Asymmetric syntheses of polyhydroxylated 1-hydroxymethylpyrrolizidines

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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 September 2012 until March 2016, 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.

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This thesis is concerned with the development of methodology for the asymmetric syntheses of polyhydroxylated 1-hydroxymethylpyrrolizidines.

Chapter 1 introduces the biological activities of pyrrolizidine alkaloids and highlights their importance both in Nature and as therapeutic agents. Selected procedures for the syntheses of these compounds are discussed, with a particular focus on the formation of 1-hydroxymethylpyrrolizidines.

Chapter 2 describes studies into the asymmetric syntheses of (–)-isoretronecanol and (–)-trachelantamidine via oxidation of the C=C double bond within two diastereoisomeric 7-aminocyclohept-3-ene-carboxylate substrates via either osmium-mediated dihydroxylation or ammonium-directed epoxidation, followed by oxidative cleavage, *N*-deprotection and in situ double reductive cyclisation to give the target pyrrolizidine alkaloids.

Chapter 3 details the syntheses of three 1-hydroxymethyl-7-hydroxypyrrolizidines via the doubly diastereoselective hydroamination of an enantiopure γ-silyloxy-α,β-unsaturated ester followed by diastereoselective enolate allylation. Oxidative cleavage of the C=C double bonds followed by the application of an *N*-deprotection and in situ double reductive cyclisation protocol, gave (**–**)-hastanecine, (–)-turneforcidine and (–)-platynecine.

Chapter 4 discusses studies into the aldol reaction of β-amino enolates derived from two differently substituted α,β-unsaturated esters culminating in the asymmetric syntheses of the four 1-hydroxymethyl-2-hydroxypyrrolizidines, (**–**)-macronecine, (–)-1-*epi*-macronecine, (**–**)-petasinecine and (+)-1-*epi*-petasinecine, and the 1-hydroxymethyl-2,7-dihydroxypyrrolizidine (+)-2-*epi*-rosmarinecine.

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

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Abbreviations

$[\alpha]_D$	Specific rotation
Δ	Gentle heat
Å	Angstroms
Ac	Acetyl
acac	Acetylacetonate
AIBN	Azobisisobutyronitrile
app	Apparent
aq	Aqueous
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflectance
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
c	Concentration
C	Celsius
^{13}C	Carbon
CAN	Ceric ammonium nitrate
cat.	Catalytic
Cbz	Carboxylbenzyl
cm^{-1}	Wavenumber
Cp	Cyclopentadienyl
CSO	Camphorsulfonyloxaziridine
d	Doublet
DBB	4,4'-di-*tert*-butylbiphenyl
DBU	1,8-Diazabicycloundec-7-ene
DCN	Dicyanonaphthalene
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
dr	Diastereoisomeric ratio
δ_H	Proton (^1H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
ent	Enantiomer
epi	epimeric
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FT	Fourier transform
GTC	Gas chromatography

h	Hours
^{1}H	Proton
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
i	Ipso
^{i}	Iso
IR	Infrared
hν	Light
J	Coupling constant
L	Litres
LDA	Lithium diisopropylamide
lit.	Literature
m	Meta
m	Multiplet
M	Molar
$[M]^+$	Molecular ion
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
Ment	Menthyl
MeOH-d_4	Deuterated methanol
mg	Milligrams
MHz	Megahertz
min	Minutes
Ms	Methanesulfonyl
MS	Molecular sieves
μL	Microlitres
mL	Millilitres
mmol	Millimoles
mol	Moles
MOM	Methoxymethyl
mp	Melting point
m/z	Mass to charge ratio
nm	Nanometre
Nu	Nucleophile
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
o	Ortho
p	Para
Ph	Phenyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
Pr	Propyl
psi	Pounds per square inch

Py	Pyridine
q	Quartet
quant	Quantitative
R	Alkyl
rt	Room temperature
s	Singlet
satd	Saturated
S_N2	Substitution, nucleophilic, bimolecular
spt	Septet
^{t}, *tert*	Tertiary
t	Triplet
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMAO	Trimethylamine *N*-oxide
TMEDA	Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium Perruthenate
Tr	Triphenylmethyl
Ts	*para*-Toluenesulfonyl
UV	Ultra-violet
ν_{max}	Infra-red absorption
v	Volume
w	Weight
W	Watt

Abstract

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Chapter 1: Introduction

1.1. Pyrrolizidine alkaloids

Pyrrolizidines **3** are commonly occurring structures, which are present in numerous natural products and display an extensive range of biological activities. As constituents of over 6000 species of plants, pyrrolizidine alkaloids are one of the most ubiquitous and abundant classes of natural products, with their various biological activities depending on the nature, position and stereochemistry of the substituents (Figure 1).[1,2]

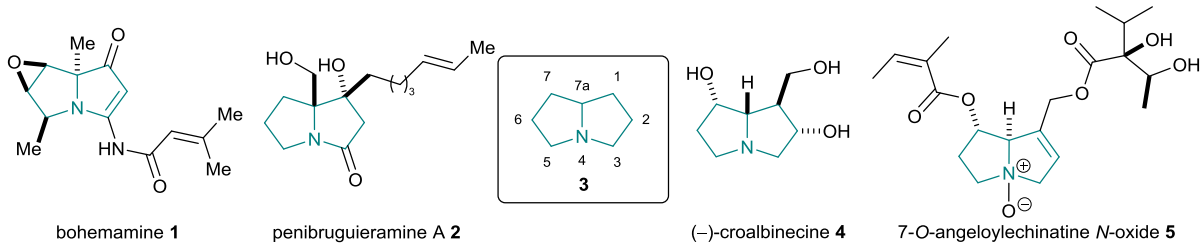
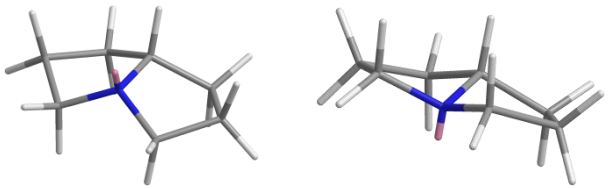


Figure 1. Selected examples of naturally occurring pyrrolizidines **1**, **2**, **4** and **5.**

Many studies on the conformational properties of this class of compounds have been published.[3] Skvortsov *et al.*[3b] studied the equilibrium between the two conformations *cis*-**3** and *trans*-**3**, relative to the *N*-lone pair and the H on C(7a), and found that unsubstituted pyrrolizidines such as **3** exhibit a preference for the *cis*-conformer over the *trans*-conformer. This particular geometry is responsible for the strong basicity of these compounds (pKa 10.88–11.94),[3a] which is one of the highest among saturated tertiary amines (Figure 2).



cis-**3** *trans*-**3**

Figure 2. Chem-3D minimised energy conformation of *cis*-**3** and *trans*-**3**.

1.2. Biological activity of pyrrolizidines

The use of plants containing pyrrolizidine alkaloids for medical purposes has caused many cases of human poisoning all over the world.[4] Despite these poisonous properties, their ability to cross link DNA and act as carbohydrate mimics allows many pyrrolizidine containing compounds to have desirable therapeutic benefits against numerous diseases. Many organisms

use these toxic properties as a defence against herbivores. The cytotoxicity of pyrrolizidine *N*-oxides has also been shown to have beneficial antitumor effects;[5] for example, indicine *N*-oxide **6** has undergone clinical trials in the treatment of leukaemia.[6] Pyrrolizidines bearing different substitution patterns have been shown to display different biological activities: for example, pilsicainide **7** (Sunrythm®) has been marketed for the treatment of cardiac arrhythmias.[7] This compound acts by protonating at physiological pH, and blocking sodium channels in the myocardial cell membrane. Furthermore, (−)-cremastrine **8** has been shown to display potential benefits in the treatment of respiratory disorders,[8,9] selectively inhibiting the muscarinic M3 receptor, while UCS1025A **9** is a pyrrolizidine alkaloid which has been shown to display antitumor and antibiotic properties (Figure 3).[10]

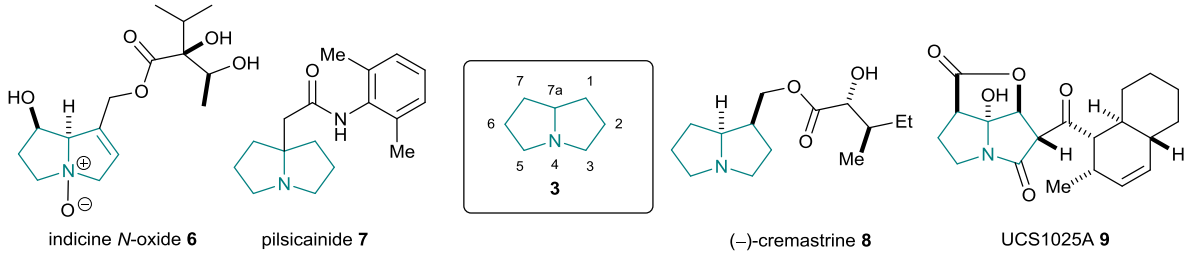


Figure 3. Selected examples of biologically active pyrrolizidines **6**–**9**.

The following sections will give an overview of three pyrrolizidine families: the loline alkaloids **10**, the 3-hydroxymethylpyrrolizidines **11**, and the 1-hydroxymethylpyrrolizidines **12** (named the necine bases) (Figure 4). Particular attention will be given to the necine bases family, these compounds being the target of the methodology reported in this thesis.

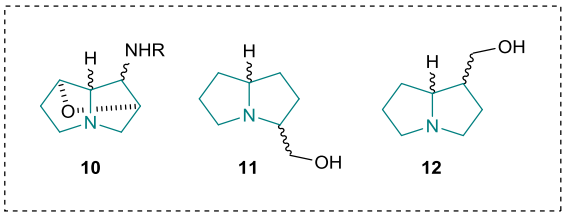


Figure 4. The substructures of the loline alkaloids **10**, the 3-hydroxymethyl pyrrolizidines **11**, and the 1-hydroxymethyl pyrrolizidines **12**.

1.3. Loline alkaloids

Loline **13**, together with congener alkaloids temuline **14** and *N*-acetyl norloline **15**, are alkaloids which are produced in endophytes and have been isolated in numerous plants playing a vital role as defences against insects and herbivores[11] (Figure 5).

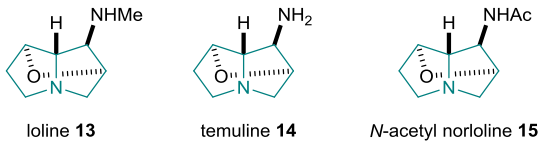


Figure 5. Structure of loline **13**, temuline **14** and *N*-acetyl norloline **15**.

Over the past 50 years there has been great interest in the biosynthesis of pyrrolizidines from the scientific community.[12] The biosynthetic pathway for the synthesis of loline alkaloids has been investigated in detail by Schardl and co-workers.[13] Analyses by deuterium labelling experiments showed that L-proline **16** and L-*O*-acetyl-homoserine **17** could be the precursors of these pyrrolizidines. In vivo incorporation of deuterium labelled **26** and **27** in the final pyrrolizidine product showed that these two compounds might also be intermediates, furnishing more support for the proposed biosynthetic pathway. It was postulated that oxidative decarboxylation of **18** affords **19** which then undergoes ring-closure towards **22**. Intermediates **20** and **21** are proposed structures of the biosynthesis because no direct experiments favour either pathway and decarboxylation might occur before or during ring formation. The ether bridge formation process in these alkaloids is still unclear, but recently it has been proposed that a mechanism involving a hydroxylation at C(2) or C(7) within **23** followed by radical H-abstraction from the other carbon and ring-closure. The mechanism of this reaction is not yet fully determined and understood but is supported by the fact that the pyrrolizidine ring is hypothesized to form prior to the ether bridge (Figure 6).[11b]

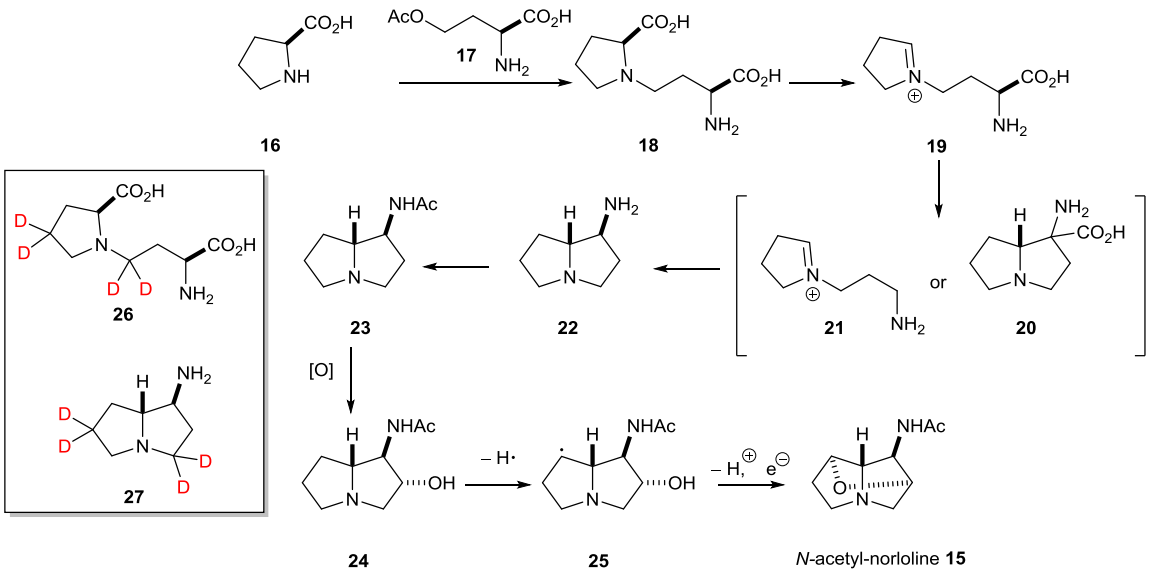
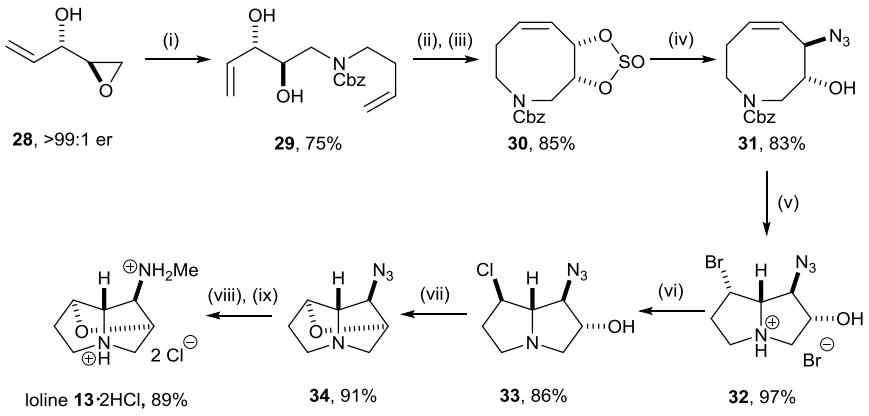


Figure 6. Proposed biosynthetic pathway for the synthesis of the pyrrolizidine ring in loline alkaloids.

Trauner *et al.*[14] reported an asymmetric synthesis of loline **13** starting from enantiopure epoxide **28** (which was obtained in >99:1 er via a Sharpless[15] epoxidation of divinyl carbinol). Nucleophilic epoxide-opening by 3-butenylamine followed by subsequent Cbz-*N*-protection, gave dihydroxy-aminodiene **29** in 75% yield. Ring-closing metathesis of **29** was followed by treatment with thionyl chloride in the presence of Et_3N to obtain cyclic sulfite **30** in 85% yield over two steps. S_N2 reaction of **30** with lithium azide gave **31** in 83% yield, which was subjected to transannular nucleophilic substitution upon treatment with Br_2 in MeOH, which gave **32** in 97% isolated yield. Finkelstein reaction of **32**, to invert the C(7) stereogenic center, gave chloropyrrolizidine **33** in 86% yield, which underwent intramolecular nucleophilic substitution to give tricycle **34** in 91% yield. Reduction of the azide functionality within **34**, *N*-Boc protection and subsequent reduction of the resultant carbamate gave loline **13** in 89% yield over 2 steps. Due to the propensity of these alkaloids to absorb CO_2 when exposed to air, the final product was isolated as the HCl salt (Scheme 1).

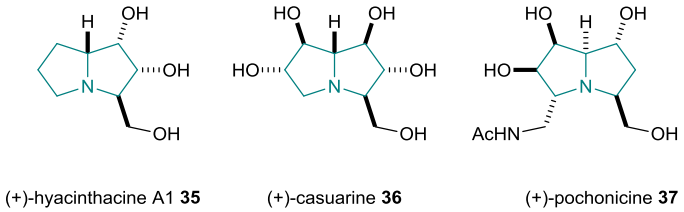


Scheme 1. *Reagents and Conditions*: (i) 3-Butenylamine, $^iPr_2EtN$, MeOH, 45 °C, 12 h then Na_2CO_3, benzyl chloroformate, H_2O/MeOH (1:1), 0 °C to rt, 3 h; (ii) Grubbs II catalyst, CH_2Cl_2, 40 °C, 1 h; (iii) Et_3N, $SOCl_2$, CH_2Cl_2, 0 °C, 1 h; (iv) LiN_3, DMF, 130 °C, 2.5 h; (v) Br_2, MeOH, 0 °C, 12 h; (vi) LiCl, DMF, 105 °C, 6 h; (vii) K_2CO_3, MeOH, 150 °C/300 W, 10 min; (viii) H_2 (1atm), Pd/C, Boc_2O, THF, rt, 48 h; (ix) $LiAlH_4$, THF, reflux, 8 h then HCl, MeOH.

1.4. 3-Hydroxymethylpyrrolizidine alkaloids

(+)-Hyacinthacine A1 **35**, (+)-casuarine **36** and (+)-pochonicine **37** are representative examples of 3-hydroxymethyl pyrrolizidines; compounds in this class often display glycosidase inhibitory properties.[16] Their mode of action is closely related to the dense oxygen functionality present on the ring which allows them to compete with carbohydrates when binding to the glycosidase enzymes.[17] Inhibition of the glycosidic bond cleavage in

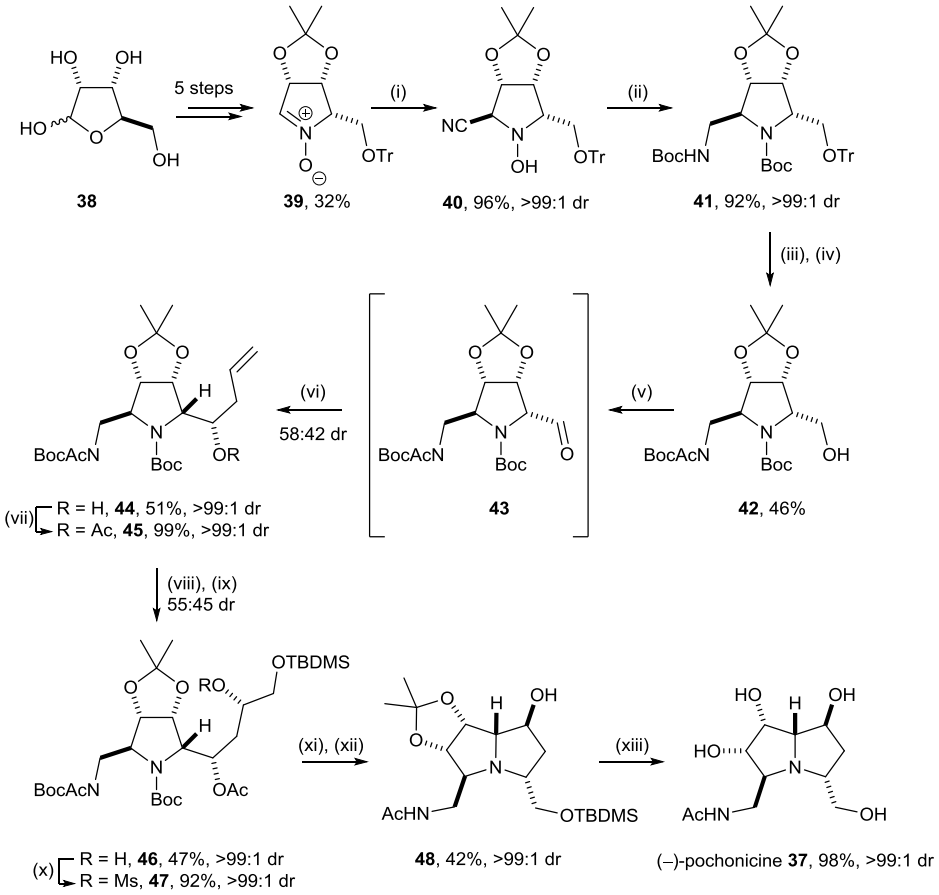
carbohydrates can give rise to various therapeutic benefits in the treatment of numerous diseases, such as cancer, diabetes and HIV (Figure 7).[18]



(+)-hyacinthacine A1 **35** (+)-casuarine **36** (+)-pochonicine **37**

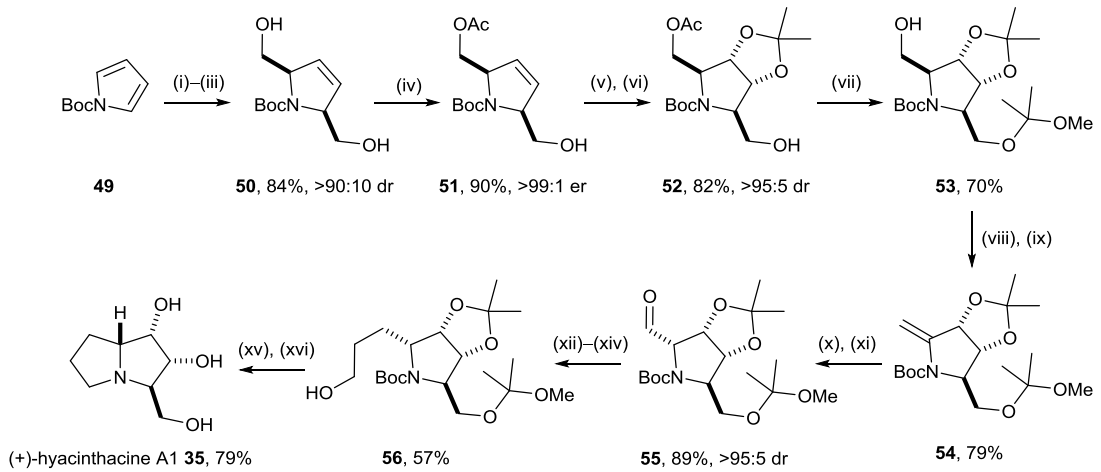
Figure 7. Structure of (+)-hyacinthacine A1 **35**, (+)-casuarine **36** and (+)-pochonicine **37**.

Only the (–)-enantiomer of pochonicine **37** has been synthesized to date with two independent routes being reported.[19] Yu and co-workers[19b] recently obtained (–)-pochonicine **37** and three of its diastereoisomers starting from D-ribose **38**. Diastereoselective addition of TMSCN to nitrone **39** (which was derived from D-ribose **38** in 5 steps and 32% overall yield) gave **40** in 96% yield and >99:1 dr which was submitted to hydrogenolytic reduction of the resultant cyano and hydroxylamine groups, in the presence of Boc_2O, to give **41** in 92% yield as a single diastereoisomer (>99:1 dr). *N*-Acetylation of **41** upon treatment with LDA and Ac_2O, and selective *O*-trityl group deprotection (upon treatment with HCO_2H) gave alcohol **42**, which was oxidized to aldehyde **43** in quantitative yield with Dess-Martin periodinane (DMP). Addition of allylzinc bromide to **43** gave a 58:42 mixture of epimers, from which the major diastereoisomer **44** was isolated in 51% yield and subjected to an acetylation protocol to give **45** in 99% yield and >99:1 dr. Dihydroxylation of **45** under Upjohn[20] conditions gave a 55:45 mixture of diastereoisomers and, following regioselective mono-*O*-silylation and subsequent mesylation, the major diastereoisomer **47** was isolated in 43% overall yield as a single diastereoisomer (>99:1 dr). Treatment of **47** with $ZnBr_2$ and *p*-cresol promoted *N*-Boc deprotection and cyclisation, and after methanolysis **48** was isolated in 42% yield. Finally (–)-pochonicine **37** was obtained in 98% yield following acid catalysed global hydrolysis of **48** (Scheme 2).



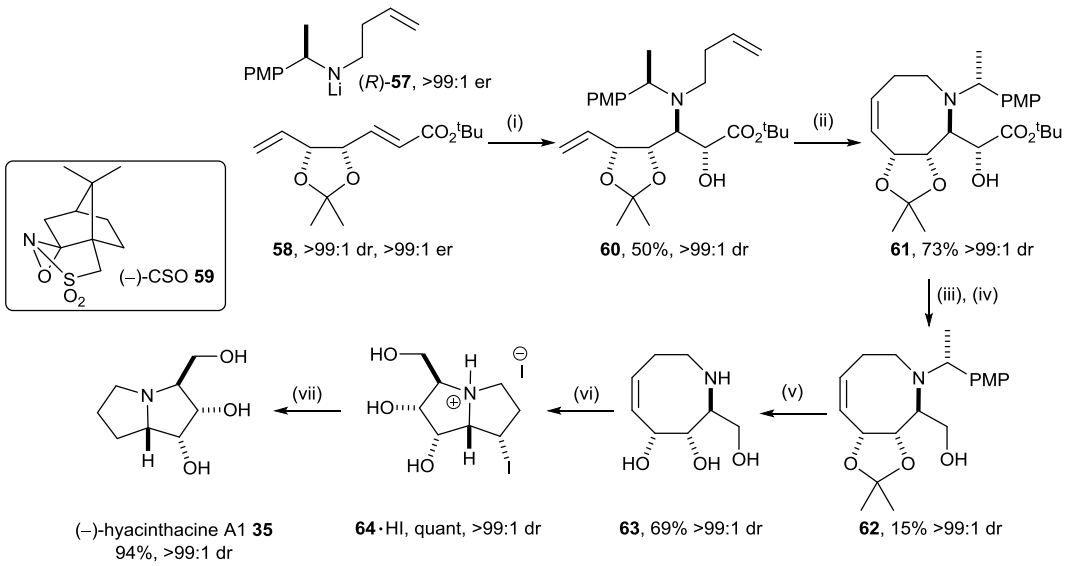
Scheme 2. *Reagents and Conditions*: (i) TMSCN, MeOH, 50 °C, 16 h; (ii) H_2 (1 atm), Raney Ni, Boc_2O, THF/MeOH (10:1), rt, 4 days; (iii) LDA, THF, −78 °C, 20 min then Ac_2O, 20 min; (iv) HCO_2H/Et_2O (1:1), 0 °C, 1 h then rt, 30 min; (v) DMP, $NaHCO_3$, CH_2Cl_2, rt, 1 h; (vi) Allyl bromide, Zn dust, THF, 4 h, rt; (vii) Ac_2O, DMAP, Py, rt, 1.5 h; (viii) OsO_4, NMO, acetone/H_2O (1:2), rt; (ix) NEt_3, DMAP, TBDMSCl, CH_2Cl_2, rt, 4 h; (x) NEt_3, MsCl, CH_2Cl_2, 0 °C, 30 min; (xi) $ZnBr_2$, *p*-cresol, CH_2Cl_2, rt, 12 h; (xii) K_2CO_3, MeOH/H_2O (17:3), 60 °C, 4 h; (xiii) HCl (6.0 M aq), MeOH, rt, 12 h.

Many syntheses of both enantiomers of hyacinthacine A1 **35** have been developed over the past 15 years.[21] For example, Donohoe *et al.*[19c] employed the bis-alkylation of *N*-Boc pyrrole **49** upon treatment of **49** with LiTMP and methyl chloroformate, followed by reduction with LiDBB to give *cis*-dihydropyrrole **50** in 84% yield and >90:10 dr. Desymmetrisation of **50** via a lipase enzymatic acetylation gave **51** in >99:1 er. *cis*-Dihydroxylation of **51** under Poli conditions,[22] and acetal-protection of the resultant 1,2-diol gave **52** in 82% yield and >95:5 dr. *O*-Protecting group manipulation of **52** gave **53**, which was subjected to mesylation and subsequent elimination with DBU to afford **54** in 55% overall yield (from **52**). Diastereoselective hydroboration of **54** and oxidation of the resultant alcohol with TPAP gave aldehyde **55**. Subsequent Wittig olefination of **55**, hydrogenation and ester reduction, gave **56** in 57% yield. Cyclisation of **56** was achieved upon mesylation of **56** and Lewis acid mediated global deprotection, giving (+)-hyacinthacine A1 **35** in 79% yield over 2 steps (Scheme 3).



Scheme 3. *Reagents and Conditions:* (i) LiTMP, THF, −78 °C, 3 h then $ClCO_2Me$, 30 min; (ii) Li, DBB, THF, −78 °C, 16 h then 2,6-di-*tert*-butylphenol, 30 min; (iii) Red-Al®, THF, 0 °C, 2 h; (iv) *Pseudomonas* lipoprotein lipase, vinyl acetate, THF, 37 °C, 30 h; (v) cat. OsO_4, TMANO, CH_2Cl_2, 16 h; (vi) *p*-TsOH, 2-methoxypropene, DMF, rt, 16 h; (vii) 2-methoxypropene, PPTS, 0 °C to rt, 16 h then K_2CO_3, MeOH, rt, 1 h; (viii) Ms_2O, DMAP, CH_2Cl_2, rt, 16 h; (ix) DBU, NaI, DME, reflux, 72 h; (x) BH_3·THF, THF, 3 h, rt then H_2O_2, NaOH (aq), 30 min; (xi) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 16 h; (xii) Ph_3PCHCO_2Me, THF, reflux, 24 h; (xiii) H_2 (1 atm), PtO_2, EtOAc, rt, 18 h; (xiv) $LiBH_4$, THF, rt, 1.5 h; (xv) Ms_2O, Py, 0 °C, 10 min then rt, 1 h; (xvi) $ZnBr_2$, CH_2Cl_2, rt, 18 h.

Davies *et al.*[19f] recently reported a different approach towards the synthesis of (–)-hyacinthacine A1 **35**. The doubly diastereoselective[23] conjugate addition of lithium amide (*R*)-**57** to α,β-unsaturated ester **58** (which was derived from D-ribose **38** in 3 steps and 55% yield) was followed by enolate oxidation[24] with (–)-CSO **59**, to afford enantiopure α-hydroxy-β-amino ester **60** as a single diastereoisomer (>99:1 dr) in 50% isolated yield. Ring-closing metathesis of **60** afforded **61** in 73% yield, and subsequent reduction of the ester and oxidative cleavage of the resultant 1,2-diol gave **62** in 15% yield over 2 steps. Global *N*- and *O*-deprotection of **62** upon treatment with aqueous HCl gave **63** in 69% yield. Subsequent transannular cyclisation, upon treatment of **63** with I_2 in MeOH, gave **64**·HI in quantitative yield. Finally, hydrogenolytic reduction of the C–I bond gave (–)-hyacinthacine A1 **35** in 94% yield after purification (Scheme 4).



Scheme 4. *Reagents and Conditions:* (i) (*R*)-**57**, THF, −78 °C, 2 h then (–)-CSO **59**, −78 °C to rt, 12 h; (ii) Grubbs I catalyst, CH_2Cl_2, rt, 12 h then $P(CH_2OH)_3$, Et_3N, SiO_2, CH_2Cl_2, rt, 12 h; (iii) $LiAlH_4$, THF, −78 °C to rt, 12 h; (iv) $NaIO_4$, MeOH, rt, 4 h then $NaBH_4$, rt, 4 h; (v) HCl (3.0 M aq), MeOH, reflux, 2 h; (vi) I_2, MeOH, rt, 12 h; (vii) H_2, Pd/C, Et_3N, MeOH, rt, 18 h.

1.5. 1-Hydroxymethylpyrrolizidines (the necine bases)

One of the largest sub-classes of pyrrolizidine alkaloids includes the 1-hydroxymethyl pyrrolizidines, which are also called the necine bases. Their biosynthesis in particular has been intensively studied and several intermediates have been isolated and characterised.[12d] The biosynthetic pathway, established by feeding experiments with ^{2}H, ^{3}H, ^{14}C and ^{13}C-labelled precursors, established that putrescine **65** is the starting point in the synthesis of 1-hydroxymethylpyrrolizidines **12**. It was reported that partial oxidation and dimerization of **65** gave, after reduction of the imine intermediate **67**, homospermidine **68**, which upon oxidation was converted into dialdehyde **69**. Cyclisation upon intramolecular Mannich reaction afforded 1-formyl-pyrrolizidine **71**, which is then reduced to give 1-hydroxymethylpyrrolizidine **12**. It has been established that deuterium labelled samples of **12** are incorporated in more complex molecules such as **72**, indicating that a possible pathway to these polyhydroxylated pyrrolizidines could be via oxidation of **12** at the C(2) or C(7) positions in vivo (Figure 8).

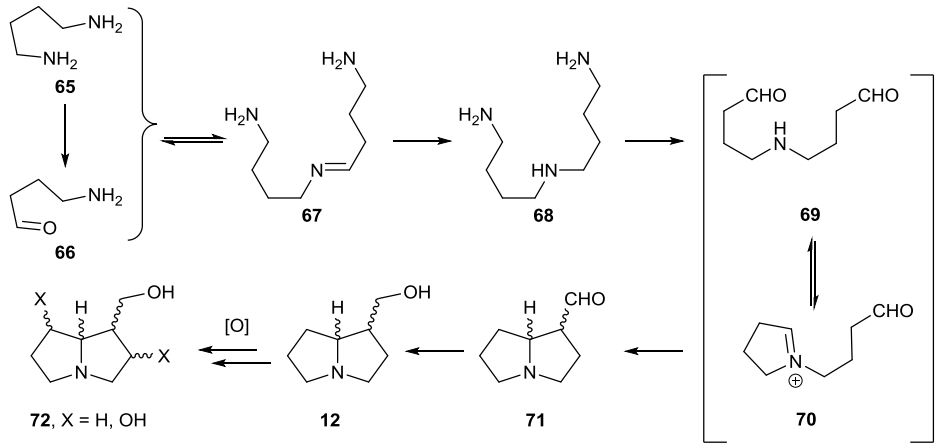


Figure 8. Biosynthetic pathway towards 1-hydroxymethylpyrrolizidines **12** and **72**.

The toxicity of these compounds is probably due to metabolic transformations occurring in the liver, making some pyrrolizidine alkaloids hepatotoxic and in some cases carcinogenic.[4] Most hepatotoxic alkaloids possess very specific structural features; in particular, to show adverse effects for the organism, the pyrrolizidine usually requires 1,2-unsaturation and acylation on the C(1)-hydroxymethyl substituent such as **73**.[25] The mechanism for their oxidation has been extensively studied and reviewed.[26] Oxidation of the unsaturated ring is postulated to afford a pyrrole derivative **74** which under acidic conditions, would promote elimination of the ester functionality to give **75** which is easily subjected to nucleophilic attack from DNA or proteins.[27] Some saturated pyrrolizidines, however, do not show the same toxic effects.[27a] The metabolic oxidation of the saturated pyrrolizidine alkaloid (–)-rosmarinine **77**, for example, has been studied and in this case pyrrole **78**, which is not susceptible to nucleophilic attack, was isolated as a result of oxidation and elimination of the ester group at C(7) (Figure 9).[27a]

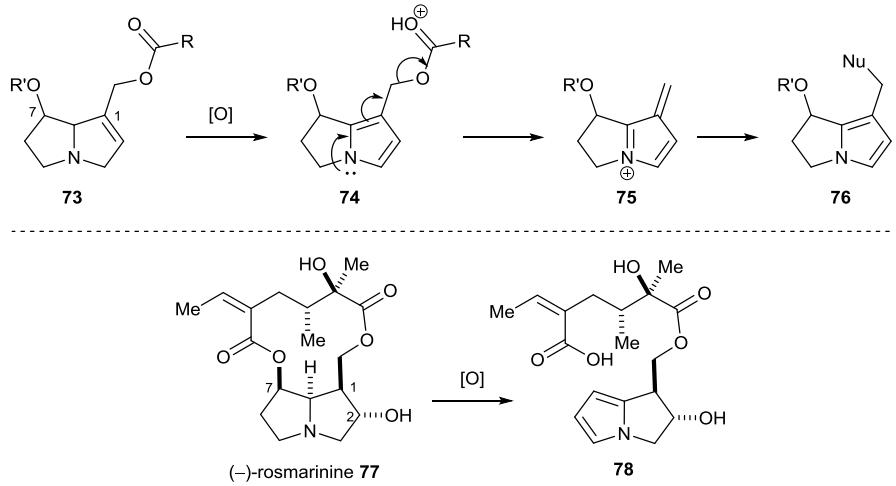


Figure 9. Metabolic oxidation of **73** and **77**.

The 1-hydroxymethylpyrrolizidines can be sub-divided in 4 different subclasses, depending on the position and the number of hydroxyl groups attached to the pyrrolizidine ring: 1-hydroxymethylpyrrolizidines **12**, 1-hydroxymethyl-2-hydroxypyrrolizidines **79**, 1-hydroxymethyl-7-hydroxypyrrolizidines **80**, and 1-hydroxymethyl-2,7-dihydroxy-pyrrolizidines **81** (Figure 10).

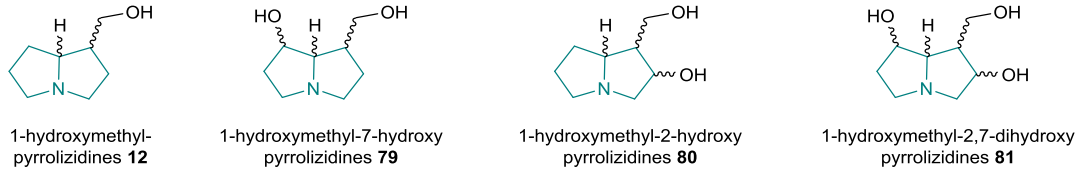


Figure 10. Structural sub-classes of the 1-hydroxymethylpyrrolizidines.

These compounds have been isolated from plants as the free bases, or as the corresponding *N*-oxides or *O*-acyl derivatives, and there has been significant interest in both their occurrence and synthesis in Nature.[28] Many procedures have been developed over the years for the syntheses of these compounds; selected illustrative examples are described in the following sections.

1.5.1. Syntheses of 1-hydroxymethylpyrrolizidines: (–)-isoretronecanol and (–)-trachelantamidine

(–)-Isoretronecanol **82** and (–)-trachelantamidine **83** [also called (–)-laburnine] represent the simplest naturally occurring 1-hydroxymethylpyrrolizidines. They are present in Nature in both enantiomeric forms and were first isolated from natural sources in 1942 and 1941, respectively[29] (Figure 11).

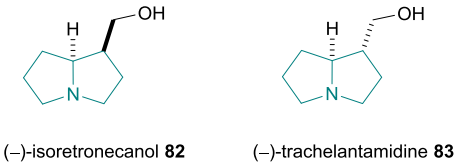
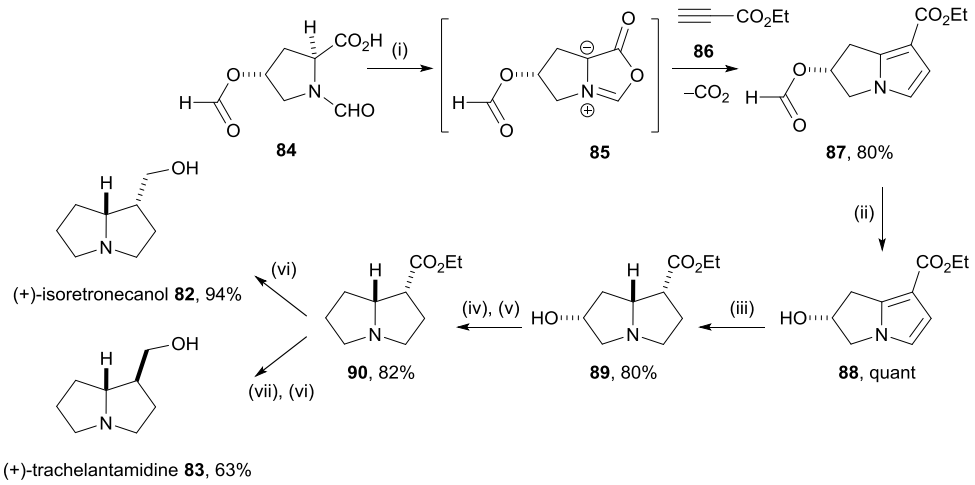


Figure 11. Structures of (–)-isoretronecanol **82** and (–)-trachelantamidine **83.**

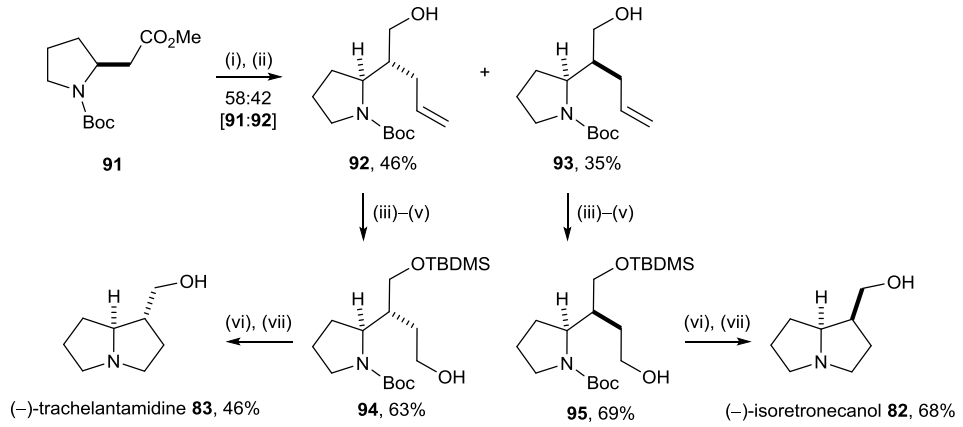
The first synthesis of these compounds in their enantiopure form was reported in 1979 by Robins and co-workers.[30] Azomethyne ylide **85** (which was formed *in situ* upon heating *N*,*O*-diformyl-4-hydroxyproline **84** in Ac_2O), was reacted via a regioselective 1,3-dipolar cycloaddition with ethyl propiolate **86**. Subsequent *in situ* decarboxylation and aromatization formed dihydropyrrolizine **87** in 80% yield. Removal of the *O*-protecting group and

diastereoselective hydrogenation on the less hindered face of **88**, gave **89** in 80% yield. Removal of the C(6)-hydroxyl group upon conversion to the corresponding chloride and reduction with Raney Ni gave **90** in 82% yield. Reduction of the ester within **90** gave (–)-isoretronecanol **82** in 94% yield, whereas sequential epimerisation of **90** upon treatment with sodium ethoxide, followed by reduction of the ester, gave (–)-trachelantamidine **83** in 63% yield (Scheme 5).



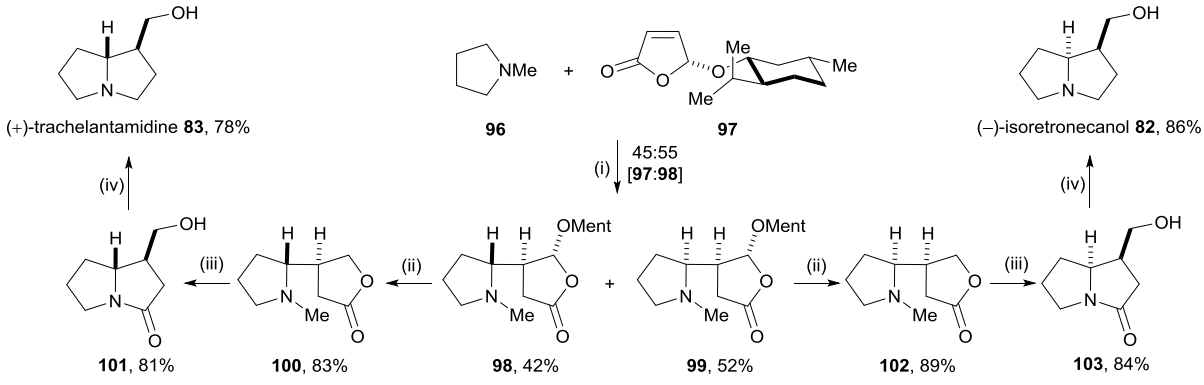
Scheme 5. *Reagents and Conditions:* (i) **86**, Ac_2O, 140 °C, 10 h; (ii) NH_3, EtOH, rt, 16 h; (iii) H_2 (21 atm), Pd/C, AcOH, rt, 2 days; (iv) $SOCl_2$, 5 °C then reflux, 5 h; (v) H_2 (15 atm), Raney Ni, EtOH, rt; (vi) $LiAlH_4$, Et_2O, rt, 2 h; (vii) NaOEt, EtOH, 58 °C, 12 h then rt, HCl (aq).

Since Robins's first synthesis of these enantiopure pyrrolizidines, many other syntheses starting from enantiopure pyrrolidines have been reported.[31] For example, Knight *et al*.[31d,e] reported syntheses of (–)-isoretronecanol **82** and (–)-trachelantamidine **83** starting from (*S*)-*N*-Boc-homoproline methyl ester **91**. Allylation of **91** followed by reduction with DIBAL-H and separation of the 58:42 epimeric mixture gave **92** and **93** in 46 and 35% yield, respectively. Both diastereoisomers were separately subjected to silyl protection of the hydroxyl functionality, dihydroxylation of the C=C double bond, oxidative cleavage of the resultant 1,2-diol, and reduction of the corresponding aldehydes with $NaBH_4$ to afford alcohols **94** and **95** in 63 and 69% yield, respectively. *O*-Mesylation and subsequent addition of trifluoroacetic acid promoted *N*-Boc deprotection and cyclisation to give (–)-isoretronecanol **82** and (–)-trachelantamidine **83** in 68 and 46% yield, respectively (Scheme 6).



Scheme 6. *Reagents and Conditions:* (i) LDA, –78 °C, THF, 15 min, then HMPA, 15 min then allyl bromide, 20 min then rt, 1 h; (ii) DIBAL-H, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –78 °C, 2.25 h; (iii) TBDMSCl, imidazole, DMF, 35 °C, 16 h; (iv) $NaIO_4$, OsO_4, Et_2O/H_2O (3:2), rt, 16 h; (v) $NaBH_4$, MeOH, 0 °C, 30 min; (vi) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (vii) TFA, CH_2Cl_2, rt, 30 min.

