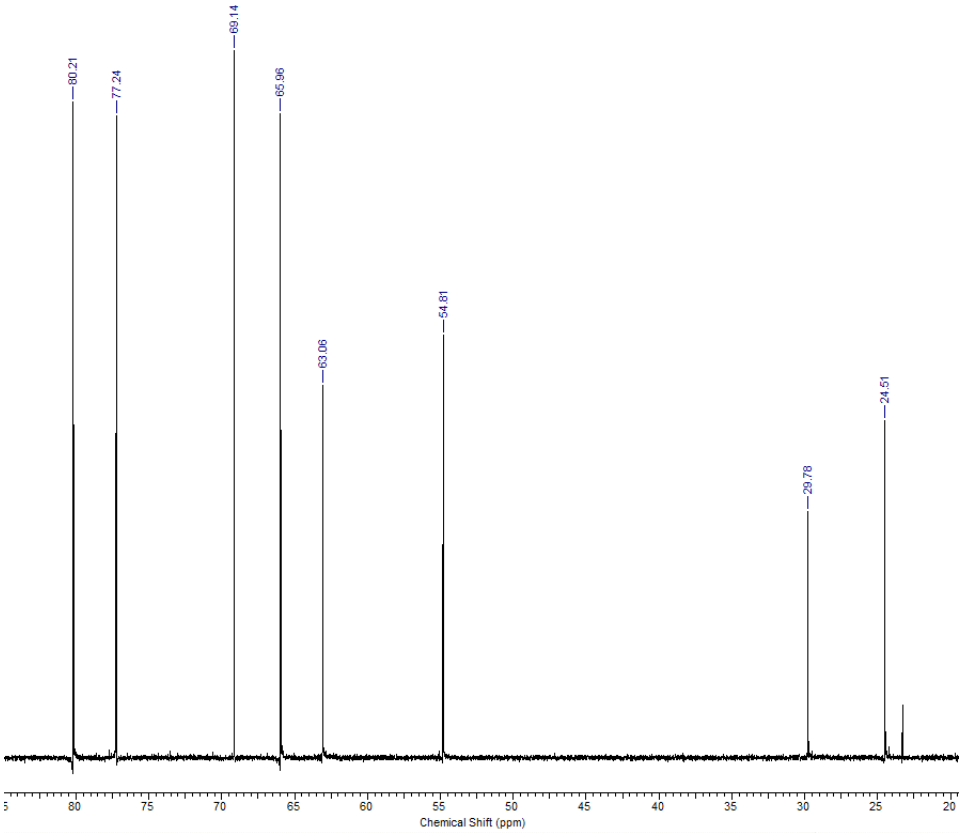
(*S*,*S*,*S*,*S*)-1,2-Dihydroxy-3-(hydroxymethyl)hexahydro-1*H*-pyrrolizidine [(–)-hyacinthacine A2] 222



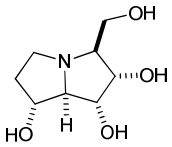
(500 MHz, ^{1}H, D_2O)



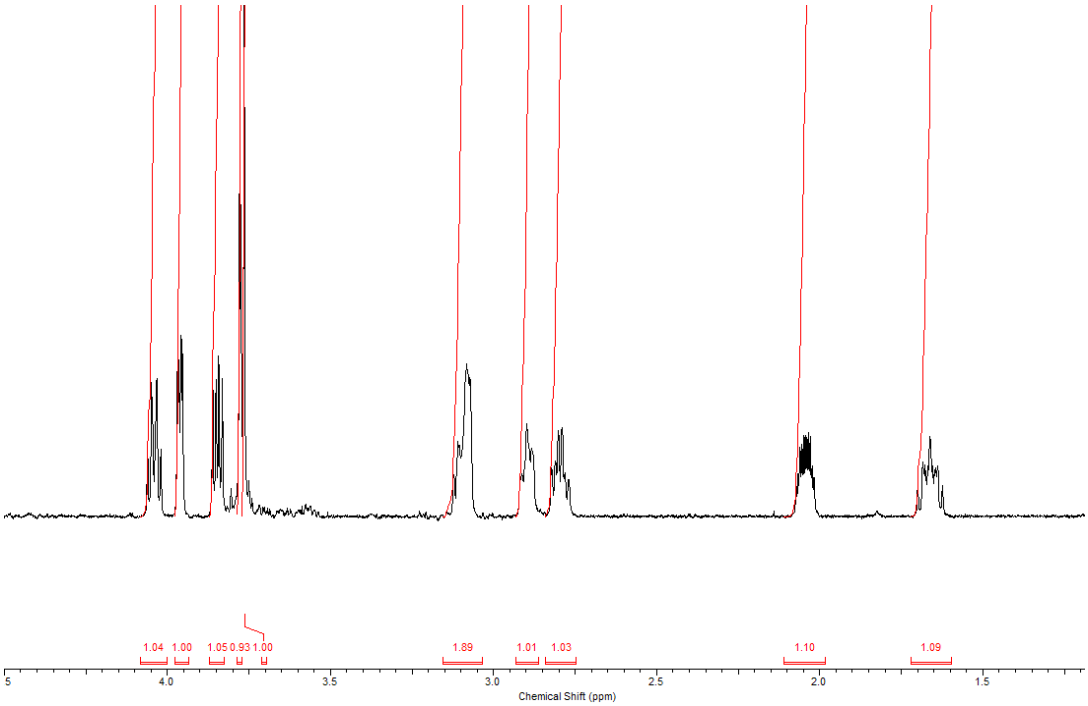
(125 MHz, ^{13}C, D_2O)



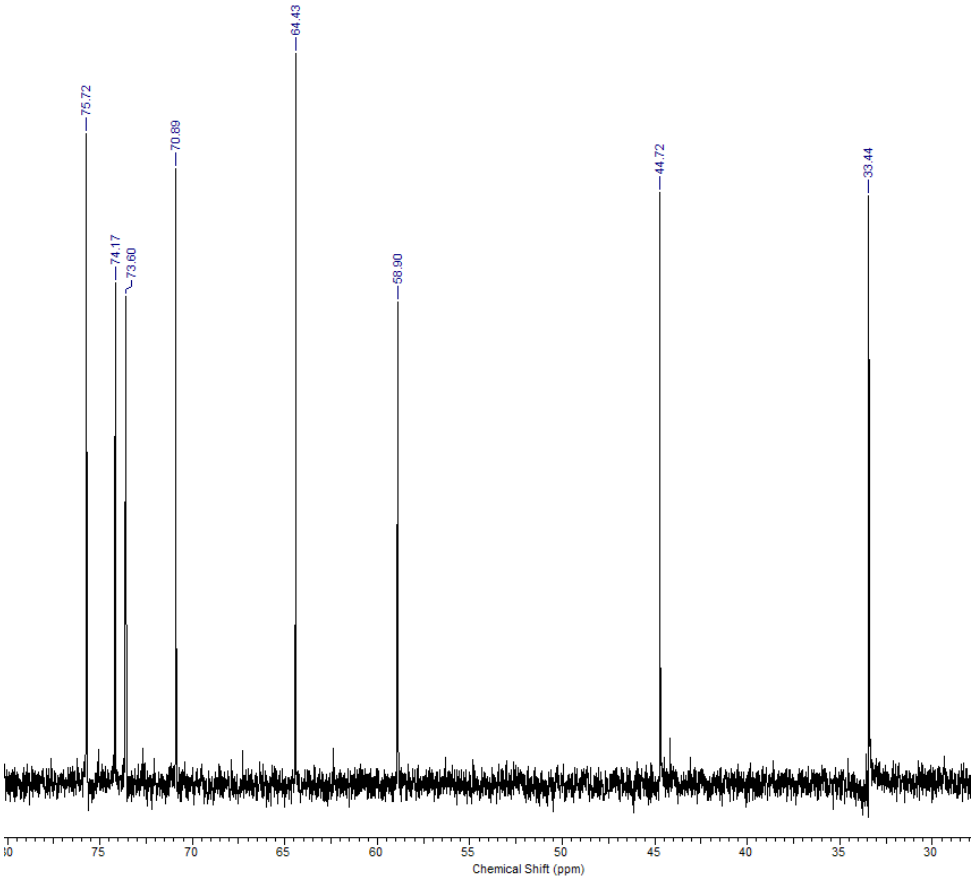
(1*R*,2*S*,3*S*,7*R*,7a*R*)-1,2-Dihydroxy-3-(hydroxymethyl)-7-(hydroxy)hexahydro-1*H*-pyrrolizidine [(–)-1-*epi*-alexine] 356