Several de novo asymmetric syntheses of (–)-isoretronecanol **82** and (–)-trachelantamidine **83** have been reported to date.[32] For example, Hoffmann and co-workers[32e,f] reported the addition of pyrrolidine **96** to enantiopure menthyloxy furanone **97** under radical conditions to give a 45:55 mixture of epimers **98** and **99**, respectively, which were isolated as single diastereoisomers in 42 and 52% yield, respectively. Reduction of **98** and **99** afforded **100** and **102** in 83 and 89% yield, respectively. *N*-Demethylation of **100** and **102** upon photosensitised oxidation afforded pyrrolizidine-3-ones **101** and **103**, in 81 and 84% yield, respectively. Finally, reduction of **101** and **103** upon treatment with $LiAlH_4$ gave (+)-trachelantamidine **83** and (–)-isoretronecanol **82** in 78 and 86% yield, respectively (Scheme 7).



Scheme 7. *Reagents and Conditions:* (i) 4,4'-dimethoxybenzophenone, MeCN, hν (300 nm); (ii) $NaBH_4$, MeOH, rt, 1 h; (iii) hν (350 nm), DCN, $LiClO_4$, O_2, 90 min then NaOH (20%, aq), 3 h; (iv) $LiAlH_4$, THF, reflux, 10 h.

1.5.2. Syntheses of 1-hydroxymethyl-2-hydroxypyrrolizidines: (–)-macronecine and (–)-petasinecine

(–)-Macronecine **105** and (–)-petasinecine **106** are the only 1-hydroxymethyl-2-hydroxypyrrolizidines isolated to date. These compounds have been isolated as their angeloyl-esters (–)-macrophylline **104** and (–)-petasinine **107** in carcinogenic plants[33] and, more recently in flea beetles,[34] in which their toxicity has been shown to be useful as a protection against potential predators[35] (Figure 12).

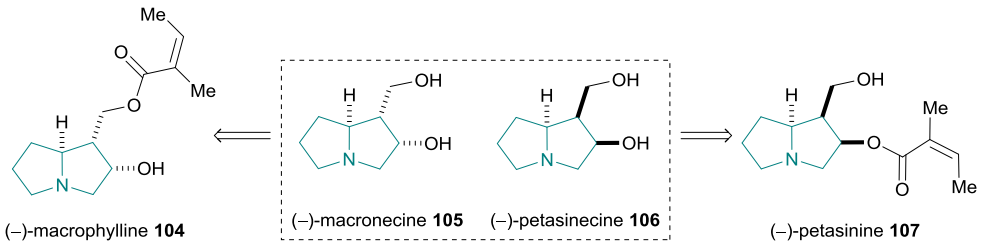
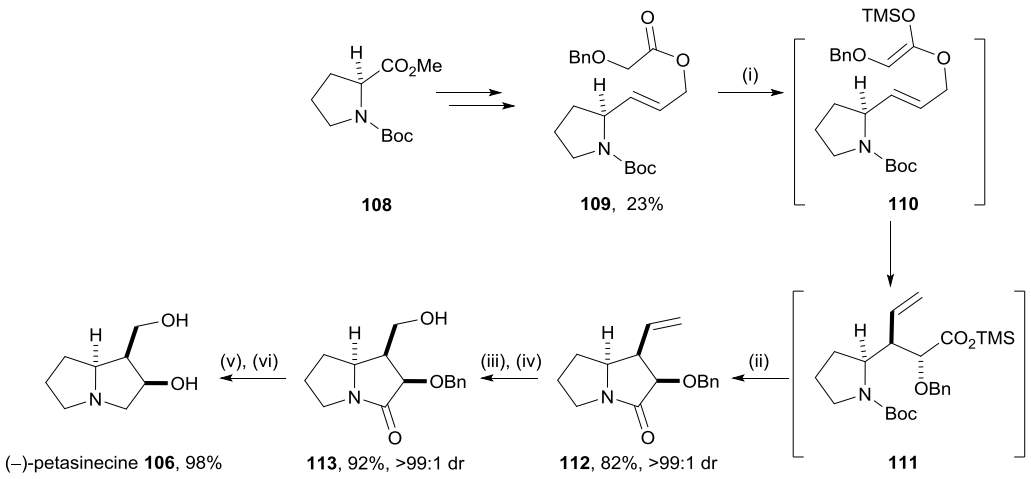


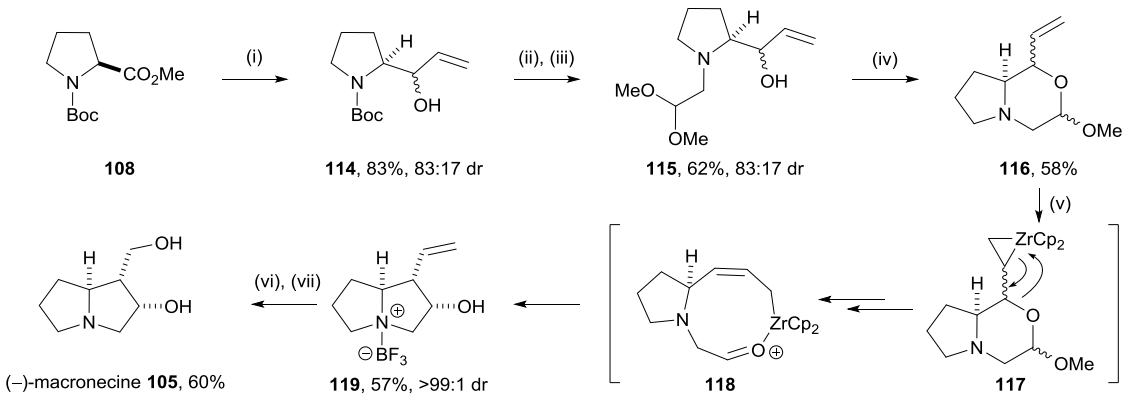
Figure 12. Structures of (–)-macronecine **105**, (–)-petasinecine **106**, (–)-macrophylline **104** and (–)-petasinine **107**.

Only 5 syntheses of enantiopure 1-hydroxymethyl-2-hydroxypyrrolizidines which involve construction of the bicyclic scaffold are known in literature.[36] Mulzer[36a] reported the synthesis of (–)-petasinecine **106** via an Ireland-Claisen-type rearrangement of **109** (which was derived from L-proline derivative **108** in 3 steps and 23% overall yield). The high diastereoselectivity observed in the rearrangement step was postulated to be due to the chair-like transition state derived from (*Z*)-silylenol ether **110**, formed upon treatment of **109** with LiHMDS and TMSCl. The relative configuration between the pyrrolidine and the stereogenic centers created upon rearrangement resulted from diastereofacial induction, with minimisation of steric interactions, via Houk's model.[37] Cyclisation towards pyrrolizidine-3-one **112** was achieved upon *N*-deprotection of **111** with TFA. Ozonolysis of **112** followed by reduction afforded **113**, which was subjected to BH_3 mediated reduction of the amide functionality and hydrogenolytic *O*-debenzylation to afford (–)-petasinecine **106** in 90% yield (Scheme 8).



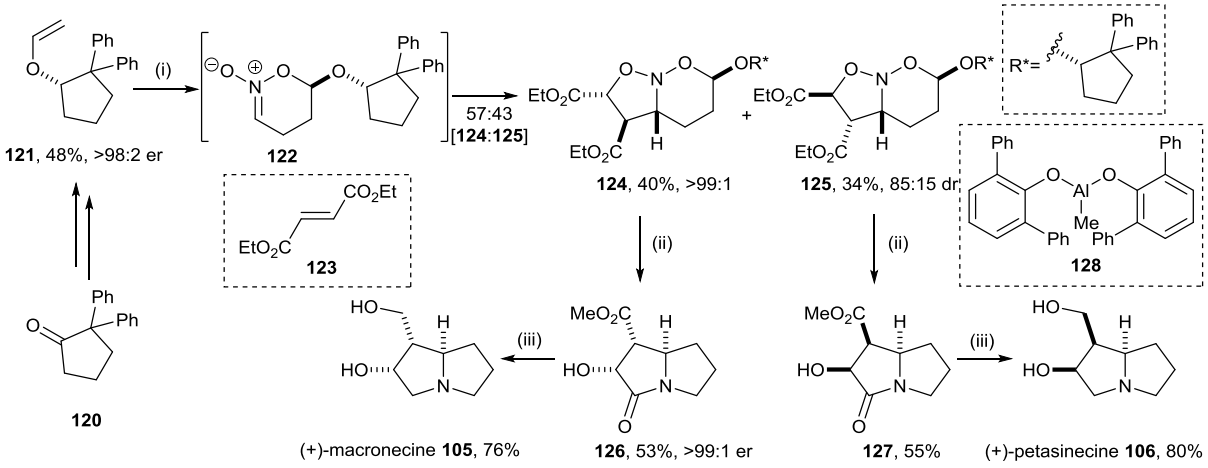
Scheme 8. *Reagents and Conditions:* (i) LiHMDS, TMSCl, THF, –110 °C, 2 h, then 0 °C, 5 h; (ii) TFA, BuOH, –20 °C, 1 h then rt, 16 h; (iii) O_3, MeOH, –78 °C, 10 min; (iv) $NaBH_4$, MeOH, –78 °C, 16 h; (v) BH_3·THF, THF, 60 °C, 48 h; (vi) H_2 (1 bar), Pd/C, MeOH, rt, 48 h.

Another L-proline based synthesis of a 1-hydroxymethyl-2-hydroxypyrrolizidine, this time (–)-macronecine **105**, was reported by Taguchi *et al.*[36b] as an application of their methodology for the zirconium-mediated ring-contraction of vinylmorpholine derivatives. Reduction of L-proline derivative **108** with DIBAL-H was followed by the addition of vinylmagnesium bromide to the resultant aldehyde, *N*-Boc deprotection and *N*-alkylation to give **115** as an 83:17 mixture of diastereoisomers. Conversion of **115** into acetal **116** in presence of TsOH was achieved in 58% yield. Subsequent treatment of **116** with "Cp_2Zr" (which was prepared in situ from Cp_2ZrCl_2 and BuLi) in the presence of BF_3·Et_2O gave **119** in 57% yield as a single diastereoisomer. The mechanism for the ring-contraction was proposed to pass through intermediate **117**, which under the acidic reaction conditions formed oxonium ion **118** that rearranged to give pyrrolizidine **119**. Ozonolysis of **119** followed by reductive work-up afforded (–)-macronecine **105** in 60% yield (Scheme 9)



Scheme 9. *Reagents and Conditions:* (i) DIBAL-H, THF, –78 °C then vinylmagnesium bromide; (ii) TFA; (iii) α-bromoacetaldehyde dimethyl acetal, $^{i}Pr_2EtN$, MeCN, reflux; (iv) TsOH, benzene, reflux; (v) Cp_2ZrCl_2, BuLi, THF, –78 °C to rt, 4 h then $BF_3{\cdot}Et_2O$, 0 °C, 1 h; (vi) O_3, –78 °C then $NaBH_4$, rt; (vii) 10% aq NaOH.

Concise methodology for the synthesis of pyrrolizidine rings has been developed by Denmark and co-workers using a [4+2] cycloaddition between nitroalkenes and chiral vinylethers as the key step.[38] Reaction of nitroethylene and chiral ether **121** (which was obtained in 2 steps and 48% overall yield from 2,2-diphenylcyclopentanone **120**) gave intermediate **122**, which was reacted with diethyl fumarate **123** via a 1,3-dipolar cycloaddition to afford a 57:43 mixture of epimers **124** and **125**, which were isolated in 40% yield as a single diastereoisomer and 34% yield in 85:15 dr, respectively. Reduction of **124** and **125** with H_2 over Raney-Nickel, afforded pyrrolizidin-3-ones **126** and **127**, which were converted to (–)-macronecine **105** and (–)-petasinecine **106** in 76 and 80% yield, respectively, upon reduction with $LiAlH_4$ (Scheme 10).



Scheme 10. *Reagents and Conditions:* (i) nitroethylene, **128**, PhMe, –78 °C, 15 min then **121**, 20 min then **123**, rt, 16 h; (ii) H_2 (180 psi), Raney Ni, MeOH, 48 h; (iii) $LiAlH_4$, THF, reflux, 3.5 h.

1.5.3. Syntheses of 1-hydroxymethyl-7-hydroxypyrrolizidines: syntheses of (–)-turneforcidine, (–)-platynecine and (–)-hastanecine

Three diastereoisomeric 1-hydroxymethyl-7-hydroxypyrrolizidines, (–)-hastanecine **129**, (–)-turneforcidine **130** and (–)-platynecine **131** have been isolated from natural sources and characterized to date (Figure 13).[39]

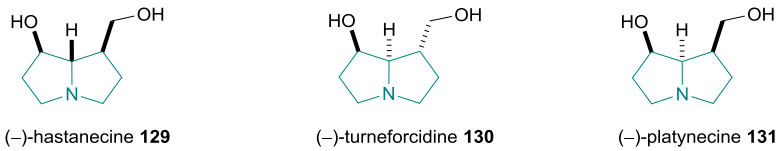
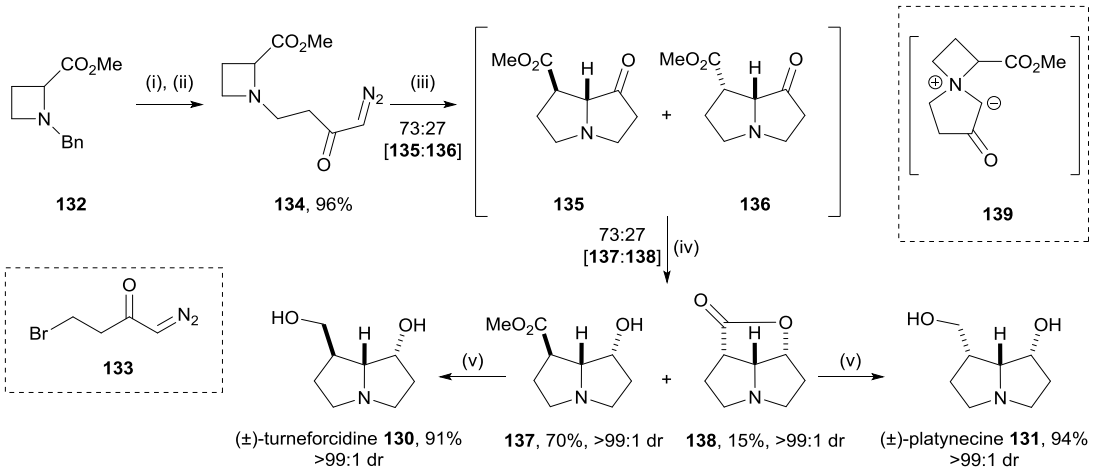


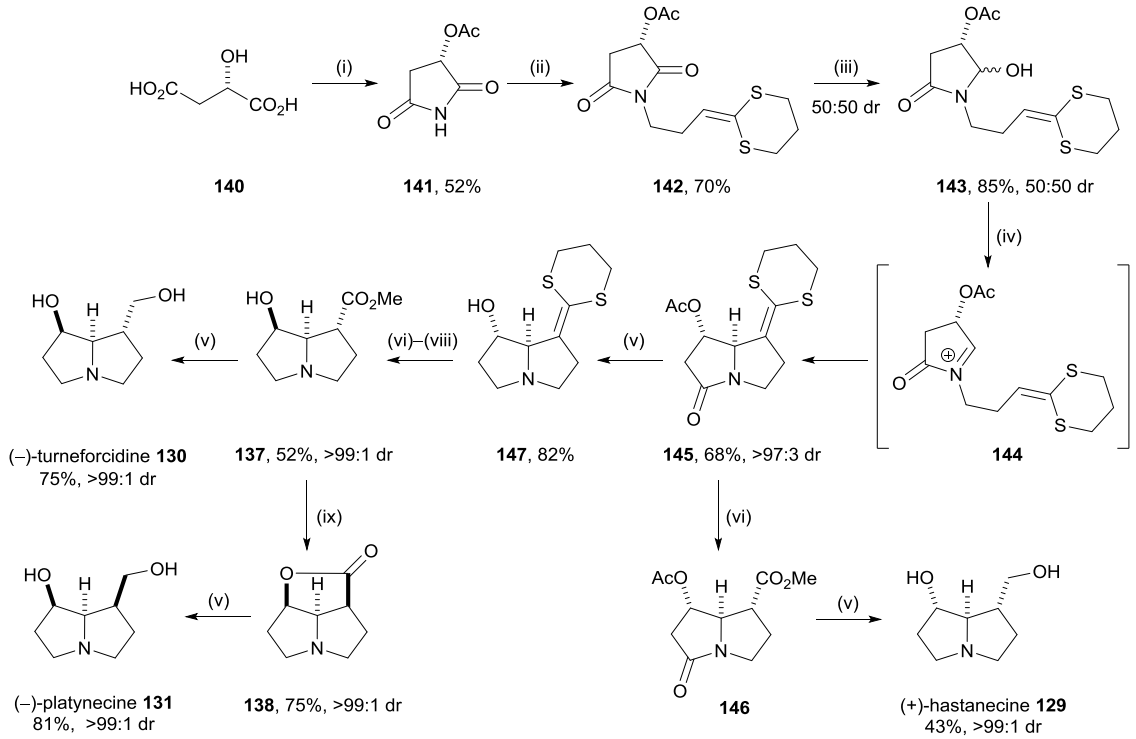
Figure 13. Structures of (–)-hastanecine **129**, (–)-turneforcidine **130** and (–)-platynecine **131**.

An interesting synthesis of (±)-turneforcidine **130** and (±)-platynecine **131** via the ring-expansion of azetidinium ylides was reported by West *et al*. in 2005.[40] Reductive debenzylation of **132** followed by coupling with 4-bromo-1-diazobutan-2-one **133** gave the cyclisation precursor **134** which, when treated with $Cu(acac)_2$, formed the transient spirocyclic ylide **139**. Rearrangement of **139** gave a 73:27 mixture of pyrrolizidin-7-ones **135** and **136**. Hydrogenation of the crude reaction mixture of **135** and **136** gave a 73:27 mixture of hydroxyester **137** and lactone **138**, respectively, which were isolated as single diastereoisomers in 70 and 15% yield, respectively. Further reduction of the ester functionality within **137** gave (±)-turneforcidine **130** and reduction of the lactone within **138** gave (±)-platynecine **131** in good yields (Scheme 11).



Scheme 11. *Reagents and Conditions:* (i) Pd/C, NH_4O_2CH, MeOH, reflux; (iii) **133**, $^{i}Pr_2NEt$, MeCN, rt, 16 h; (iii) $Cu(acac)_2$, PhMe, reflux, 10 min then rt; (iv) H_2 (1 atm), PtO_2, MeOH, rt, 4 h; (v) $LiAlH_4$, THF, 0 °C then reflux, 4 h.

Chamberlin and co-workers obtained all three natural products by functionalisation of a single pyrrolizidine-5-one intermediate **145**, which was obtained from L-malic acid **140**.[41] Conversion of **140** into succinimide **141** in 52% yield, was followed by Mitsunobu reaction of **141** with 2-(3-hydroxypropylidene)-1,3-dithiane and partial reduction with $NaBH_4$, which gave **143** as a 50:50 mixture of epimers in 59% yield (over 2 steps from **141**). Mesylation of **143** and concomitant formation of iminium ion **144** was followed by cyclisation to give **145** in 68% yield and >97:3 dr. Treatment of **145** with mercuric chloride in acidic methanol afforded ester **146** which was reduced with $LiAlH_4$ to give (+)-hastanecine **129** in 43% yield over 2 steps. Alternatively, reduction of **145** with $LiAlH_4$ gave **147** in 82% yield. Hydrolysis of the dithiane within **147** was followed by Swern oxidation and diastereoselective hydrogenation to yield **137** in 52% yield (over 3 steps from **147**). Reduction of the ester within **137** gave (–)-turneforcidine **130** in 75% yield, while (–)-platynecine **131** was obtained following epimerisation at the C(1) stereogenic center (upon treatment with NaOEt in EtOH), followed by reduction of lactone **138**, which gave (–)-platynecine **131** in 61% overall yield from **137** (Scheme 12).



Scheme 12. *Reagents and Conditions:* (i) AcCl, reflux, 1.5 h then NH_3, THF, rt, 30 min then AcCl, reflux, 2 h; (ii) 2-(3'-hydroxypropylidene)-1,3-dithiane, PPh_3, THF, rt, 16 h; (iii) $NaBH_4$, MeOH, –4 °C, 10 min; (iv) MsCl, NEt_3, –20 °C to rt, 16 h; (v) $LiAlH_4$, THF, reflux, 2 h; (vi) HCl (6.0 M aq), $HgCl_2$, TFA, MeOH, Δ, 8 h; (vii) $(COCl)_2$, DMSO, CH_2Cl_2, –70 °C then –65 °C, 1 h then NEt_3, rt, 30 min; (viii) H_2 (1 atm), PtO_2, MeOH, rt, 1.5 h; (v) $LiAlH_4$, THF, reflux; (ix) EtONa, EtOH, Δ, 2.5 h.

1.5.4. Syntheses of 1-hydroxymethyl, 2,7-dihydroxypyrrolizidines: (–)-rosmarinecine and (–)-croalbinecine

Only four stereoisomers of 1-hydroxymethyl-2,7-dihydroxypyrrolizidines have been synthesized and fully characterized (out of 8 possible diastereoisomers). (–)-Rosmarinecine **148** has been isolated after hydrolysis of an ester derivative *viz.* rosamarinine **77**[42] while the structure of (+)-croalbinecine **4** was determined in 1980[43] after having been isolated after hydrolysis of an ester derivative. The asymmetric syntheses of (+)-2-*epi*-rosmarinecine **149** and (+)-7-*epi*-croalbinecine **150** were independently reported and syntheses of the remaining stereoisomers are yet to be disclosed (Figure 14).[44,45]

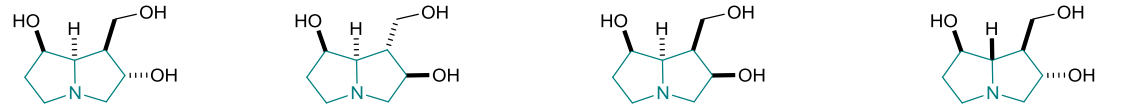
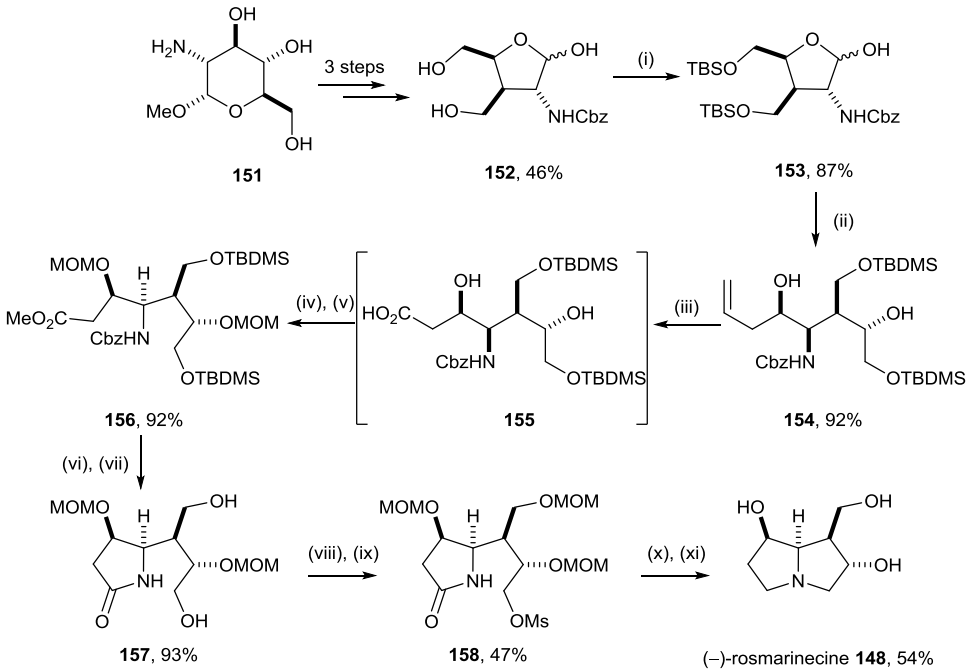


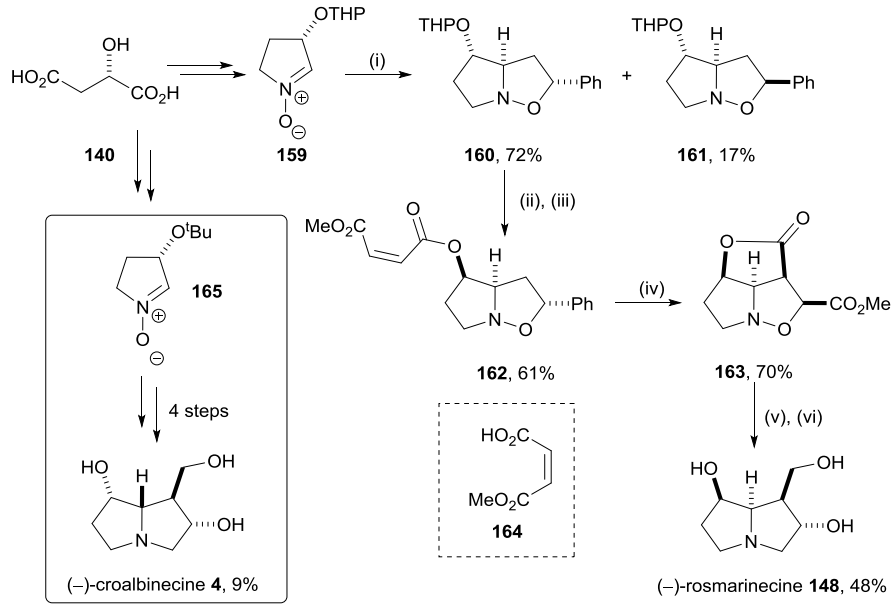
Figure 14. Structures of naturally occurring 1-hydroxymethyl-2,7-dihydroxypyrrolizidines (–)-rosmarinecine **148** and (–)-croalbinecine **4**, and their synthetic diastereoisomers **149** and **150**.

Most synthetic efforts towards these polyhydroxylated compounds have targeted (–)-rosmarinecine **148**, which has been synthesised by four different groups using various approaches.[38b,c,46] The first synthesis of this alkaloid was reported by Tatsuta in 1983.[46a] The synthetic approach for the construction of the four contiguous stereogenic centers, relied on the stereochemistry of the amino-sugar precursor **152** (which was obtained in 46% overall yield from methyl α-D-glucosamine **151**). Protection of the hydroxy functionality with TBDMSCl followed by the addition of allyl magnesium bromide, afforded **154** in 80% yield (over 2 steps from **152**). Oxidation of the double bond within **154** to the corresponding carboxylic acid was achieved upon treatment of **154** with a solution of $KMnO_4$ and $NaIO_4$ in ^tBuOH.[47] Esterification of **155** with diazomethane followed by *O*-protection gave **156** in 92% yield (over 3 steps from **154**). Cyclisation of **156** upon treatment with H_2 in the presence of Pd/C followed by treatment with TBAF, gave lactam **157** in 93% yield. Subsequent methoxymethylation of **157** gave a 60:40 regioisomeric mixture of triprotected *O*-MOM tetrols, from which the major product was isolated and mesylated to afford **158** in 47% yield. Deprotection of the *O*-MOM group and S_N2-type displacement of the mesylate gave (–)-rosmarinecine **148** in 54% yield (Scheme 13).



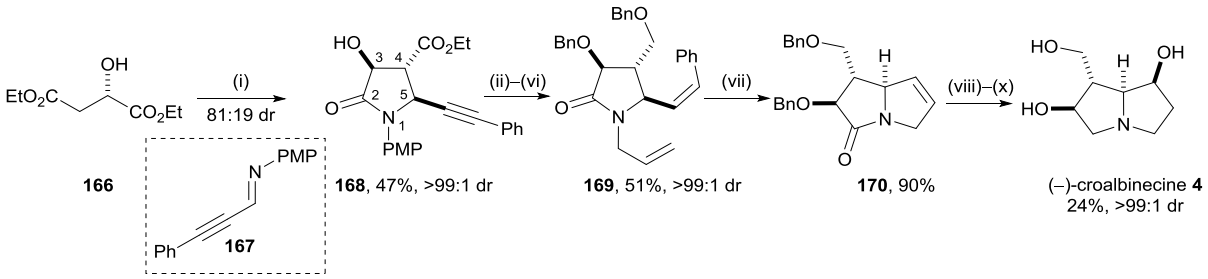
Scheme 13. *Reagents and Conditions:* (i) TBDMSCl, Py, rt, 15 h; (ii) AllylMgBr, Et_2O, 5 °C, 30 min; (iii) $NaIO_4$, $KMnO_4$, aqueous ^tBuOH then 5% K_2CO_3, 15 h; (iv) CH_2N_2, Et_2O; (v) MOMCl, $^iPr_2NEt$, $CHCl_3$, 60 °C; (vi) H_2 (3 atm), Pd/C, THF/AcOH, 3 h; (vii) TBAF, THF, 5 °C, 30 min; (viii) MOMCl (1.0 eq), $^iPr_2NEt$, THF, rt, 6 h; (ix) MsCl, Py, rt, 1 h; (x) BH_3, DMS, THF, 60 °C, 5 h; (xi) 0.5 M HCl, dioxane, 80 °C, 6 h.

Goti *et al*. have used chiral nitrones **159** and **165** (derived from L-malic acid **140**) as chiral precursors in the syntheses of azabicycles.[45,46b] In their synthesis of (–)-rosmarinecine **148**, *O*-THP protected enantiopure nitrone **159** was reacted with styrene to yield **160** and **161** in 72 and 17% yield, respectively. The major product was subjected to *O*-THP deprotection, using PPTS, and Mitzunobu reaction with monomethyl maleate **164** gave **162** in 61% yield (over 2 steps from **160**). Cycloreversion and intramolecular cycloaddition of the corresponding nitrone upon reflux in *o*-dichlorobenzene, gave **163** in 70% yield. Hydrogenolysis of **163** followed by reduction with Red-Al® gave (–)-rosmarinecine **148** in good yield. A similar sequence of reactions applied to nitrone **165** gave (–)-croalbinecine **4** in 9% overall yield (Scheme 14).



Scheme 14. *Reagents and Conditions:* (i) Styrene, PhMe, 80 °C, 11 h; (ii) PPTS, EtOH, reflux, 3 h then Ambersep 900-OH, 3 h; (iii) **164**, PPh_3, DEAD, THF, 0 °C then rt, 2 days; (iv) *o*-Dichlorobenzene, reflux, 14 h; (v) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h; (vi) Red-Al®, THF, reflux, 3 h.

Ha and co-workers reported a synthesis of (–)-croalbinecine **4** via a malate enolate-imine condensation followed by ring-closing metathesis.[48] The enolate dianion obtained from diethyl L-malate **166** upon treatment with sodium bis(trimethylsilyl)amide was reacted with imine **167** to give an 81:19 mixture of C(5)-epimers from which the major pyrrolidin-2-one **168** was isolated in 47% yield. Stereoselective reduction of the triple bond with Lindlar's catalyst, CAN mediated *N*-deprotection and subsequent *N*-allylation, gave **169** in 51% yield over 3 steps. Subsequent ring-closing metathesis of diene **169** gave pyrrolizidin-3-one **170**, which was obtained in 90% yield. Epoxidation of the resultant C=C double bond followed by regioselective epoxide-opening of the major diastereoisomer with $LiAlH_4$ and global deprotection, afforded (–)-croalbinecine **4** in 24% yield over 3 steps (Scheme 15).



Scheme 15. *Reagents and Conditions:* (i) $NaN(TMS)_2$, **167**, THF, –78 °C; (ii) $LiBH_4$, diglyme, rt; (iii) NaH, DMF, 0 °C then BnBr, rt, 1 h; (iv) H_2 (40 psi), Lindlar catalyst, benzene, rt, 40 min; (v) CAN, MeCN/H_2O (4:1), 0 °C, 1 h; (vi) NaH, THF, then allyl bromide and TBAI, 1 h; (vii) Grubbs II catalyst, benzene, 12 h; (viii) *m*-CBPA, $NaHCO_3$, benzene, rt, 36 h; (ix) $LiAlH_4$, THF, rt, 12 h; (x) H_2 (45 psi), $Pd(OH)_2$/C, EtOH, rt, 10 days.

1.6. Thesis aim

The aim of this thesis was to develop broadly applicable and efficient asymmetric methodology to access all classes of naturally occurring 1-hydroxymethylpyrrolizidines **12**, **79**, **80**, **81** and their diastereoisomers starting from inexpensive precursors. It was envisaged that the chemo-, regio- and diastereoselective conjugate addition of an enantiopure lithium amide **171** to differently substituted α,β,ε,ζ-diunsaturated esters **172**, followed by alkylation (Y = H) or aldol reaction (Y = OH), could be used to synthesize enantiopure amino dienes such as **173**. The construction of the pyrrolizidine ring could then be achieved upon oxidative cleavage of the double bonds within **173**, to afford dialdehyde **174**, followed by hydrogenolytic *N*-deprotection and in situ double reductive cyclisation to give the target pyrrolizidine scaffolds **175** (Figure 15).

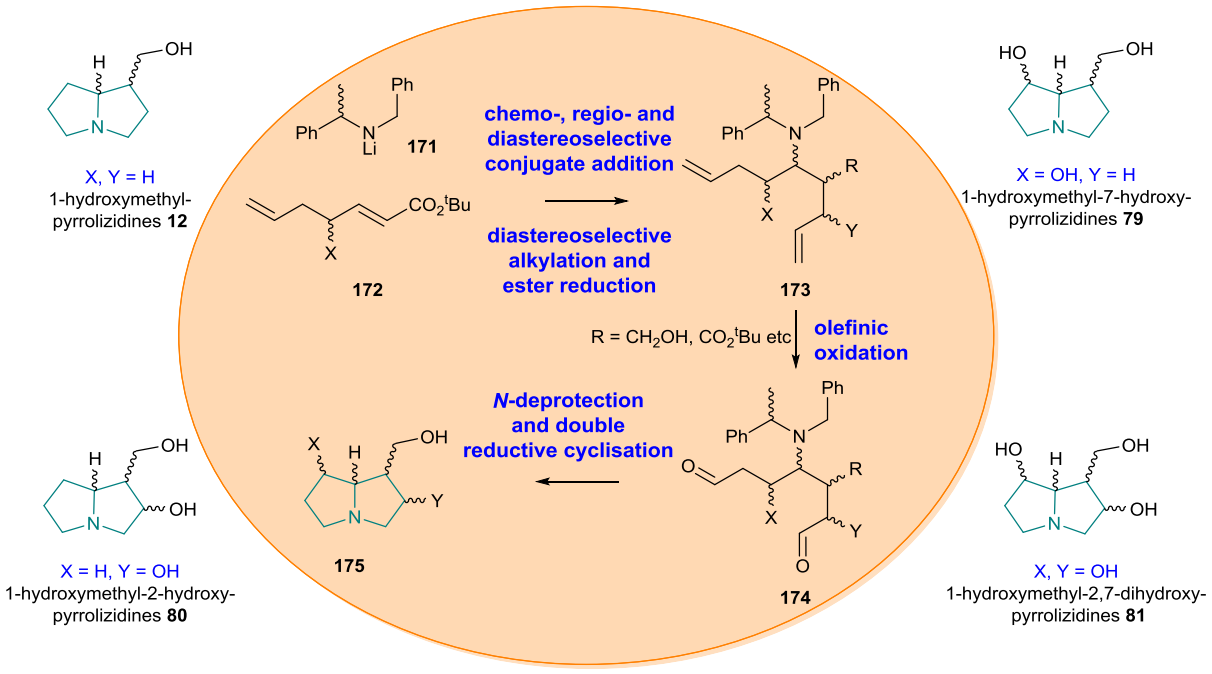


Figure 15. Proposed synthetic route to pyrrolizidines **12, 79, 80** and **81**.

1.7. References and notes

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Chapter 2: Asymmetric Syntheses of (–)-Isoretronecanol and (–)-Trachelantamidine

This chapter describes investigations towards the development of methodology to access 1-hydroxymethylpyrrolizidines **12**, which culminate in the total asymmetric syntheses of the pyrrolizidine alkaloids (–)-isoretronecanol **82** and (–)-trachelantamidine **83** (Figure 16).

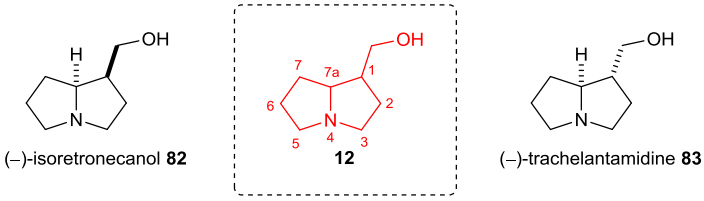
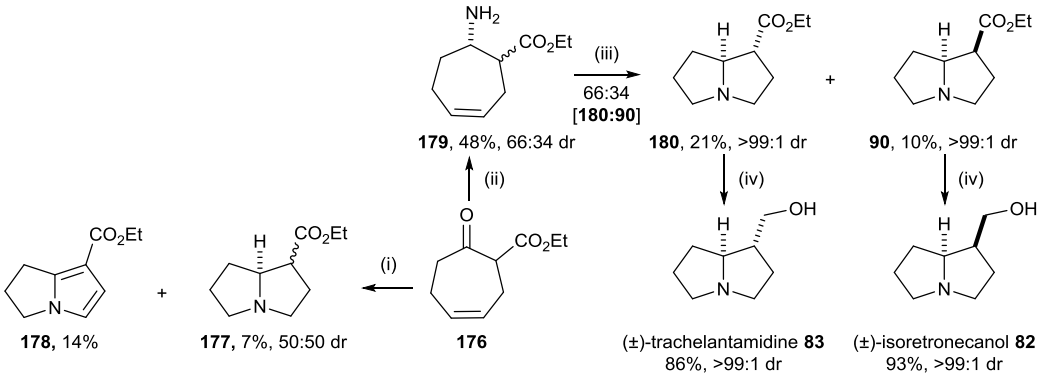


Figure 16. The structures of the 1-hydroxymethylpyrrolizidine alkaloids (–)-isoretronecanol **82** and (–)-trachelantamidine **83**.

2.1. Previous work

In 1977, Borch *et al.*[1] reported the first attempts at double reductive cyclisation approaches towards (±)-isoretronecanol **82** and (±)-trachelantamidine **83**. Ozonolysis of cyclohept-4-enone **176** followed by addition of NH_4NO_3 and $NaBH_3CN$ gave a complex mixture from which a 50:50 mixture of diastereoisomers **177** was isolated in only 7% yield, along with pyrrole **178** in 14% isolated yield. The low yield and poor diastereoselectivity in the cyclisation step prompted development of another route towards pyrrolizidines **82** and **83**. Thus, oxidation of **179** (which was obtained as a 66:34 diastereoisomeric mixture in 48% combined yield upon reductive amination of **176**) upon treatment with $OsO_4/NaIO_4$, followed by reduction with $NaBH_3CN$ afforded a 66:34 epimeric mixture of **180** and **90**, which were isolated in 21 and 10% yield, respectively. (±)-Isoretronecanol **82** and (±)-trachelantamidine **83** were subsequently obtained after reduction of the ester functionalities within **90** and **180**, which gave **82** and **83** in 93 and 86% yield, respectively (Scheme 16).



Scheme 16. *Reagents and Conditions*: (i) O_3, CH_2Cl_2, −78 °C then DMS, 0 °C, 1 h then NH_4NO_3, $NaBH_3CN$, MeOH, 0 °C, 5 h then rt, 48 h; (ii) NH_4NO_3, $NaBH_3CN$, MeOH, rt, 48 h; (iii) OsO_4, $NaIO_4$, Et_2O, 0 °C, 3 h then $NaBH_3CN$, MeOH, 0–5 °C, 4 days; (iv) $LiAlH_4$, Et_2O, reflux, 3 h.

2.2. Chapter aim

The aim of this chapter is to develop efficient asymmetric methodology for the synthesis of pyrrolizidine scaffolds. It was envisaged that the rapid construction of the 1-hydroxymethyl-substituted pyrrolizidine motif **191** in enantiopure form could be achieved via hydrogenolytic removal of the *N*-benzyl protecting groups within a dialdehyde **184**, promoting cyclisation and *in situ* reduction (via intermediates **185**–**189**, R = H, Bn, α-MeBn) to give pyrrolizidine **190**. Subsequent reduction of the ester within **190** would then reveal the target 1-hydroxymethylpyrrolizidine **191**. It was proposed that the key intermediate dialdehyde **184** could be obtained via oxidative cleavage of enantiopure aminodiene **183**, which can be readily prepared via the chemo-, regio- and diastereoselective conjugate addition of lithium amide[2] (*S*)-**171** to α,β-unsaturated ester **181** followed by diastereoselective allylation of **182** (Figure 17).

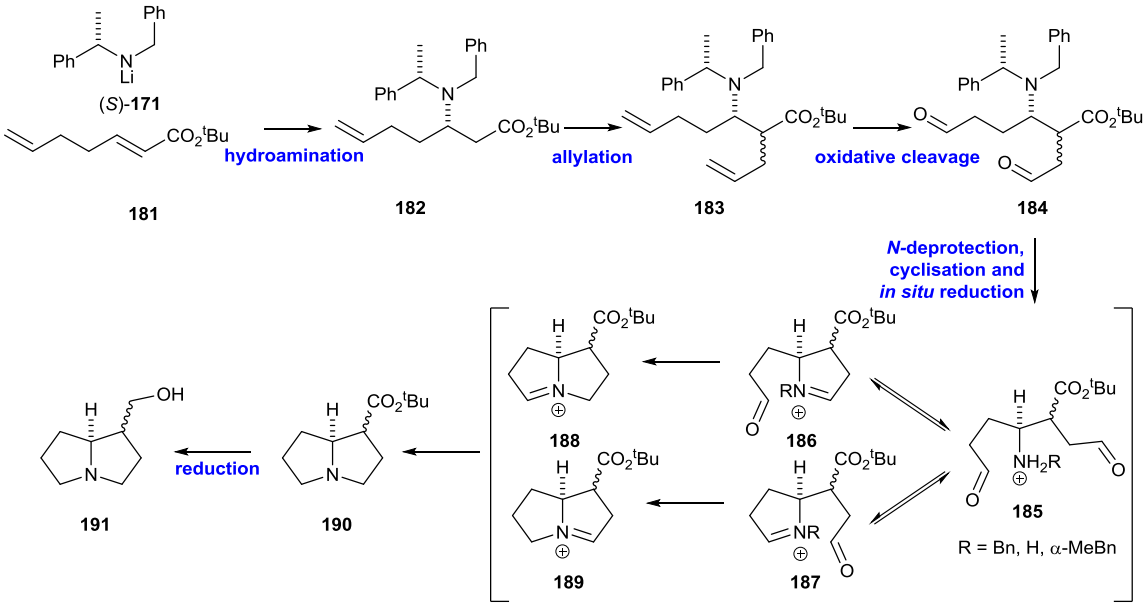
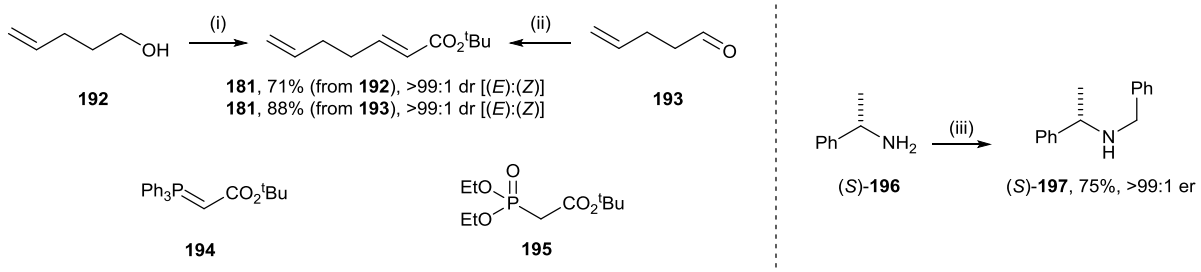


Figure 17. Proposed route for the formation of pyrrolyzidines **191**.

2.3. Syntheses of unsaturated amine precursors

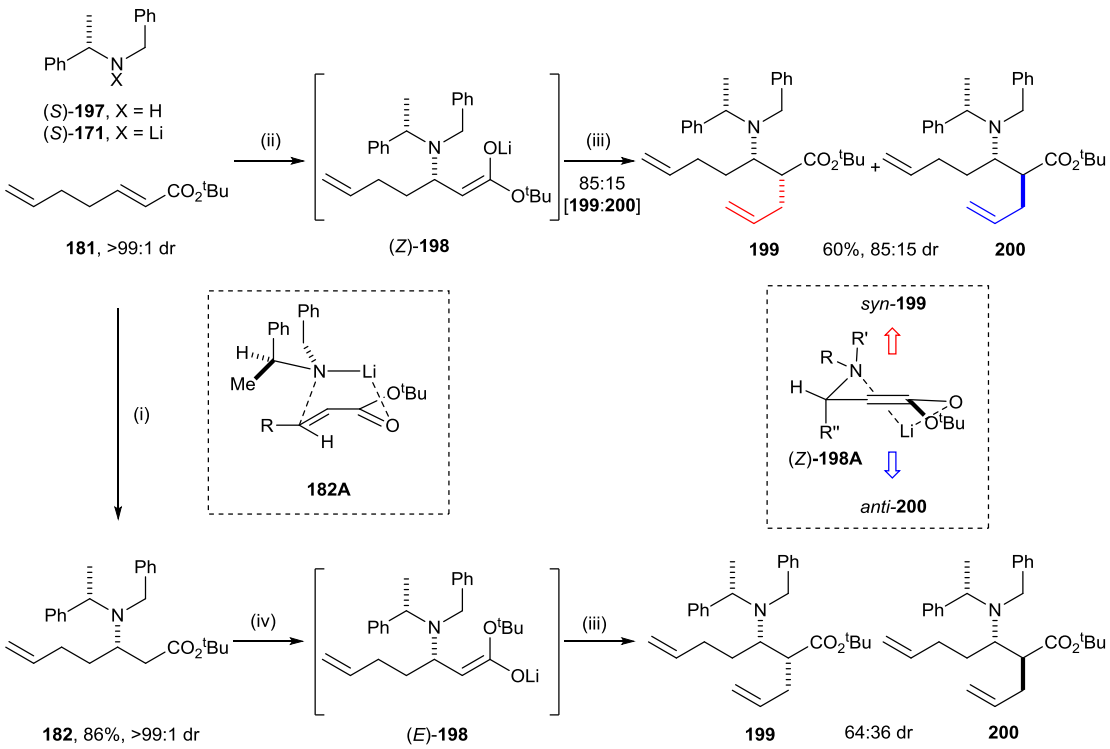
The α,β-unsaturated ester **181** was prepared from 4-penten-1-ol **192** via a one pot Swern oxidation/Wittig olefination, which gave **181** in 71% isolated yield and >99:1 dr [(*E*):(*Z*)]. However, a superior yield of **181** was obtained via reaction of commercially available 4-pentenal **193** with the anion derived from *tert*-butyl diethylphosphonoacetate **195**, according to a modified Wadsworth-Emmons reaction,[3] which gave **181** in 88% isolated yield and >99:1 dr [(*E*):(*Z*)]. (*S*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine (*S*)-**197** was synthesised by reductive alkylation of commercially available (*S*)-α-methylbenzylamine (*S*)-**196** with benzaldehyde which gave (*S*)-**197**[4] in 75% yield and >99:1 er[5] (Scheme 17).



Scheme 17. *Reagents and Conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 15 min then **192**, 1 h, Et_3N then **194**, −78 °C to rt, 16 h; (ii) **195**, MeMgBr, THF, rt, 15 min then **193**, rt to 80 °C, 2.5 h then NH_4Cl (satd aq); (iii) PhCHO, $NaBH_4$, EtOH, rt, 72 h.

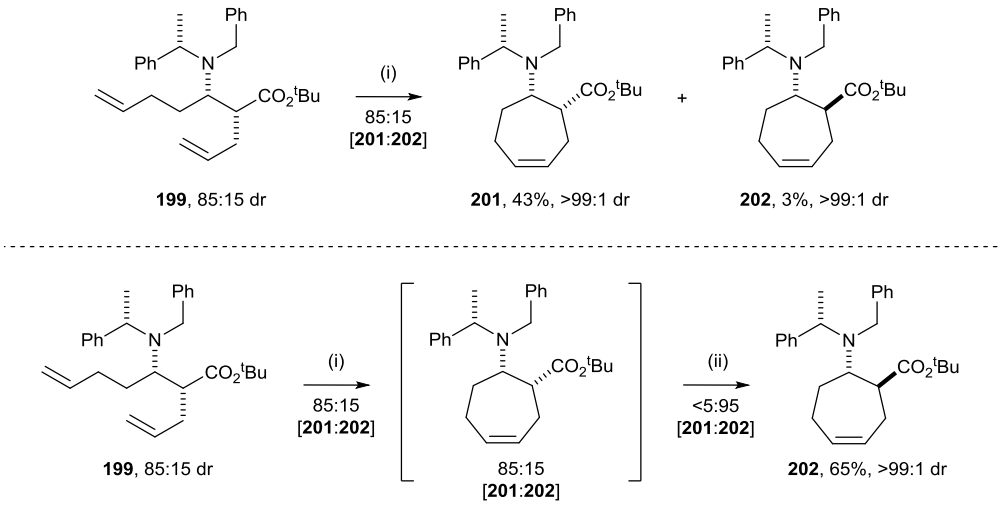
Following established literature procedures,[6,7] the conjugate addition and enolate allylation protocols were investigated via both a tandem [i.e., conjugate addition of (*S*)-**171** to α,β-unsaturated ester **181** and *in situ* allylation of the resultant expected lithium (*Z*)-β-amino enolate[8]] or a stepwise [i.e., deprotonation of β-amino ester **182** and allylation of the resultant expected lithium (*E*)-β-amino enolate[8]] approach. Thus, conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**171** [resulting from treatment of amine (*S*)-**197** with BuLi] to α,β-unsaturated ester **181** followed by the addition of satd aq NH_4Cl gave the known β-amino ester **182**[9] in 86% isolated yield as a single diastereoisomer (>99:1 dr). Repetition of the conjugate addition reaction, but treating the enolate (*Z*)-**198**[10] with allyl bromide gave an 85:15 mixture of diastereoisomers *syn*-**199** and *anti*-**200**, respectively, which were isolated as an inseparable mixture in 60% combined yield (Scheme 18). Given the total stereocontrol observed upon conjugate addition in the formation of **182**, *via* the known transition state **182A** for the formation of the C(3) stereocenter, the diastereoisomeric mixture of **199** and **200** was assigned as being a mixture of C(2)-epimers, and the configuration of the

major diastereoisomer *syn*-**199** was subsequently assigned by single crystal X-ray diffraction analyses of several derivatives (*vide infra*). Following the alternative stepwise procedure, deprotonation of β-amino ester **182** with LDA gave the corresponding lithium (*E*)-β-amino enolate (*E*)-**198**.[11] Upon repetition of the reaction, treatment of enolate (*E*)-**198** with allyl bromide gave a 64:36 mixture of *syn*-**199** and *anti*-**200**, respectively. The use of LiHMDS under the same conditions slightly increased the diastereoisomeric ratio to 77:23 in favour of *syn*-**199**, whereas the use of KHMDS gave a mixture of *syn*-**199** and *anti*-**200** in 67:33 dr, respectively. The high preference for *syn*-**199** from (*Z*)-**198** could be explained looking at the possible reactive conformation adopted after lithium amide addition; hypothesising a lithium chelation from the amino substituent and the enolate, **198A** could then react with allyl bromide from the top or the bottom face, giving *syn*-**199** or *anti*-**200**, respectively. The observed preference for *syn*-**199** could be due to the chair-like conformation adopted for the formation of *syn*-**199** preferred over the boat-like conformation adopted to obtain *anti*-**200** (Scheme 18). The inseparability of the two diastereoisomers at this stage, and the poor diastereoselectivity of the allylation step necessitated another way to access diastereoisomerically pure samples.



Scheme 18. *Reagents and Conditions*: (i) (*S*)-**171**, THF, −78 °C, 2 h then satd aq NH_4Cl; (ii) (*S*)-**171**, THF, −78 °C, 2 h; (iii) Allyl bromide, −78 °C to rt, 16 h; (iv) LDA, THF, −78 °C, 30 min.

Previous work conducted in the Davies group on similar substrates employed a strategy of converting to the corresponding cycloheptene via ring-closing metathesis followed by epimerisation at the C(1) stereogenic center of the 7-aminocycloheptene-3-carboxylate to enrich the diastereoisomeric purity.[12] Following this approach, ring-closing metathesis of the 85:15 diastereoisomeric mixture of *syn*-**199** and *anti*-**200** with Grubbs I catalyst in CH_2Cl_2 at 35 °C resulted in complete conversion to an 85:15 mixture of *syn*-**201** and *anti*-**202**, respectively. Purification, upon treatment with $P(CH_2OH)_3$ in the presence of Et_3N and silica gel to remove ruthenium residues, followed by flash column chromatography, gave *syn*-**201** and *anti*-**202** in 43 and 3% yield, respectively, and >99:1 dr in each case, along with a 55:45 mixture of *syn*-**201** and *anti*-**202** in 33% yield. However treatment of the crude 85:15 mixture of *syn*-**201** and *anti*-**202** with a solution of KO^{t}Bu in THF for 16 h, resulted in complete conversion (>95:5 dr) to *anti*-**202**. Following purification, *anti*-**202** was isolated as a single diastereoisomer (>99:1 dr) in 65% overall yield from **199** (Scheme 19).

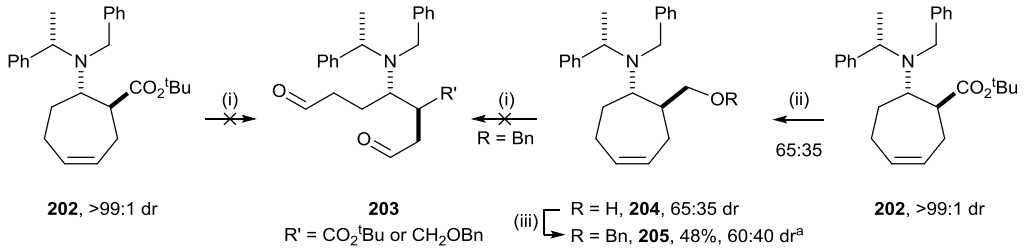


Scheme 19. *Reagents and Conditions*: (i) Grubbs I catalyst, CH_2Cl_2, 35 °C, 16 h then $P(CH_2OH)_3$, SiO_2, Et_3N, CH_2Cl_2, rt, 16 h; (ii) KHMDS, ^{t}BuOH, THF, rt, 16 h.

2.4. Conversion of unsaturated amines to the corresponding dialdehydes

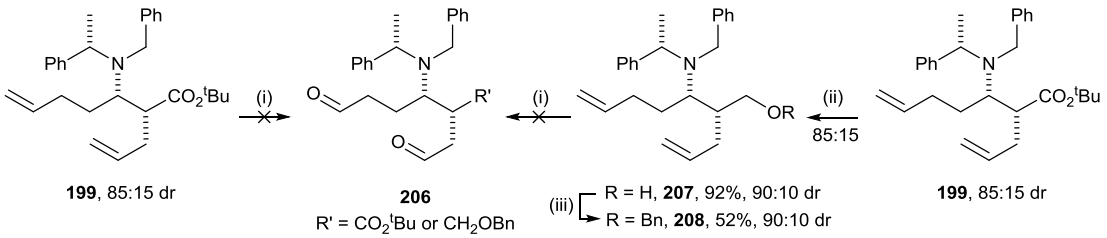
With diastereoisomerically pure samples of both *syn*-**201** and *anti*-**202** in hand, initial ozonolysis to give dialdehydes **203**, were carried out on *anti*-**202**. The HCl salt of **202** (>99:1 dr) was formed to avoid *N*-oxidation in the subsequent ozonolysis step, then **202**·HCl was treated with O_3 in CH_2Cl_2 at −78 °C followed by the addition of DMS, which promoted complete consumption of the starting material to give a complex mixture of products in poor mass return. The effect of reduction of the ester on the reaction outcome was investigated.

Thus, reduction of **202** with $LiAlH_4$ afforded alcohol **204** in 65:35 dr, which was *O*-benzylated to give **205** as a 60:40 mixture of diastereoisomers in 48% isolated yield, along with a 5% yield of **205** in 95:5 dr (over 2 steps from **202**). Presumably, the erosion in diastereoisomeric purity is due to epimerisation under the basic conditions. **205** was then submitted to the ozonolysis reaction conditions. However, also in this case, the reaction gave complete consumption of starting material and formation of a complex mixture (Scheme 20).



Scheme 20. *Reagents and Conditions*: (i) HCl (2.0 M in Et_2O), O_3, CH_2Cl_2, –78 °C then DMS, −78 °C to rt, 16 h; (ii) $LiAlH_4$, THF, 0 °C then 0 °C to rt, 16 h; (iii) NaH then BnBr, 15-crown-5, THF, rt, 16 h. [[a] a further fraction containing **205** (95:5 dr) was also isolated in 5% yield].

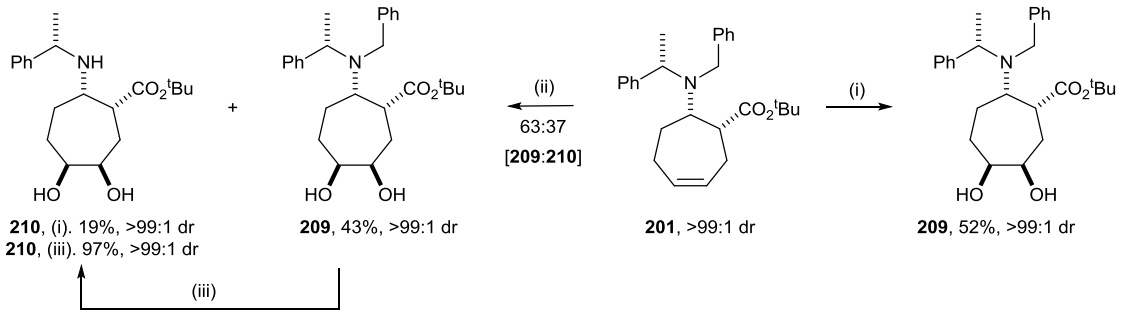
The same sequence of reactions was applied to the epimeric mixture of open chain α-allyl-β-amino esters *syn*-**199** and *anti*-**200** and to the mixture of the benzylated alcohols **208** (90:10 dr). Reduction of the 85:15 mixture of *syn*-**199** and *anti*-**200** with $LiAlH_4$ afforded **207** in ~85:15 dr, which was increased to 90:10 dr upon chromatographic purification and benzylated giving **208** in 48% yield over 2 steps (90:10 dr). Unfortunately, ozonolysis of both mixtures of **199**·HCl and **200**·HCl (85:15 dr) and **208**·HCl (90:10 dr) gave complex mixtures (Scheme 21).



Scheme 21. *Reagents and Conditions*: (i) HCl (2.0 M in Et_2O), O_3, CH_2Cl_2, –78 °C then DMS, −78 °C to rt, 16 h; (ii) $LiAlH_4$, THF, 0 °C then 0 °C to rt, 16 h; (iii) NaH then BnBr, 15-crown-5, THF, rt, 16 h.

Due to the poor results under the ozonolysis conditions, other procedures for the oxidative cleavage of the C=C bond within **201** were investigated. The reaction of an olefin with OsO_4 followed by treatment with $NaIO_4$ is a reliable method to access aldehydes in good yield either using a one pot or a stepwise procedure.[13] A stepwise OsO_4 dihydroxylation followed

by oxidative cleavage to the corresponding dialdehydes with $NaIO_4$ was first trialled, to check the feasibility and efficiency of each step. Standard Upjohn conditions,[14] requiring the addition of catalytic amount of OsO_4 and 3.0 equiv of NMO, applied to *syn*-**201** gave a 63:37 mixture of **209** and the *N*-debenzylated derivative **210** which were isolated in 43 and 19% yield, respectively (Scheme 22). The relative configuration within **210** was confirmed by single crystal X-ray diffraction analysis[15] and the absolute (1*R*,3*R*,4*S*,7*S*,α*S*)-configuration within **210** was assigned by the reference to the known (*S*)-configuration of the α-methylbenzyl fragment (Figure 18). The configuration of **209** was established via chemical correlation with **210** upon treatment of **209** with CAN in a 5:1 mixture of $MeCN/H_2O$ for 2 h, which gave **210** in 97% yield and as a single diastereoisomer (>99:1 dr). The spectroscopic data, mp and specific rotation of this sample of **210** debenzylation, were entirely consistent with those for **210** obtained from the Os-mediated dihydroxylation. Presumably, **210** is formed from **209** upon oxidation of the amino substituent, followed by elimination of H_2O and hydrolysis of the resultant iminium ion. Alternatively, addition of 1.1 equiv of OsO_4 and 3.0 equiv of TMEDA to **201** in CH_2Cl_2 at −78 °C (Donohoe dihydroxylation conditions[16]) gave complete conversion to *syn*-diol **209**, which was obtained in 52% yield and >99:1 dr upon chromatographic purification (Scheme 22).



Scheme 22. *Reagents and Conditions*: (i) OsO_4, TMEDA, CH_2Cl_2, –78 °C, 1 h then −78 °C to rt then $P(CH_2OH)_3$, SiO_2, Et_3N, CH_2Cl_2, rt, 48 h; (ii) OsO_4, NMO, THF, rt, 16 h; (iii) CAN (2.1 equiv), $MeCN/H_2O$ (5:1), rt, 2 h.

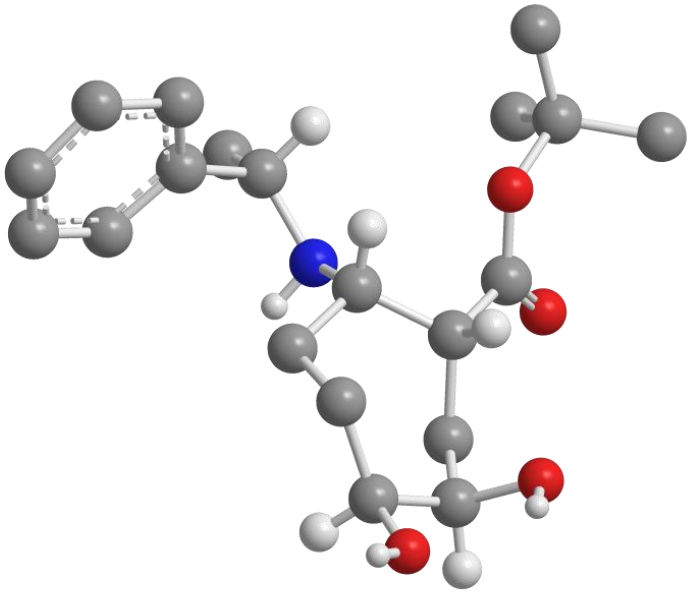
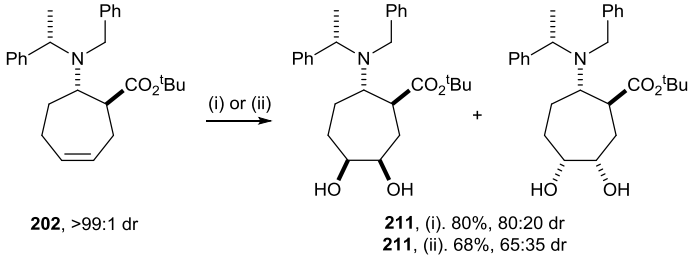


Figure 18. X-ray crystal structure of (1*R*,3*R*,4*S*,7*S*,α*S*)-**210** (selected H atoms are omitted for clarity).

Treatment of *anti*-**202** under Donohoe dihydroxylation conditions (OsO_4 and TMEDA)[16] afforded, after treatment of the intermediate osmate ester with $P(CH_2OH)_3$ and NEt_3, an 80:20 mixture of *syn*-diols **211** in 80% combined yield. Oxidation of **202** under Upjohn conditions (OsO_4, NMO)[14] gave a 65:35 mixture of *syn*-diols **211** in 68% combined yield (Scheme 23). An analytically pure sample of the major diastereoisomer **211** was crystallized from the mixture and the relative configuration within **211** was unambiguously established by single crystal X-ray diffraction analysis,[15] with the absolute (1*S*,3*R*,4*S*,7*S*,α*S*)-configuration of **211** being assigned by reference to the known (*S*)-configuration of the α-methylbenzyl fragment (Figure 19). The relative (and hence the absolute) configuration of the minor diastereoisomer was assigned on the basis that it is the alternative diol resulting from the stereospecific *cis*-dihydroxylation of **202**. The formation of both diastereoisomeric diols was not envisaged to be problematic because of the elimination of both C(3) and C(4) stereogenic centers in the oxidative cleavage step.



Scheme 23. *Reagents and Conditions*: (i) OsO_4, TMEDA, CH_2Cl_2, –78 °C, 1 h then −78 °C to rt then $P(CH_2OH)_3$, SiO_2, Et_3N, CH_2Cl_2, rt, 48 h; (ii) OsO_4, NMO, THF, rt, 16 h.

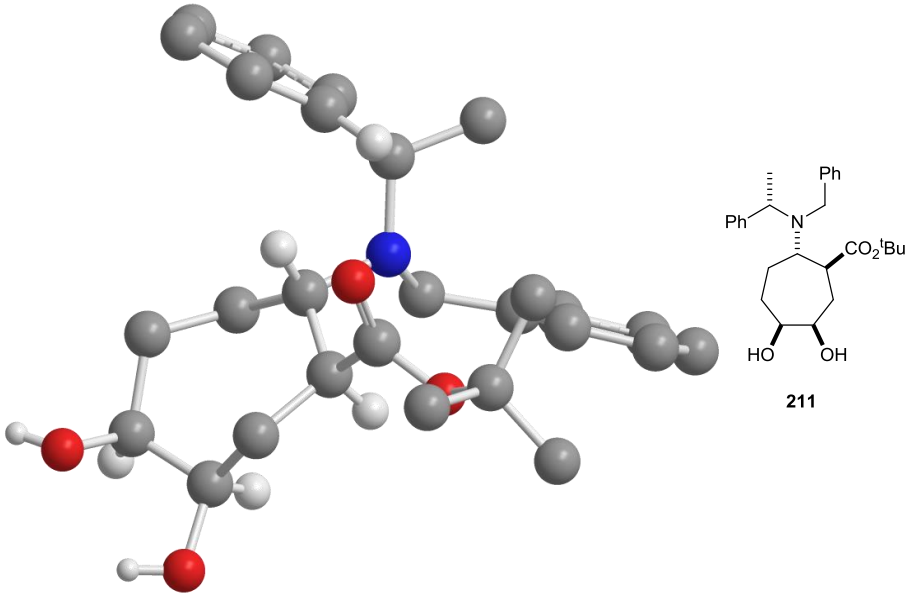
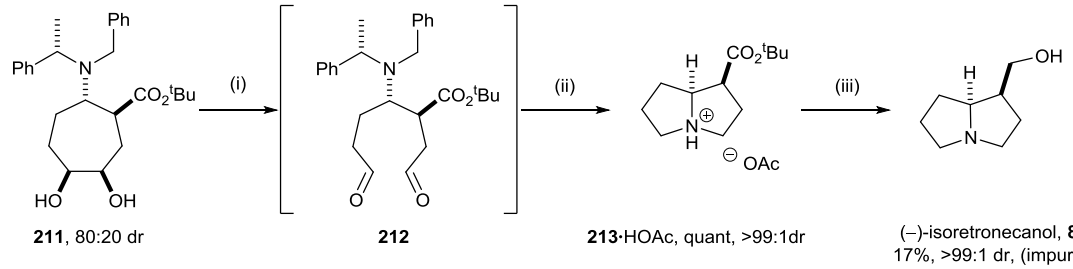


Figure 19. X-ray crystal structure of (1*S*,3*R*,4*S*,7*S*,α*S*)-**211** (selected H atoms are omitted for clarity).

Previous observations on the diastereoselectivity of the Upjohn conditions[14] are usually consistent with the diol formation being governed by either steric or stereoelectronic interactions between the substrate and the osmium reagent.[17] In these cases, the lack of an allylic substituent suggests steric control would be predominant. Under the Donohoe[16] conditions, the presence of a strong H-bond donor group (i.e., N–H of an amide, a carbamate, sulfonamide or O–H from an alcohol), usually affords the product resulting from a hydrogen bond-directed dihydroxylation.[16] However in cases lacking a strong H-bond donor (as in **201** and **202**), it has been observed that steric control is dominant.[18] Therefore, dihydroxylation of both **201** and **202** under either set of conditions (Upjohn or Donohoe) would be expected to give the same major diastereoisomeric product, as observed experimentally. The relatively high diasteroselectivity in these dihydroxylations is consistent with the sterically demanding *N*-benzyl-*N*-α-methylbenzyl substituent enforcing a well-defined 7-membered chair-like ground state conformation with the amino substituent in a pseudo-equatorial position.[19] If this is also the reactive conformation, then the dihydroxylation would be predicted to occur on the less hindered face of the C=C double bond opposite the ring. The superior diastereoselectivity in the oxidation of *syn*-**201** (>99:1 dr for both Upjohn and Donohoe conditions) in comparison to *anti*-**202** (Upjohn: 65:35 dr; Donohoe: 80:20 dr) is consistent with an enhance in sterics due to the pseudeo-axial ester substituent. Moreover, dihydroxylation of **202** under Donohoe conditions,[16] in which the OsO_4-TMEDA complex is larger and so even more sensitive to steric effects, results in a greater diastereoselectivity.

2.5. Double reductive cyclisation towards (–)-isoretronecanol and (–)-trachelantamidine

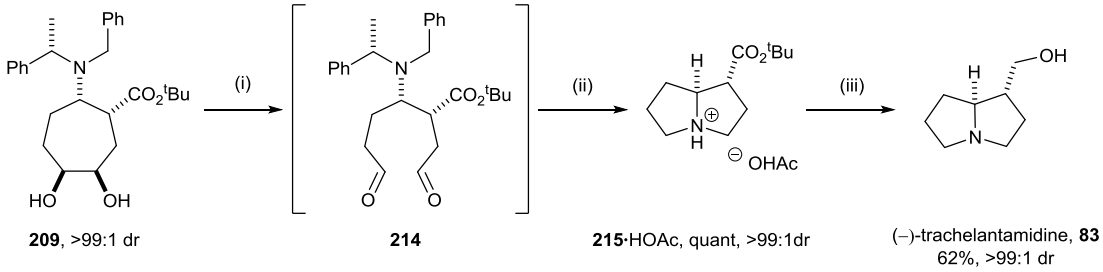
With *cis*-diols **209** and **211** in hand, attention was turned to the synthesis of the corresponding dialdehydes (via oxidative cleavage of the 1,2-diol units) and subsequent double reductive cyclisation. Treatment of **211** with $NaIO_4$ gave dialdehyde **212**, which was partially characterized by ^{1}H-NMR spectroscopy and mass spectrometry analyses and used immediately in the next step without further purification. Unfortunately, submission of **212** under H_2 (1 atm), in the presence of Pearlman's catalyst [$Pd(OH)_2$/C, (40% w/w)] in MeOH for 24 h did not afford pyrrolizidine **213**, and gave a complex mixture of degradation products. Reaction of **212** under H_2 (5 atm) in the presence of $Pd(OH)_2$/C (40% w/w) at rt for 24 h in MeOH gave a complex mixture of products, showing partially *N*-debenzylated intermediates by ^{1}H-NMR spectroscopy and mass spectrometry analyses, but no cyclisation products were isolated. Carrying out the reaction in EtOAc resulted in a complex mixture containing, as observed by ^{1}H-NMR spectroscopy, products containing aromatic peaks and including the aldehyde starting material. However, conversion towards pyrrolizidine **213** was obtained using a 10:1 mixture of MeOH and AcOH as the reaction solvent which gave **213**·HOAc in quantitative yield. Reduction of **213**·HOAc with DIBAL-H in THF gave (–)-isoretronecanol **82** in only 17% isolated yield (from **211**) with impurities present after purification by ion exchange chromatography (Scheme 24).



Scheme 24. *Reagents and Conditions*: (i) $NaIO_4$, MeOH, rt, 1 h; (ii) $Pd(OH)_2$/C, H_2 (5 atm), MeOH/AcOH (10:1), rt, 24 h; (iii) DIBAL-H, THF, 0 °C, 2 h, then 0 °C to rt, 16 h.

The same sequence of reactions was applied to *syn*-**209**. Oxidative cleavage of the 1,2-diol **209** furnished dialdehyde **214** which was partially characterized by ^{1}H-NMR spectroscopy and mass spectrometry analyses and submitted to the hydrogenolytic *N*-debenzylation and *in situ* double reductive cyclisation conditions in MeOH and AcOH, which gave **215**·HOAc in quantitative yield. (–)-Trachelantamidine **83** was subsequently obtained in 62% yield and

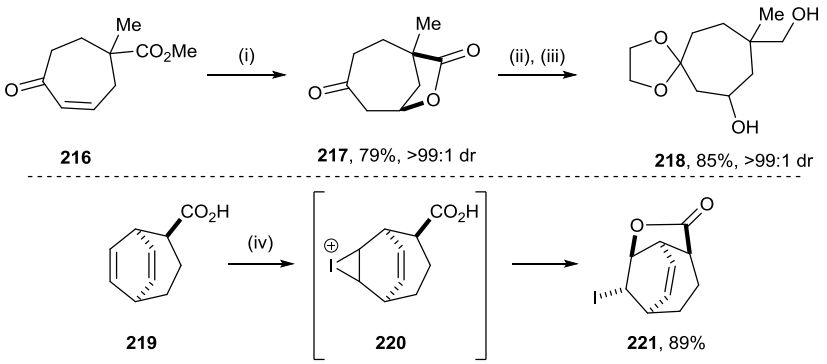
>99:1 dr after reduction and subsequent purification by ion exchange chromatography (Scheme 25).



Scheme 25. *Reagents and Conditions*: (i) $NaIO_4$, MeOH, rt, 1 h; (ii) $Pd(OH)_2/C$, H_2 (5 atm), MeOH/AcOH (10:1), rt, 24 h; (iii) DIBAL-H, THF, 0 °C, 2 h then 0 °C to rt, 16 h.

2.6. Alternative route towards (–)-isoretronecanol and (–)-trachelantamidine

The final reduction step of **213** towards the 1-hydroxymethylpyrrolizidines proved to be more problematic than expected, giving low mass return and impurities which were present even after attempted purification. A different route towards the dialdehydes with prior reduction of the *tert*-butyl ester within aminocycloheptene **202** to alcohol **204** proved to be problematic as well, being accompanied by epimerisation at the C(1) stereogenic center, therefore an alternative route towards the products was required. Previous work by Davies *et al*.[20] reported an epoxidation procedure for γ,δ-unsaturated β-amino esters occurring with *in situ* intramolecular lactonisation, employing HBF_4 and *m*-CPBA in CH_2Cl_2 and it was envisaged that this protocol could be used for the oxidation of **201** and **202**. A search in the literature revealed that lactonisation of cycloheptene-type substrates occurs regioselectively; for example, Baldwin *et al*.[21] showed that treatment of cycloheptenone **216** with aqueous HCl resulted in lactonisation towards the 5-membered ring **217** which was reduced to give alcohol **218**, after protection of the ketone. Moreover, Kirmse and coworkers[22] observed iodolactonisation to give **221** upon treatment of carboxylic acid **219** with iodine (Scheme 26).



Scheme 26. *Reagents and Conditions*: (i) HCl (aq.), dimethoxyethane, 50 °C, 14 h; (ii) ethylene glycol, $TsOH{\cdot}H_2O$, C_6H_6, reflux, 7 h; (iii) $LiAlH_4$, THF, 0 °C, 30 min then rt, 16 h; (iv) I_2, KI, satd aq $NaHCO_3$, rt, 16 h.

Accordingly, it was anticipated that application of this protocol to *cis*- or *trans*-**222** followed by subsequent reduction of lactone **224** would give triol **225**, and that oxidative cleavage of the 1,2-diol unit within **225**, may then give dialdehyde **226** (Figure 20).

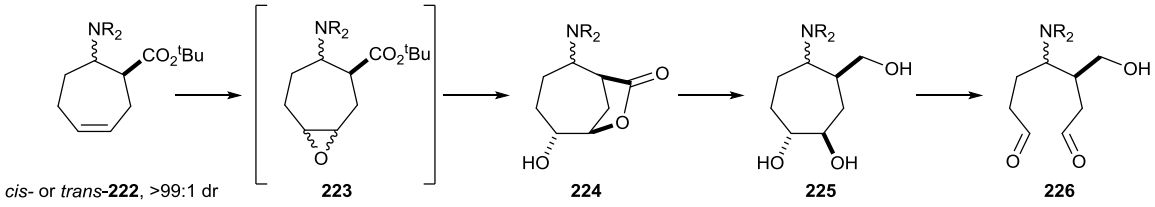
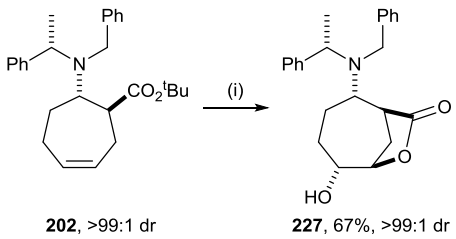


Figure 20. Possible pathway for formation of aldehyde **226**.

Treatment of **202** with HBF_4 (to protect the nitrogen from oxidation) followed by *m*-CPBA in CH_2Cl_2 for 48 h promoted exclusive formation of lactone **227**, which was isolated in 67% yield and >99:1 dr after chromatographic purification (Scheme 27). The relative configuration within **227** was unambiguously established by single crystal X-ray diffraction analysis[15] and the absolute (1*S*,2*S*,5*R*,6*R*,α*S*)-configuration of **227** was assigned relative to the known (*S*)-configuration of the α-methylbenzyl fragment (Figure 21)



Scheme 27. *Reagents and Conditions*: (i) HBF_4, *m*-CPBA, CH_2Cl_2, rt, 48 h.

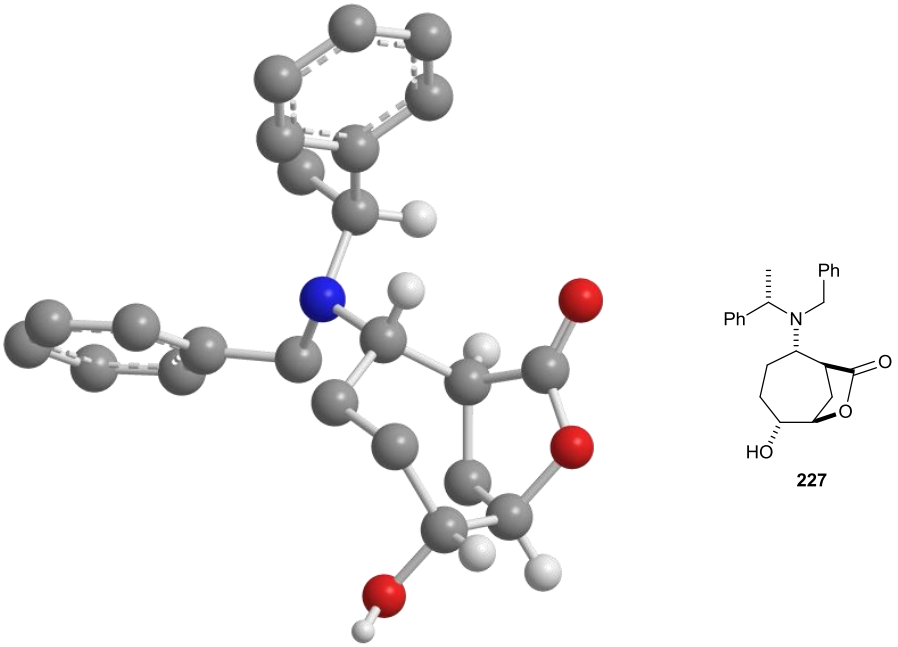


Figure 21. X-ray crystal structure of (1*S*,2*S*,5*R*,6*R*,α*S*)-**227** (selected H atoms are omitted for clarity).

This reaction outcome is consistent with several different scenarios: (i) epoxidation occurs on the bottom face of **202**, followed by regioselective ring opening by attack of H_2O at C(3) and subsequent lactonisation; (ii) epoxidation occurs on the top face of **202**, followed by regioselective ring opening by attack of H_2O at C(4) and subsequent lactonisation; (iii) epoxidation occurs on the bottom face of **202**, followed by regioselective ring-opening by attack of the ester carbonyl at C(3) giving direct lactonisation; (iv) a combination of all three possibilities. The possibilities outlined in (i), (ii) and (iv) involve intermolecular ring-opening by H_2O and it is unlikely that this would be a completely regioselective process, although this possibility cannot be completely ruled out. In scenario (iii), the diastereoselective formation of epoxide **229** on the bottom face is opposite to the steric preference in the previously discussed dihydroxylations. A mechanism can be hypothesized whereby hydrogen-bonding directed control is in operation as shown in **228**, as already observed for similar substrates.[23] In this conformation, the pseudo-axial positioning of the ester would facilitate an intramolecular ring opening at C(3) within **229** to then give lactone **227**. (Figure 22).

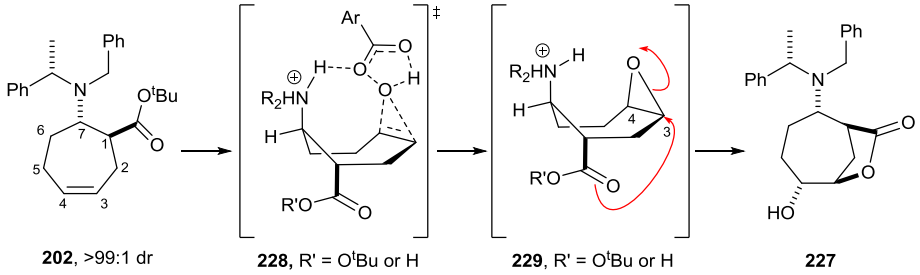
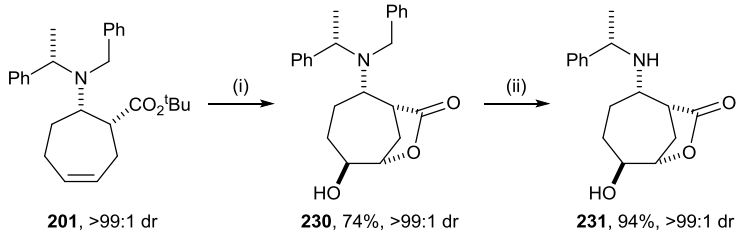


Figure 22. Possible pathway for formation of lactone **227**.

The same reaction conditions were applied to **201** and furnished the diastereoisomeric 5-membered ring lactone **230** in 74% isolated yield and >99:1 dr after chromatographic purification. Mono-*N*-debenzylated derivative **231** was obtained in 94% yield and >99:1 dr upon treatment of **230** with CAN in MeCN (Scheme 28). The relative configuration within **231** was confirmed by single crystal X-ray diffraction analysis[15] and the absolute (1*R*,2*S*,5*S*,6*R*,α*S*)-configuration of **231** was assigned relative to the known (*S*)-configuration of the α-methylbenzyl fragment (Figure 23). This analysis therefore also established the relative configuration, and hence also the absolute configuration of **230**. Also in this case, the highly diastereoselective reaction outcome is consistent with the formation of only one epoxide followed by regioselective ring-opening by the ester at the C(3)-position. The epoxidation step therefore occurs with opposite diastereofacial selectivity to that observed upon reaction of **202**, but is consistent with epoxidation of **201** occuring under steric control as in the case of the dihydroxylation under the Upjohn[14] or Donohoe[16] conditions, on the opposite face to the *tert*-butyl ester group. In this case it is feasible that the enhanced steric compression between the bulky ester and the bulky amino groups may preclude an ammonium-directed pathway during epoxidation (Figure 24).



Scheme 28. *Reagents and Conditions*: (i) HBF_4, *m*-CPBA, CH_2Cl_2, rt, 48 h; (ii) CAN (2.1 equiv), $MeCN/H_2O$ (5:1), rt, 2 h.

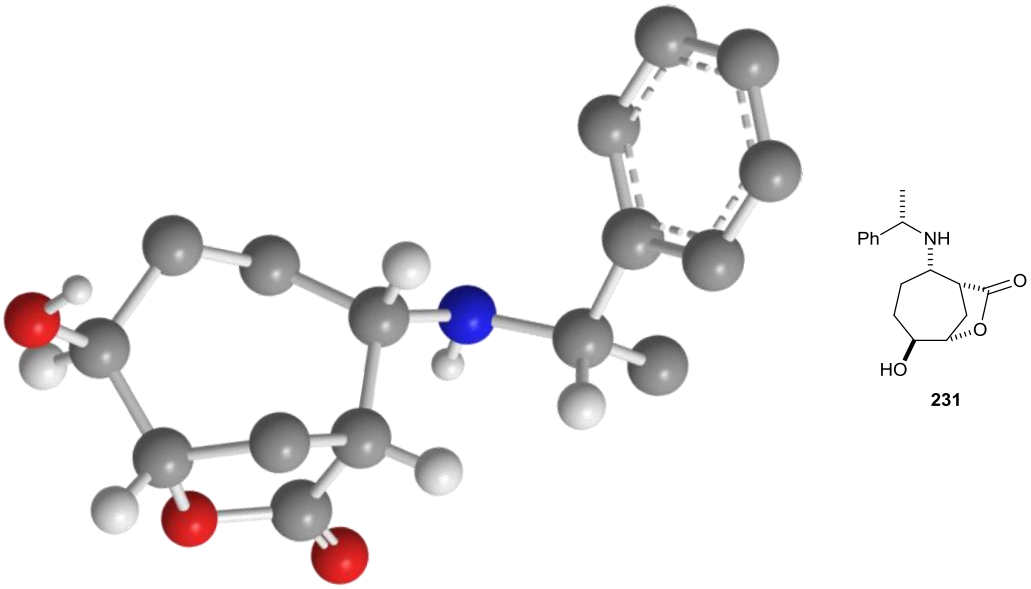


Figure 23. X-ray crystal structure of (1*R*,2*S*,5*S*,6*R*,α*S*)-**231** (selected H atoms are omitted for clarity).

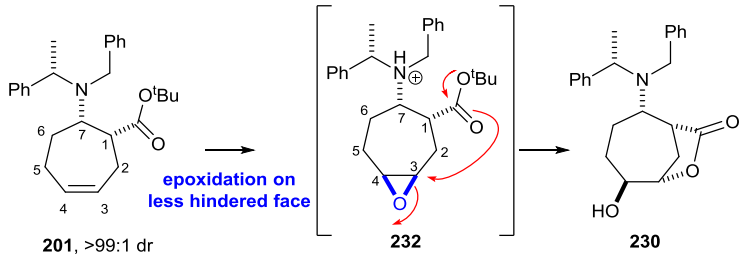
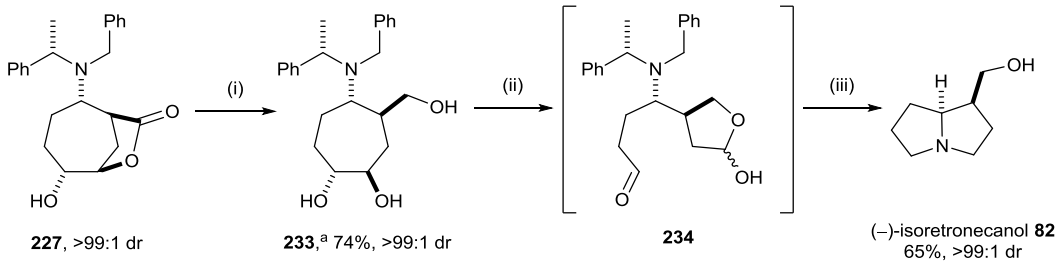


Figure 24. Possible pathway for formation of lactone **230**.

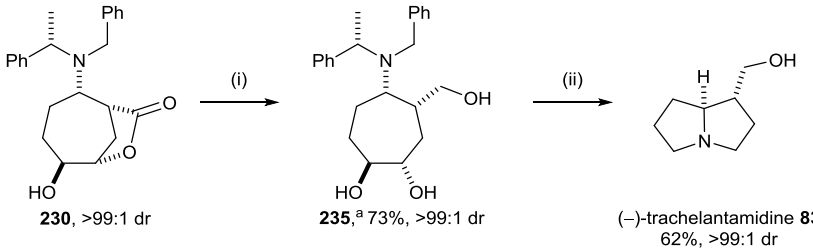
2.7. Improved syntheses of (–)-isoretronecanol and (–)-trachelantamidine

Reduction of lactone **227** with $LiAlH_4$ in THF at 0 °C gave, after 2 h, triol **233** in 74% yield and >99:1 dr. An optimized route towards triol **233** from olefin **202** without the isolation of intermediates increased the overall yield of **233** to 80%. Oxidative cleavage of the 1,2-diol unit within **233** afforded intermediate lactol **234** which was subjected to hydrogenation conditions without further purification. Although lactol **234** was not fully characterized, the outcome of the oxidation step was confirmed by ^{1}H–NMR spectroscopy and mass spectrometry analyses of the crude reaction mixture. Lactol **234** was subjected to the previously optimized conditions without further purification and afforded the desired azabicycle **82**·HOAc. Treatment with HCl followed by purification on DOWEX ion exchange resin gave (–)-isoretronecanol **82** in 65% yield (from **233**) and >99:1 dr (Scheme 29). The specific rotation and ^{1}H and ^{13}C NMR spectroscopic data of this sample of **82** were entirely consistent with those reported in literature[24,25] {$[\alpha]_D^{20}$ –70.1 (*c* 1.0 in EtOH); lit.[25] for a sample isolated from a natural source $[\alpha]_D^{20}$ –65.7 (c 1.88 in EtOH)}.



Scheme 29. *Reagents and Conditions*: (i) $LiAlH_4$, THF, 0 °C, 2 h; (ii) $NaIO_4$, MeOH, rt, 1 h; (iii) $Pd(OH)_2/C$, H_2 (5 atm), MeOH/AcOH (10:1), rt, 24 h. [[a] **233** was also isolated in 80% yield and >99:1 dr (from **202**) over 2 steps without purification of the intermediates].

Following the same sequence of reactions, treatment of lactone **230** with $LiAlH_4$ in THF furnished triol **235** in 73% yield and >99:1 dr. Alternatively, **235** was isolated in 65% yield and >99:1 dr from olefin **201** (without purification of **230**). Oxidative cleavage of the 1,2-diol unit within **235** followed hydrogenolytic *N*-deprotection and *in situ* double reductive cyclisation gave **83**·HOAc. Subsequent treatment of **83**·HOAc with HCl followed by purification on DOWEX ion exchange resin, gave (–)-trachelantamidine **83** in 62% yield (from **235**) and >99:1 dr (Scheme 30). Also in this case, the specific rotation and ^1H and ^{13}C NMR spectroscopic data of this sample of **83** were entirely consistent with those reported in literature[26,27] {$[\alpha]_D^{20}$ −13.0 (*c* 0.2 in EtOH); lit.[27] for a sample isolated from a natural source $[\alpha]_D^{20}$ −13.8 (*c* 1.28 in EtOH)}.