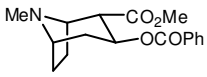
(500 MHz, ^{1}H, D_2O)



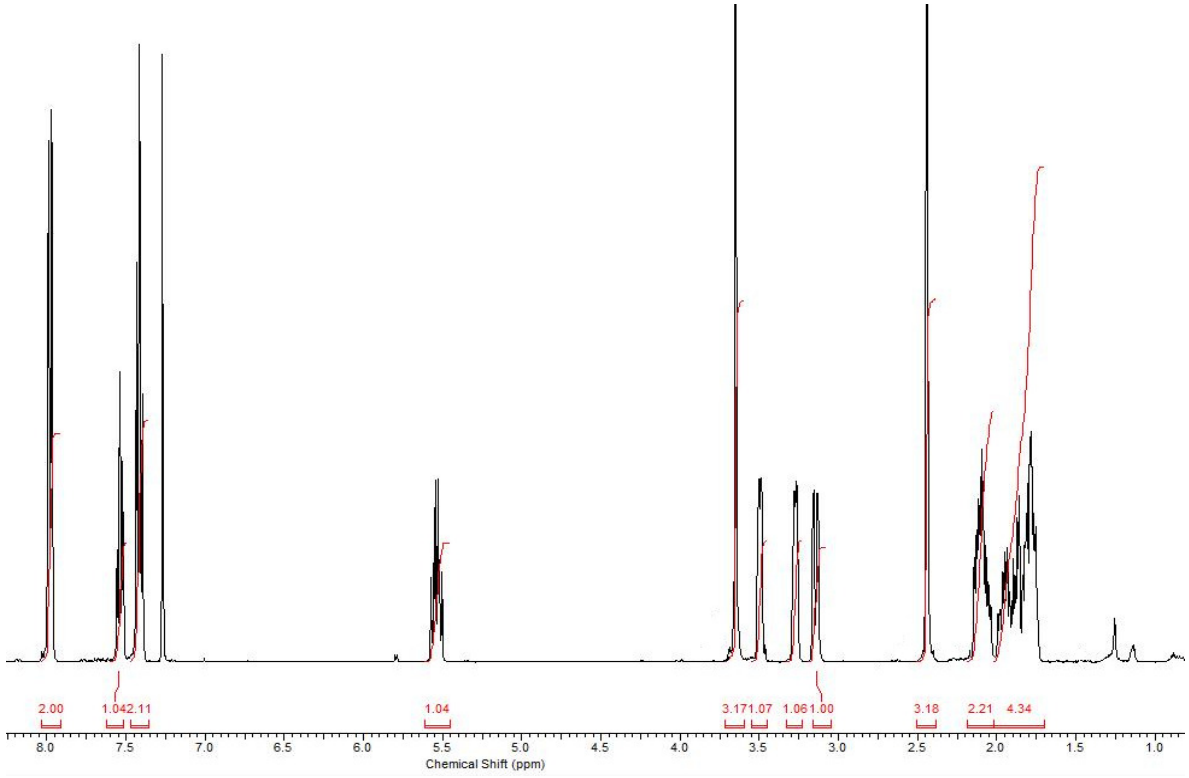
(125 MHz, ^{13}C, D_2O)



Methyl (1*R*,2*S*,3*S*,5*S*)-3-benzoyloxy-*N*(8)-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate [(+)-pseudococaine] 419



(500 MHz, ^{1}H, $CDCl_3$)



(125 MHz, ^{13}C, $CDCl_3$)