Scheme 30. *Reagents and Conditions*: (i) $LiAlH_4$, THF, 0 °C, 2 h; (ii) $NaIO_4$, MeOH, rt, 1 h then $Pd(OH)_2/C$, H_2 (5 atm), MeOH/AcOH (10:1), rt, 24 h. [[a] **235** was also isolated in 65% yield and >99:1 dr (from **201**) over 2 steps without purification of the intermediates]

2.8. Summary

The rapid assembly of the 1-hydroxymethyl pyrrolidizine scaffold was achieved from two epimeric 7-aminocyclohept-3-ene-carboxylate substrates *syn*-**201** or *anti*-**202**. Oxidation of the C=C double bond via Donohoe[16] or Upjohn[14] dihydroxylation conditions or an improved ammonium-directed[23] epoxidation protocol (followed by reduction of the resultant lactone), gave vicinal diols **236** and **237**. Subsequent oxidative cleavage of the 1,2-diol units within **236** and **237**, gave the corresponding dialdehydes **238**. Subsequent hydrogenolytic *N*-deprotection and *in situ* double reductive cyclisation, gave (–)-isoretronecanol **82** and (–)-trachelantamidine **83**. The total asymmetric syntheses of these two alkaloids, (–)-isoretronecanol **82** and (–)-trachelantamidine **83**, were achieved in 17 and 9% overall yield, respectively, via the improved ammonium directed epoxidation route, from commercially available starting materials (Figure 25).[28]

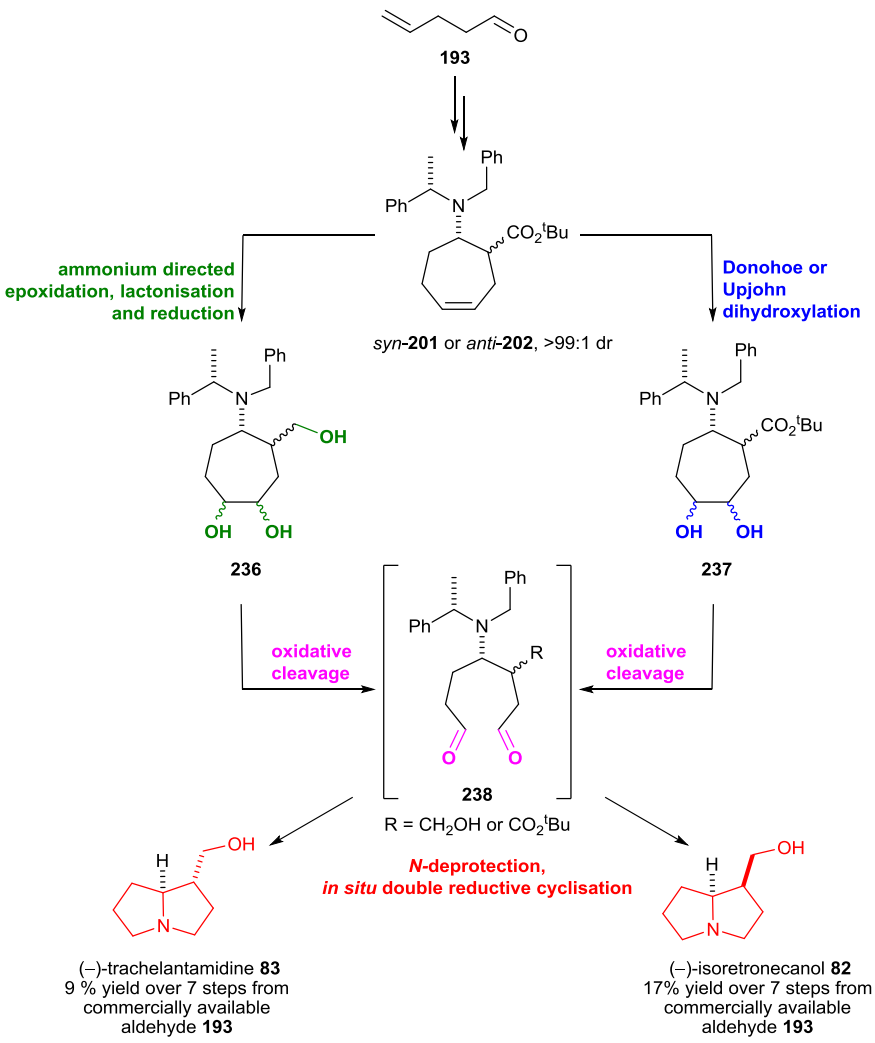


Figure 25. Scheme of syntheses of pyrrolizidines (–)-isoretronecanol **82** and (–)-trachelantamidine **83**.

2.9. References and notes

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(11) The (*E*)-enolate geometry was confirmed by trapping the (*E*)-**198** with TMSCl and analysing the resultant silyl ketene acetal by 1H-NMR and NOESY spectroscopic analysis

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Chapter 3: Asymmetric Syntheses of 1-hydroxymethyl-7-hydroxypyrrolizidines

This chapter describes investigations towards the synthesis of 1-hydroxymethyl-7-hydroxypyrrolizidines **79** and culminates in the asymmetric syntheses of (–)-hastanecine **129**, (–)-turneforcidine **130** and (–)-platynecine **131** (Figure 26).

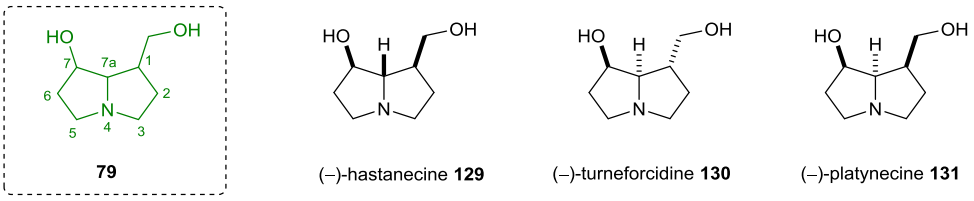


Figure 26. The structures of the 1-hydroxymethyl-7-hydroxypyrrolizidine alkaloids: (–)-hastanecine **129**, (–)-turneforcidine **130** and (–)-platynecine **131**.

3.1. Chapter aim

Following the successful results obtained in the syntheses of the 1-hydroxymethylpyrrolizidines (–)-isoretronecanol **82** and (–)-trachelantamidine **83**, delineated in the previous chapter, it was envisaged that the syntheses of the structurally more complex 1-hydroxymethyl-7-hydroxypyrrolizidines **242** could be achieved starting from the conjugate addition of either (*R*)-**171** or (*S*)-**171** to a suitably *O*-protected derivative of enantiopure γ-hydroxy-α,β-unsaturated ester (*R*)-**239**. Diastereoselective enolate allylation and subsequent oxidative cleavage of the C=C double bonds within **240** would then afford dialdehyde **241**. Subsequent hydrogenolytic *N*-debenzylation and double reductive cyclisation was predicted to give the corresponding 1-hydroxymethyl-7-hydroxypyrrolizidines **242** (Figure 27).

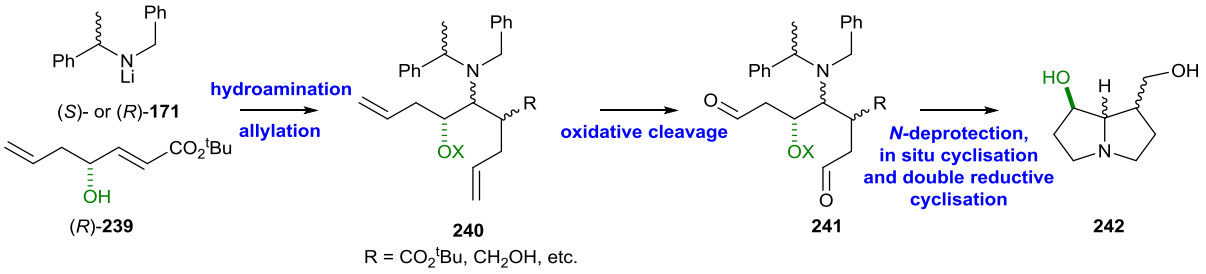
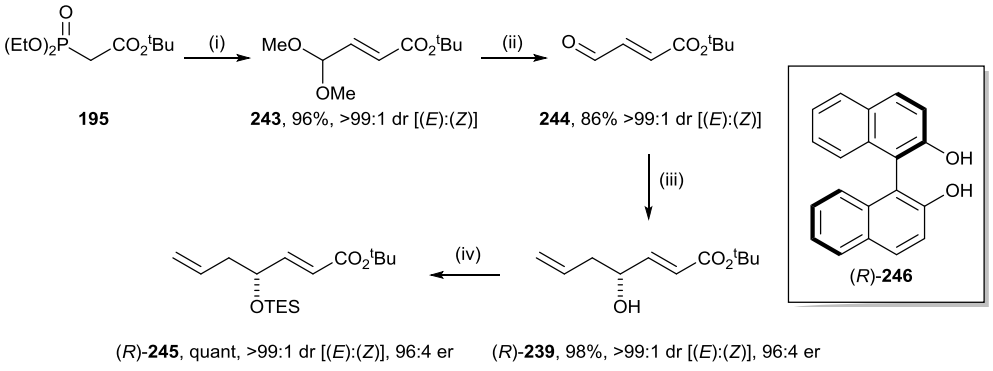


Figure 27. Proposed synthetic route towards 1-hydroxymethyl-7-hydroxypyrrolizidines **242**.

3.2. Conjugate addition of lithium amides to an enantiopure γ-hydroxy-α,β-unsaturated ester derivative

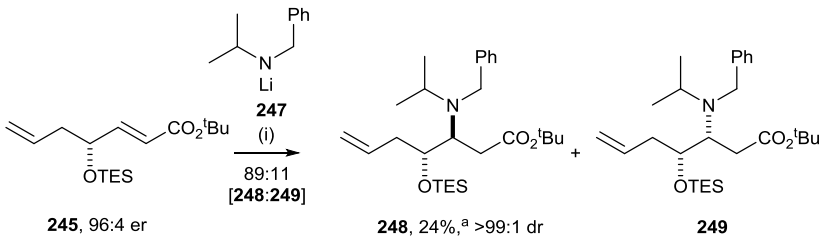
The required γ-hydroxy-α,β-unsaturated ester (*R*)-**239** was prepared via a literature procedure for the synthesis of the corresponding ethyl ester.[1,2] Wadsworth-Emmons olefination of dimethoxyacetaldehyde with *tert*-butyl diethylphosphonoacetate **195** in the presence of K_2CO_3 gave α,β-unsaturated ester **243** in 96% isolated yield and >99:1 dr [(*E*):(*Z*)]. Hydrolysis of the acetal within **243** upon treatment with TsOH in a 1:1 mixture of acetone and H_2O afforded **244** in 86% isolated yield and >99:1 dr [(*E*):(*Z*)]. Treatment of **244** with $Ti(O^iPr)_4$, TFA and (+)-(*R*)-BINOL **246** followed by allyltributylstannane afforded (*R*)-**239** in 98% yield, >99:1 dr [(*E*):(*Z*)] and 96:4 er. The enantiomeric excess of **239** was determined by chiral HPLC analysis, upon comparaison with an authentic racemic standard (which was synthesized in 67% yield upon treatment of **244** with allyl magnesium chloride).[3] The stereochemistry of **239** was assigned by analogy with literature precedent and subsequently established by single crystal X-ray diffraction analysis of a derivative (*vide infra*). The hydroxyl functionality within **239** was then protected upon treatment of (*R*)-**239** with TESCl, which afforded **245** in quantitative yield after chromatographic purification. (Scheme 31).



Scheme 31. *Reagents and Conditions*: (i) K_2CO_3, dimethoxyacetaldehyde, cyclohexane, 60 °C, 16 h; (ii) TsOH, acetone/H_2O (1:1), 70 °C, 1.5 h; (iii) $Ti(O^iPr)_4$, TFA, (+)-(*R*)-BINOL **246**, 4 Å MS, rt, 1 h then allyltributylstannane, CH_2Cl_2, –78 °C to –20 °C then –20 °C, 72 h; (iv) TESCl, imidazole, DMAP, CH_2Cl_2, rt, 16 h.

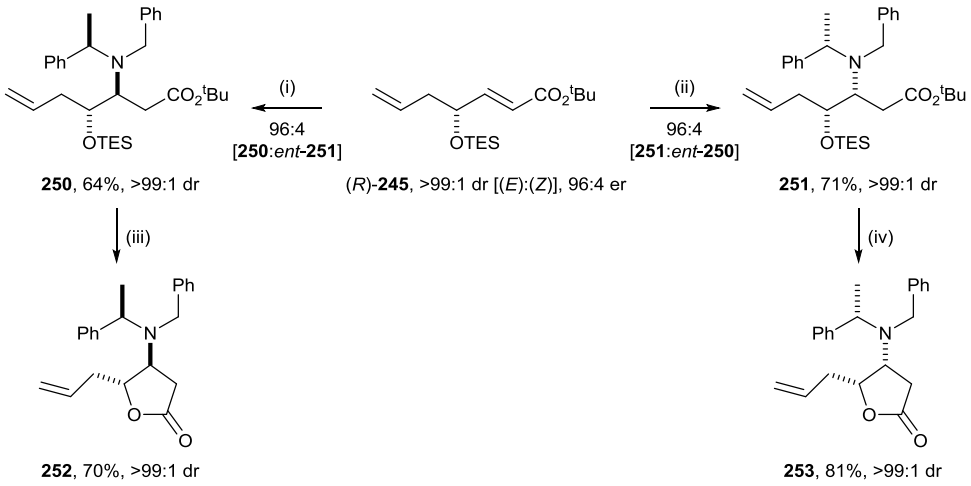
With γ-silyloxy-α,β-unsaturated ester (*R*)-**245** in hand, attention was turned to the doubly diastereoselective[4] conjugate additions of (*R*)-**171** or (*S*)-**171** to (*R*)-**245**. However, when both the reagent and the substrate are chiral, the stereochemical outcome of a reaction can be described by two possible situations; firstly if the intrinsic stereocontrol of both components

of the reaction favour the same stereochemical outcome then the doubly diastereoselective pairing of the two (i.e., reagent and substrate) is named 'matched' and the reaction is usually highly diastereoselective. Secondly, when the two components favour different stereochemical outcomes then the doubly diastereoselective pairing is defined as 'mismatched' and the diastereoselectivity of the reaction may be low, and the major product is the one resulting from the dominant component.[4] Davies *et al.* have extensively studied and reported many examples of doubly diastereoselective lithium amide conjugate additions of (*R*)-**171** or (*S*)-**171** to chiral α,β-unsaturated esters.[5] It has been shown that for an analogue γ-silyloxy-α,β-unsaturated ester the conjugate addition resulted in total control from the amide reagent, overcoming the substrate preference.[5a] It was found that lithium *N*-benzyl-*N*-isopropylamide **247** was the optimal achiral mimic for the behaviour of antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **171** in the evaluation of the inherent level of substrate control exerted by enantiopure α,β-unsaturated esters.[6] Thus, it was decided to investigate the substrate control offered by (*R*)-**245** upon addition of *N*-benzyl-*N*-isopropylamide **247**. Reaction of **247** with (*R*)-**245** gave an 89:11 diastereoisomeric mixture of **248** and **249**, respectively, from which **248** was isolated in 24% as a single diastereoisomer, along with an 85:15 mixture of **248** and **249** in 67% combined yield (Scheme 32). The configuration within **248** and **249** were assigned subsequently by chemical correlation (*vide infra)*. This result, combined with the established sense of diastereocontrol elicited by the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide,[7] suggested that the reaction between lithium amide (*R*)-**171** and α,β-unsaturated ester (*R*)-**245** (i.e., where both components favour the formation of the 3,4-*anti*-diastereoisomer) is predicted to be the doubly diastereoselective "matched" pairing, and the reaction between (*S*)-**171** and (*R*)-**245** (i.e., where the two components have inherent preference for different outcomes) would be the doubly diastereoselective "mismatched" pairing of substrate and reagent.



Scheme 32. *Reagents and Conditions*: (i) **247**, THF, –78 °C, 2 h. [[a] an 85:15 mixture of **248** and **249** was also isolated in 67% combined yield].

Conjugate addition of (*R*)-**171** to γ-silyloxy-α,β-unsaturated ester (*R*)-**245** gave a 96:4 diastereoisomeric mixture of **250** and *ent*-**251**, respectively, from which **250** was isolated in 64% yield and >99:1 dr, while conjugate addition of (*S*)-**171** to (*R*)-**245** afforded a 96:4 diastereoisomeric mixture of **251** and *ent*-**250**, respectively, from which **251** was isolated in 71% yield and >99:1 dr (Scheme 33). It was also observed that, while reaction of (*R*)-**171** with (*R*)-**245** proceeded with full conversion using 1.6 equiv of the lithium amide reagent, the same conditions applied to the conjugate addition of (*S*)-**171** to (*R*)-**245** gave only 66% conversion; in this case 100% conversion was achieved using 2.0 equivalents of the lithium amide reagent. The relative configurations within **250** and **251** were unambiguously established by conversion to the corresponding lactones **252** and **253** and subsequent single crystal X-ray diffraction analyses of **252** and **253**: treatment of **250** with HF in py. for 16 h gave poor conversion to lactone **252**, which was obtained in 30% yield and >99:1 dr. However, treatment of **250** with TBAF for 24 h promoted 100% conversion to lactone **252**, which was isolated as the only product in 70% yield as a single diastereoisomer (>99:1 dr). The same conditions were applied to **251** and also in this case, lactonisation was observed. However, full conversion towards **253** could only be achieved after 48 h and **253** was subsequently isolated in 81% yield and as a single diastereoisomer (>99:1 dr) (Scheme 33). The relative configurations within **252** and **253** were confirmed by single crystal X-ray diffraction analysis[8] and the absolute (4*S*,5*R*,α*R*)-configuration within **252** and the (4*R*,5*R*,α*S*)-configuration within **253** were assigned by the reference to the known (*R*)- and (*S*)-configurations of the α-methylbenzyl fragments, respectively. These analyses therefore also confirmed the assigned relative configurations of β-amino esters **250** and **251** and the absolute configurations of the α,β-unsaturated ester precursors (*R*)-**239** and (*R*)-**245** (Figures 28 and 29). The spectroscopic data for the minor compounds *ent*-**250** and *ent*-**251** were identical to those for **250** and **251**, respectively, both conjugate addition reactions proceeding under the completely dominant control of the lithium amide reagent (overwhelming the inherent substrate bias), with the minor compound in both cases being derived from the minor enantiomeric component of the starting material (*S*)-**245**.



Scheme 33. *Reagents and Conditions*: (i) (*R*)-**171**, THF, –78 °C, 2 h; (ii) (*S*)-**171**, THF, –78 °C, 2 h; (iii) TBAF (1.0 M in THF), THF, rt, 24 h; (iv) TBAF (1.0 M in THF), THF, rt, 48 h.

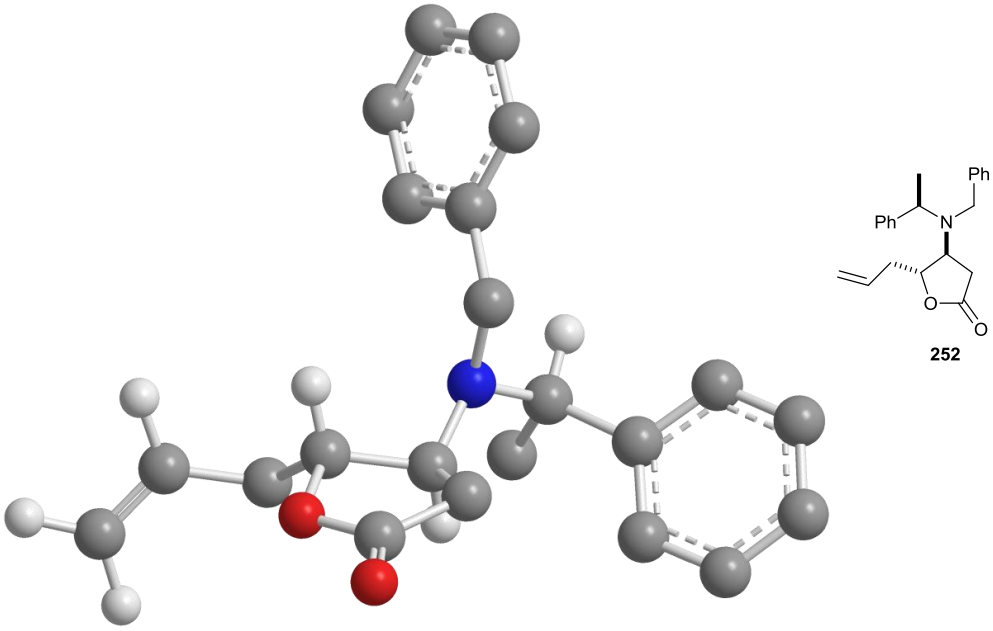


Figure 28. X-ray crystal structure of (4*S*,5*R*,α*R*)-**252** (selected H atoms are omitted for clarity)

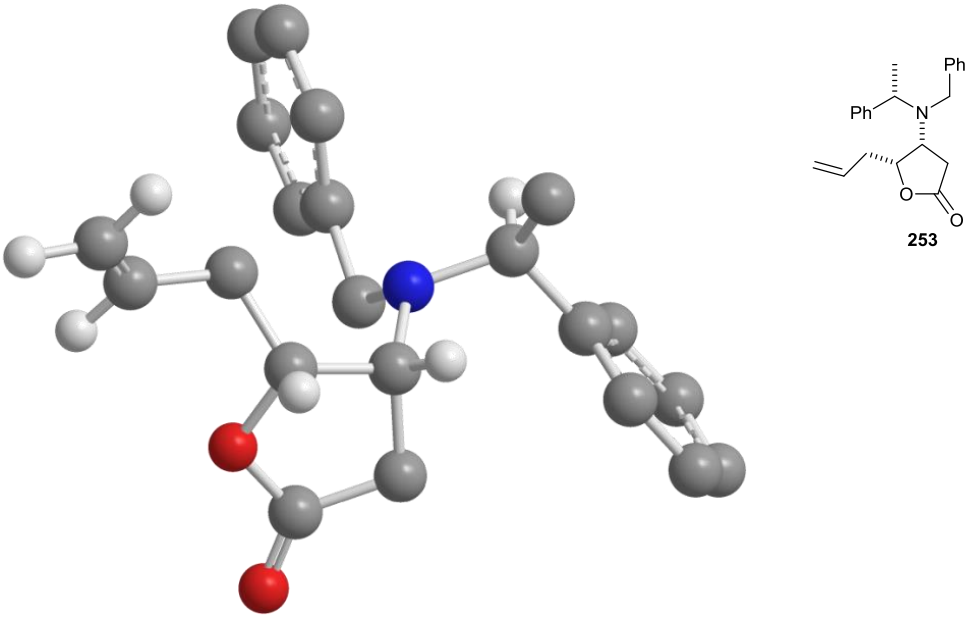
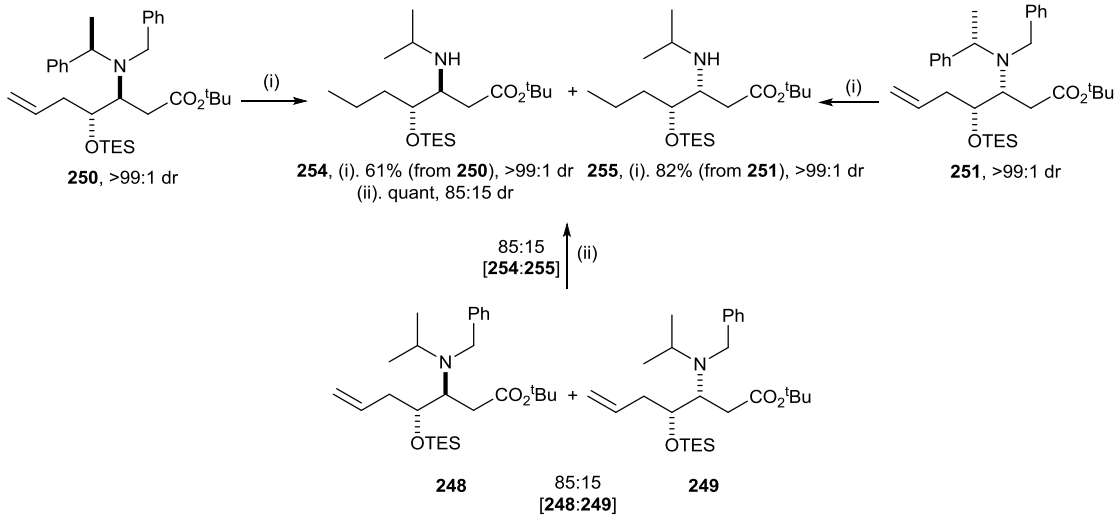


Figure 29. X-ray crystal structure of (4*R*,5*R*,α*S*)-**253** (selected H atoms are omitted for clarity).

Having assigned the configurations of β-amino esters **250** and **251** [derived from the conjugate addition of (*R*)-**171** and (*S*)-**171** to α,β-unsaturated ester (*R*)-**245**], chemical correlation of β-amino esters **248** and **249** [derived from the conjugate addition of achiral lithium amide **247** to α,β-unsaturated ester (*R*)-**245**] with **250** and **251** was carried out in order to establish unambiguously the configurations of **248** and **249**. Hydrogenolytic *N*-debenzylation of a sample of **250** (>99:1 dr) and a sample of **251** (>99:1 dr) were carried out in a 10:1 mixture of MeOH/acetone in the presence of Pearlman's catalyst [$Pd(OH)_2/C$], which also promoted *in situ* reductive alkylation to afford *N*-isopropyl β-amino esters **254** and **255** in 61 and 82% isolated yield, respectively. Submission of the 85:15 mixture of **248** and **249** to hydrogenolytic conditions, gave an 85:15 mixture of **254** and **255**, respectively, in quantitative yield (Scheme 34). The spectroscopic data for **254** and **255** obtained from **248** and **249** were entirely consistent with those obtained for the authentic sample of **254** and **255** obtained from **250** and **251**, establishing unambiguously the configurations within the precursors **248** and **249**, respectively.

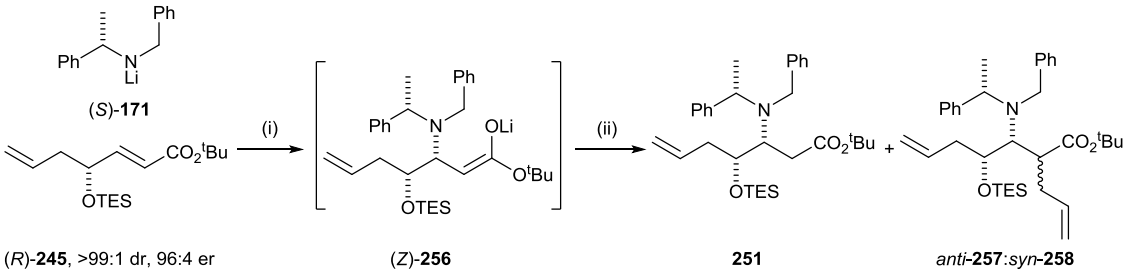


Scheme 34. *Reagents and Conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH/acetone (10:1), rt, 24 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$,MeOH, rt, 24 h.

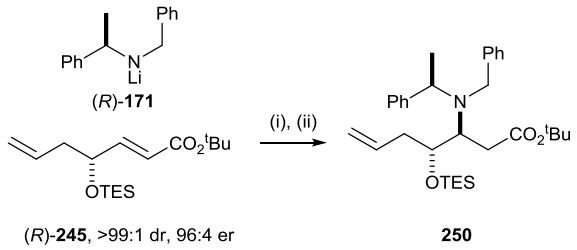
3.3. α-Allylation

Next, as for the γ-unsubstituted substrate described in Chapter 2, the allylation protocol was investigated via both a tandem [i.e., conjugate addition of the requisite antipode of **171** to α,β-unsaturated ester **245** and allylation of the resultant lithium (*Z*)-β-amino enolate[9]] and a stepwise [i.e., deprotonation of β-amino ester **250** or **251** and allylation of the resultant lithium (*E*)-β-amino enolate[9]] approach. Following the tandem approach, conjugate addition

of (*S*)-**171** to (*R*)-**245** followed by *in situ* treatment with allyl bromide gave a 79:21 mixture of γ-silyloxy-β-amino ester **251** and α-allyl-β-amino esters **257** and **258**, respectively. Addition of 12-crown-4 or DMPU resulted, in both cases, in a higher percentage of α-allyl-β-amino esters **257** and **258**, but poor diastereoselectivity was observed. Similarly, conjugate addition of lithium amide (*R*)-**171** to α,β-unsaturated ester (*R*)-**245** followed by addition of allyl bromide gave 80% conversion towards only γ-silyloxy-β-amino ester **250** (Scheme 35).



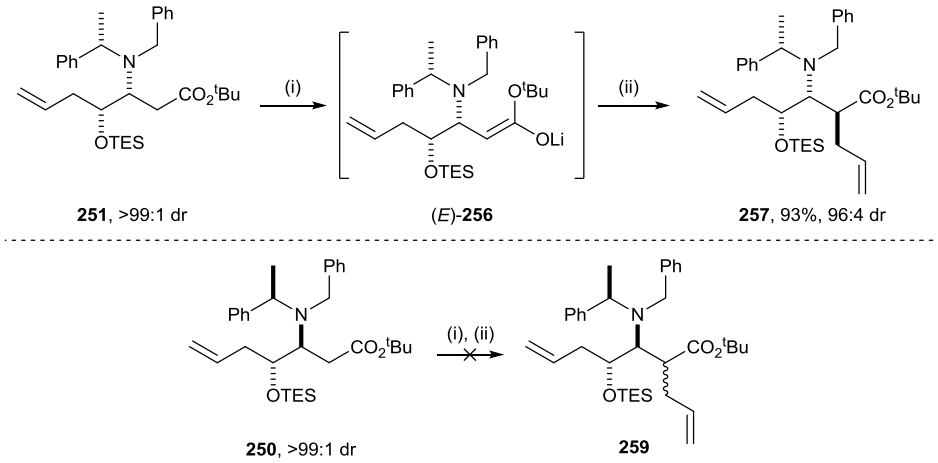
Additive (X)	conversion	251:[*anti*-257:*syn*-258]	*anti*-257:*syn*-258
-	100%	79:21	71:29
12-crown-4	100%	11:89	47:53
DMPU	87%	37:63	70:30



Scheme 35. *Reagents and Conditions*: (i) THF, –78 °C, 2 h then **X**, 1 h; (ii) allyl bromide, –78 °C to rt, 16 h.

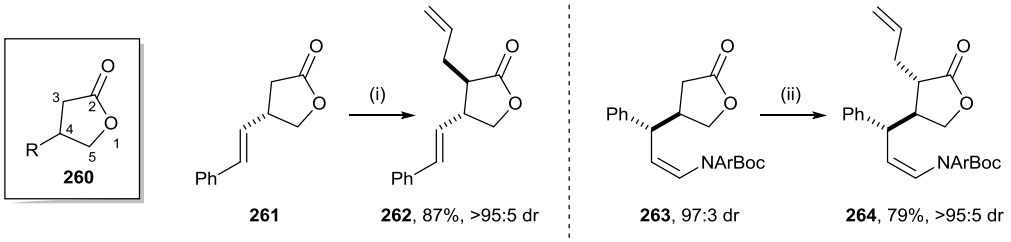
Due to the low diastereoselectivity and poor conversion encountered in the tandem approach, the stepwise approach was investigated next. Thus, deprotonation of γ-silyloxy-β-aminoester **251** with LDA followed by the addition of allyl bromide gave **257** in 93% yield and 96:4 dr. The relative configuration within **257** was unambiguously established by single crystal X-ray diffraction analysis of a derivative (*vide infra*). Attempted allylation under different conditions (i.e., by changing the base to LiTMP, KHMDS and LiHMDS, or using additives such as 12-crown-4 or DMPU) was also attempted, but did not improve or dramatically change the stereochemical outcome. In contrast, submission of **250** to the best stepwise allylation conditions found for the reaction of **251** gave incomplete conversion of the starting material and complex mixture of unidentified products (Scheme 36). The highly substrate dependent

outcomes of enolate allylation reactions of β-amino esters has been reported previously by Davies *et al.* in similar systems.[10]



Scheme 36. *Reagents and Conditions*: (i) LDA, THF, 0 °C, 1 h; (ii) allyl bromide, 0 °C to rt, 16 h

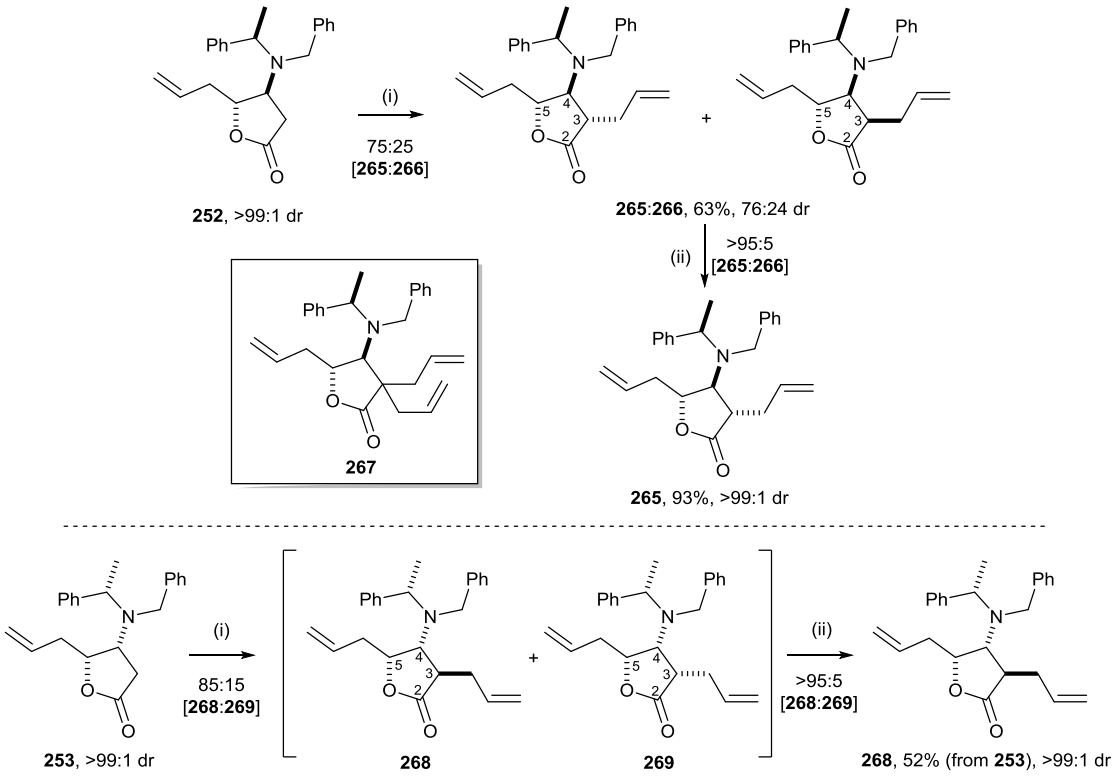
Examples of the allylation of β-substituted γ-butyrolactones such as **260** have been previously reported in the literature.[11] For example, Fürstner *et al.*[11a] showed that treatment of **261** with LDA followed by allyl iodide addition gave α-allylated lactone **262** in 87% yield as a single diastereoisomer (>95:5 dr), bearing the newly installed allylic functionality *anti* to the β-substituent. The same stereochemical preference during the allylation of **263** was shown by Beak and co-workers,[11b] upon treatment of **263** (97:3 dr) with LDA and allyl bromide, which gave **264** as a single diastereoisomer (>95:5 dr) in 79% yield (Scheme 37).



Scheme 37. *Reagents and Conditions*: (i) LDA, THF, –78 °C, 30 min then allyl iodide, THF, –78 °C, 45 min; (ii) LDA, THF, –78 °C, 1 h then allyl bromide, –78 °C to rt, 2 h.

Following this literature precedent, it was envisaged that the allylation of lactones **252** and **253** could also be investigated in the hope of increasing the stereochemical diversity of aminodiene templates available for elaboration to the final pyrrolizidines. In contrast to failure in the open chain, treatment of lactone **252** with LDA and allyl bromide gave an inseparable 76:24 mixture of C(3)-epimers **265** and **266** in 63% combined yield. Attempts to improve the diastereoselectivity or the yield were then undertaken. Increasing the temperature from 0 °C

gave mixture of products containing amine **197** which was isolated in 46% yield after purification, consistent with an E1cb-type elimination of the intermediate enolate; increasing the equivalents of allyl bromide from 2.0 to 5.0 resulted in the formation of double-allylation product **267**, which was isolated in 16% yield along with a 90:10 mixture of diastereoisomers **265** and **266**, respectively, in 52% yield. However, treatment of the 76:24 diastereoisomeric mixture of **265** and **266**, respectively, with KO^{t}Bu afforded **265** as the only product (>99:1 dr) in 93% isolated yield after chromatographic purification. Allylation of lactone **253** under the same conditions gave an 85:15 mixture of **268** and **269**, respectively and as before, submission of the crude 85:15 mixture of C(3)-epimers to KO^{t}Bu afforded **268** as a single diastereoisomer (>99:1 dr) in 52% yield after chromatographic purification (over 2 steps from **253**) (Scheme 38). Also in this case, attempts were undertaken to improve the diastereoselectivity and yield of the allylation reaction (i.e., by changing the base or the metal counterion from Li to B or Ti) but no better results were obtained. The relative configurations within **265** and **268** were tentatively assigned by ^{1}H NMR NOE analyses and by analogy to literature examples (Figure 30) and these assignments were subsequently confirmed by chemical correlation to (−)-hastanecine **129** and (−)-turneforcidine **130**, respectively.



Scheme 38. *Reagents and Conditions*: (i) LDA, THF, 0 °C, 1 h then allyl bromide, 0 °C to rt, 2 h; (ii) KO^{t}Bu, THF, rt, 18 h.

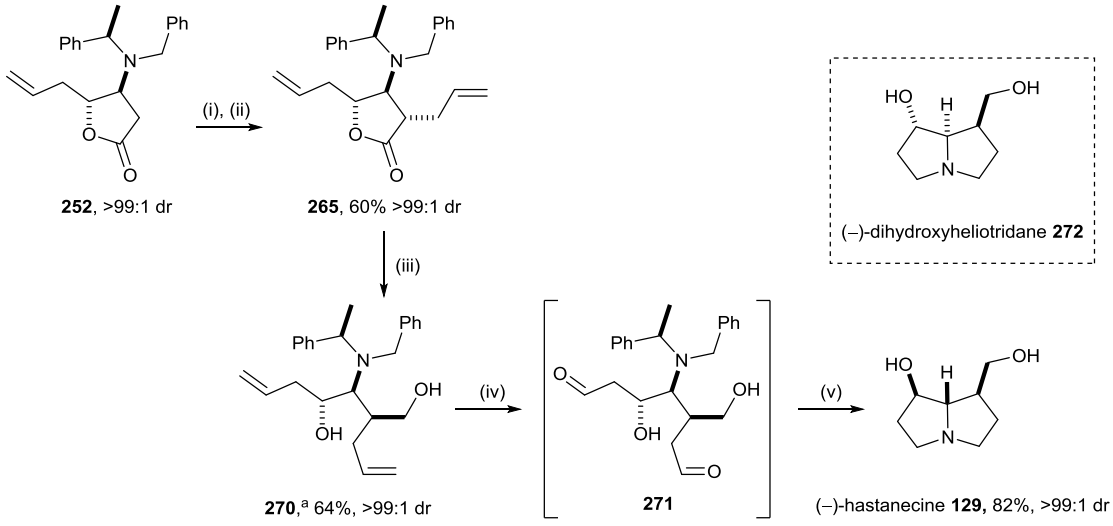


Figure 30. Representation of ^{1}H NMR NOE correlations observed within **265** and **268**. [‘‘↔’’ represents reciprocal interaction].

3.4. Syntheses of (–)-hastanecine, (–)-turneforcidine and (–)-platynecine

With diastereoisomerically pure samples of dienes **257**, **265** and **268** in hand, attention was turned to the syntheses of the corresponding 1-hydroxymethyl-7-hydroxypyrrolizidines via oxidation of the olefinic units followed by hydrogenolytic *N*-debenzylation and double reductive cyclisation. Reduction of **265** with $LiAlH_4$ afforded **270** in 64% yield and >99:1 dr. An improved 57% yield of **270** from **252** was obtained by submission of the crude reaction mixture of **265** and **266** to KO^{t}Bu and subsequent reduction, without isolation of the intermediates, over 3 steps. Ozonolysis employing polymer supported PPh_3[12] was trialled on **270**. Treatment of **270** with HCl and O_3 in a 1:1 mixture of MeOH and CH_2Cl_2 was followed by the addition of polymer supported PPh_3. Simple filtration of the reaction mixture gave dialdehyde **271** (which was not isolated or characterized but observed by mass spectrometry). Treatment of **271** with H_2 (5 atm) in the presence of Pearlman’s catalyst [$Pd(OH)_2$/C] in MeOH and AcOH gave (–)-hastanecine **129** after purification on DOWEX ion exchange resin, in 82% yield and as a single diastereoisomer (>99:1 dr) (Scheme 39). The absolute and relative configurations of C(3) and C(4) within **270**, and therefore of C(7) and C(7a) within the final pyrrolizidine, were previously established via single crystal X-ray diffraction analysis of lactone **252**. The melting point, specific rotation and ^{1}H and ^{13}C NMR data of this sample of **129** were therefore compared with (–)-hastanecine **129** and the C(1)-epimer (–)-dihydroxyheliotridane **272** to confirm the stereochemistry of the C(1). The melting point and specific rotation of this sample of **129** were in good agreement with literature data[13] {mp 109–110 °C; lit.[14] 113–114 °C; lit.[15] 113–114 °C; lit.[13j] 113–114 °C; lit.[13g] mp 112.5–113.5 °C; lit.[13e] mp 113–114 °C; lit.[13d] mp 111–112 °C; lit.[13i] mp 113–114 °C; lit.[13c] mp 110 °C; $[\alpha]_D^{20}$ −8.3 (*c* 0.9 in EtOH); lit.[14] $[\alpha]_D^{20}$ –9.1 (in EtOH); lit.[15] $[\alpha]_D^{25}$ –10.0 (*c* 0.43 in EtOH); lit.[13g] $[\alpha]_D^{25}$ –10.0 (*c* 0.7 in EtOH); lit.[13e] $[\alpha]_D^{20}$ –9.7 (*c* 0.9 in EtOH); lit.[13d] $[\alpha]_D^{23}$ –10.4 (c

0.4 in EtOH); lit.[13c] for *ent*-**129**: $[\alpha]_D^{25}$ +8.5 (*c* 0.6 in EtOH); lit.[13e] for *ent*-**129**: $[\alpha]_D^{20}$ +9.0 (*c* 0.49 in EtOH); lit.[13i] for *ent*-**129**: $[\alpha]_D^{20}$ +8.2 (*c* 1.43 in EtOH); lit.[13j] for *ent*-**129**: $[\alpha]_D^{18}$ +8.5 (*c* 2.2 in EtOH)}, and distinct from those known for the C(1)-epimer (–)-dihydroxyheliotridane **272**[16] {lit.[16b] mp 69–73 °C; lit.[16c] mp 72.5–74.0 °C; lit.[16c] $[\alpha]_D^{25}$ −36.0 (*c* 0.67 EtOH); lit.[13e] $[\alpha]_D^{20}$ –31.7 (*c* 0.55 EtOH); lit.[16a] for *ent*-**272**: $[\alpha]_D^{20}$ +19.2 (*c* 0.56 EtOH); lit.[13e] for *ent*-**272**: $[\alpha]_D^{20}$ +32.0 (*c* 0.50 EtOH)}. Comparison of the ^{1}H and ^{13}C NMR spectroscopic data for this synthetic sample of (–)-hastanecine **129** showed excellent agreement with data previously reported by Denmark *et al.*[13d] and Mulzer[13e] for synthetic samples of (–)-hastanecine **129.** Unfortunately, although (–)-hastanecine **129** has been isolated from a natural source, no NMR spectroscopic data for a natural sample of **129** has been reported in the literature (Tables 1 and 2). Crucially, the ^{1}H and ^{13}C NMR data reported by Mulzer[13e] and Hartmann[13a] for the C(1)-epimer (–)-dihydroxyheliotridane **272** displayed significant differences associated with the C(1)*H*, C(7)*H* and C(7a)*H* and the *C*(1), *C*(7) and *C*(7a) resonances, confirming the assigned configuration of the synthetic sample of (–)-hastanecine **129** obtained in this study. These data therefore also confirmed the assigned configurations within the synthetic precursors **270** and **265**.



Scheme 39. *Reagents and Conditions*: (i) LDA, THF, 0 °C, 1 h then allyl bromide, 0 °C to rt, 2 h; (ii) KO^{t}Bu, THF, rt, 18 h; (iii) $LiAlH_4$, THF, 0 °C, 2 h; (iv) HCl (2.0 M in Et_2O) then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 2 h; (v) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 48 h. [[a] **270** was also isolated in 57% yield and >99:1 dr (from **252**) over 3 steps without purification of the intermediates].

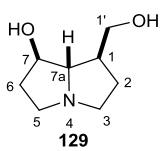
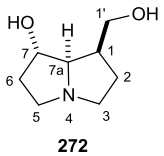
^{1}H NMR data for (–)-hastanecine 129 in MeOH-d_4  **129**			**^{1}H NMR data for (–)-dihydroxyheliotridane 272 in MeOH-d_4**  **272**	
H	**This study** (400 MHz)	**Denmark[13d]** (500 MHz)	**Mulzer[13e]** (270 MHz)	**Hartmann[13a]** (400 MHz)
C(1)*H*	1.75−2.00 m	1.87−2.06 m	2.60−2.70 m	2.44
C(2)H_A	1.40−1.55 m	1.50 −1.58 m	1.90 −1.95 m	1.81
C(2)H_B	1.75−2.00 m	1.87−2.06 m	2.25−2.35 m	1.53
C(3)H_A	2.46 dt (*J* 10.1, 5.6)	2.53 dt (*J* 10.2, 5.5)	3.10−3.20 m	2.89
C(3)H_B	2.98−3.10 m	3.04−3.30 m	3.50 m	2.65
C(5)H_A	2.63 ddd (*J* 11.2, 6.9, 4.1)	2.70 ddd (*J* 11.2, 6.9, 4.2)	3.05−3.15 m	3.19
C(5)H_B	2.98−3.10 m	3.04−3.30 m	3.80 m	2.59
C(6)H_A	1.58−1.68 m	1.67−1.73 m	1.95−2.05 m	1.74
C(6)H_B	1.75−2.00 m	1.87−2.06 m	2.05−2.15 m	2.06
C(7)*H*	3.96−4.01 m	4.06 dt (*J* 4.9, 2.7)	4.55 q (*J* 6.0)	4.12
C(7a)*H*	2.90 dd (*J* 7.5, 2.0)	2.96 dd (*J* 7.5, 2.5)	4.00 dd (*J* 9.0, 6.0)	3.25
C(1')H_2	3.45−3.55 m	3.54−3.63 m	3.80 m	3.85, 3.67

Table 1. Comparison of ^{1}H NMR data for (–)-hastanecine **129** and the C(1)-epimer (–)-dihydroxyheliotridane **272** in MeOH-d_4 [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

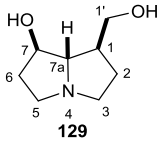
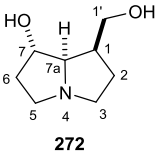
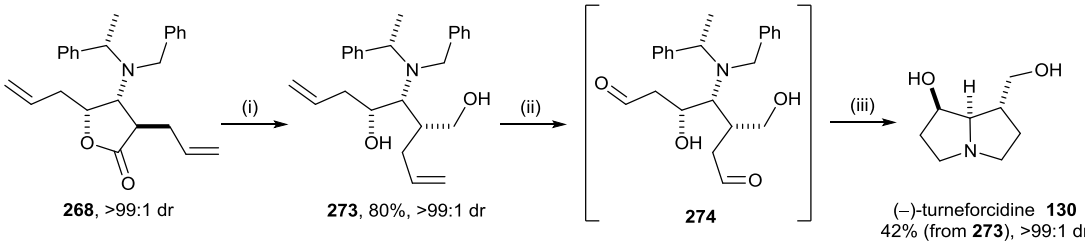
^{13}C NMR data for (–)-hastanecine 129 in MeOH-d_4  **129**				**^{13}C NMR data for (–)-dihydroxyheliotridane 272 in MeOH-d_4**  **272**	
C	**This study** (100 MHz)	**Denmark[13d]** (125 MHz)	**Mulzer[13e]** (63 MHz)	**Mulzer[13e]** (63 MHz)	**Hartmann[13a]** (100 MHz)
C(1)	47.6	47.77	47.8	44.8	44.9
C(2)	30.8	30.87	30.8	28.6	28.6
C(3)	55.6	55.36	55.4	55.0	55.1
C(5)	53.3	53.00	53.1	53.9	53.9
C(6)	33.5	33.50	33.5	35.7	35.8
C(7)	77.5	77.82	77.8	71.8	72.0
C(7a)	77.3	76.79	76.8	73.2	73.2
C(1')	65.0	65.27	65.3	63.0	63.2

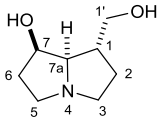
Table 2. Comparison of ^{13}C NMR data for (–)-hastanecine **129** and the C(1)-epimer (–)-dihydroxyheliotridane **272** in MeOH-d_4 [chemical shifts (δ_C) are reported in ppm].

The same sequence of reactions was applied to lactone **268**: reduction of **268** with $LiAlH_4$ gave **273** in 80% yield as a single diastereoisomer (>99:1 dr). Subsequent ozonolysis of the C=C double bonds within **273** and double reductive cyclisation gave (–)-turneforcidine **130** in 42% yield and >99:1 dr (over 2 steps from **273**) after purification (Scheme 40). To allow complete conversion towards (–)-turneforcidine **130** it was necessary to heat the reaction mixture at 50 °C for 48 h which could also be responsible for degradation or by-product formation. The lower yield compared with the one obtained for the C(7)-epimer (–)-hastanecine **129** could be due to the unfavourable position of the C(7) substituent being in the concave face of the pyrrolizidine. Also in this case, the spectroscopic data, melting point and specific rotation of (–)-turneforcidine **130** were in good agreement with literature data, confirming the previous assignment of lactone **268**[17] {mp 109–110 °C; lit.[13i] mp 118–120 °C; lit.[17f] mp 119–120 °C; $[\alpha]_D^{20}$ –10.0 (*c* 0.8 in MeOH); lit.[13i] $[\alpha]_D^{24}$ –11.4 (*c* 1.2 in MeOH); lit.[17b] $[\alpha]_D^{24}$ –13.9 (*c* 0.36 in MeOH); lit.[13j] $[\alpha]_D^{24}$ –12.5 (*c* 1.3 in MeOH); lit.[17f] $[\alpha]_D^{24}$ –12.0 (*c* 0.82 in MeOH)}. Comparison of the ^1H and ^{13}C NMR data for this synthetic sample of (–)-turneforcidine **130** showed excellent agreement with data previously reported by Wee and coworkers[17b] for a synthetic sample of (–)-turneforcidine **130** and for a sample of (–)-turneforcidine **130** isolated from a natural source[13a] (Tables 3–6).



Scheme 40. *Reagents and Conditions*: (i) $LiAlH_4$, THF, 0 °C, 2 h; (ii) HCl (2.0 M in Et_2O) then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 2 h; (iii) H_2 (5 atm), $Pd(OH)_2/C$, MeOH/AcOH (10:1), rt, 48 h then 50 °C, 72 h.

^{1}H NMR data for (–)-turneforcidine 130 in MeOH-d_4

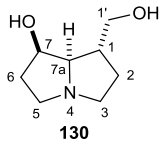


130

H	**This study** (400 MHz)	**Wee**[17b] (300 MHz)	**Hartmann**[13a] (400 MHz)
C(1)*H*	2.46−2.60 m	2.48−2.66 m	2.53
C(2)H_A	1.66 dtd (*J* 12.4, 9.3, 6.8)	1.66 dddd (*J* 12.2, 12.2, 9.7, 6.8)	1.68
C(2)H_B	2.07 dtd (*J* 12.4, 6.8, 3.0)	2.09 dddd (*J* 12.6, 6.6, 6.6, 3.3)	2.10
C(3)H_A	2.46−2.60 m	2.48−2.66 m	2.58
C(3)H_B	2.97−3.08 m	3.03−3.16 m	3.08
C(5)H_A	2.68 q (*J* 8.9)	2.73 q (*J* 9.1)	2.70
C(5)H_B	2.97−3.08 m	3.03−3.16 m	3.03
C(6)H_A	1.93−1.99 m	1.85−2.20 m	2.00
C(6)H_B	1.93−1.99 m	1.85−2.20 m	1.99
C(7)*H*	4.14 q (*J* 3.7)	4.17 q (*J* 3.3)	4.18
C(7a)*H*	3.14 dd (*J* 6.9, 4.6)	3.21 dd (*J* 6.6, 4.5)	3.16
C(1')H_A	3.49 dd (*J* 10.6, 7.1)	3.51 dd (*J* 10.5, 7.2)	3.53
C(1')H_B	3.14 dd (*J* 10.6, 6.6)	3.56 dd (*J* 10.5, 6.6)	3.57

Table 3. Comparison of ^{1}H NMR data in MeOH-d_4 for **(–)**-turneforcidine **130** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

^{1}H NMR data for turneforcidine 130 in $CDCl_3$



130

H	**This study** (400 MHz)	**West**[17a] (500 MHz)	**Livinghouse**[17c] (300 MHz)	**Niwa**[13b] (270 MHz)	**Knight**[17e] (400 MHz)[a]
C(1)*H*	2.46−2.57 m	2.61 ddd (*J* 10.3, 10.3, 6.0)	2.42−2.72 m	2.43−2.74 m	2.70−2.90 m
C(2)H_A	1.60−1.72 m	1.60 dddd (*J* 12.1, 10.6, 10.6, 7.3)	1.59 m	1.55−1.71 m	1.85−2.05 m
C(2)H_B	1.83−2.14 m	2.03 m	1.86−2.07 m	1.55−1.71 m	2.05−2.40 m
C(3)H_A	2.62 td (*J* 10.3, 6.2)	2.49 m	2.42−2.72 m	2.43−2.74 m	3.00−3.15 m
C(3)H_B	3.07 ddd (*J* 10.3, 6.9, 4.1)	3.03 ddd (*J* 10.4, 6.9, 5.0)	3.00 m	3.06 m	3.15−3.40 m
C(5)H_A	2.70 td (*J* 9.5, 6.4)	2.68 ddd (*J* 10.2, 8.5, 6.5)	2.42−2.72 m	2.43−2.74 m	3.15−3.40 m
C(5)H_B	3.23 ddd (*J* 9.4, 7.4, 1.8)	3.20 ddd (*J* 9.6, 7.3, 2.2)	3.20 m	3.21 m	3.15−3.40 m
C(6)H_A	1.83−2.14 m	1.92 m	1.86−2.07 m	1.88−2.11 m	2.05−2.40 m
C(6)H_B	1.83−2.14 m	2.03 m	1.86−2.07 m	1.88−2.11 m	2.05−2.40 m
C(7)*H*	4.37 dd (*J* 9.2, 5.4)	4.32 dd (*J* 10.0, 5.6)	4.30 dd (*J* 7.5, 5.1)	4.34 dd (*J* 10.0, 5.6)	4.30−4.40 m
C(7a)*H*	3.38 dd (*J* 8.3, 5.4)	3.32 dd (*J* 8.3, 5.6)	3.37 m	3.32 dd (*J* 8.2, 5.6)	3.50−3.85 m
C(1')H_A	3.49 t (*J* 9.8)	3.41 dd (*J* 9.8, 9.8)	3.37 m	3.56 dd (*J* 10.5, 6.6)	3.50−3.85 m
C(1')H_B	3.87 dd (*J* 9.8, 4.6)	3.80 dd (*J* 10.0, 4.5)	3.76 dd (*J* 10.2, 4.8)	3.85 dd (*J* 9.9, 4.6)	3.50−3.85 m

Table 4. Comparison of ^{1}H NMR data in $CDCl_3$ for (**−**)-turneforcidine **130** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz]; [a][an additional signal was reported at 3.90–4.10 ppm]

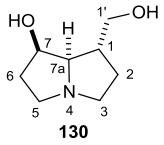
^{13}C NMR data for (–)-turneforcidine 130 in MeOH-d_4  **130**			
C	**this study** (100 MHz)	**Wee[17b]** (100 MHz)	**Hartmann[13a]** (100 MHz)
C(1)	40.9	40.7	40.8
C(2)	32.6	32.4	32.6
C(3)	52.9	52.8	52.8
C(5)	56.4	56.3	56.2
C(6)	37.6	37.4	37.5
C(7)	72.1	71.8	72.0
C(7a)	73.8	73.9	73.7
C(1')	65.8	65.5	65.6

Table 5. Comparison of ^{13}C NMR data in MeOH-d_4 for (**–**)-turneforcidine **130** [chemical shifts (δ_C) are reported in ppm].

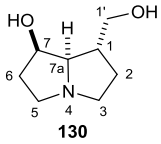
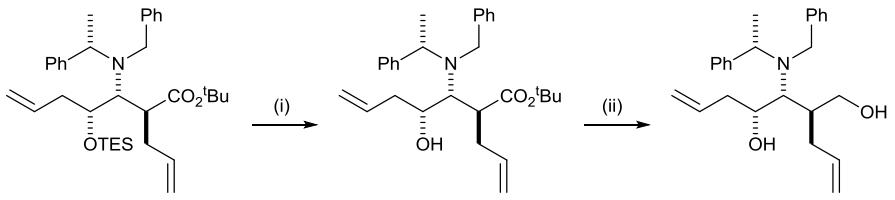
^{13}C NMR data for (–)-turneforcidine 130 in $CDCl_3$  **130**				
C	**this study** (100 MHz)	**West[17a]** (125 MHz)	**Livinghouse[17c]** (75 MHz)	**Knight[17e]** (100 MHz)
C(1)	40.0	40.5	40.2	40.4
C(2)	31.0	31.0	30.8	31.1
C(3)	52.1	52.3	52.1	53.5
C(5)	55.0	55.2	55.0	56.3
C(6)	35.7	35.4	35.3	37.0
C(7)	71.5	71.5	71.2	70.7
C(7a)	74.3	74.3	74.2	75.7
C(1')	65.4	65.3	64.9	63.7

Table 6. Comparison of ^{13}C NMR data in $CDCl_3$ for (**–**)-turneforcidine **130** [Chemical shifts (δ_C) are reported in ppm].

O-Deprotection and reduction followed by the same cyclisation reaction were applied to **257** to complete the synthesis of (–)-platynecine **131**: *O*-deprotection of **257** (96:4 dr) with TBAF gave low conversion even after 48 h under the reaction conditions. However, treatment of **257** with HF·py afforded γ-hydroxy-β-amino ester **275** in 92% yield and 96:4 dr. Subsequent reduction of the ester functionality within **275** gave diol **276** in 95:5 dr and, after chromatographic purification, in 91% isolated yield (Scheme 41). Differences between the ^{1}H NMR spectra of diol **276** and diol **273** (resulting from reduction of allyl-lactone **268**) established that the two compounds are epimeric, differing at the C(2)-configuration, because of the previous unambiguous assignment of the C(3) and C(4) configurations via the single crystal X-ray diffraction analysis of lactone **253**.



257, 96:4 dr **275**, 92%, 96:4 dr **276**, 91%, 95:5 dr

Scheme 41. *Reagents and Conditions*: (i) HF·py, THF, rt, 18 h; (ii) $LiAlH_4$, THF, –78 °C to rt, 18 h.

Submission of **276** to ozonolysis followed by hydrogenolytic *N*-debenzylation and double reductive cyclisation gave a complex mixture of products. ^{1}H NMR spectroscopic and mass spectrometric analyses of the crude reaction mixture showed many components present in the reaction mixture consistent with intermediates resulting from mono-cyclisation and by-products formed upon dehydration or *N*-methylation. It was hypothesized that the steric hindrance of both substituents in the concave face of the final pyrrolizidine was responsible for the slower rate of the cyclisation compared with the cyclisations of dialdehydes **271** and **274** to give (–)-hastanecine **129** and (–)-turneforcidine **130**, respectively. In this case, it is possible that the residual formaldehyde from the ozonolysis reaction, if still present in the solution, could react with *N*-H intermediates, giving rise to undesired *N*-methyl by-products[18] at competitive rate under these reductive conditions. To test this hypothesis it was decided to submit **277** to ring-closing metathesis and then treat the resultant 7-aminocyclohept-3-ene-carboxylate **278** to ozonolysis (which would not yield formaldehyde as a by-product) and subsequent conditions for hydrogenolytic *N*-debenzylation and double reductive cyclisation (Figure 31).

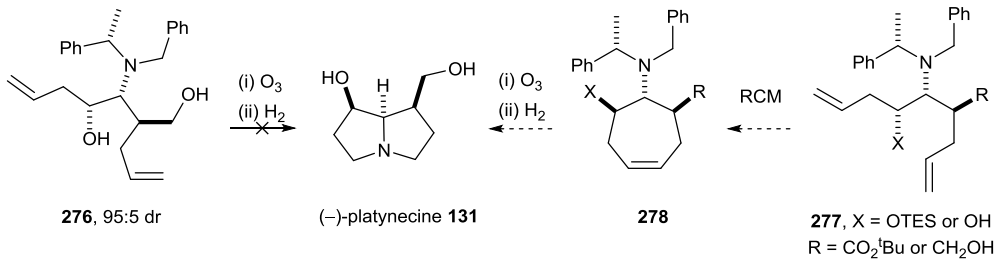
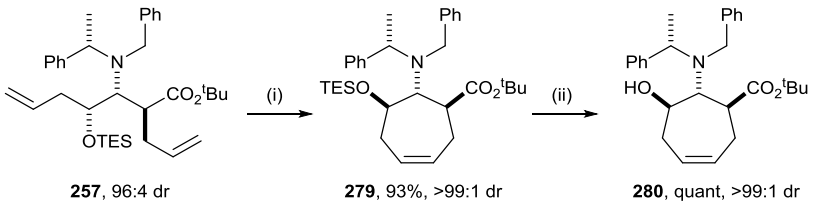


Figure 31. Revised strategy for the synthesis of (–)-platynecine **131**.

Attempted ring-closing metathesis of olefins within **276** was unsuccessful. However, ring-closing metathesis of the *O*-TES protected precursor **257** upon treatment with Grubbs I catalyst at 35 °C gave cycloheptene **279**, which was isolated in 93% yield as a single diastereoisomer (>99:1 dr) after chromatographic purification. Subsequent HF-mediated *O*-deprotection gave **280** in quantitative yield and >99:1 dr (Scheme 42). The relative configuration of **280** was confirmed by single crystal X-ray diffraction analysis[8] and the absolute (1*R*,6*R*,7*R*,α*S*)-configuration within **280** was assigned by reference to the known (*S*)-configuration of the α-methylbenzyl fragment (Figure 32). This analysis therefore also confirmed the assigned configurations within the *O*-TES precursors **257**, **279** and diol **276** resulting from its reduction. The unambiguous assignment of the configuration within **280** confirms also the stereochemistry of the open chain diols **276** and therefore of the C(2)-epimeric diol **273**.



Scheme 42. *Reagents and Conditions*: (i) Grubbs I catalyst, CH_2Cl_2, 35 °C, 18 h; (ii) HF·py, THF, rt, 18 h.

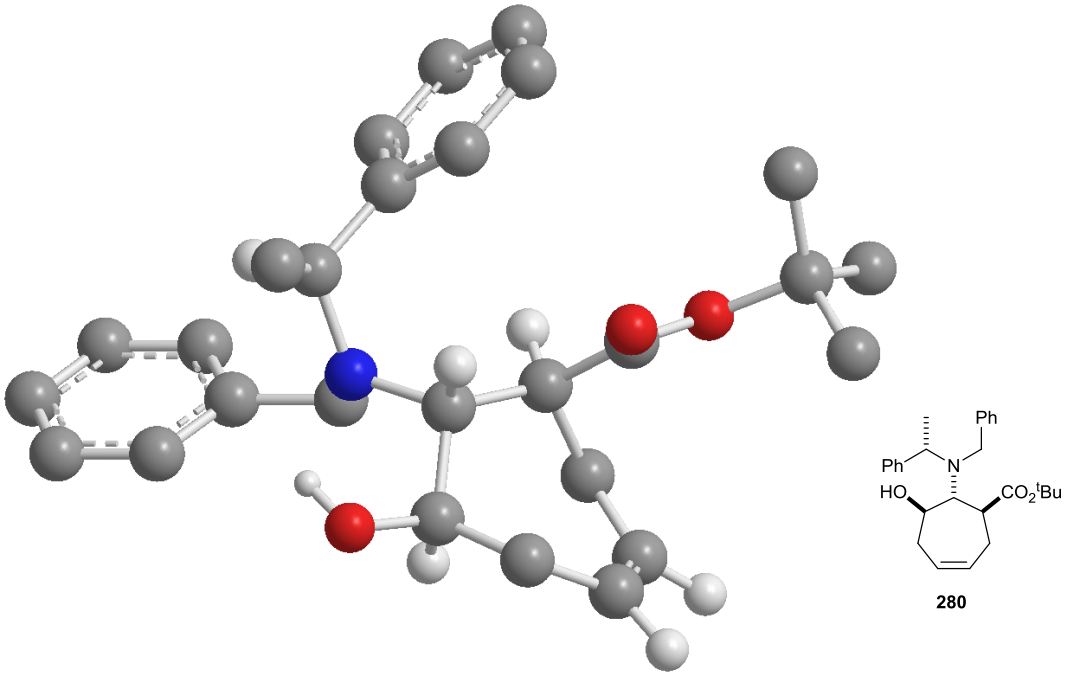
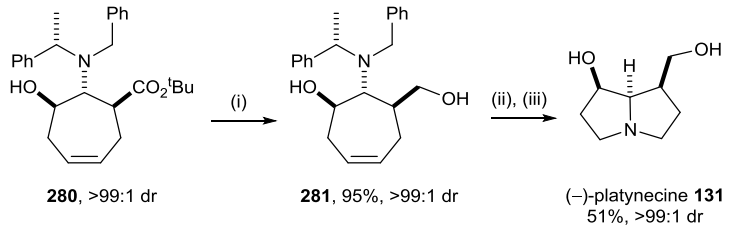


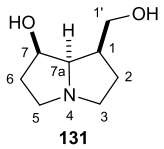
Figure 32. X-ray crystal structure of (1*R*,6*R*,7*R*,α*S*)-**280** (selected H atoms are omitted for clarity).

Reduction of the ester moiety within **280** gave diol **281** in 95% yield as a single diastereoisomer (>99:1 dr). Subsequent submission of **281** to the ozonolysis and hydrogenolytic *N*-debenzylation and double reductive cyclisation conditions gave, as expected from the previous stereochemical assignments, (–)-platynecine **131**, which was isolated in 51% yield and as a single diastereoisomer after chromatographic purification (Scheme 43). The melting point and specific rotation for this sample of (–)-platynecine **131** were in good agreement with literature data[19] {mp 140–142 °C; lit.[19k] mp 145–146 °C; lit.[19h] mp 146–147 °C; lit.[13i] mp 151–153 °C; lit.[19e] mp 147–148 °C; lit.[19g] mp 149–151 °C; lit.[19a] mp 147–148 °C; lit.[19f] mp 147.5–149 °C; $[\alpha]_D^{20}$ –58.8 (*c* 0.9 in EtOH) ; $[\alpha]_D^{20}$ –55.0 (*c* 0.2 in $CHCl_3$); lit.[13i] $[\alpha]_D^{20}$ –55.1 (*c* 2.14 in $CHCl_3$); lit.[19h] $[\alpha]_D^{20}$ –63.4 (*c* 0.15 in $CHCl_3$); lit.[19k] $[\alpha]_D^{20}$ –61.5 (*c* 1.0 in $CHCl_3$); lit.[13a] $[\alpha]_D^{20}$ –51 (*c* 0.9 in EtOH); lit.[19e] $[\alpha]_D^{20}$ –60.3 (*c* 0.3 in $CHCl_3$); lit.[19g] $[\alpha]_D^{20}$ –58.0 (*c* 1.0 in EtOH); lit.[19f] $[\alpha]_D^{20}$ –65.5 (*c* 0.75 in $CHCl_3$)}. Comparison of the ^1H and ^{13}C NMR spectroscopic data for this synthetic sample of (–)-platynecine **131** showed excellent agreement with data previously reported[17a,13a] for two synthetic samples of (–)-platynecine **131**. Unfortunately, although (–)-platynecine **131** has been isolated from a natural source, no NMR data for a natural sample of **131** has been reported in the literature (Tables 7 and 8).[20]



Scheme 43. *Reagents and Conditions*: (i) $LiAlH_4$, THF, –78 °C to rt, 18 h; (ii) HCl (2.0 M in Et_2O), rt then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 15 min then polymer-bound PPh_3, rt, 2 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 48 h.

^{1}H NMR data for (–)-platynecine 131 in MeOH-d_4



131

H	**This study** (400 MHz)	**West**[17a] (500 MHz)	**Hartmann**[13a] (400 MHz)
C(1)*H*	2.42−2.57 m	2.47 m	2.45 m
C(2)H_A	1.78 dtd (*J* 11.8, 7.2, 2.3)	1.77 dddd (*J* 9.6, 7.1, 7.1, 2.5)	1.74 m
C(2)H_B	1.99−2.11 m	2.91 m	1.98 m
C(3)H_A	2.85−3.00	2.87 ddd (*J* 11.3, 9.1, 2.5)	2.79 m
C(3)H_B	3.20 td (*J* 10.5, 7.2)	3.17 ddd (*J* 10.7, 10.7, 7.1)	3.10 m
C(5)H_A	2.85−3.00	2.93 ddd (*J* 11.3, 11.3, 7.1)	2.86 m
C(5)H_B	3.33−3.38 m	3.31 m	3.23 m
C(6)H_A	1.89−1.96 m	1.91 m	1.88 m
C(6)H_B	1.89−1.96 m	2.03 m	1.90 m
C(7)*H*	4.30 q (*J* 2.7)	4.29 m	4.25 m
C(7a)*H*	3.43 dd (*J* 8.1, 3.2)	3.38 dd (*J* 8.0, 3.3)	3.29 m
C(1')H_A	3.90−4.00 m	3.95 dddd (*J* 11.0, 11.0, 11.0, 5.9)	3.94 m
C(1')H_B			3.93 m

Table 7. Comparison of ^{1}H NMR data in MeOH-d_4 for (**–**)-platynecine **131** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

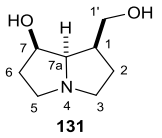
^{13}C NMR data for (–)-platynecine 131 in MeOH-d_4  **131**			
C	**This study** 100 MHz	**West**[17a] (125 MHz)	**Hartmann**[13a] (100 MHz)
C(1)	45.0	45.1	45.0
C(2)	29.0	29.0	28.9
C(3)	56.7	56.7	56.5
C(5)	55.1	55.1	54.8
C(6)	37.4	37.4	37.3
C(7)	73.0	73.1	72.6
C(7a)	73.2	72.9	73.2
C(1')	61.6	61.7	61.6

Table 8. Comparison of ^{13}C NMR data in MeOH-d_4 for (**–**)-platynecine **131** [chemical shifts (δ_C) are reported in ppm].

3.5. Summary

The syntheses of three 1-hydroxymethyl-7-hydroxypyrrolizidines have been achieved via the doubly diastereoselective hydroamination of (*R*)-**245** which gave the diastereoisomeric γ-silyloxy-β-amino esters **250** and **251** in >99:1 dr. Lactonisation of **250** and subsequent allylation resulted in the synthesis of **265**, which after reduction, ozonolysis, hydrogenolytic *N*-debenzylation and double reductive cyclisation gave (**–**)-hastanecine **129** in 17% overall yield from commercially available starting materials. The same lactonisation/allylation protocol was applied to **251** and gave, after lactone reduction, ozonolysis and hydrogenolytic *N*-debenzylation and double reductive cyclisation, (–)-turneforcidine **130** in 8% overall yield from commercially available starting materials, while direct allylation of β-amino ester **251** gave the other diastereoisomeric 1-hydroxymethyl-7-hydroxypyrrolizidine (–)-platynecine **131**, following ring closing metathesis, ester reduction, ozonolysis and hydrogenolytic *N*-debenzylation and double reductive cyclisation, which was obtained in 24% overall yield from commercially available starting materials (Figure 33).

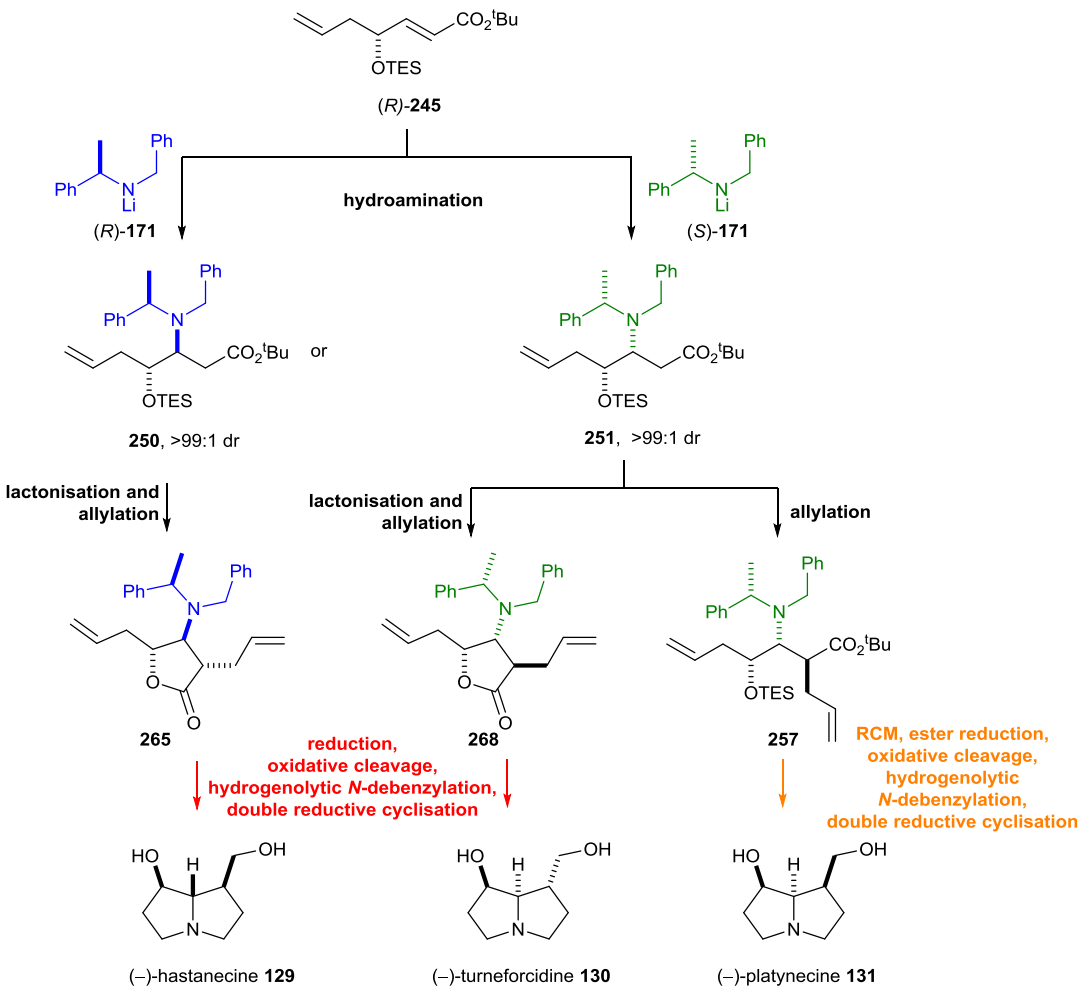


Figure 33. Summary of syntheses of the 1-hydroxymethyl-7-hydroxypyrrolizidine alkaloids (–)-hastanecine **129**, (–)-turneforcidine **130** and (–)-platynecine **131**.

3.6. References and notes

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(20) Further 1H and 13C NMR spectroscopic data for (−)-platynecine **131** are reported in Appendix II.

Chapter 4: Asymmetric syntheses of 1-hydroxymethyl-2-hydroxypyrrolizidines

This chapter details investigations into the syntheses of 1-hydroxymethyl-2-hydroxypyrrolizidines **80** and 1-hydroxymethyl-2,7-dihydroxypyrrolizidines **81** (Figure 34).

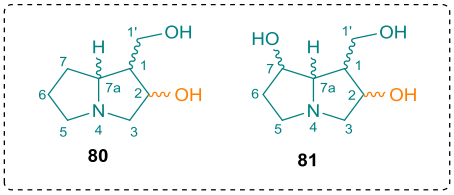
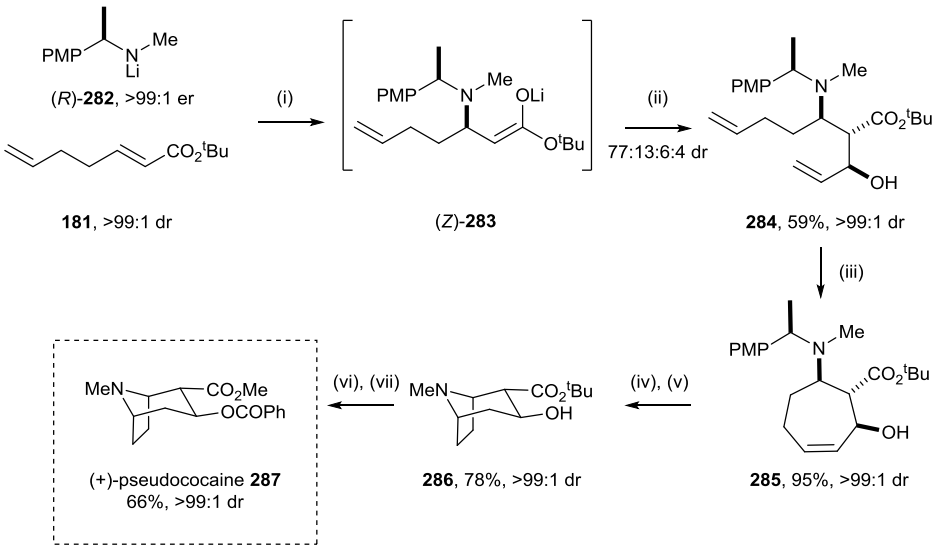


Figure 34. The structures of 1-hydroxymethyl-2-hydroxypyrrolizidines **80** and 1-hydroxymethyl-2,7-dihydroxypyrrolizidines **81**.

4.1. Previous work on aldol reactions of β-amino enolates

The aldol reaction is a reliable and efficient method for the construction of C–C bonds with concomitant formation of two contiguous stereogenic centers.[1] Despite the fact that this reaction has been widely studied and reviewed,[1] relatively few examples of aldol reactions of β-amino enolates are reported in literature.[2] Previous studies in the Davies group utilised the aldol reaction of lithium (*Z*)-β-amino enolate **283**[3] with acrolein as the key step in an asymmetric synthesis of (+)-pseudococaine **287**.[4] Treatment of α,β-unsaturated ester **181** with lithium amide (*R*)-**282** followed by reaction of the intermediate enolate (*Z*)-**283** with acrolein gave a 77:13:6:4 mixture of diastereoisomers from which the major diastereoisomer **284** was isolated in 59% yield and >99:1 dr. Ring-closing metathesis of **284** gave **285** in 95% yield, and subsequent transannular iodoamination of **285** upon treatment with I_2 constructed the tropane scaffold. A sequence of deiodination, transesterification and *O*-benzoylation then gave (+)-pseudococaine **287** in 51% overall yield (from **285**) and >99:1 dr (Scheme 44).



Scheme 44. *Reagents and Conditions:* (i) THF, −78 °C, 2 h; (ii) acrolein, −78 °C to rt, 12 h; (iii) Grubbs I catalyst, CH_2Cl_2, 30 °C, 12 h; (iv) I_2, CH_2Cl_2 (EtOH-stabilised), rt, 18 h; (v) Bu_3SnH, AIBN, PhMe, 80 °C, 5 h; (vi) $SOCl_2$, MeOH, 60 °C, 5 h; (vii) PhCOCl, DMAP, Et_3N, CH_2Cl_2, rt, 12 h.

4.2. Chapter aim

It was envisaged that the aldol reaction of β-amino enolates, followed by *N*-deprotection and *in situ* double reductive cyclisation could be employed in syntheses of 1-hydroxymethyl-2-hydroxypyrrolizidines and 1-hydroxymethyl-2,7-dihydroxypyrrolizidines. As the outcome of aldol reactions of β-amino enolates have been shown to be highly dependent on numerous factors, including the enolate geometry and identity of the metal counterion,[2] both "stepwise" and "tandem" protocols were investigated. The synthetic strategy for the syntheses of 1-hydroxymethyl-2-hydroxypyrrolizidines and 1-hydroxymethyl-2,7-dihydroxypyrrolizidines would then employ reduction of the ester functionality within **290** followed by oxidative cleavage of the C=C double bonds within the resultant alcohol **291**. Hydrogenolytic *N*-debenzylation and double reductive cyclisation would then afford the 1-hydroxymethyl-2-hydroxypyrrolizidines **292** (X = H) and 1-hydroxymethyl-2,7-dihydroxypyrrolizidines **292** (X = OH) (Figure 35).

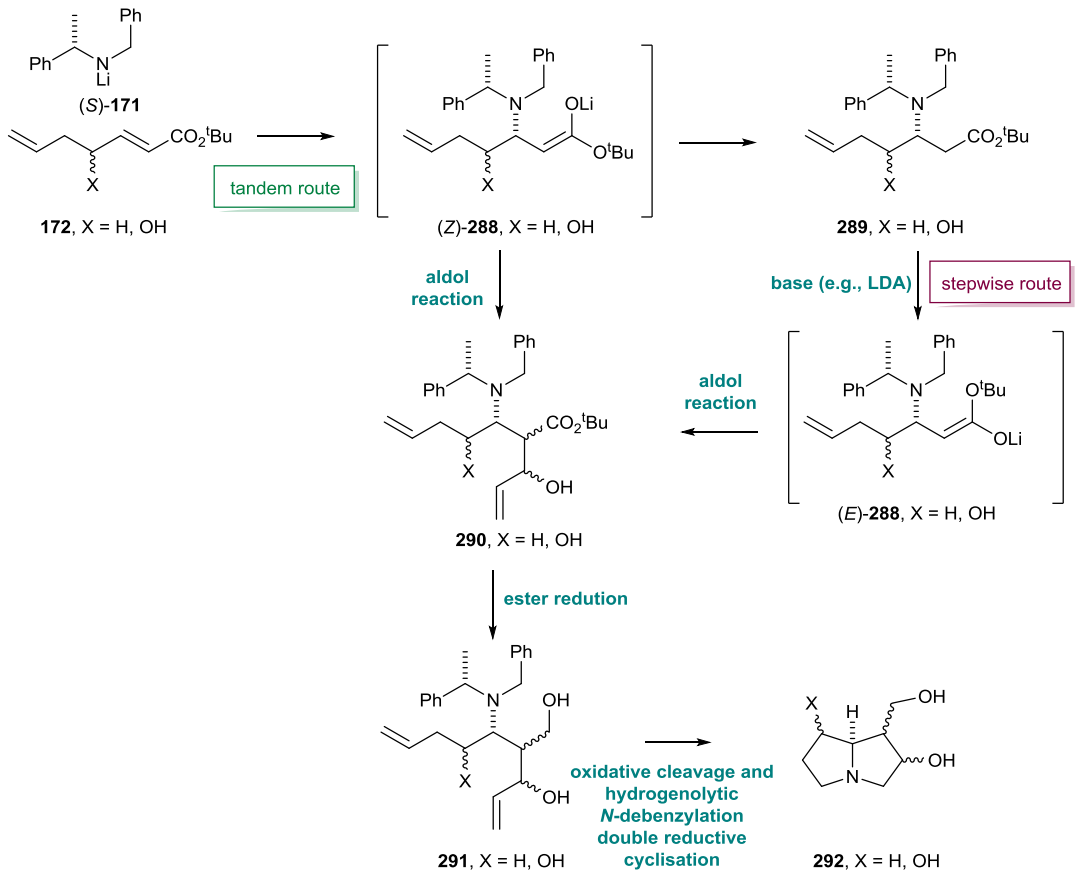
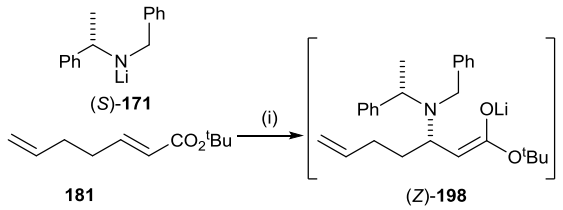


Figure 35. Proposed route towards 1-hydroxymethyl-2-hydroxypyrrolizidines **292** (X = H) and 1-hydroxymethyl-2,7-dihydroxypyrrolizidines **292** (X = OH).

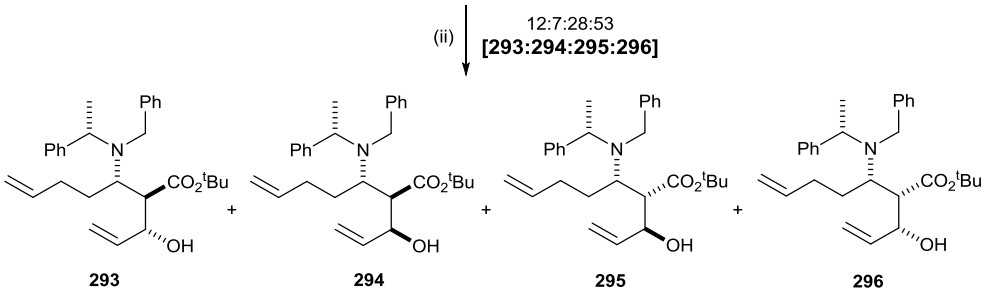
4.3. Aldol reactions

The "tandem" protocol involving the conjugate addition of (*S*)-**171** to α,β-unsaturated ester **181** followed by the addition of acrolein to the corresponding lithium (*Z*)-β-amino enolate[5] **198** was investigated initially. Maintaining the reaction temperature at −78 °C for 2 h resulted in the formation of all four possible diastereoisomers **293**, **294**, **295** and **296** (31:13:29:27 dr, respectively) in 54% yield, from which **296** was isolated in 12% yield and >99:1 dr. Different reaction temperatures and times were investigated in an attempt to increase both the yield and diastereoselectivity, with full conversion being observed after 2 h in all cases. Increasing the temperature from −78 °C to −20 °C over 2 h resulted in an improved ratio in favour of **296** (19:10:32:39 dr) which was isolated in 20% yield. Raising the temperature to 0 °C and also increasing the time from 2 to 3 h gave the best results and afforded **293**, **294**, **295**, and **296** in 12:7:28:53 dr, respectively, from which **296** was isolated in 41% yield and >99:1 dr along with a 28:24:40:7 mixture of **293**, **294**, **295** and **296**, respectively, in 38% combined yield. Unfortunately, attempts to increase the temperature to rt resulted in only β-amino ester **182**, as

determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Scheme 45). Presumably **182** is formed, in this case, as a result of a retroaldol pathway. The absolute configurations of **293**, **294**, **295**, and **296** were established either by chemical correlation or single crystal X-ray diffraction analyses of their derivatives (*vide infra*).

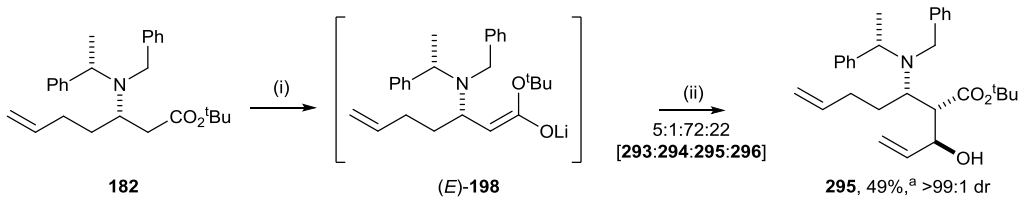


T (°C)	Time (h)	dr [293:294:295:296]	Yield 296 (>99:1 dr)	Total yield 293-296
–78	2	31:13:29:27	12%	54%
–78 to –20	2	19:10:32:39	20%	53%
–78 to 0	3	12:7:28:53	41%	79%
–78 to rt	16	-	-	-



Scheme 45. *Reagents and Conditions:* (i) THF, −78 °C, 2 h; (ii) acrolein, THF, see table.

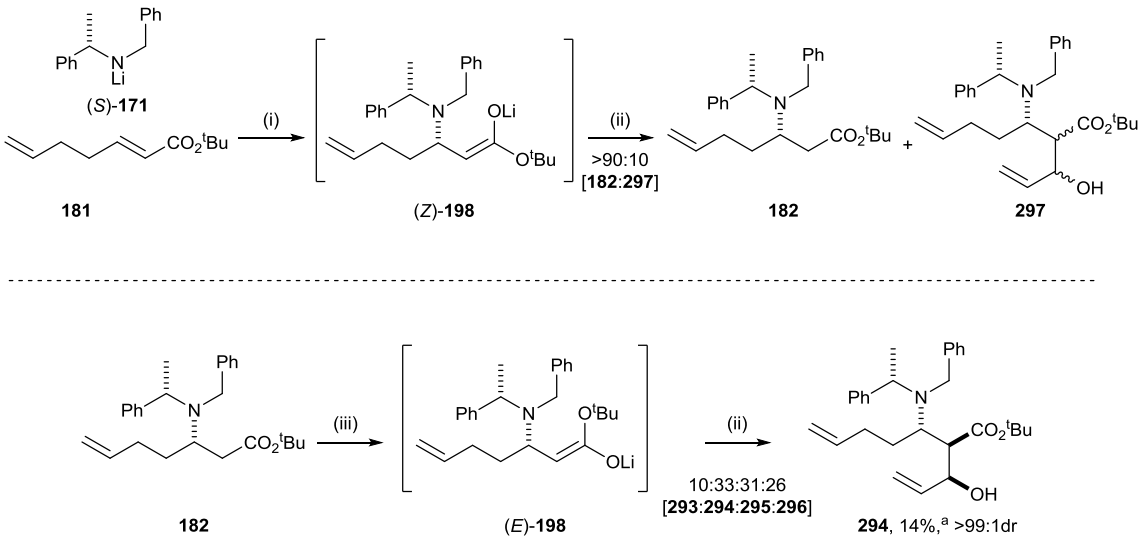
Investigations into the alternative "stepwise" protocol, whereby deprotonation of β-amino ester **182** with a lithium base followed by reaction of the resultant lithium (*E*)-β-amino enolate[5] **198** with acrolein were also attempted. The use of LDA in THF at 0 °C gave an 8:16:51:25 mixture of **293**, **294**, **295** and **296**, respectively, while superior diastereoselectivity in the formation of **295** was obtained using LiTMP as the base, resulting in the formation of a 5:1:72:22 mixture of **293**, **294**, **295** and **296**, respectively, from which **295** was isolated in 49% yield and >99:1 dr upon chromatographic purification (Scheme 46).



Scheme 46. *Reagents and Conditions:* (i) LiTMP, THF, 0 °C, 1 h; (ii) acrolein, −78 °C to 0 °C, 3 h. [[a] a 16:4:32:44 mixture of **293**, **294**, **295** and **296** was also isolated in 24% total yield].

Transmetallation of lithium to a different metal counterion after enolate formation was also investigated in the hope that the aldol reaction could be optimised for the formation of the remaining two diastereoisomers, **293** and **294**. Boron enolates have been widely used in aldol

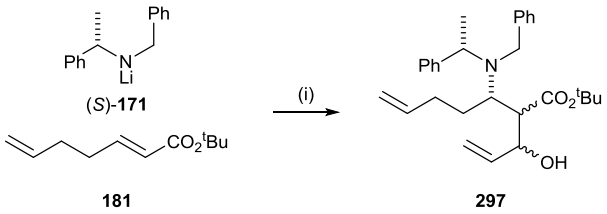
reactions to improve the diastereoselectivity[1e] and, in particular, Davies and co-workers employed a boron mediated aldol reaction of a β-amino enolate in their synthesis of (+)-thienamycin.[2b] Using these established conditions for transmetallation, treatment of (*Z*)-β-amino enolate[5] **198**, resulting from the "tandem" protocol, with $B(OMe)_3$ prior to the addition of acrolein, gave β-amino ester **182** as the major component, as determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. Similarly, treatment of lithium (*E*)-β-amino enolate[5] **198** (which was generated from deprotonation of **182** with LDA) with $B(OMe)_3$, according to the literature reaction conditions,[2b] before the addition of acrolein, gave **293**, **294**, **295** and **296** in 10:33:31:26 dr, respectively (Scheme 47). The increased ratio of **294** compared with the other previous conditions however, allowed its isolation as a single diastereoisomer in 14% yield. The use of LiTMP as the base to generate the enolate (*E*)-**198** followed by treatment with $B(OMe)_3$, gave a 21:20:51:8 mixture of **293**, **294**, **295** and **296**, respectively.



Scheme 47. *Reagents and Conditions:* (i) THF, −78 °C, 2 h; (ii) $B(OMe)_3$, −78 °C, 1 h, then acrolein, −78 to 0 °C, 3 h; (iii) LDA, THF, −78 to 0 °C, 2 h. [[a] a 10:25:48:17 mixture of **293**, **294**, **295** and **296** was also isolated in 52% total yield].

Transmetallation to Zn, Zr, Mo or Ti was also attempted in both "tandem" and "stepwise" protocols. In the "tandem" cases, the addition of $ZnCl_2$ or $ZrCp_2Cl_2$ to the lithium (*Z*)-β-amino enolate (generated upon treatment of α,β-unsaturated ester **181** with lithium amide (*S*)-**171**) gave only β-amino ester **182**, while the use of $MoCp_2Cl_2$ gave **295** and **296** as the major products. Addition of $TiCl(O^iPr)_3$ gave a mixture of **293**, **294**, **295** and **296** in

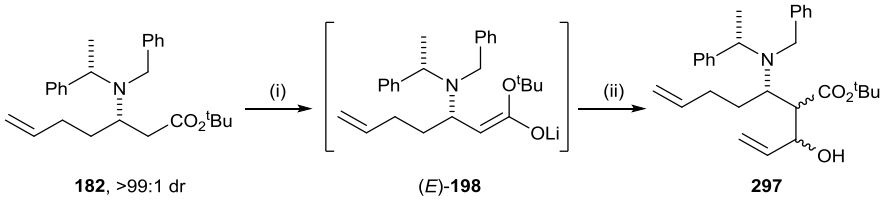
49:15:23:13 dr, respectively, from which **293** was isolated in 22% yield as a single diastereoisomer (Scheme 48).



X	Conversion to 297 %	dr [293:294:295:296]	Yield
$ZnCl_2$	<5	-	-
$ZrCp_2Cl_2$	<5	-	-
$MoCp_2Cl_2$	44	21:12:34:33	-
$TiCl(OiPr)_3$	80	49:15:23:13	22% [a] (**293**)

Scheme 48. *Reagents and Conditions:* (i) THF, −78 °C, 2 h then **X** (see table), −78 °C, 1 h then acrolein, −78 to 0 °C, 3 h. [[a] a 28:21:33:18 mixture of **293**, **294**, **295** and **296** was also isolated in 48% total yield].

In the "stepwise" protocol, treatment of the lithium (*E*)-β-amino enolate[5] **198**, obtained upon deprotonation of **182** with LDA, with $ZnCl_2$, $ZrCp_2Cl_2$ or $TiCl(O^iPr)_3$ gave only starting material, while treatment of (*E*)-**198** with $MoCp_2Cl_2$ gave a 22:1:39:38 mixture of **293**, **294**, **295** and **296**, respectively (Scheme 49).



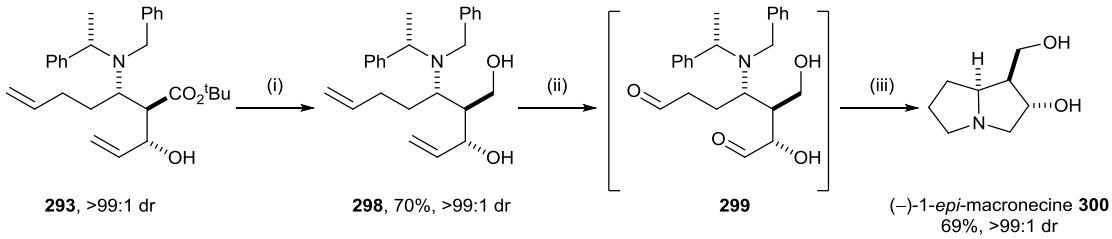
X	Conversion %	dr [293:294:295:296]
$TiCl(OiPr)_3$	<5	-
$ZnCl_2$	<5	-
$ZrCp_2Cl_2$	<5	-
$MoCp_2Cl_2$	>95	22:1:39:38

Scheme 49. *Reagents and Conditions:* (i) LDA, THF, 0 °C, 1 h; (ii) **X** (see table), −78 °C, 1 h then acrolein, −78 °C to 0 °C, 3 h.

4.4. Syntheses of 1-hydroxymethyl-2-hydroxypyrrolizidines

With the four enantiopure diastereoisomeric products **293**–**296** in hand, attention was turned to the syntheses of the corresponding 1-hydroxymethyl-2-hydroxypyrrolizidines. Reduction of β-amino ester **293** with $LiAlH_4$ gave aminodiol **298** in 70% yield and >99:1 dr. The relative configuration within **298** was confirmed by single crystal X-ray diffraction analysis[6]

of **298**·HBF_4 and the absolute (1*S*,2*S*,1'*R*,α*S*)-configuration of **298** was assigned by reference to the known (*S*)-configuration of the α-methylbenzyl fragment (Figure 36). This assignment also secured the configuration of the β-amino ester precursor **293**. Submission of **298** to the ozonolysis conditions, followed by hydrogenolytic *N*-deprotection and *in situ* double reductive cyclisation of dialdehyde **299** gave, after treatment with HCl followed by purification on DOWEX ion exchange resin, (–)-1-*epi*-macronecine **300** in 69% yield and >99:1 dr (Scheme 50). No NMR spectroscopic data for (–)-1-*epi*-macronecine **300** have been reported to date, although the melting point and specific rotation for this sample of **300** were in good agreement with literature data {mp 90–91 °C; lit.[7] mp 91–93 °C; $[\alpha]_D^{20}$ –96.0 (*c* 0.1 in EtOH); lit.[8] $[\alpha]_D^{25}$ –115 (EtOH); lit.[7] $[\alpha]_D^{25}$ –114 (*c* 0.9 in EtOH)}.



Scheme 50. *Reagents and Conditions*: (i) $LiAlH_4$, THF, –78 °C to rt, 16 h; (ii) HCl (2.0 M in Et_2O) then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 2 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 24 h.

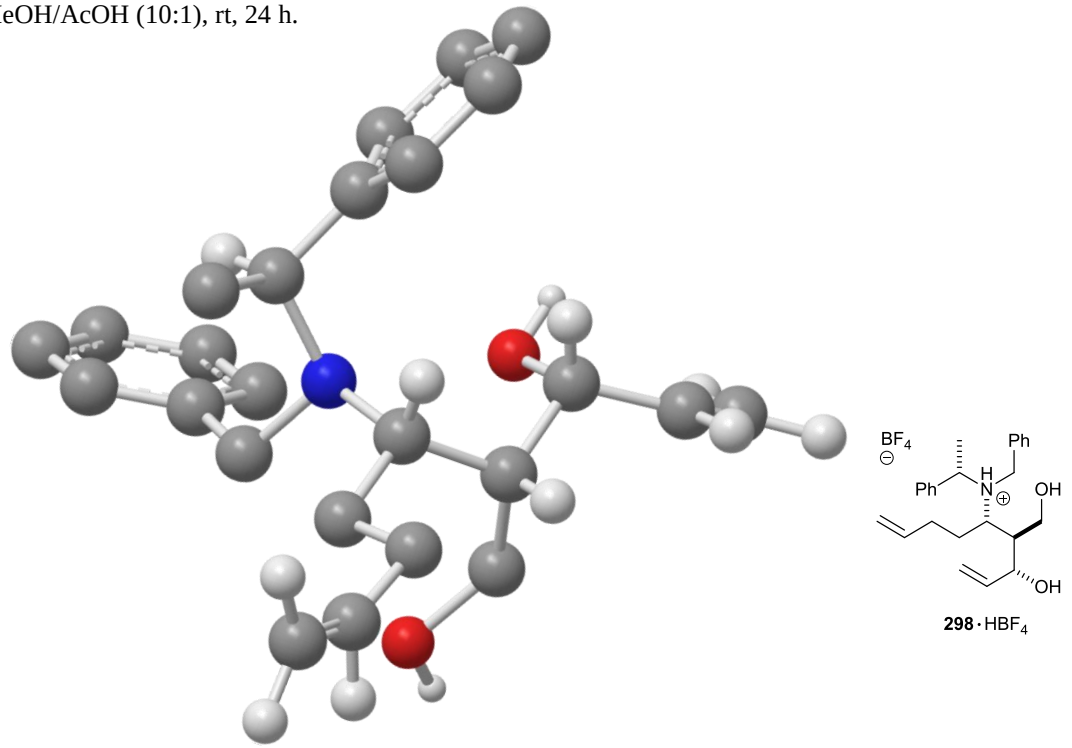
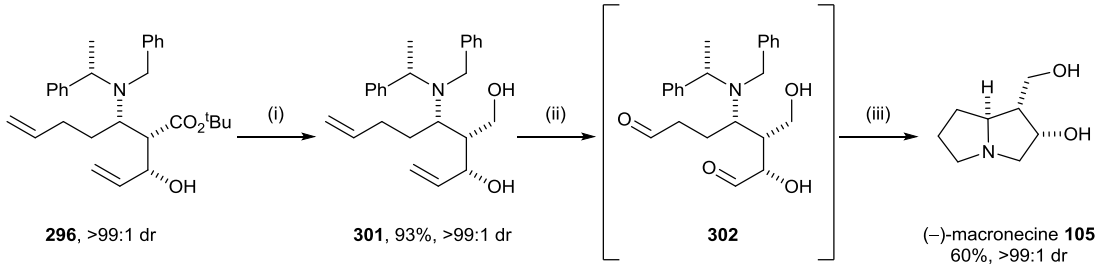


Figure 36. X-ray crystal structure of (1*S*,2*S*,1'*R*,α*S*)-**298**·HBF_4 (selected H atoms and the BF_4 counterion are omitted for clarity).

Similarly, reduction of β-amino ester **296** with $LiAlH_4$ at −78 °C gave aminodiol **301** in 93% yield and >99:1 dr after chromatographic purification. Submission of **301** to the ozonolysis conditions upon prior *N*-protection with HCl gave dialdehyde **302** which was submitted to the hydrogenoytic *N*-deprotection and *in situ* double reductive cyclisation. Purification of **105** upon treatment with HCl followed by ion DOWEX ion exchange resin, gave (−)-macronecine **105** in 60% yield and >99:1 dr (Scheme 51). The melting point and specific rotation for this sample of **105** were in good agreement with literature data {mp 120–123 °C; lit.[9] mp 124–127 °C; lit.[10] mp 128–129 °C; lit.[11] mp 126–128 °C; $[\alpha]_D^{20}$ –40.0 (*c* 0.6 in EtOH); lit.[9] $[\alpha]_D^{20}$ –49.4 (*c* 1.0 in EtOH); lit.[12] $[\alpha]_D^{20}$ –42.1 (*c* 1.0 in EtOH); lit.[10] for *ent*-**105**: $[\alpha]_D^{20}$ +42.7 (*c* 1.0 in EtOH); lit.[11] for *ent*-**105**: +49.3 (*c* 0.5 in EtOH)}. Comparison of the ^1H and ^{13}C NMR spectroscopic data for this synthetic sample of (−)-macronecine **105** showed excellent agreement with data previously reported[13] for both enantiomerically pure[10] and racemic[13a,b] samples of **105** (Tables 9 and 10). Moreover, the relative configuration within **105** was confirmed by single crystal X-ray diffraction analysis[6] and the absolute (1*R*,2*S*,7a*S*)-configuration of **105** was assigned by the reference to the known (*S*)-configuration of the C(7a)-stereogenic center[14] (Figure 37). This assignment also established the configurations of β-amino ester **296** and aminodiol **301**.



Scheme 51. *Reagents and Conditions*: (i) $LiAlH_4$, THF, –78 °C to rt, 16 h; (ii) HCl (2.0 M in Et_2O) then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 2 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 24 h.

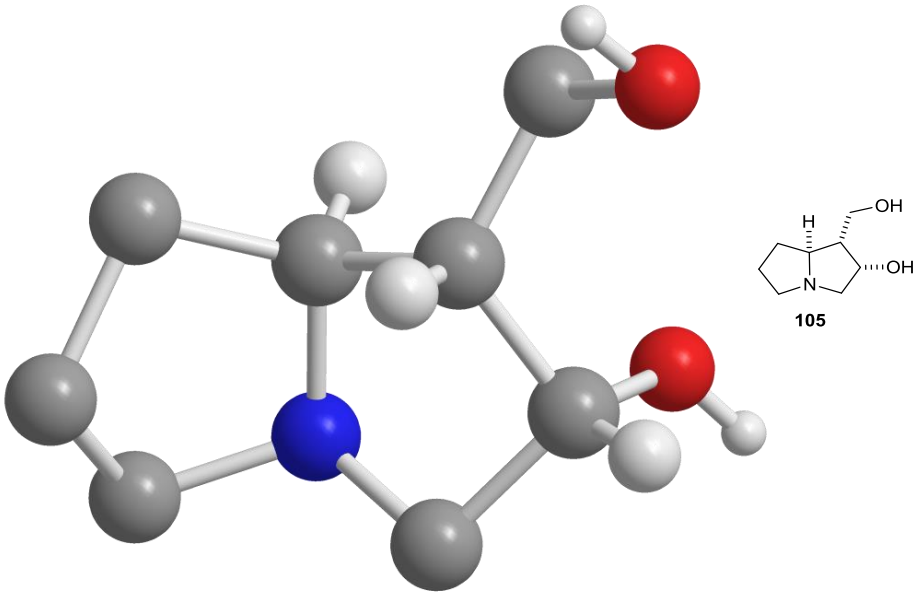


Figure 37. X-ray crystal structure of (1*R*,2*S*,7a*S*)-**105** [(–)-macronecine] (selected H atoms are omitted for clarity).

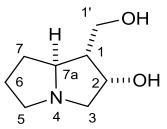
^{1}H NMR data for macronecine 105 				
H	**This study** [a](400 MHz)	**Denmark**[10] [b](500 MHz)	**Sarkar**[13a] [c](400 MHz)	**Yoda**[13b] [c](300 MHz)
C(1)*H*	1.92-2.05 m	1.95 dq (*J* 12.2, 7.2)	1.63−2.04 m	1.97 m
C(2)*H*	4.51 t (*J* 3.7)	4.49 t (*J* 3.7)	4.36−4.54 m	4.50 t (*J* 3.9)
C(3)H_A	2.71 dd (11.0, 3.7)	2.67 dd (*J* 11.0, 3.4)	2.40−2.73 m	2.71 dd (*J* 11.4, 3.9)
C(3)H_B	3.23 d (*J* 11.0)	3.17 d (*J* 11.0)	3.18 d (*J* 11.0)	3.22 d (*J* 11.4)
C(5)H_A	2.56-2.65 m	2.57 m	2.40−2.73 m	2.60 dt (J 10.8, 6.3)
C(5)H_B	3.01 dt (*J* 11.0, 6.6)	2.95 td (*J* 10.6, 6.5)	2.80−3.04 m	3.00 dt (*J* 10.8, 6.6)
C(6)H_A	1.78-1.90	1.76−1.86 m	1.63−2.04 m	1.77−1.90 m
C(6)H_B	1.78-1.90	1.76−1.86 m	1.63−2.04 m	1.77−1.90 m
C(7)H_A	1.55 dq (*J* 11.9, 6.1)	1.52 dq (*J* 12.2, 6.0)	1.39−1.63 m	1.54 m
C(7)H_B	1.78-1.90	1.76−1.86 m	1.63−2.04 m	1.77−1.90 m
C(7a)*H*	3.56-3.65 m	3.51−3.57 m	3.39−3.60 m	3.59 m
C(1')H_A	3.80−3.92 m	3.82−3.88 m	3.71−3.85 m	3.84 dd (*J* 11.4, 6.9)
C(1')H_B	3.80−3.92 m	3.82−3.88 m	3.71−3.85 m	3.91 dd (*J* 11.4, 4.8)

Table 9. Comparison of ^{1}H NMR spectroscopic data in $CDCl_3$ for macronecine **105** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz]. [[a]data for (–)-macronecine **105**; [b]data for (+)-macronecine **105**; [c]data for (±)-macronecine **105**].

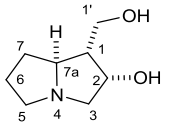
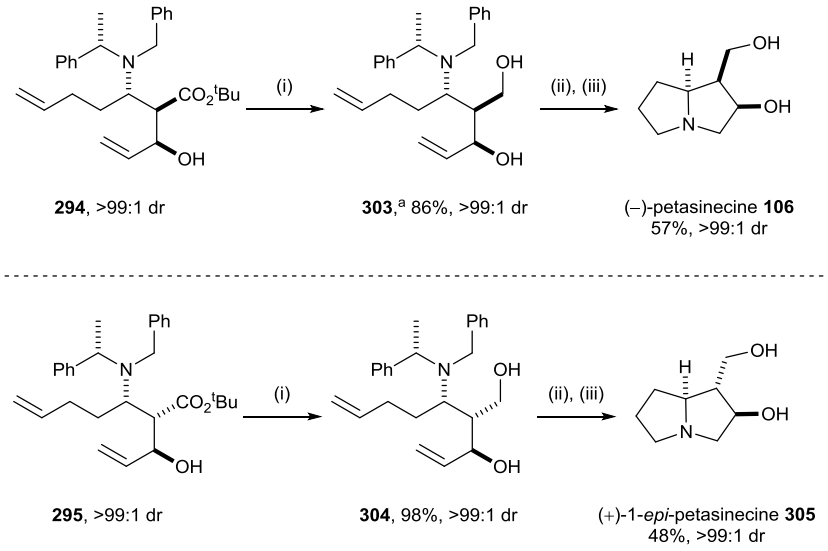
^{13}C NMR data for macronecine 105 				
C	**This study** [a](100 MHz)	**Denmark**[10] [b](125 MHz)	**Sarkar**[13a] [c](50 MHz)	**Yoda**[13b] [c](75 MHz)
C(1)	52.4	52.5	52.5	52.2
C(2)	75.6	75.3	75.1	75.6
C(3)	62.9	62.9	63.0	62.8
C(5)	54.9	55.0	54.9	54.7
C(6)	25.5	25.4	25.4	25.5
C(7)	31.2	31.2	31.2	31.0
C(7a)	64.2	64.0	63.9	64.5
C(1')	60.9	60.6	60.4	60.8

Table 10. Comparison of ^{13}C NMR spectroscopic data in $CDCl_3$ for (–)-macronecine **105** [chemical shifts (δ_C) are reported in ppm]. [[a]data for (–)-macronecine **105**; [b]data for (+)-macronecine **105**; [c]data for (±)-macronecine **105**].

The same sequence of reactions was applied to **294** and **295**; reduction of **294** with $LiAlH_4$ gave **303** in 86% yield as a single diastereoisomer (>99:1 dr). However, a superior yield of **303** was obtained from β-amino ester **182** following boron-mediated aldol reaction of **182** and acrolein, and reduction of a 55:45 mixture of **294** and **295**, respectively, which gave **303** in 31% yield (from **182**) after chromatographic purification. Ozonolysis of **303**·HCl followed by hydrogenoytic *N*-deprotection and *in situ* double reductive cyclisation gave, after purification on DOWEX ion exchange resin, (–)-petasinecine **106** in 57% yield and >99:1 dr. The melting point and specific rotation for this sample of **106** were in good agreement with literature data {mp 128–130 °C; lit.[10] mp 132–134 °C; lit.[15] mp 134–135 °C; lit.[16] mp 135 °C; lit.[17] mp 132–134 °C; $[\alpha]_D^{20}$ –26.0 (*c* 0.8 in EtOH); lit.[15] $[\alpha]_D^{25}$ –32.0 (*c* 1.3 in EtOH); lit.[16] $[\alpha]_D^{20}$ –21.0 (*c* 0.3 in EtOH); lit.[17] $[\alpha]_D^{20}$ –20 (*c* 0.3 in EtOH); lit.[18] $[\alpha]_D^{25}$ –27 (*c* 0.3 in EtOH); lit.[10] for *ent*-**106**: $[\alpha]_D^{20}$ +24.8 (*c* 0.25 in EtOH)}. Similarly, reduction of the ester functionality within β-amino ester **295** afforded aminodiol **304** in 98% yield and >99:1 dr. Ozonolysis of **304**·HCl followed by hydrogenoytic *N*-deprotection and *in situ* double reductive cyclisation gave, after purification on DOWEX ion exchange resin, (+)-1-*epi*-petasinecine **305** in 48% yield and >99:1 dr (Scheme 52). Also in this case, the melting point and specific rotation for this sample of **305** were in good agreement with literature data {mp 98–100 °C; lit.[13b] mp 94–96 °C; lit.[19]

mp 104–105 °C; lit.[15] mp 114–115 °C $[\alpha]_D^{20}$ +30.0 (*c* 0.8 in EtOH); lit.[15] $[\alpha]_D^{25}$ +40.0 (*c* 1.0 in EtOH); lit.[19] for *ent*-**305** $[\alpha]_D^{25}$ −29.4 (*c* 0.5 in EtOH)}.



Scheme 52. *Reagents and Conditions*: (i) $LiAlH_4$, THF, –78 °C to rt, 16 h; (ii) HCl (2.0 M in Et_2O) then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 2 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 24 h. [[a]**303** was also isolated in 31% yield (from **182**) and >99:1 dr].

The configurations of **106** and **305** were assigned by comparison of their ^{1}H and ^{13}C NMR spectroscopic data with those in the literature for (−)-petasinecine **106** and (+)-1-*epi*-petasinecine **305**. Crucially, the ^{1}H and ^{13}C NMR spectroscopic data reported for (−)-petasinecine **106** displayed excellent agreement with literature data (Tables 11 and 12). Comparison of the ^{1}H and ^{13}C NMR spectroscopic data previously reported for (+)-1-*epi*-petasinecine **305** also showed good agreement with the data observed for this sample of (+)-1-*epi*-petasinecine **305** (Tables 13 and 14). These assignments therefore also established the configurations of the synthetic precursors **294**, **295**, **303** and **304**.

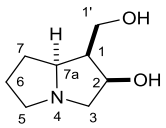
^{1}H NMR data for petasinecine 106 						
	MeOH-d_4			**$CDCl_3$**		
H	**This study** [a](400 MHz)	**Mulzer**[16] [a](250 MHz)	**Denmark**[10] [b](500 MHz)	**This study** [a](400 MHz)	**Ma**[18] [a](500 MHz)	[a]**Yamada**[17]
C(1)*H*	2.25−2.35 m	2.22−2.37 m	2.31 m	2.34−2.43 m	2.40 m	1.50−3.70 m
C(2)*H*	4.27 t (*J* 3.7)	4.29 m	4.30 dt (*J* 4.4, 1.25)	4.47−4.54 m	4.53 m	4.54 dt (*J* 5.5, 5.0)
C(3)H_A	2.90 d (*J* 12.7)	2.79 ddd (*J* 12.7, 1.25, 0.5)	2.83 dd (*J* 12.7, 1.2)	2.69−2.82 m	2.75 m	1.50−3.70 m
C(3)H_B	3.19 dd (*J* 12.7, 3.7)	3.10 ddd (*J* 12.7, 5.0, 4.5)	3.13 dd (*J* 12.7, 3.9)	3.09−3.17 m	3.11 m	1.50−3.70 m
C(5)H_A	2.90−3.00 m	2.86−2.95 m	2.91 dt (*J* 9.9, 5.7)	2.69−2.82 m	2.75 m	1.50−3.70 m
C(5)H_B	3.32 t (*J* 7.9)	3.19 ddd (*J* 12.7, 5.0, 4.5)	3.21 ddd (*J* 9.5, 7.0, 2.5)	3.24 dd (*J* 11.7, 5.0)	3.23 dd (*J* 11.6, 7.1)	1.50−3.70 m
C(6)H_A	1.61−1.73 m	1. 57−1.81 m	1. 67−1.79 m	1.62−1.89 m	1.66−1.99 m	1.50−3.70 m
C(6)H_B	1.93−2.08 m	1.87−2.08 m	1.96−2.04 m	1.62−1.89 m	1.66−1.99 m	1.50−3.70 m
C(7)H_A	1.75−1.83 m	1. 57−1.81 m	1. 67−1.79 m	1.62−1.89 m	1.66−1.99 m	1.50−3.70 m
C(7)H_B	1.93−2.08 m	1.87−2.08 m	1.96−2.04 m	1.93−2.02 m	1.66−1.99 m	1.50−3.70 m
C(7a)*H*	3.75−3.90 m	3.46−3.62 m	3.59 m	3.45−3.53 m	3.48 m	1.50−3.70 m
C(1')H_A	3.68 dd (*J* 11.0, 7.5)	3.76 dd (*J* 7.5, 7.0)	3.76 dd (*J* 10.8, 7.3)	3.82 dd (*J* 10.8, 5.0)	3.86 dd (*J* 10.8, 5.2)	3.89 dd (*J* 11.0, 6.0)
C(1')H_B	3.83 dd (*J* 11.0, 7.3)	3.92 dd (*J* 8.0, 7.5)	3.92 dd (*J* 10.8, 7.3)	3.94 dd (*J* 10.8, 9.3)	3.96 dd (*J* 10.8, 8.8)	3.94 dd (*J* 11.0, 8.0)

Table 11. Comparison of ^{1}H NMR spectroscopic data in MeOH-d_4 and $CDCl_3$ for petasinecine **106** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].[[a]data for **(−)**-petasinecine **106**; [b]data for (+)-petasinecine **106**].

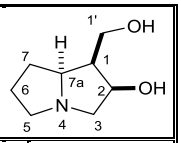
^{13}C NMR data for petasinecine 106 			
C	**This study** [a](100 MHz)	**Denmark**[10] [b](125 MHz)	**Mulzer**[16] [a](63 MHz)
C(1)	49.4	49.7	49.6
C(2)	74.0	74.5	74.3
C(3)	62.9	63.5	63.3
C(5)	58.1	57.8	57.7
C(6)	27.8	27.9	27.8
C(7)	28.5	28.6	28.5
C(7a)	68.8	67.8	67.7
C(1')	59.3	59.8	59.6

Table 12. Comparison of ^{13}C NMR spectroscopic data in MeOH-d_4 for **(−)**-petasinecine **106** [chemical shifts (δ_C) are reported in ppm]. [[a]data for **(−)**-petasinecine **106**; [b]data for (+)-petasinecine **106**].

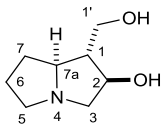
^{1}H NMR data for 1-*epi*-petasinecine 305 			
H	**This study** [a](400 MHz)	**Ha**[19] [b](300 MHz)	**Yoda**[13b] [c](300 MHz)
C(1)*H*	1.89−2.03 m	1. 63−1.92 m	2.31 m
C(2)*H*	4.30−4.38 m	4.30 m	4.33 m
C(3)H_A	2.54 t (*J* 9.1)	2.67 m	2.83 dd (*J* 12.7, 1.2)
C(3)H_B	2.97−3.05 m	3.29 m	3.13 dd (*J* 12.7, 3.9)
C(5)H_A	2.69−2.77 m	2.90 m	2.91 dt (*J* 9.9, 5.7)
C(5)H_B	3.26−3.34 m	3.29 m	3.21 ddd (*J* 9.5, 7.0, 2.5)
C(6)H_A	1.58−1.71 m	1.63−1.92 m	1. 67−1.79 m
C(6)H_B	1.72−1.89 m	1.63−1.92 m	1.96−2.04 m
C(7)H_A	1.72−1.89 m	1.63−1.92 m	1. 67−1.79 m
C(7)H_B	1.89−2.03 m	1.63−1.92 m	1.96−2.04 m
C(7a)*H*	3.42 dd (*J* 9.8, 5.6)	-	3.59 m
C(1')H_A	3.72 dd (*J* 10.7, 6.9)	3.67 dd (*J* 11.0, 5.0)	3.59 m
C(1')H_B	3.87 dd (*J* 10.7, 4.5)	3.84 dd (*J* 11.0, 4.0)	3.76 dd (*J* 10.8, 7.3)

Table 13. Comparison of ^{1}H NMR spectroscopic data in $CDCl_3$ for 1-*epi*-petasinecine **305** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz]. [[a]data for (+)-1-*epi*-petasinecine **305**; [b]data for (–)-1-*epi*-petasinecine **305**; [c]data for (±)-1-*epi*-petasinecine **305**].

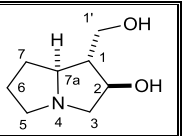
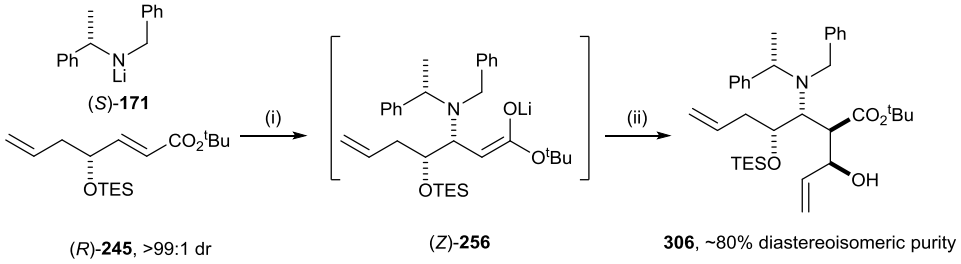
^{13}C NMR data for 1-*epi*-petasinecine 305 			
C	**This study** (100 MHz)	**Ha**[19] [a](75 MHz)	**Yoda**[13b] [b](75 MHz)
C(1)	56.2	56.1	56.2
C(2)	74.7	74.5	74.7
C(3)	62.0	62.9	63.0
C(5)	56.5	56.3	56.4
C(6)	26.4	26.3	26.3
C(7)	33.4	33.3	33.3
C(7a)	67.6	67.5	67.7
C(1')	63.1	61.8	61.9

Table 14. Comparison of ^{13}C NMR spectroscopic data in MeOH-d_4 for 1-*epi*-petasinecine **305** [chemical shifts (δ_C) are reported in ppm]. [[a]data for (+)-1-*epi*-petasinecine **305**; [b]data for **(–)**-1-*epi*-petasinecine **305**; [c]data for (±)-1-*epi*-petasinecine **305**].

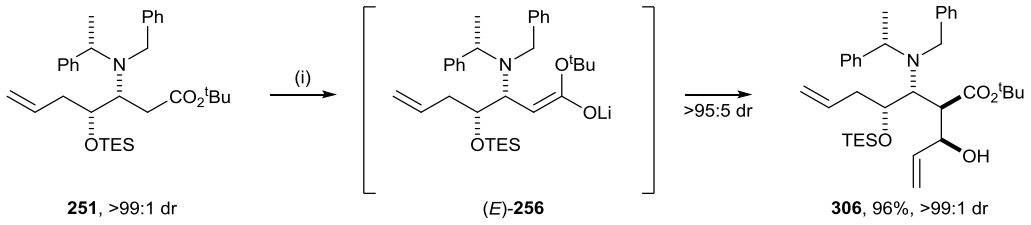
4.5. Synthesis of (+)-2-*epi*-rosmarinecine

Following the successful syntheses of the four diastereoisomeric 1-hydroxymethyl-2-hydroxypyrrolizidines, it was decided to investigate the synthesis of 1-hydroxymethyl-2,7-dihydroxypyrrolizidines using the same sequence of reactions, starting from enantiopure γ-silyloxy-α,β-unsaturated ester (*R*)-**245**. Given the results obtained upon enolate allylation of the (*R*)-**245** discussed in Chapter 3, it was decided to investigate the aldol reactions of lithium β-amino enolates (*Z*)-**256** and (*E*)-**256** which result from either conjugate addition of (*S*)-**171** to α,β-unsaturated ester (*R*)-**245**, or upon deprotonation of the β-amino ester **251** with LiTMP, respectively. Upon addition of acrolein to enolate (*Z*)-**256**[20] a complex mixture of products was observed, in which **306** was present as the major species (Scheme 53).



Scheme 53. *Reagents and Conditions:* (i) THF, −78 °C, 2 h, then acrolein.

However, treatment of γ-silyloxy-β-amino ester **251** with LiTMP in THF at 0 °C gave lithium (*E*)-β-amino enolate[21] **256**; the geometry of **256** was confirmed by trapping the enolate with TESCl and analysing the resultant silyl ketene acetal by ^{1}H NMR and NOESY spectroscopy. Subsequent addition of acrolein gave, surprisingly, only one product, out of the four possible diastereoisomers, in >95:5 dr. Chromatographic purification afforded **306** in 96% yield and >99:1 dr (Scheme 54). Attempts to change of the conditions (i.e., base, metal counterion or reaction temperature) did not dramatically change the diastereoisomeric outcome. The absolute configuration of **306** was later established by single crystal X-ray diffraction analysis of a derivative (*vide infra*).



Scheme 54. *Reagents and Conditions:* (i) LiTMP, THF, 0 °C, 1 h; (ii) acrolein, −78 °C to 0 °C, 3 h.

The high diastereoselectivity in this aldol reaction, giving **306** as the only product, suggests a well-defined transition state which is much lower in energy than the other possibilities. Assuming a reactive conformation for enolate (*E*)-**256** which minimises the 1,3-allylic strain (i.e., the C(3)-H atom lies parallel to the C(1)-O^{t}Bu bond) then the stereochemical outcome of this reaction with acrolein is consistent with addition of the less hindered face of the enolate (i.e., opposite to the bulky amino group). Invoking a chelated Zimmerman-Traxler type transition state,[22] then gives two possibilities: **307** and **308**. Presumably, **307** is disfavoured by large *syn*-pentane interactions between the C(3)-R' bulky substituent and the pseudo-equatorial vinyl group of the aldehyde. Placing the vinyl group of acrolein pseudo-axial, as in **308**, relieves this strain and gives rise to **306**. It is the delicate interplay between the various *syn*-pentane type interactions which, presumably, renders the aldol reactions of enolates (*E*)-**198** and (*Z*)-**198** only modestly selective.The configuration of **251** also allows a favourable positioning of the C(4) substituents in the transition state, placing the C(4)*H* "inside" towards the aldehyde when the silyloxy bulky substituent is antiperiplanar to the C(3)*H*. The relative configuration between C(3) and C(4) could be therefore responsible for the good reactivity and stereoselectivity of β-aminoester **251** compared to **250** which showed poor reactivity towards both the allylation[23a] and aldol reactions (Figure 38).

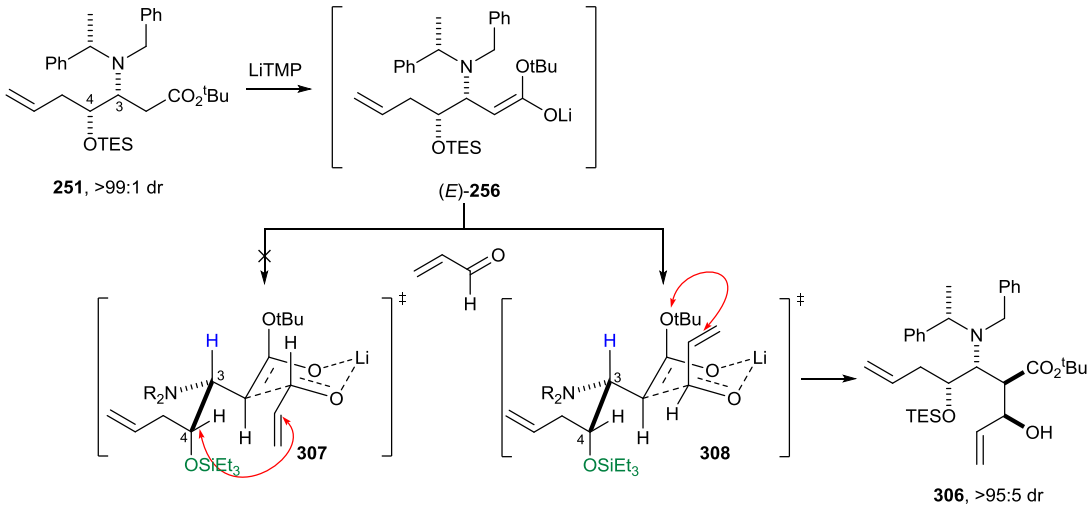
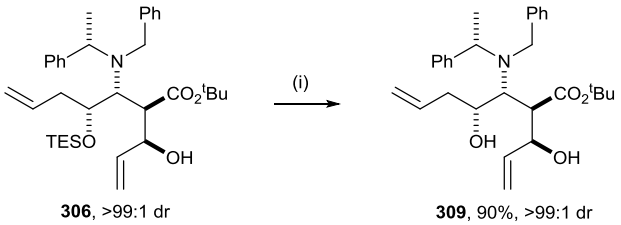


Figure 38. Proposed Zimmermann-Traxler transition state model for the addition of (*E*)-**256** to acrolein.[''↔'' represents steric interaction].

O-Deprotection of **306** with HF in pyridine afforded **309** in 90% yield as a single diastereoisomer (>99:1 dr) after chromatographic purification (Scheme 55). The relative configuration within **309** was confirmed by single crystal X-ray diffraction analysis[6] and the

absolute (2*R*,3*R*,4*R*,1'*S*,α*S*)-configuration of **309** was assigned by reference to the known (*S*)-configuration of the α-methylbenzyl fragment and the established (*R*)-configurations of both the C(3) and C(4) stereogenic centres[23b] (Figure 39). This analysis therefore also confirmed the assigned configurations within the *O*-TES substituted precursor **306**.



Scheme 55. *Reagents and Conditions:* (i) HF·py, THF, rt, 18 h.

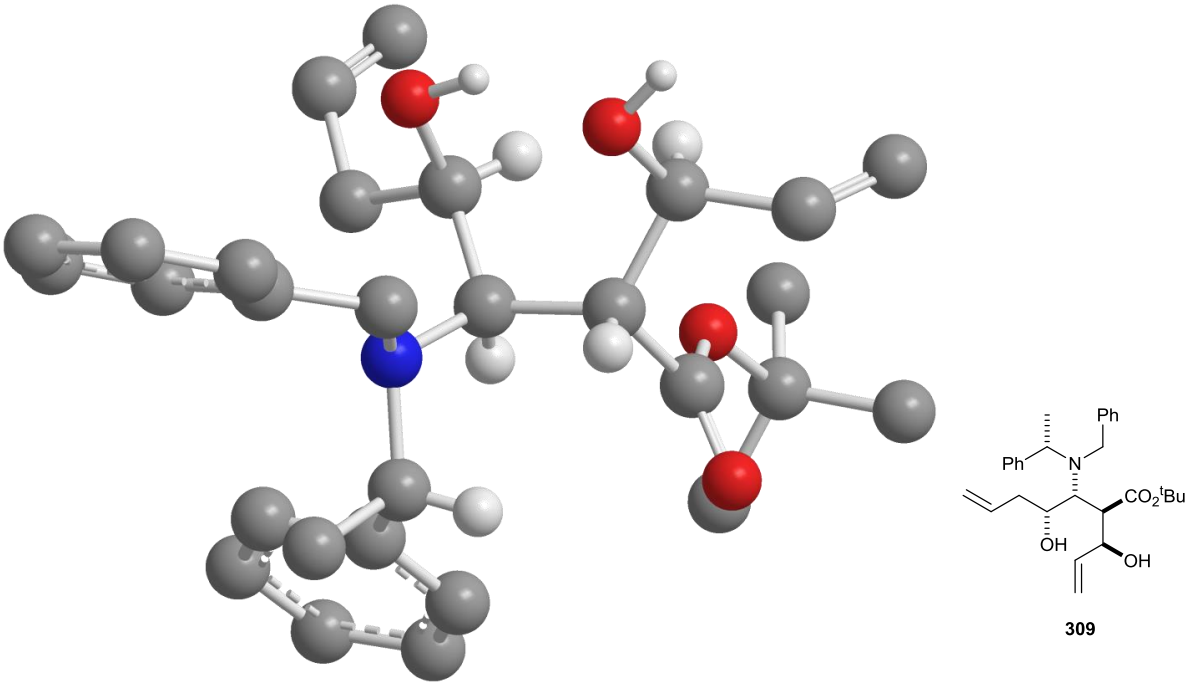
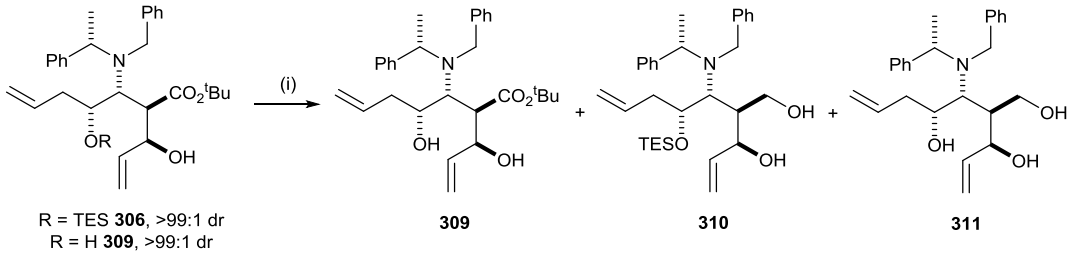


Figure 39. X-ray crystal structure of (2*R*,3*R*,4*R*,1'*S*,α*S*)-**309** (selected H atoms are omitted for clarity).

Reduction of β-amino ester **309** with $LiAlH_4$ under the same conditions used for **293–296** (–78 °C to rt, 16 h) gave an impure sample of **311** in 81% yield (~70% purity). Reduction of **309** with DIBAL-H for 24 h (–78 °C to rt) gave poor conversion, while increasing the temperature to 35 °C gave rise to a complex mixture of products. It was decided to attempt the reduction on the *O*-TES protected ester **306**, trying to improve the yield and the purity of the resultant alcohols **310** or **311**; reduction of **306** with $LiAlH_4$ gave **310** in 23% yield along with the formation of triol **311** which was isolated in 30% yield. Decreasing the equivalents of the reducing agent from 5.0 to 1.0 gave *O*-deprotected ester **309** in 28%

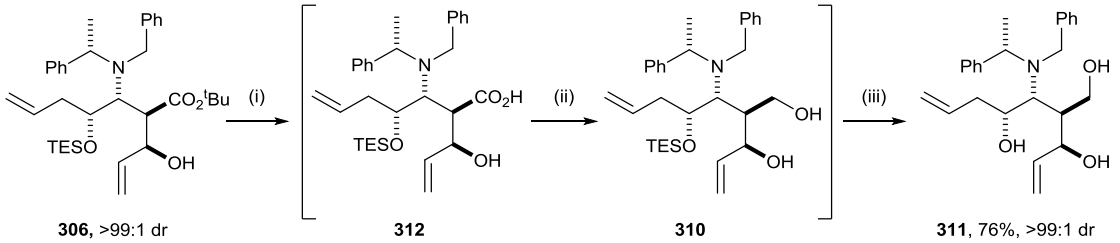
yield and >99:1 dr along with an impure sample of **310** in 9% yield. Reduction of **306** with DIBAL-H gave complete conversion to **310** which was isolated in 23% yield and >99:1 dr; however, the ^{1}H NMR spectrum of **310** showed the presence of impurities (~20% of the total). Attempted one-pot reduction/*O*-deprotection was also attempted, but reduction of **306** with DIBAL-H followed by HF mediated deprotection resulted in a complex mixture containing **311** (~80% purity) in low mass return (Scheme 56). The low conversions and the problematic purification upon reduction of either **306** or **309** required a different route towards triol **311**.



R	Reducing agent	equiv	T (°C)	309:310:311	Yield (%)		Purity %	
					310	311	310	311
H	$LiAlH_4$	4.0	–78 °C to rt	0:0:100		81	-	70
H	DIBAL-H	10.0	0 °C to 35 °C	-	-	-	-	-
TES	$LiAlH_4$	5.0	–78 °C to rt	10:54:46	23	30	90	90
TES	$LiAlH_4$	1.0	–78 °C to rt	38:62:0	37[a]	-	90	-
TES	DIBAL-H	5.0	0 °C to rt	0:100:0	23	-	80	-

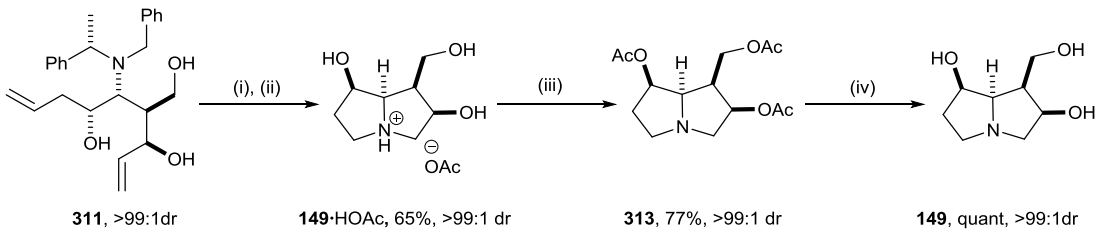
Scheme 56. *Reagents and Conditions*: (i) see table, THF, 24 h. [[a] **309** was also isolated in 28% yield and >99:1 dr]

It was decided to hydrolyse the ester functionality within **306** and submit the resultant carboxylic acid to reduction and *O*-deprotection to obtain triol **311**. Hydrolysis of β-amino ester **306** with TFA gave carboxylic acid **312**, which was used as an intermediate without further purification in the next step (attempted column chromatography of **312** gave rise to unidentifiable products and poor mass return). Reduction of **312** was achieved with $LiAlH_4$ at reflux in THF followed by HF mediated *O*-deprotection which gave **311** in 76% yield (over 3 steps) and >99:1 dr (Scheme 57).

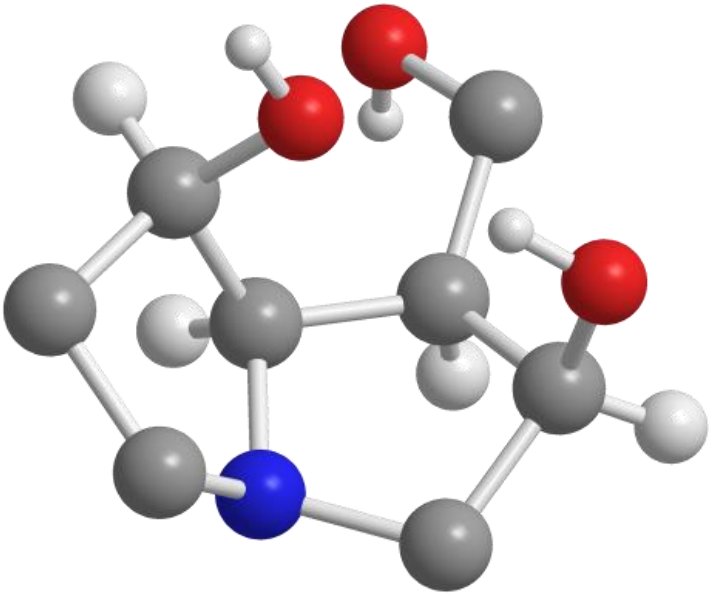


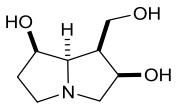
Scheme 57. *Reagents and Conditions:* (i) TFA, CH_2Cl_2, 16 h, rt; (ii) $LiAlH_4$, THF, –78 °C to rt, 16 h; (iii) HF·py, THF, rt, 18 h.

Ozonolysis of **311**·HCl followed by hydrogenolytic *N*-deprotection and *in situ* double reductive cyclisation gave **149**·HOAc which was isolated in 65% yield upon chromatographic purification. Difficulties in the purification of this type of compound have been previously reported in literature,[24] so to simplify the purification of **149**, it was decided to treat **149**·HOAc with Ac_2O in pyridine, which yielded **313** in 77% isolated yield and >99:1 dr. Global deprotection of the masked hydroxyl functionalities within **313** in the presence of K_2CO_3 revealed the 1-hydroxymethyl-2,7-dihydroxypyrrolizidine, (+)-2-*epi*-rosmarinecine **149**, which was obtained in quantitative yield after chromatographic purification (Scheme 58). The relative configuration within **149** was confirmed by single crystal X-ray diffraction analysis[6] and the absolute (1*S*,2*R*,7*R*,7a*R*)-configuration within **149** was assigned by the reference to the previously established (*R*)-configurations of the C(7) and C(7a) stereogenic centers[23] (Figure 40). Comparison of the ^{1}H and ^{13}C NMR spectroscopic data for this sample of (+)-2-*epi*-rosmarinecine **149** with those reported by Chakraborty *et al.*[25] for a sample of (±)-2-*epi*-rosmarinecine **149** revealed several discrepancies; the major differences in the ^{1}H-NMR spectroscopic data can be observed for the C(3)*H* and C(5)*H*, which differ in both multiplicity and chemical shifts, and for C(6)H_2 and C(7a)*H* and C(7)*H* which display a difference of almost 0.5 ppm in the chemical shift. Similarly, the ^{13}C NMR spectroscopic data shows important differences in chemical shifts for the *C*(2), *C*(7), *C*(7a) and *C*(1') resonances (Tables 15 and 16). The origin of these discrepancies is unclear, although the stereochemical assignment of this sample of (+)-2-*epi*-rosmarinecine **149** remains secure.



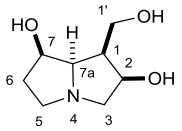
Scheme 58. *Reagents and Conditions*: (i) HCl (2.0 M in Et_2O) then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, min then polymer supported PPh_3, rt, 2 h; (ii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 24 h; (iii) Ac_2O, Py, DMAP, CH_2Cl_2, rt, 16 h; (iv) K_2CO_3, MeOH, rt, 16 h.

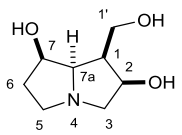




149

Figure 40. X-ray crystal structure of (1*S*,2*R*,7*R*,7a*R*)-**149** [(+)-2-*epi*-rosmarinecine] (selected H atoms are omitted for clarity).

^{1}H NMR data for 2-*epi*-rosmarinecine 149 		
H	**This study (+)-149** (400 MHz)	**Chakraborty[25] (±)-149** (500 MHz)
C(1)*H*	2.40−2.50 m	2.68 m
C(2)*H*	4.13−4.21 m	4.45 m
C(3)H_A	2.70−2.83 m	3.86 dd (*J* 11.5, 6.0)
C(3)H_B	3.08 dd (*J* 13.4, 4.0)	3.08 dd (*J* 11.5, 7.9)
C(5)H_A	2.70−2.83 m	3.35 dd (*J* 11.4, 6.4)
C(5)H_B	3.14−3.23 m	3.81-3.74 m
C(6)H_A	1.71−1.92 m	2.22-2.34 m
C(6)H_B	1.71−1.92 m	2.22-2.34 m
C(7)*H*	4.13−4.21 m	4.60 m
C(7a)*H*	3.49 dd (*J* 9.1, 3.6)	4.03 dd (*J* 7.4, 5)
C(1')H_A	3.81 dd (*J* 11.0, 6.3)	3.81-3.74 m
C(1')H_B	3.95 dd, (*J* 11.1, 8.5)	3.81-3.74 m

^{13}C NMR data for 2-*epi*-rosmarinecine 149 		
H	**This study (+)-149** (100 MHz)	**Chakraborty[25] (±)-149** (125 MHz)
C(1)	47.1	48.4
C(2)	70.6	74.7
C(3)	62.0	62.7
C(5)	53.4	55.8
C(6)	36.1	37.4
C(7)	71.5	75.4
C(7a)	69.8	72.3
C(1')	57.0	62.1

Tables 15 and 16. Comparison of ^{1}H and ^{13}C NMR data in D_2O for (+)-2-*epi*-rosmarinecine **149**[chemical shifts (δ_H and δ_C) are reported in ppm and coupling constants (*J*) in Hz].

4.6. Summary

The syntheses of four diastereoisomeric 1-hydroxymethyl-2-hydroxypyrrolizidines and one 1-hydroxymethyl-2,7-dihydroxypyrrolizidine have been achieved using aldol reactions of β-amino enolates and a double reductive cyclisation as the key steps. Aldol reaction of the β-amino enolates resulting from either a "tandem" or a "stepwise" protocol [starting from either α,β-unsaturated ester **314** (X = H) or β-amino ester **315** (X = H), respectively] gave all four possible diastereoisomers of **316** (X = H) each isolated in >99:1 dr. In each case, reduction of the ester functionality followed by ozonolysis, hydrogenolytic *N*-debenzylation and *in situ* double reductive cyclisation gave (–)-1-*epi*-macronecine **300**, (–)-petasinecine **106**, (+)-1-*epi*-petasinecine **305** and (–)-macronecine **105** in 9, 14, 19 and 20% yield, respectively, from commercially available starting materials, as single diastereoisomers in each case. Alternatively, the aldol reaction of β-amino ester **315** (X = OTES) proved to be highly diastereoselective, giving only one diastereoisomeric product. Ester hydrolysis of **316** (X = OTES) followed reduction and *O*-deprotection gave triol **311** which was submitted to oxidative cleavage, hydrogenolytic *N*-debenzylation and *in situ* double reductive cyclisation to afford (+)-2-*epi*-rosmarinecine **149** in 21% yield from commercially available starting materials (Figure 41).

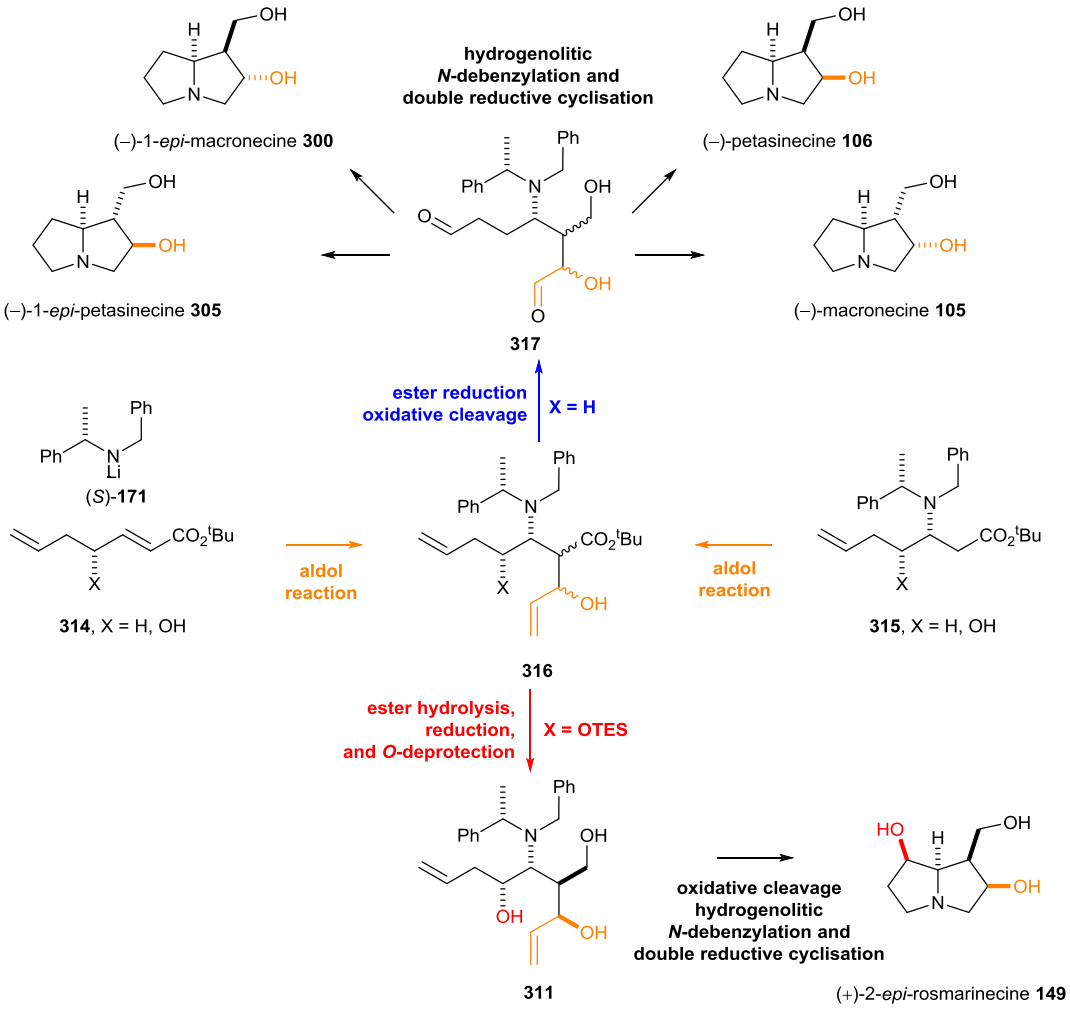


Figure 41. Summary of syntheses of the 1-hydroxymethyl-2-hydroxypyrrolizidines **105**, **106**, **300**, and **305** and 1-hydroxymethyl-2,7-dihydroxypyrrolizidine **149**.

4.7. Conclusions and future work

The syntheses of ten 1-hydroxymethylpyrrolizidines have been achieved via efficient and broadly applicable methodology employing the highly diastereoselective lithium amide conjugate addition reaction followed by either allylation or aldol reaction of β-amino enolates as the key steps for the installation of the stereochemistry. Subsequent oxidative cleavage of the olefinic units and *N*-deprotection and *in situ* double reductive cyclisation constructed the azabicyclic ring system. The application of this methodology resulted in the total asymmetric syntheses of (–)-isoretronecanol **82**, (–)-trachelantamidine **83**, (**–**)-hastanecine **129**, (–)-turneforcidine **130**, (–)-platynecine **131**, (–)-1-*epi*-macronecine **300**, (–)-petasinecine **106**, (+)-1-*epi*-petasinecine **305**, (–)-macronecine **105** and (+)-2-*epi*-rosmarinecine **149** (Figure 42).

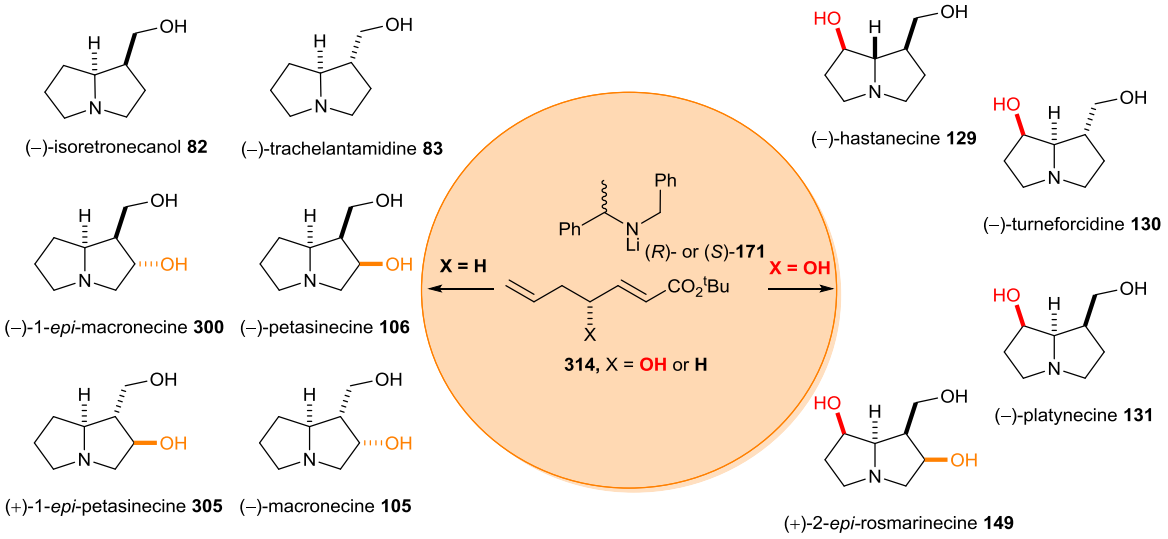


Figure 42. Syntheses of the 1-hydroxymethylpyrrolizidines **82** and **83**, 1-hydroxymethyl-7-hydroxypyrrolizidines **129**-**131**, 1-hydroxymethyl-2-hydroxypyrrolizidines **105**, **106**, **300** and **305**, and 1-hydroxymethyl-2,7,dihydroxypyrrolizidine **149**.

Future work will focus on the application of this methodology in the total asymmetric syntheses of various analogues including polyhydroxylated deoxyfluoro- and deoxyamino-pyrrolizidines, as well as other [x.y.0] azabicyclic scaffolds. For example, a deoxyfluorination[26] protocol could be used in the syntheses of fluorinated pyrrolizidines such as **320**; the use of a protected γ,δ-dihydroxy-α,β-unsaturated ester (which can, for example, be derived from carbohydrates[27]) would afford the 1-hydroxymethyl-6,7-dihydroxypyrrolizidines **319**. Alternatively, the use of a protected γ-amino-α,β-unsaturated ester (which can, for example, be obtained from α-amino acids[28]) would afford the 1-hydroxymethyl-7-

aminopyrrolizidines **321**; the use of but-3-enyl bromide, or 4-butenal in the corresponding enolate allylation/aldol reaction would allow access to polyhydroxylated indolizidines (n = 1, m = 2 or n = 2, m = 1) or quinolizidines (n = m = 2) **322** (Figure 43).

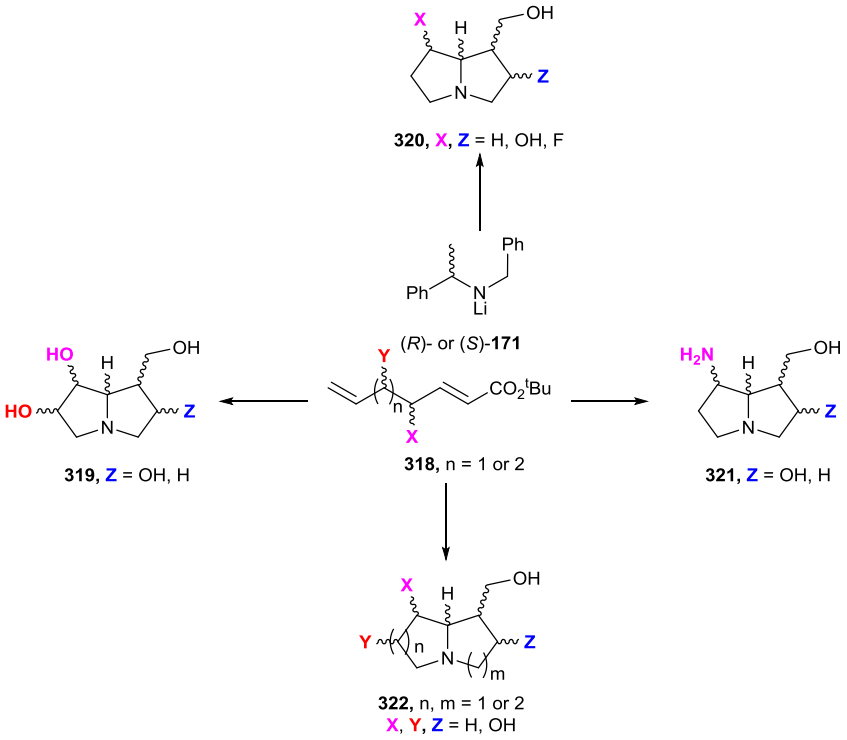


Figure 43. Future work towards differently substituted 1-hydroxymethylpyrrolizidines, indolizidines and quinolizidines **319**–**322**.

4.8. References and notes

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

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(21) The geometry of (*E*)-**256** was confirmed by trapping the lithium enolates with TESCl and analysing the resultant silyl ketene acetals by 1H NMR and NOESY spectroscopic analyses.

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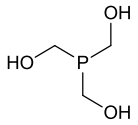
Chapter 5: Experimental

5.1 General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs *et al*.[1] Water was purified by an Elix® UV-10 system. BuLi was supplied as a solution in hexanes and titrated against Ph_2CHCO_2H before use. All other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), 1% aq $KMnO_4$, or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Elemental analyses were recorded by the microanalysis service of the London Metropolitan University, U.K. Melting points were recorded on a Gallenkamp Hot Stage or Leica Gallen III apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film), a KBr disc (KBr) or on a diamond ATR module (ATR), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated and at rt unless otherwise specified. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. When the diastereotopic methyl groups of acetonide and isopropyl functionalities could not be unambiguously assigned, the descriptors *Me*CMe and *Me*CHMe were employed, respectively. In the ^1H and ^{13}C NMR spectra, these descriptors are intended to convey neither that the resonances are attributable to methyl groups that reside on the same, nor on different carbon atoms. Low-resolution mass spectra were recorded on either a Micromass LCT Premier or Agilent Quadrupole 6120 LC/MS spectrometer. Accurate mass measurements were run on a Bruker MicroToF internally calibrated with polyalanine.

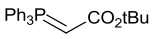
5.2 Experimental data for Chapter 2

Tris(hydroxymethyl)phosphine[2]



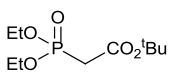
Dry tetrakis(hydroxymethyl)phosphonium chloride[3] (64.0 g, 340 mmol) was dissolved in Et_3N (600 mL). The resultant mixture was stirred and heated at 60 °C for 1 h then allowed to cool to rt, filtered (eluent Et_3N) and concentrated *in vacuo* to give $P(CH_2OH)_3$ as a colourless oil (29.0 g, 69%); δ_H (400 MHz, MeOH-d_4) 4.12 (6H, d, *J* 6.0, $P(CH_2OH)_3$).

tert-Butyl (triphenylphosphoranylidene)acetate 194[4]



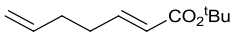
tert-Butyl bromoacetate (37.9 mL, 256 mmol) was added to a stirred solution of PPh_3 (67.1 g, 256 mmol) in EtOAc (500 mL) at rt. After 18 h the white precipitate was collected by vacuum filtration and washed with Et_2O (300 mL). The solid residue was dissolved in CH_2Cl_2 (800 mL), the resultant solution was cooled to 0 °C, and 2.0 M aq NaOH (256 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 400 mL) and the combined organic extracts were dried and concentrated *in vacuo* to a total volume of 100 mL. The resultant mixture was stirred at rt for 16 h, then filtered to give **194** as a white solid (55.0 g, 57%); mp 147–150 °C; δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 2.78 (1H, br s, PC*H*), 7.20–8.10 (15H, m, *Ph*).

tert-Butyl (diethylphosphono)acetate 195



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 **195** as a colourless oil (60.1 g, 94%); δ_H (400 MHz, $CDCl_3$) 1.33 (6H, t, *J* 7.2, $P(OCH_2CH_3)_2$), 1.46 (9H, s, C*Me*$_3$), 2.87 (2H, d, *J* 21.5, PCH_2), 4.08–4.19 (4H, m, $P(OCH_2CH_3)_2$).

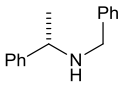
tert-Butyl (*E*)-hepta-2,6-dienoate 181[5]



Method A: A solution of $(COCl)_2$ (1.2 mL, 14.0 mmol) in CH_2Cl_2 (20 mL) at –78 °C was treated with DMSO (1.1 mL, 15.0 mmol). After stirring for 10 min a solution of 4-penten-1-ol **192** (4.37 g, 11.6 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred for 1 h before the addition of Et_3N (3.2 mL, 26.2 mmol). The resultant mixture was allowed to warm to rt, **194** (4.37 g, 11.6 mmol) was added and the mixture was stirred at rt for 18 h. Satd aq Na_2CO_3 (25 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), then dried and concentrated *in vacuo* to give **181** in >99:1 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **181** as a colourless oil (1.50 g, 71%, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 2.18–2.31 (4H, m, C(4)*H*$_2$, C(5)*H*$_2$), 4.99–5.08 (2H, m, C(7)*H*$_2$), 5.74–5.85 (2H, m, C(2)*H*, C(6)*H*), 6.87 (1H, dt, *J* 15.6, 6.7, C(3)*H*).

Method B: MeMgBr (2.86 M in Et_2O, 3.8 mL, 10.7 mmol) was added dropwise to a stirred solution of **195** (2.70 g, 10.7 mmol) in THF (20 mL) at rt and the resultant mixture was stirred for 15 min. 4-Pentenal **193** (1.00 g, 11.9 mmol) was then added dropwise and the reaction mixture was heated at reflux for 2.5 h. The reaction mixture was then allowed to cool to rt, quenched with satd aq NH_4Cl (10 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), then dried and concentrated *in vacuo* to give **181** as a colourless oil (1.62 g, 88%, >99:1 dr).

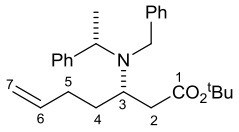
(*S*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine (*S*)-197



Benzaldehyde (41.8 mL, 0.41 mol) was added to a stirred solution of (*S*)-α-methylbenzylamine (*S*)-**196** (50 mL, 0.39 mol) in EtOH (250 mL) at rt. The resultant mixture was heated at reflux for 2 h before being allowed to cool to rt, and then cooled to 0 °C. $NaBH_4$ (14.8 g, 0.39 mol) was added and the resultant suspension was stirred at rt for 3 days. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (150 mL) and CH_2Cl_2 (150

mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were washed with brine (100 mL) dried and concentrated *in vacuo*. The residue was added dropwise to a stirred mixture of Et_2O (150 mL) and aq 10 M HCl (40 mL) at 0 °C. The resultant precipitate was filtered and re-dissolved in CH_2Cl_2, and the resultant solution was dried and concentrated *in vacuo* to afford, after purification *via* recrystallisation (CH_2Cl_2/pentane) (*S*)-**197**·HCl as a white crystalline solid. The free amine was regenerated as required by stirring (*S*)-**197**·HCl with 2.0 M aq NaOH and CH_2Cl_2 (1:1, 500 mL) for 1 h. The aqueous layer was then extracted with two portions of CH_2Cl_2, and the combined organic extracts were dried, filtered and concentrated *in vacuo* to furnish amine (*S*)-**197** (61.3 g, 75%, >99:1 er[6]) as a colourless oil. $[\alpha]_D^{20}$ –49.7 (*c* 1.0 in $CHCl_3$) {lit.[7] $[\alpha]_D^{25}$ –53.6 (*c* 3.8 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.5, C(α)*Me*), 1.60 (1H, br s, N*H*), 3.62 (1H, d, *J* 13.1, NCH_AH_BPh), 3.69 (1H, d, *J* 13.1, NCH_AH_BPh), 3.84 (1H, q, *J* 6.5, C(α)*H*), 7.23–7.40 (10H, m, *Ph*).

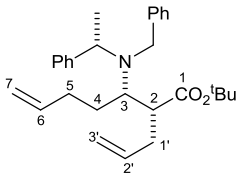
tert-Butyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methyl-benzyl)amino]hept-6-enoate 182[8]



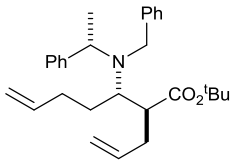
BuLi (2.2 M in hexanes, 0.77 mL, 1.70 mmol) was added dropwise to a stirred solution of (*S*)-**197** (371 mg, 1.76 mmol, >99:1 er) in THF (5 mL) at –78 °C. The resultant mixture was stirred at –78 °C for 30 min, then solution of **181** (200 mg, 1.10 mmol, >99:1 dr) in THF (5 mL) at –78 °C was then added dropwise *via* cannula. The resultant reaction mixture was stirred at –78 °C for 2 h, then 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 Et_2O (10 mL) and 10% aq citric acid solution (10 mL). The aqueous layer was extracted with Et_2O (2 × 20 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 **182** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave **182** as a colourless oil (370 mg, 86%, >99:1 dr); $[\alpha]_D^{20}$ –9.2 (*c* 3.46 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.2, C(α)*Me*), 1.41 (9H, s, CMe_3), 1.49–1.61 (2H, m, C(4)H_2), 1.84–1.90 (2H, m,

C(2)H_2), 2.10−2.19 (1H, m, C(5)H_A), 2.36−2.44 (1H, m, C(5)H_B), 3.33−3.40 (1H, m, C(3)*H*), 3.50 (1H, app d, *J* 14.9, CH_AH$_B$Ph), 3.79−3.85 (2H, m, C(α)*H*, CH$_A$$H_B$Ph), 4.93−4.96 (1H, m, C(7)H_A), 4.99−5.05 (1H, m, C(7) H_B), 5.76−5.86 (1H, m, C(6)*H*), 7.24−7.46 (10H, m, *Ph*).

tert-Butyl (2*R*,3*S*,α*S*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate 199 and _tert_-Butyl (*S*,*S*,*S*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate 200



199



200

Method A: BuLi (2.2 M in hexanes, 1.70 mL, 4.26 mmol) was added dropwise *via* syringe to a stirred solution of (*S*)-**197** (930 mg, 4.40 mmol, >99:1 er) in THF (10 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **181** (500 mg, 2.75 mmol, >99:1 dr) in THF (10 mL) at −78 °C was added dropwise *via* cannula. The resultant reaction mixture was stirred at −78 °C for 2 h, then freshly distilled allyl bromide (700 μL, 8.23 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h, then concentrated *in vacuo*. The residue was partitioned between Et_2O (15 mL) and 10% aq citric acid solution (15 mL). The aqueous layer was extracted with Et_2O (2 × 20 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, 100:1) gavea 85:15 mixture of **199** and **200**, respectively, as a colorless oil (714 mg, 60%, 85:15 dr). Data for mixture: ν_{max} (ATR) 2975, 2933 (C–H), 1721 (C=O), 1640 (C=C); *m/z* (ESI$^+$) 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{39}NNaO_2^+$ ([M+Na]$^+$) requires 456.2873; found 456.2865. Data for **199**: δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.9, C(α)*Me*), 1.31 (9H, s, CMe_3), 1.41–1.43 (1H, m, C(4)H_A), 1.43–1.70 (1H, m, C(4)H_B), 1.81–2.00 (2H, m, C(5)H_A, C(1')H_A), 2.01–2.10 (1H, m, C(1')H_B), 2.14–2.28 (2H, m, C(2)*H*, C(5)H_B), 2.70–2.77 (1H, m, C(3)*H*), 3.74 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 3.85 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.78–4.93 (4H, m, C(7)H_2, C(3')H_2), 5.35–5.48 (1H, m, C(2')*H*), 5.59–5.74 (1H, m, C(6)*H*), 7.06–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7 (C(α)*Me*), 28.1 (CMe_3), 29.8 (*C*(4)), 32.2

(*C*(5)), 36.3 (*C*(1')), 49.5 (*C*(2)), 51.2 (N*C*H_2Ph), 59.1 (*C*(α)), 59.6 (*C*(3)), 80.3 (*C*Me_3), 114.4 (*C*(7)), 116.1 (*C*(3')), 126.6, 127.9, 128.2, 128.3 (*o,m,p-Ph*), 135.9 (*C*(2')), 138.9 (*C*(6)), 142.2, 144.6 (*i-Ph*), 174.3 (*C*(1)). Data for **200**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.21 (3H, d, *J* 6.8, C(α)*Me*), 1.33 (9H, s, C*Me*$_3$), 2.29–2.39 (1H, m, C(2)*H*), 2.91–2.99 (1H, m, C(3)*H*), 4.78–4.93 (4H, m, C(7)*H*$_2$, C(3')*H*$_2$), 5.35–5.48 (1H, m, C(2')*H*), 5.59–5.74 (1H, m, C(6)*H*), 7.06–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 17.6 (C(α)*Me*), 28.2 (C*Me*$_3$), 48.5 (*C*(2)), 50.9 (N*C*H_2Ph), 114.5, 115.7 (*C*(7), *C*(3')), 126.5, 128.4, 128.6, (*o,m,p-Ph*), 136.5, 138.6 (*C*(6), *C*(2')), 142.2, 144.4 (*i-Ph*), 174.0 (*C*(1)).

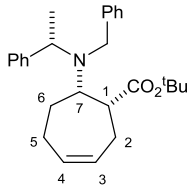
Method B: BuLi (2.2 M in hexanes, 230 μL, 0.50 mmol) was added dropwise to a stirred solution of $^{i}Pr_2NH$ (70 μL, 0.50 mmol) in THF (2.5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then **182** (100 mg, 0.25 mmol, >99:1 dr) in THF (2.5 mL) at −78 °C was added dropwise. The resultant reaction mixture was stirred at −78 °C for 1 h, then freshly distilled allyl bromide (40 μL, 0.50 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo*. The residue was partitioned between Et_2O (5 mL) and 10% aq citric acid solution (5 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to givea 64:36 mixture of **199** and **200**.

Method C: KHMDS (0.5 M in PhMe, 2.50 mL, 1.25 mmol) was added dropwise to a stirred solution of **182** (100 mg, 0.25 mmol, >99:1 dr) in THF (5 mL) at −78 °C was added dropwise. The resultant reaction mixture was stirred at −78 °C for 1 h, then freshly distilled allyl bromide (40 μL, 0.50 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo*. The residue was partitioned between Et_2O (5 mL) and 10% aq citric acid solution (5 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to givea 67:33 mixture of **199** and **200**.

Method D: LiHMDS (1.0 M in THF, 1.25 mL, 1.25 mmol) was added dropwise to a stirred solution of **182** (100 mg, 0.25 mmol, >99:1 dr) in THF (5 mL) at −78 °C was added dropwise. The resultant reaction mixture was stirred at −78 °C for 1 h, then freshly distilled allyl bromide

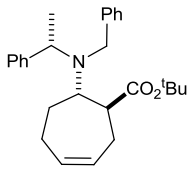
(40 μL, 0.50 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo*. The residue was partitioned between Et_2O (5 mL) and 10% aq citric acid solution (5 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to givea 77:23 mixture of **199** and **200**.

tert-Butyl (1*R*,7*S*,α*S*)-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclohept-3-ene-1-carboxylate 201



Grubbs I catalyst (152 mg, 0.18 mmol) was added to a stirred solution of an 85:15 mixture of **199** and **200** (800 mg, 1.85 mmol, 85:15 dr) in degassed CH_2Cl_2 (60 mL) at 35 °C. The resultant mixture was stirred at 35 °C for 16 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (40 mL) and $P(CH_2OH)_3$ (4.10 g, 33.2 mmol), Et_3N (500 μL, 3.50 mmol) and excess silica gel 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, 75:1) gave **201** as a white solid (320 mg, 43%, >99:1 dr); mp 30–32 °C; $[\alpha]_D^{25}$ –86.4 (*c* 0.25 in $CHCl_3$); ν_{max} (ATR) 1723 (C=C), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.6, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 1.70–1.84 (2H, m, C(2)H_A, C(6)H_A), 1.85–1.96 (1H, m, C(5)H_A), 2.18–2.34 (3H, m, C(2)H_B, C(5)H_B, C(6)H_B), 2.47–2.52 (1H, m, C(1)*H*), 2.81 (1H, dt, *J* 12.0, 3.1, C(7)*H*), 3.82 (1H, d, *J* 14.5, NCH_AH_BPh), 3.97 (1H, q, *J* 6.6, C(α)*H*), 4.18 (1H, d, *J* 14.5, NCH$_A$$H_B$Ph), 5.48–5.58 (1H, m, C(3)*H*), 5.79–5.88 (1H, m, C(4)*H*), 7.10–7.50 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 26.5 (*C*(6)), 26.8 (*C*(5)), 28.1 (C*Me*$_3$), 29.6 (*C*(2)), 48.3 (*C*(1)), 51.3 (N*C*H$_2$Ph), 57.1 (*C*(α)), 62.5 (*C*(7)), 79.8 (*C*Me$_3$), 127.8 (*C*(3)), 126.4, 126.5, 127.9, 128.5 (*o,m,p-Ph*), 132.6 (*C*(4)), 142.5, 144.6 (*i-Ph*), 173.9 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_2^+$ ([M+H]$^+$) requires 406.2741; found 406.2726. Further elution gave a mixture of **201** and **202** (250 mg, 33%, 55:45 dr) and **202** (18 mg, 3%, >99:1 dr).

tert-Butyl-(1*S*,7*S*,α*S*)-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclohept-3-ene-1-carboxylate 202



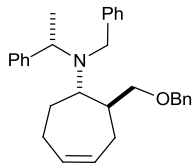
Method A: KHMDS (0.5 M in PhMe, 500 μL, 0.25 mmol) was added to a solution of freshly distilled ^{t}BuOH (25 μL, 0.25 mmol) in THF (5.0 mL) at rt. After 15 min a solution of **201** (100 mg, 0.25 mmol, >99:1 dr) in THF (5 mL) was added. The resultant solution was left to stir at rt for 16 h then concentrated *in vacuo*. The residue was then partitioned between satd aq NH_4Cl (5 mL) and Et_2O (5 mL), and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ and brine, then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 75:1) gave **202** as a colourless oil (80 mg, 80%, >99:1 dr); $[\alpha]_D^{25}$ –38.8 (*c* 1.4 in $CHCl_3$); ν_{max}(ATR) 2974, 2933 (C–H), 1722 (C=O), 1648 (C=C); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 7.1, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 1.51–1.61 (1H, m, C(6)*H*$_A$), 1.71–1.82 (1H, m, C(6)*H*$_B$), 1.94–2.06 (1H, m, C(5)*H*$_A$), 2.24–2.39 (3H, m, C(2)*H*$_2$, C(5)*H*$_B$), 2.5 (1H, td, *J* 8.3, 3.5, C(1)*H*), 3.5 (1H, td, *J* 10.3, 3.5, C(7)*H*), 3.72 (2H, s, NC*H*$_2$Ph), 4.05 (1H, q, *J* 7.1, C(α)*H*), 5.50–5.65 (1H, m, C(3)*H*), 5.65–5.80 (1H, m, C(4)*H*), 7.05–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.5 (C(α)*Me*), 26.0 (*C*(5)), 28.0 (*C*(6)), 28.1 (C*Me*$_3$), 28.9 (*C*(2)), 49.9 (*C*(1)), 50.0 (N*C*H$_2$Ph), 60.6 (*C*(α)), 62.5 (*C*(7)), 79.6 (*C*Me$_3$), 127.8 (*C*(3)), 126.4, 126.6, 127.8, 127.9, 128.9 (*o*,*m*,*p*-*Ph*) 133.1 (*C*(4)), 141.8, 144.2 (*i*-*Ph*), 174.6 (*C*O$_2^{t}$Bu); *m/z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_2^+$ ([M+H]$^+$) requires 406.2741; found 406.2724.

Method B: Step 1: Grubbs I catalyst (210 mg, 0.25 mmol) was added to a stirred solution of an 85:15 mixture of **199** and **200** (1.10 g, 2.50 mmol, 85:15 dr) in degassed CH_2Cl_2 (80 mL) at 35 °C. The resultant mixture was stirred at 35 °C for 16 h then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (40 mL) and $P(CH_2OH)_3$ (6.20 g, 50.0 mmol), Et_3N (700 μL, 5.00 mmol) and excess silica gel were added sequentially. The resultant mixture

was left to stir at rt for 12 h, then filtered and concentrated *in vacuo* to give a 85:15 mixture of **201** and **202** (1.40 g).

Step 2: KHMDS (0.5 M in PhMe, 13.6 mL, 6.80 mmol) was added to a solution of freshly distilled ^{t}BuOH (650 μL, 6.80 mmol) in THF (35 mL) at rt. After 15 min a solution of a mixture of **201** and **202** (1.40 g, 2.50 mmol, 85:15 dr) in THF (35 mL) was added. The resultant solution was left to stir at rt for 16 h then concentrated *in vacuo*. The residue was then partitioned between satd aq NH_4Cl (20 mL) and Et_2O (20 mL), and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 75:1) gave **202** as a colourless oil (660 mg, 65%, >99:1 dr).

(1*S*,7*S*,α*S*)-1-((Benzyloxymethyl)-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclohept-3-ene 205

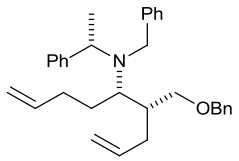


Step 1: $LiAlH_4$ (1.0 M in THF, 2.70 mL, 2.70 mmol) was added to a stirred solution of **202** (270 mg, 0.67 mmol, >99:1 dr) in THF (20 mL) at 0 °C. The resultant solution was allowed to warm to rt, then stirred at rt for 16 h. 2.0 M aq NaOH (1.35 mL, 2.70 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo* to give **204** (150 mg, 65:35 dr).

Step 2: The residue of **204** (140 mg, 0.42 mmol, 65:35 dr) was dissolved in THF (5 mL) and the resultant solution was added to a stirred solution of NaH (60%, 37 mg, 0.84 mmol) in THF (5 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 1 h, then BnBr (140 mg, 0.82 mmol) and 15-crown-5 (180 mg, 0.82 mmol) were added. The resultant solution was left to stir at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between Et_2O (15 mL) and satd aq NH_4Cl (15 mL), the aqueous layer was extracted with Et_2O (2 × 20 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, 90:10) gave **205** as a colourless oil (90 mg, 48%, 60:40 dr). Data for minor [selected peaks]: δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 6.8, C(α)*Me*), 3.48 (1H, d, *J* 13.5, NCH_AH$_B$Ph), 3.63 (1H, d, *J* 13.5, NCH$_A$$H_B$Ph). Further elution gave an analytically pure sample of the major diastereoisomer **205** (10 mg, 5%, 95:5 dr). $[\alpha]_D^{25}$ + 4.2 (*c* 0.5 in $CHCl_3$); ν_{max}(ATR) 2969, 2926 (C–H), 1720 (C=C); δ_H (400 MHz, $CDCl_3$) 1.30–1.40 (1H, m, C(6)H_A), 1.36 (3H, d, *J* 7.1, C(α)*Me*), 1.80–2.14 (4H, m, C(1)*H*, C(2)H_A, C(5)H_A, C(6)H_B), 2.30–2.52 (3H, m, C(2)H_B, C(5)H_B, C(7)*H*), 2.72 (1H, t, *J* 9.5, C(1')H_A), 3.34 (1H, app dd, *J* 9.5, 3.5, C(1')H_B), 3.73 (1H, d, *J* 13.9, NCH_AH$_B$Ph), 3.87 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 3.95 (1H, q, *J* 7.1, C(α)*H*), 4.27–4.38 (2H, m, OCH_2Ph), 5.52–5.60 (2H, m, C(3)*H*, C(4)*H*), 7.17–7.53 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.3 (C(α)*Me*), 26.4 (*C*(5)), 27.5 (*C*(2)), 28.2 (*C*(6)), 43.2 (*C*(1)), 50.7 (N*C*H$_2$Ph), 56.7 (*C*(α)), 58.7 (*C*(7)), 72.3, 72.6 (*C*(1'), O*C*H$_2$Ph), 126.5, 126.6, 127.3, 127.6, 127.8, 128.2, 128.8 (*o,m,p-Ph*), 130.7, 139.1 (*C*(3), *C*(4)), 141.6, 144.8 (*i-Ph*). *m/z* (ESI$^+$) 426 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{36}NO^+$ ([M+H]$^+$) requires 426.2791; found 426.2788.

(2*R*,3*S*,*αS*)-1-((Benzyloxy)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-ene 208

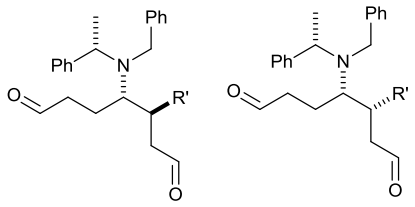


Step 1: $LiAlH_4$ (1.0 M in THF, 4.6 mL, 4.6 mmol) was added to a stirred solution of an 85:15 mixture of **199** and **200** (500 mg, 1.15 mmol, 85:15 dr) in THF (30 mL) at 0 °C. The resultant solution was allowed to warm to rt, then stirred at rt for 16 h, 2.0 M aq NaOH (2.3 mL, 4.6 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **207** as a colourless oil (383 mg, 92%, 90:10 dr); Data for mixture: ν_{max}(ATR) 3420 (O–H), 3028, 2972, 2930 (C–H) 1684 (C=C); *m/z* (ESI$^+$) 364 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO^+$ ([M+H]$^+$) requires 364.2635; found 364.2633. Data for **207**: δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.33–1.43 (1H, m, C(2)*H*), 1.60–1.77 (2H, m, C(4)H_2), 1.92–2.16 (3H, m, C(5)H_2, C(1')H_A),

2.14–2.28 (1H, m, C(1')H_B), 2.88–2.97 (2H, m, C(1)H_A, C(3)*H*), 3.22–3.31 (1H, m, C(1)H_B), 3.68 (1H, d, *J* 13.9, NCH_AH$_B$Ph), 3.82 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 3.83 (1H, q, *J* 6.8, C(α)*H*), 4.81–5.02 (4H, m, C(7)H_2, C(3')H_2), 5.48–5.64 (1H, m, C(2')*H*), 5.69–5.84 (1H, m, C(6)*H*), 7.09–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.1 (C(α)*Me*), 28.3 (*C*(4)), 30.6 (*C*(1')), 32.0 (*C*(5)), 42.4 (*C*(2)), 52.4 (N*C*H$_2$Ph), 56.3 (*C*(3)), 57.5 (*C*(α)), 65.4 (*C*(1)), 115.1, 116.0 (*C*(7), (*C*(3')), 127.2, 128.1, 128.6, 128.9, (*o,m,p-Ph*), 138.0 (*C*(2')), 139.1 (*C*(6)), 140.8, 143.5 (*i-Ph*).

Step 2: The residue of **207** (150 mg, 0.41 mmol, 90:10 dr) was dissolved in THF (5 mL) and the resultant solution was added to a stirred solution of NaH (60% in mineral oil, 33 mg, 0.82 mmol) in THF (5 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 1 h, then BnBr (100 μL, 0.82 mmol) and 15-crown-5 (160 μL, 0.82 mmol) were added. The resultant solution was left to stir at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between Et_2O (15 mL) and satd aq NH_4Cl (15 mL), the aqueous layer was extracted with Et_2O (2 × 20 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, 9:1) gave **208** as a colourless oil (98 mg, 52%, 90:10 dr); Data for mixture: $[\alpha]_D^{25}$ + 9.1 (*c* 1.2 in $CHCl_3$); ν_{max}(ATR) 1640 (C=C); *m/z* (ESI$^+$) 454 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{40}NO^+$ ([M+H]$^+$) requires 454.3104; found 454.3102. Data for **208**: δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.9, C(α)*Me*), 1.39–1.72 (3H, m, C(2)*H*, C(4)H_2), 1.81–2.04 (2H, m, C(5)H_A, C(1')H_A), 2.04–2.22 (2H, m, C(5)H_B, C(1')H_B), 2.73 (1H, app q, *J* 5.9, C(3)*H*), 3.16 (2H, d, *J* 4.9, C(1)H_2), 3.70–3.80 (2H, m, NCH_2Ph), 3.87 (1H, q, *J* 6.9 C(α)*H*), 4.19 (2H, m, OCH_2Ph), 4.68–4.96 (4H, m, C(7)H_2, C(3')H_2), 5.38–5.52 (1H, m, C(2')*H*), 5.62–5.77 (1H, m, C(6)*H*), 7.06–7.46 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.3 (C(α)*Me*), 29.1 (*C*(4)), 32.5 (*C*(5)), 34.1 (*C*(1')), 41.9 (*C*(2)), 51.3 (N*C*H$_2$Ph), 57.8 (*C*(3)), 58.9 (*C*(α)), 70.5 (*C*(1)), 72.7 (O*C*H$_2$Ph), 114.4 (*C*(7)), 115.6 (*C*(3')), 127.4, 127.9, 128.1, 128.2, 128.4 (*o,m,p-Ph*), 138.0 (*C*(2')), 139.1 (*C*(6)), 142.4, 144.9 (*i-Ph*).

Attempted synthesis of dialdehydes 203 and 206



Method A: **202** (150 mg, 0.37 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 2.0 mL), then dissolved in CH_2Cl_2 (10 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then DMS (250 μl, 3.50 mmol) was added and the reaction mixture was allowed to cool to rt and stirred for 16 h. The resultant mixture was then washed with H_2O (5 × 10 mL), dried and concentrated *in vacuo* to give a dark brown oil.

Method B: An 85:15 mixture of **199** and **200** (150 mg, 0.35 mmol, 85:15 dr) was coevaporated three times with HCl (2.0 M in Et_2O, 3 × 2.0 mL), then dissolved in CH_2Cl_2 (10 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then DMS (250 μl, 3.50 mmol) was added and the reaction mixture was allowed to cool to rt and stirred for 16 h. The resultant mixture was then washed with H_2O (5 × 10 mL), dried and concentrated *in vacuo* to give a dark brown oil.

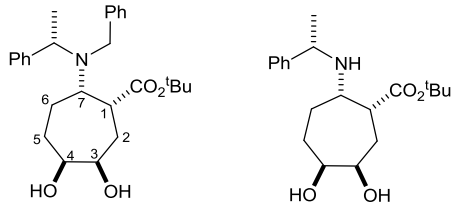
Method C:[9] An 85:15 mixture of **199** and **200** (150 mg, 0.35 mmol, 85:15 dr) was coevaporated three times with HCl (2.0 M in Et_2O, 3 × 2.0 mL), then dissolved in CH_2Cl_2 (10 ml) and NMO (123 mg, 1.05 mmol) was added. The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then DMS (250 μl, 3.50 mmol) was added and the reaction mixture was allowed to cool to rt and stirred for 16 h. The resultant mixture was then washed with H_2O (5 × 10 mL), dried and concentrated *in vacuo* to give a dark brown oil.

Method D: **208** (90 mg, 0.21 mmol, 90:10 dr) was coevaporated three times with HCl (2.0 M in Et_2O, 3 × 2.0 mL), then dissolved in CH_2Cl_2 (10 mL). The resultant solution was cooled to

−78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then DMS (250 μl, 3.50 mmol) was added and the reaction mixture was allowed to cool to rt and stirred for 16 h. The resultant mixture was then washed with H_2O (5 × 10 mL), dried and concentrated *in vacuo* to give a dark brown oil.

Method E: **205** (90 mg, 0.21 mmol, 60:40 dr) was coevaporated three times with HCl (2.0 M in Et_2O, 3 × 2.0 mL), then dissolved in CH_2Cl_2 (10 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then DMS (250 μl, 3.50 mmol) was added and the reaction mixture was allowed to cool to rt and stirred for 16 h. The resultant mixture was then washed with H_2O (5 × 10 mL), dried and concentrated *in vacuo* to give a dark brown oil.

tert-Butyl (1*R*,3*R*,4*S*,7*S*,α*S*)-3,4-dihydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino] cycloheptanecarboxylate 209 and _tert_-butyl (1*S*,3*R*,4*S*,7*S*,α*S*)-3,4-dihydroxy-7-[*N*-(α-methylbenzyl)amino]cycloheptanecarboxylate 210



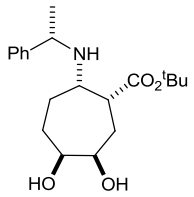
Method A: OsO_4 (62 mg, 0.25 mmol) was added to a stirred solution of **201** (1.00 g, 2.47 mmol) in THF (17.5 mL), followed by a solution of NMO (1.16 g, 9.88 mmol) in H_2O (4.4 mL). The reaction mixture was stirred at rt for 16 h. Satd aq Na_2SO_3 (20 mL) was then added and the resultant mixture was left to stir at rt for 1 h. The reaction mixture was then extracted with EtOAc (3 × 30 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 63:37 mixture of **209** and **210**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **209** as a white solid (470 mg, 43%, >99:1 dr); mp: 102–104 °C; $[\alpha]_D^{25}$ –56.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O–H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 1.55–1.70 (2H, m,

C(2)H_A, C(5)H_A), 1.70–1.85 (2H, m, C(2)H_B, C(5)H_B), 1.82 (1H, dt, *J* 9.8, 1.2, C(6)H_A), 2.06 (1H, m, C(6)H_B), 2.56 (1H, dt, *J* 7.6, 4.3 C(1)*H*), 3.13 (1H, dt, *J* 11.1, 4.3, C(7)*H*), 3.84 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.83–3.96 (3H, m, C(3)*H*, C(4)*H*, C(α)*H*), 4.05 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 7.18–7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.5 (C(α)*Me*), 24.5 (*C*(6)), 28.1 (C*Me*$_3$), 29.7 (*C*(5)), 32.2 (*C*(2)), 46.4 (*C*(1)), 51.1 (N*C*H$_2$Ph), 57.5 (*C*(α)), 58.7 (*C*(7)), 71.3 (*C*(3)), 74.1 (*C*(4)), 80.4 (*C*Me$_3$), 126.4, 126.6, 127.8, 127.9, 128.0, 128.4 (*o,m,p-Ph*), 142.2, 144.3 (*i-Ph*), 174.7 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 440 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{37}NNaO_4^+$ ([M+Na]$^+$) requires 462.2615; found 462.2592.

Further elution gave **210** as a white solid (160 mg, 19%, >99:1 dr); mp: 106–108 °C; $[\alpha]_D^{25}$ –26.8 (*c* 1.2 in $CHCl_3$); ν_{max} (ATR) 3397 (O–H), 1715 (C=O); δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.6, C(α)*Me*), 1.30–1.38 (1H, m, C(6)H_A), 1.58 (9H, s, C*Me*$_3$), 1.52–1.57 (1H, m, C(5)H_A), 1.56–1.66 (1H, m, C(5)H_B), 1.83–1.92 (2H, m, C(2)H_A, C(6)H_B), 1.93–2.00 (1H, m, C(2)H_B), 3.04–3.10 (2H, m, C(1)*H*, C(7)*H*), 3.70 (1H, td, *J* 9.8, 3.5, C(4)*H*), 3.83 (1H, q, *J* 6.6, C(α)*H*), 4.06 (1H, td, *J* 7.3, 3.5, C(3)*H*), 7.20–7.33 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 24.0 (C(α)*Me*), 27.9 (*C*(5)), 28.2 (C*Me*$_3$), 28.9 (*C*(2)), 29.4 (*C*(6)), 42.2 (*C*(1)), 55.4 (*C*(α)), 55.8 (*C*(7)), 70.4 (*C*(3)), 74.6 (*C*(4)), 80.5 (*C*Me$_3$), 126.5, 126.6, 128.3 (*o,m,p-Ph*), 146.4 (*i-Ph*), 174.1 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 350 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{32}NO_4^+$ ([M+H]$^+$) requires 350.2326; found 350.2321.

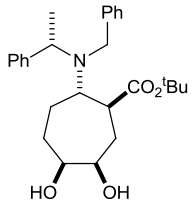
Method B: OsO_4 (125 mg, 0.49 mmol) was added to a stirred solution of **201** (150 mg, 0.44 mmol) and TMEDA (95 μL, 0.62 mmol) in CH_2Cl_2 (10 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then allowed to warm to rt over 15 min before being concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and $P(CH_2OH)_3$ (5.50 g, 45.0 mmol), Et_3N (1.20 mL, 8.80 mmol) and excess silica gel were added sequentially. The resultant mixture was left to stir at rt for 48 h, then filtered through a short plug of silica gel (eluent CH_2Cl_2) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **209** as a white solid (100 mg, 52%, >99:1 dr).

tert-Butyl (1*S*,3S,4*R*,7*S*,α*S*)-3,4-dihydroxy-7-[*N*-(α-methylbenzyl)amino] cycloheptanecarboxylate 210



CAN (150 mg, 0.22 mmol) was added to a stirred solution of **209** (60 mg, 0.13 mmol, >99:1 dr) in MeCN (2.25 mL) and H_2O (0.45 mL) and the resultant mixture was stirred at rt for 2 h. Then satd aq $NaHCO_3$ (5 mL) was added and the reaction mixture was left to stir at rt for 10 min. The resultant mixture was then extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **210** as a white solid (42 mg, 97%, >99:1 dr).

tert-Butyl (1*S*,3*R*,4*S*,7*S*,α*S*)-3,4-dihydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino] cycloheptane-1-carboxylate 211

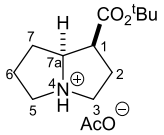


Method A: OsO_4 (141 mg, 0.55 mmol) was added to a stirred solution of **202** (202 mg, 0.50 mmol, >99:1 dr) and TMEDA (100 μL, 0.70 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to rt over 15 min before being concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 (50 mL) and $P(CH_2OH)_3$ (6.20 g, 50 mmol), Et_3N (1.4 mL, 10 mmol) and excess silica gel were added sequentially. The resultant mixture was left to stir at rt for 48 h, then filtered and concentrated *in vacuo* to give **211** in 80:20 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **211** (175 mg, 80%, 80:20 dr).

Method B: OsO_4 (50 mg, 0.20 mmol) was added to a stirred solution of **202** (800 mg, 1.98 mmol, >99:1 dr) in THF (14 mL), followed by a solution of NMO (930 mg, 7.92 mmol) in H_2O (3.50 mL). The reaction mixture was stirred at rt for 16 h. Satd aq Na_2SO_3 (15 mL) was then added and the resultant mixture was left to stir at rt for 1 h. The reaction mixture was then extracted with

EtOAc (3 × 15 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **211** in 65:35 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **211** as a white solid (590 mg, 68%, 65:35 dr). Data for mixture: mp: 115–116°C; ν_{max} (ATR) 3412 (O–H), 1723 (C=O); *m/z* (ESI^+) 440 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{38}NO_4^+$ ($[M+H]^+$) requires 440.2795; found 440.2774. Data for major **211**: δ_H (400 MHz, $CDCl_3$) 1.17 (1H, m, C(6)H_A), 1.25 (3H, d, *J* 6.9, C(α)*Me*), 1.42 (9H, s, CMe_3), 1.45–1.60 (2H, m, C(2)H_A, C(5)H_A), 1.56–1.70 (1H, m, C(6)H_B), 1.79–1.94 (2H, m, C(2)H_B, C(5)H_B), 2.25–2.57 (2H, broad s, 2 × O*H*), 2.58 (1H, dt, *J* 11.2, 5.8, C(1)*H*), 3.38 (1H, td, *J* 10.0, 2.5, C(7)*H*), 3.50–3.58 (3H, m, C(3)*H*, NCH_2Ph), 3.71 (1H, dd, *J* 9.1, 2.0, C(4)*H*), 3.89 (1H, q, *J* 6.9, C(α)*H*), 7.06–7.23 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.5 (C(α)*Me*), 22.0 (*C*(6)), 28.1 (CMe_3), 30.5 30.6 (*C*(2), *C*(5)), 49.1 (*C*(1)), 49.6 (N*C*H_2Ph), 60.7 (*C*(α)), 62.4 (*C*(7)), 80.8 (*C*Me_3), 72.7 (*C*(4)) , 73.3 (*C*(3)), 126.4, 126.6, 127.8, 128.1, 128.8 (*o,m,p-Ph*), 141.5, 143.7 (*i-Ph*), 176.7 (*C*$O_2{}^t$Bu). Data for minor: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.50 (9H, s, CMe_3) 2.29 (1H, ddd, *J* 14.9, 9.7, 5.5 C(2)H_A), 2.78 (1H, dt, *J* 9.1, 4.8 C(1)*H*), 3.36 (1H, td, *J* 9.1, 2.6 C(7)*H*). δ_C (100 MHz, $CDCl_3$) 18.2 (C(α)*Me*), 21.6 (*C*(6)), 28.2 (CMe_3), 30.1, 31.9 (*C*(2), *C*(5)), 44.6 (*C*(1)), 50.1 (N*C*H_2Ph), 59.4, 60.6 (*C*(α), *C*(7)), 70.2, 72.6 (*C*(3), *C*(4)), 80.1 (*C*Me_3), 126.4, 126.6, 128.0, 128.5 (*o,m,p-Ph*), 141.6, 144.3 (*i-Ph*), 175.3 (*C*$O_2{}^t$Bu).

(1*S*,7a*S*)-1-(*tert*-Butoxycarbonyl)octahydropyrrolizin-4-ium acetate 213·HOAc

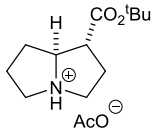


Step 1: $NaIO_4$ (690 mg, 3.20 mmol) was added to a solution of **211** (470 mg, 1.07 mmol, 65:35 dr) in MeOH (30 mL) and the resultant suspension was stirred at rt for 1 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) then concentrated *in vacuo*. The residue was dissolved in Et_2O (30 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) then concentrated *in vacuo* to give **212**. δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.38 (9H, s, CMe_3), 3.79 (2H, s, NCH_2Ph), 3.92 (1H, q, *J* 6.9, C(α)*H*), 7.20–7.48 (10H, m,

Ph), 9.19 (1H, s, CO*H*$_A$), 9.82 (1H, s, CO*H*$_B$). *m/z* (ESI$^+$) 470 ([M+H+MeOH]$^+$, 100%), 502 ([M+Na+MeOH]$^+$, 80%).

Step 2: Pd(OH)$_2$/C (75 mg, 0.54 mmol) was then added to a stirred solution of **212** in MeOH (10 mL) and AcOH (0.5 mL) at rt. The resultant mixture was degassed with N_2 and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 24 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give **213**·HOAc as pale yellow oil (350 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ −14.1 (*c* 0.78 in $CHCl_3$); ν_{max} (ATR) 3381 (N^+–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$), 1.25−1.45 (10H, m, C*Me*$_3$, C*H*$_A$), 1.51–1.64 (1H, m, C*H*$_B$), 1.80–1.95 (4H, m, C*H*$_A$, C*H*$_3$CO$_2$), 2.00–2.02 (3H, m, C*H*$_B$, C*H*$_2$), 2.60–2.80 (1H, m, C(5)*H*$_A$), 2.95–3.01 (1H, m, C(3)*H*$_A$), 3.21 (1H, q, *J* 8.2, C(1)*H*), 3.47–3.58 (1H, m, C(3)*H*$_B$), 3.70–3.78 (1H, m, C(5)*H*$_B$), 4.35 (1H, q, *J* 8.3, C(7a)*H*); δ_C (100 MHz, $CDCl_3$) 22.0 (*C*H$_3$CO$_2^-$), 25.9 26.7 27.8 (3 × *C*H$_2$), 27.8 (C*Me*$_3$), 46.4 (*C*(1)), 52.6 55.0 (*C*(3), *C*(5)), 66.5 (*C*(7a)), 82.1 (*C*Me$_3$), 169.9 (*C*O$_2^t$Bu), 176.3 (CH$_3$*C*O$_2^-$); *m/z* (ESI$^+$) 212 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_2^+$ ([M+H]$^+$) requires 212.1645; found 212.1637.

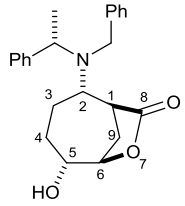
(1*R*,7a*S*)-1-(*tert*-Butoxycarbonyl)octahydropyrrolizin-4-ium acetate 215·HOAc



Step 1: $NaIO_4$ (220 mg, 1.03 mmol) was added to a solution of **209** (150 mg, 0.34 mmol, >99:1 dr) in MeOH (10 mL) and the resultant suspension was stirred at rt for 1 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) then concentrated *in vacuo*. The residue was dissolved in Et_2O (20 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and then concentrated *in vacuo* to give **214**. δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.34 (3H, d, *J* 6.8, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 3.84 (1H, d, *J* 15.2, NCH$_A$H$_B$Ph), 3.95–3.42 (2H, m, NCH$_A$*H*$_B$Ph, C(α)*H*), 7.22–7.38 (10H, m, *Ph*), 9.45 (1H, s, CO*H*$_A$), 9.67 (1H, s, CO*H*$_B$). *m/z* (ESI$^+$) 502 ([M+Na+MeOH]$^+$, 100%), 470 ([M+H+MeOH]$^+$ 15%).

Step 2: $Pd(OH)_2/C$ (24 mg, 0.17 mmol) was then added to a stirred solution of **214** in MeOH (5 mL) and AcOH (0.25 mL) at rt. The resultant mixture was degassed with N_2 and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 24 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give **215**·HOAc as pale yellow oil (350 mg, quant, >99:1 dr). $[\alpha]_D^{25}$ –11.9 (*c* 0.7 in $CHCl_3$); ν_{max} (ATR) 3401 (N^+–H), 1719 (C=O); δ_H (400 MHz, $CDCl_3$), 1.39 (9H, s, C*Me*$_3$), 1.72–1.85 (1H, m, C*H*$_A$H$_B$), 1.88–1.96 (4H, m, CH$_A$*H*$_B$, C*H*$_3$CO$_2^-$), 1.99–2.08 (1H, m, C*H*$_A$H$_B$), 2.15–2.28 (3H, m, CH$_A$*H*$_B$, C*H*$_2$), 2.65 (1H, app q, *J* 8.1, C(1)*H*), 2.69–2.86 (2H, m, C(3)*H*$_A$, C(5)*H*$_A$), 3.52–3.64 (1H, m, C(3)*H*$_B$), 3.81–3.90 (1H, m, C(5)*H*$_B$), 4.25–4.34 (1H, m, C(7a)*H*); δ_C (100 MHz, $CDCl_3$) 21.9 (*C*H$_3$CO$_2^-$), 24.6, 29.2, 30.3 (*C*(2), *C*(6), *C*(7)), 27.9 (C*Me*$_3$), 50.1 (*C*(1)), 53.9, 54.5 (*C*(3), *C*(5)), 67.9 (*C*(7a)), 82.3 (*C*Me$_3$), 169.7 (*C*O$_2^t$Bu), 176.6 (CH$_3$*C*O$_2^-$); *m/z* (ESI$^+$) 212 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_2^+$ ([M+H]$^+$) requires 212.1645; found 212.1646.

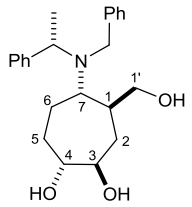
(1*S*,2*S*,5*R*,6*R*,α*S*)-2-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxy-7-oxabicyclo[4.2.1]--nonan-8-one 227



HBF_4 (48% in H_2O, 160 μL, 1.25 mmol) was added to a stirred solution of **202** (100 mg, 0.25 mmol, >99:1 dr) in CH_2Cl_2 (0.7 mL). After 5 min *m*-CPBA (70% in H_2O, 120 mg, 0.50 mmol) was added and the resultant mixture was left to stir at rt for 48 h. CH_2Cl_2 (10 mL), satd aq Na_2SO_3 (5 mL) and satd aq $NaHCO_3$ (5 mL) were added sequentially and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **227** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **227** as a white solid (60 mg, 67%, >99:1 dr); mp 191–193 °C; $[\alpha]_D^{25}$ +20.8 (*c* 0.9 in $CHCl_3$); ν_{max} (ATR) 3463 (O–H), 1750 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.1, C(α)*Me*), 1.34–1.48 (1H, m, C(4)*H*$_A$), 1.49–1.63 (1H, m, C(3)*H*$_A$) 1.63–1.83 (1H, m, C(4)*H*$_B$), 1.49–1.83 (1H, m, O*H*), 1.82–2.34 (1H, m, C(9)*H*$_A$),

2.00−2.18 (1H, app q, *J* 12.3, C(3)H_B), 2.31 (1H, app d, *J* 13.7, C(9)H_B), 2.41 (1H, app d, *J* 9.3 C(1)*H*), 3.39 (1H, app dd, *J* 12.0, 4.9, C(2)*H*), 3.43 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.82 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 3.83 (1H, q, *J* 7.1, C(α)*H*), 3.97 (1H, app q, *J* 4.0, C(5)*H*), 4.46 (1H, app dd, *J* 7.8, 4.7, C(6)*H*), 7.15−7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(α)*Me*), 24.4 (*C*(4)), 24.8 (*C*(9)), 27.9 (*C*(3)), 39.5 (*C*(1)), 50.0 (N*C*H$_2$Ph), 59.2 (*C*(α)), 59.6 (*C*(2)), 68.4 (*C*(5)), 79.4 (*C*(6)), 126.7, 127.1, 127.8, 128.3, 128.4 (*o,m,p-Ph*), 141.6, 142.6 (*i-Ph*), 180.8 (*C*(8)); *m/z* (ESI$^+$) 366 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{28}NO_3^+$ ([M+H]$^+$) requires 366.2064; found 366.2053.

(1*S*,3*R*,4*R*,7*S*,α*S*)-1-Hydroxymethyl-3,4-dihydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino] cycloheptane 233



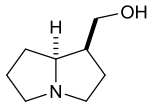
Method A: $LiAlH_4$ (1.0 M in THF, 0.88 mL, 0.88 mmol) was added to a stirred solution of **227** (80 mg, 0.22 mmol, >99:1 dr) in THF (6 mL) at 0 °C. The resultant solution was left to stir at 0 °C for 2 h, then 2.0 M aq NaOH (0.44 mL, 0.88 mmol) was added and the reaction mixture was left to stir at rt for 1 h. The resultant mixture was then filtered through Celite® (eluent THF), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **233** as a white solid (60 mg, 74%, >99:1 dr); mp 56–57 °C; $[\alpha]_D^{25}$ +32.7 (*c* 0.67 in $CHCl_3$); ν_{max} (ATR) 3362 (O–H); δ_H (400 MHz, $CDCl_3$) 1.26–1.31 (1H, m, C(2)H_A), 1.41 (3H, d, *J* 7.0, C(α)*Me*), 1.55 (1H, dt, *J* 14.4, 2.2, C(2)H_B), 1.69–1.90 (4H, m, C(1)*H*, C(5)H_2, C(6)H_A), 1.93–2.04 (1H, m C(6)H_B), 2.83 (1H, dt, *J* 10.1, 5.0, C(7)*H*), 3.04 (1H, dd, *J* 10.6, 6.3, C(1')H_A), 3.20 (3H, br s, 3 × O*H*), 3.36–3.42 (2H, m, C(4)*H*, C(1')H_B), 3.47 (1H, m, C(3)*H*), 3.61 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.99 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 3.97 (1H, q, *J* 7.0, C(α)*H*), 7.10–7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6 (C(α)*Me*), 24.0 (*C*(6)), 29.6 (*C*(5)), 33.8 (*C*(2)), 39.3 (*C*(1)), 50.3 (N*C*H$_2$Ph), 56.3 (*C*(α)), 57.8 (*C*(7)), 67.9 (*C*(1')), 76.9 (*C*(3)), 77.6 (*C*(4)), 127.2, 127.3, 128.1, 128.3, 128.5, 129.4 (*o,m,p-Ph*), 139.5, 143.1 (*i-Ph*);

m/z (ESI^+) 370 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{32}NO_3^+$ ($[M+H]^+$) requires 370.2377; found 370.2370.

Method B: Step 1: HBF_4 (48% in H_2O, 900 μL, 6.75 mmol) was added to a stirred solution of **202** (550 mg, 1.35 mmol, >99:1 dr) in CH_2Cl_2 (3.5 mL). After 5 min *m*-CPBA (70% in H_2O, 1.00 g, 4.05 mmol) was added and the resultant mixture was left to stir at rt for 48 h. CH_2Cl_2 (20 mL), satd aq Na_2SO_3 (5 mL) and satd aq $NaHCO_3$ (5 mL) were added sequentially and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **227** in >95:5 dr (600 mg).

Step 2: $LiAlH_4$ (1.0 M in THF, 5.4 mL, 5.40 mmol) was added to a stirred solution of **227** (600 mg, 1.35 mmol, >95:5 dr) in THF (30 mL) at 0 °C. The resultant solution was left to stir at 0 °C for 2 h, then 2.0 M aq NaOH (2.7 mL, 2.70 mmol) was added and the reaction mixture was left to stir at rt for 1 h. The resultant mixture was then filtered through Celite® (eluent THF), dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **233** as a white solid (400 mg, 80%, >99:1 dr).

(1*S*,7a*S*)-1-Hydroxymethyl-hexahydro-1*H*-pyrrolizine[(–)-isoretronecanol] 82



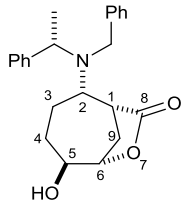
Method A: *Step 1:* $NaIO_4$ (174 mg, 0.81 mmol) was added to a solution of **233** (100 mg, 0.27 mmol, >99:1 dr) in MeOH (10 mL) and the resultant suspension was stirred at rt for 1 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the resultant solution was concentrated *in vacuo*. The residue was dissolved in Et_2O (30 mL) and filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo* to give **234**. δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.23-1.38 (3H, m, C(α)*Me*), 5.35–5.40 (1H, m, C(2')*H*), 7.18–7.48 (10H, m, *Ph*), 9.65–9.71 (1H, m, CO*H*). *m/z* (ESI^+) 400 ($[M+H+MeOH]^+$, 100%).

Step 2: The residue was dissolved in MeOH (5 mL) and AcOH (0.25 mL) and $Pd(OH)_2/C$ (19 mg, 0.13 mmol) was added. The resultant mixture was degassed with N_2 and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) at rt for 24. The reaction mixture was

then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification *via* ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **82** as a colourless oil (23 mg, 65%, >99:1 dr); $[\alpha]_D^{20}$ −70.1 (*c* 1.0 in EtOH); lit.[10] $[\alpha]_D^{20}$ −65.7 (*c* 1.88 in EtOH); lit.[11] $[\alpha]_D^{21}$ −76.4 (*c* 1.14 in EtOH), lit.[12] $[\alpha]_D^{20}$ −74.0 (*c* 0.2 in EtOH); ν_{max} (film) 3331 (O−H), 2871 (C−H); δ_H (400 MHz, $CDCl_3$), 1.30−1.60 (2H, m, CH_2), 1.63−1.95 (4H, m, 2 × CH_2), 2.36−2.54 (2H, m, C(1)*H*, C(3)H_A), 2.58−2.72 (1H, m, C(5)H_A), 2.90−3.01 (1H, m, C(5)H_B), 3.12−3.27 (1H, m, C(3)H_B), 3.36 (1H, br s, O*H*), 3.40−3.55 (1H, m, C(7a)*H*), 3.60−3.71 (2H, m, CH_2OH); δ_C (100 MHz, $CDCl_3$) 25.9, 26.6, 27.3 (*C*(2), *C*(6), *C*(7)), 43.8 (*C*(1)), 53.9, 55.5 (*C*(3), *C*(5)), 63.6 (*C*H_2OH), 66.5 (*C*(7a)); *m/z* (ESI^+) 142 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO^+$ ($[M+H]^+$) requires 142.1226; found 142.1229.

Method B: DIBAL-H (1.0 M in THF, 7.00 mL, 7.00 mmol) was added to a stirred solution of **213**·HOAc (150 mg, 0.70 mmol) in THF (15 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 18 h. 2.0 M aq NaOH (3.5 mL, 7.00 mmol) was then added and the resultant mixture was heated at reflux for 1 h. The reaction mixture was then filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification *via* ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **82** as an impure pale yellow oil (11 mg, 17%, >99:1 dr).

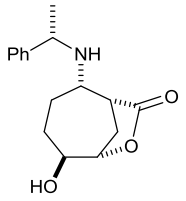
(1*R*,2*S*,5*S*,6*S*,α*S*)-2-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxy-7-oxabicyclo[4.2.1] nonan-8-one 230



HBF_4 (48% in H_2O, 320 μL, 2.50 mmol) was added to a stirred solution of **201** (200 mg, 0.5 mmol, >99:1 dr) in CH_2Cl_2 (1.3 mL). After 5 min *m*-CPBA (70% in H_2O, 240 mg, 1.00 mmol) was added and the resultant mixture was left to stir at rt for 48 h. CH_2Cl_2 (20 mL), satd aq

Na_2SO_3 (10 mL) and satd aq $NaHCO_3$ (10 mL) were added sequentially and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **230** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **230** as a white solid (120 mg, 74%, >99:1 dr); mp 39–40 °C; $[\alpha]_D^{25}$ –30.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3433 (O–H), 1772 (C=O); δ_H (400 MHz, $CDCl_3$), 1.27 (3H, d, *J* 6.7, C(α)*Me*), 1.31–1.45 (1H, m, C(9)H_A), 1.60–1.80 (3H, m, C(4)H_A, C(3)H_A, O*H*), 1.93–2.02 (1H, m, C(3)H_B), 2.18 (1H, app dt, *J* 13.6, 8.1, C(4)H_B), 2.00–2.62 (1H, app d, *J* 8.8, C(1)*H*), 2.86 (1H, app dt, *J* 10.3, 2.8, C(2)*H*), 3.83 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 4.01 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.94–4.00 (1H, m, C(5)*H*), 4.04 (1H, q, *J* 6.7, C(α)*H*), 4.49 (1H, app q, *J* 8.1, C(6)*H*), 7.20–7.60 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$), 15.4 (C(α)*Me*), 25.7 (*C*(3)), 28.0 (*C*(4)), 31.5 (*C*(9)), 43.6 (*C*(1)), 51.0 (N*C*H_2Ph), 57.4 (*C*(α)), 62.1 (*C*(2)), 71.8 (*C*(5)), 81.9 (*C*(6)), 126.6, 126.8, 127.6, 128.2, 128.4 (*o,m,p-Ph*), 142.0, 144.0 (*i-Ph*), 178.5 (*C*(8)); *m/z* (ESI^+) 366 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{27}NNaO_3^+$ ($[M+Na]^+$) requires 388.1883; found 366.1871.

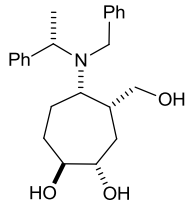
(1*R*,2*S*,5*S*,6*S*,*αS*)-2-[*N*-(α-Methylbenzyl)amino]-5-hydroxy-7-oxabicyclo[4.2.1]nonan-8-one 231



CAN (620 mg, 1.13 mmol) was added to a stirred solution of **230** (200 mg, 0.54 mmol, >99:1 dr) in MeCN/H_2O (5:1, 9 mL) and the resultant mixture was stirred at rt for 2 h. Satd aq $NaHCO_3$ (10 mL) was then added and the reaction mixture was left to stir at rt for 10 min. The resultant mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **231** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1) gave **231** as a white solid (140 mg, 94%, >99:1 dr); mp 107–109 °C; $[\alpha]_D^{25}$ –64.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3403 (O–H), 1756 (C=O); δ_H (400 MHz, $CDCl_3$), 1.27 (3H, d, *J* 6.6, C(α)*Me*), 1.20–1.30 (1H, m, C(3)H_A), 1.34–1.43 (1H,

m, C(4)H_A), 1.89–2.05 (3H, m, C(3)H_B, C(4)H_B, C(9)H_A), 2.17 (2H, br s, N*H*, O*H*), 2.36 (1H, app dt, *J* 13.7, 8.6, C(9)H_B), 2.60 (1H, app dt, *J* 10.3, 3.8, C(2)*H*), 2.99 (1H, app dd, *J* 8.6, 3.8, C(1)*H*), 3.91–3.97 (1H, m, C(5)*H*), 4.02 (1H, q, *J* 6.6, C(α)*H*), 4.61 (1H, app d, *J* 8.1, C(6)*H*), 7.22–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$), 25.5 (*C*(9)), 26.0 (C(α)*Me*), 28.5 (*C*(3)), 28.7 (*C*(4)), 39.5 (*C*(1)), 54.7 (*C*(α)), 57.3 (*C*(2)), 70.6 (*C*(5)), 82.7 (*C*(6)), 126.7, 127.1, 128.6 (*o,m,p-Ph*), 145.4 (*i-Ph*), 177.8 (*C*(8)); *m/z* (ESI^+) 276 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{22}NO_3^+$ ($[M+H]^+$) requires 276.1594; found 276.1596.

(1*R*,3*S*,4*S*,7*S*,α*S*)-3,4-Hydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-1-(hydroxymethyl)cycloheptane 235



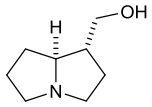
Method A: $LiAlH_4$ (1.0 M in THF, 2.20 mL, 2.20 mmol) was added to a stirred solution of **230** (200 mg, 0.55 mmol, >99:1 dr) in THF (20 mL) at 0 °C. The resultant mixture was left stirring at 0 °C for 2 h, then 2.0 M aq NaOH (1.1 mL, 2.2 mmol) was added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was then filtered through Celite® (eluent THF), dried and concentrated *in vacuo.* Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **235** as a white solid (150 mg, 73%, >99:1 dr); mp 52−54 °C; $[\alpha]_D^{25}$ +14.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3356 (O–H); δ_H (400 MHz, $CDCl_3$) 1.23–1.43 (1H, m, C(5)H_A), 1.36 (3H, d, *J* 7.1, C(α)*Me*), 1.49–1.59 (1H, m, C(2)H_A), 1.59–1.71 (2H, m, C(2)H_B, C(1)*H*), 1.71–1.84 (1H, m, C(6)H_A), 1.83–1.94 (1H, m, C(5)H_B), 1.94–2.05 (1H, m, C(6)H_B), 3.00–3.11 (1H, m, C(7)*H*), 3.13–3.26 (2H, m, C(3)*H,* C(1')H_A), 3.27–3.38 (1H, m, C(4)*H*), 3.46–3.56 (1H, m, C(1')H_B), 3.38−4.00 (3H, br s, 3 × O*H*), 3.80 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.89 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.95 (1H, q, *J* 7.1 C(α)*H*),7.17–7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.1 (C(α)*Me*), 23.3 (*C*(6)), 30.4 (*C*(5)), 32.6 (*C*(2)), 39.6 (*C*(1)), 52.6 (NCH_2Ph), 55.7 (*C*(7)), 56.4 (*C*(α)), 65.3 (*C*(1')), 77.5 (*C*(3)), 79.0 (*C*(4)), 127.2, 127.4, 128.1, 128.3, 128.7,

129.0 (*o,m,p-Ph*), 139.6, 143.0 (*i-Ph*); *m/z* (ESI^+) 370 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{32}NO_3^+$ ($[M+H]^+$) requires 370.2377; found 370.2375.

Method B: Step 1: HBF_4 (48% in H_2O, 1.0 mL, 7.50 mmol) was added to a stirred solution of **201** (610 mg, 1.50 mmol, >99:1 dr) in CH_2Cl_2 (4.0 mL). After 5 min *m*-CPBA (70% in H_2O, 740 mg, 3.00 mmol) was added and the resultant mixture was left to stir at rt for 48 h. CH_2Cl_2 (20 mL), satd aq Na_2SO_3 (5 mL) and satd aq $NaHCO_3$ (5 mL) were added sequentially and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **230** in >95:5 dr (600 mg).

Step 2: $LiAlH_4$ (1.0 M in THF, 6.0 mL, 6.00 mmol) was added to a stirred solution of **230** (600 mg, 1.50 mmol, >95:5 dr) in THF (30 mL) at 0 °C. The resultant solution was left to stir at 0 °C for 2 h, then 2.0 M aq NaOH (3.0 mL, 6.00 mmol) was added and the reaction mixture was left to stir at rt for 1 h. The resultant mixture was then filtered through Celite® (eluent THF), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **235** as a white solid (360 mg, 65%, >99:1 dr).

((1*R*,7a*S*)-1-Hydroxymethyl-hexahydro-1*H*-pyrrolizine [(–)-trachelantamidine] 83



Method A: *Step 1:* $NaIO_4$ (260 mg, 1.23 mmol) was added to a solution of **235** (150 mg, 0.41 mmol, >99:1 dr) in MeOH (15 mL) and the resultant suspension was stirred at rt for 1 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in Et_2O (30 mL) and filtered through a short plug of Celite® (eluent Et_2O) and concentrated *in vacuo* to give the intermediate aldehyde. δ_H (400 MHz, $CDCl_3$) [selected peaks] 5.32–5.36 (1H, m, C(2')*H*), 7.07–7.48 (10H, m, *Ph*), 9.67–9.69 (1H, m, CO*H*). *m/z* (ESI^+) 400 ($[M+H+MeOH]^+$, 100%).

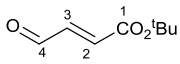
Step 2: The residue was dissolved in MeOH (5 mL) and AcOH (0.25 mL) and $Pd(OH)_2/C$ (28 mg, 0.19 mmol) was added. The resultant solution was degassed with N_2 and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) at rt for 24 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The

reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification *via* ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **83** as a colourless oil (35 mg, 62%, >99:1 dr); $[\alpha]_D^{20}$ −13.0 (*c* 0.2 in EtOH); lit.[13] $[\alpha]_D^{20}$ −13.8 (*c* 1.28 in EtOH); lit.[14] $[\alpha]_D^{20}$ −10.3 (*c* 0.65 in EtOH); lit[15] $[\alpha]_D^{25}$ −13.5 (*c* 2.0 in EtOH); ν_{max} (ATR) 3349 (O−H), 2869 (C−H); δ_H (400 MHz, $CDCl_3$) 1.50−1.61 (1H, m, CH_AH_B), 1.63−1.73 (1H, m, CH_AH_B), 1.74−1.92 (2H, m, CH_2), 1.93−2.08 (3H, m, CH_AH_B, CH_AH_B, C(1)*H*), 2.57 (1H, app td, *J* 9.5, 6.3, C(5)H_A), 2.63 (1H, app td, *J* 10.7, 6.6, C(3)H_A), 3.04 (1H, dt, *J* 10.8, 6.3, C(3)H_B), 3.22 (1H, ddd, *J* 10.1, 6.8, 3.2, C(5)H_B), 3.31 (1H, q, *J* 6.3, C(7a)*H*), 3.55−3.75 (2H, m, *C*H_2OH); δ_C (100 MHz, $CDCl_3$) 25.7 29.9 31.9 (*C*(2), *C*(6), *C*(7)),48.3 (*C*(1)), 54.5, 54.7 (*C*(3), *C*(5)), 65.0 (*C*H_2OH), 67.7 (*C*(7a)); *m/z* (ESI^+) 142 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO^+$ ($[M+H]^+$) requires 142.1226; found 142.1226.

Method B: DIBAL-H (1.0 M in THF, 4.0 mL, 4.0 mmol) is added to a stirred solution of **215**·HOAc (80 mg, 0.40 mmol) in THF (8 mL) at 0°C. The solution is allowed to warm and stirred at rt 18 h. Then 2.0 M aq NaOH (2 mL, 4 mmol) was added and the resultant mixture was refluxed for a further 1 h. The mixture was then filtered through Celite®, dried and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification *via* ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 35% NH_4OH in H_2O) gave **83** as a pale yellow oil (35 mg, 62%, >99:1dr).

5.3. Experimental data for Chapter 3

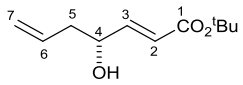
tert-Butyl (*E*)-3-formyl-2-propenoate 244[16]



Step 1: K_2CO_3 (7.90 g, 57.1 mmol) was added to a stirred solution of **195** (8.00 g, 31.7 mmol) in cyclohexane (50 mL) and the resultant suspension was stirred at 60 °C for 2 h. 2,2-Dimethoxyacetaldehyde (60% in H_2O, 12 mL, 69.3 mmol) was added, and the resultant mixture was stirred at 60 °C for 16 h, then allowed to cool to rt before satd aq NH_4Cl (50 mL) was added. The aqueous layer was extracted with Et_2O (3 × 50 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* to give **243** in >99:1 dr [(*E*):(*Z*)]. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **243** as a colourless oil (7.00 g, 96%, >99:1 dr [(*E*):(*Z*)]);[16] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 3.34 (6H, s, CH(O*Me*)$_2$), 4.92 (1H, dd, *J* 4.3, 1.3, C(4)*H*), 6.06 (1H, dd, *J* 15.9, 1.3, C(2)*H*), 6.67 (1H, dd, *J* 15.9, 4.3, C(3)*H*).

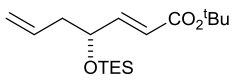
Step 2: *p*-Toluenesulfonic acid monohydrate (1.98 g, 10.4 mmol) was added to a stirred solution of **243** (18.1 g, 89.6 mmol, >99:1 dr [(*E*):(*Z*)]) in a 1:1 mixture of H_2O and acetone (400 mL). The resultant mixture was heated at reflux for 1.5 h, then satd aq $NaHCO_3$ (100 mL) was added. The aqueous layer was extracted with Et_2O (3 × 150 mL) and the combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo* to give **244** in >99:1 dr [(*E*):(*Z*)]. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **244** as a colourless oil (14.0 g, 86%, >99:1 dr [(*E*):(*Z*)]);[16] δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 6.65 (1H, d, *J* 15.9, C(2)*H*), 6.88 (1H, dd, *J* 15.9, 7.8, C(3)*H*), 9.73 (1H, d, *J* 7.8, C(4)*H*).

tert-Butyl (*R*,*E*)-4-hydroxy-hepta-2,6-dienoate 239[17]



(*R*)-(+)-BINOL **246** (733 mg, 2.56 mmol), $Ti(O^iPr)_4$ (1.0 M in CH_2Cl_2, 1.28 mL, 1.28 mmol) and CF_3CO_2H (0.5 M in CH_2Cl_2, 0.18 mL, 0.098 mmol) were added to a stirred mixture of 4 Å molecular sieves (2.00 g) in CH_2Cl_2 (40 mL). The resultant mixture was heated at reflux for 1 h, then allowed to cool to rt. **244** (2.00 g, 12.8 mmol) was added and the resultant mixture was stirred at rt for 30 min, then cooled to –78 °C and allyltributyltin (6.00 mL, 1.93 mmol) was added. The reaction mixture was stirred for 10 min at –78 °C then transferred to a –20 °C freezer. After 72 h, satd aq $NaHCO_3$ (5 mL) was added and the resultant mixture was purified *via* flash column chromatography (10% KF in SiO_2,[18] eluent 30–40 °C petrol/acetone, 95:5 increased to 90:10) to give **239** as a colourless oil (2.50 g, 98%, >99:1 dr [(*E*):(*Z*)], 96:4 er);[17] $[\alpha]_D^{20}$ +1.4 (*c* 1.6 in $CHCl_3$); ν_{max} (ATR) 3433 (O–H), 2983 (C–H), 1718 (C=O) 1658 (C=C); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 2.23–2.36 (1H, m, C(5)*H*$_A$), 2.37–2.48 (1H, m, C(5)*H*$_B$), 4.31–4.38 (1H, m, C(4)*H*), 5.14–5.24 (2H, m, C(7)*H*$_2$), 5.74–5.87 (1H, m, C(6)*H*), 5.98 (1H, dd, *J* 15.7, 1.5, C(2)*H*), 6.84 (1H, dd, *J* 15.7, 4.7, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 41.1 (*C*(5)), 69.9 (*C*(4)), 80.6 (*C*Me$_3$), 119.4 (*C*(7)), 122.5 (*C*(2)), 133.2 (*C*(6)), 147.8 (*C*(3)), 165.8 (*C*(1)); HRMS (ESI^+) $C_{11}H_{19}O_3^+$ ($[M+H]^+$) requires 199.1329; found 199.1333. HPLC Chiralpack AD-H (eluent hexane/iso-propanol 95:5, λ 210, 1 mL/min) t_R [(*R*)-isomer] = 8.82 min; t_R [(*S*)-isomer] = 9.55 min.

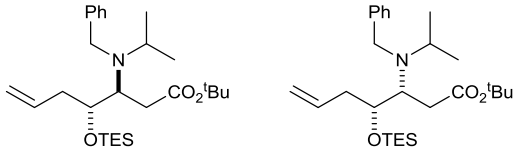
tert-Butyl (*R*,*E*)-4-(triethylsilyloxy)hepta-2,6-dienoate 245



TESCl (4.4 mL, 26.1 mmol), imidazole (3.0 g, 43.4 mmol) and DMAP (530 mg, 4.34 mmol) were added to a stirred solution of **239** (4.20 g, 21.7 mmol, >99:1 dr [(*E*):(*Z*)], 96:4 er) in CH_2Cl_2 (70 mL). The reaction mixture was stirred at rt for 16 h, then washed with 1.0 M aq HCl (3 × 20 mL). Purification *via* flash column chromatography (eluent 30–40°C petrol/Et_2O, 40:1) gave **245**

as a colourless oil (6.75 g, quant, >99:1 dr [(*E*):(*Z*)], 96:4 er); $[\alpha]_D^{20}$ −3.8 (*c* 1.5 in $CHCl_3$); ν_{max} (ATR) 2878, 2957 (C–H), 1715 (C=O), 1658 (C=C); δ_H (400 MHz, $CDCl_3$) 0.53 (6H, q, *J* 8.0, $Si(CH_2CH_3)_3$), 0.88 (9H, t, *J* 8.0, $Si(CH_2CH_3)_3$), 1.41 (9H, s, CMe_3), 2.20–2.28 (2H, m, C(5)H_2), 4.24 (1H, tdd, *J* 6.3, 4.9, 1.6, C(4)*H*), 4.99–5.04 (2H, m, C(7)H_2), 5.65–5.77 (1H, m, C(6)*H*), 5.82 (1H, dd, *J* 15.5, 1.6, C(2)*H*), 6.74 (1H, dd, *J* 15.5, 4.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 4.8 ($Si(CH_2CH_3)_3$), 6.8 ($Si(CH_2CH_3)_3$), 28.1 (CMe_3), 42.1 (*C*(5)), 71.4 (*C*(4)), 80.2 (CMe_3), 117.7 (*C*(7)), 121.9 (*C*(2)), 133.8 (*C*(6)), 148.9 (*C*(3)), 166.0 (*C*(1)); HRMS (ESI^+) $C_{17}H_{33}O_3Si^+$ ($[M+H]^+$) requires 313.2194; found 313.2196.

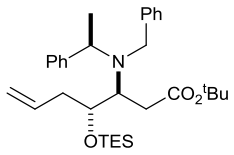
tert-Butyl (3*S*,4*R*)-3-(*N*-benzyl-*N*-isopropylamino)-4-(triethylsilyloxy)hept-6-enoate 248 and _tert_-butyl (*R*,*R*)-3-(*N*-benzyl-*N*-isopropylamino)-4-(triethylsilyloxy)hept-6-enoate 249



BuLi (2.2 M in hexanes, 0.43 mL, 0.99 mmol) was added dropwise to a stirred solution of *N*-benzyl-*N*-isopropylamine (0.17 mL, 1.02 mmol) in THF (1.5 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **245** (200 mg, 0.64 mmol, >99:1 dr [(*E*):(*Z*)], 96:4 er) in THF (1.5 mL) at −78 °C was added dropwise *via* cannula. The resultant mixture was stirred at −78 °C for 2 h, then satd aq NH_4Cl (15 mL) was added. The resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (5 mL) and 10% aq citric acid (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give an 89:11 mixture of **248** and **249**, respectively. Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave an 85:15 mixture of **248** and **249**, respectively, as a colourless oil (200 mg, 67%). Data for mixture: ν_{max} (ATR) 2960, 2877 (C–H), 1730 (C=O) 1640 (C=C); *m/z* (ESI^+) 462 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{48}NO_3Si^+$ ($[M+H]^+$) requires 462.3398; found 462.3393. Data for **249**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.39 (9H, s, CMe_3), 2.98 (1H, septet, *J* 6.7, $NCHMe_2$), 3.04 (1H, ddd, *J* 8.9, 4.0, 2.4, C(3)*H*), 4.00 (1H, d, *J*

14.8, NC*H*$_A$H$_B$Ph), 4.85–4.93 (1H, m, C(7)*H*$_A$), 5.53 (1H, ddt, *J* 17.2, 10.2, 6.9, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 5.1 (Si(*C*H$_2$CH$_3$)$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 17.2 (NCH*Me*$_A$Me$_B$), 22.6 (NCHMe$_A$*Me*$_B$), 28.1 (C*Me*$_3$), 34.7, 38.5 (*C*(2), *C*(5)), 49.5 (*C*HMe$_2$), 51.7 (N*C*H$_2$Ph), 80.2 (*C*Me$_3$), 116.4 (*C*(7)), 136.0 (*C*(6)). Further elution gave **248** as a colourless oil (70 mg, 24%, >99:1dr); $[\alpha]_D^{20}$ −4.0 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2960, 2878 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.52 (6H, q, *J* 8.0, Si(C*H*$_2$CH$_3$)$_3$), 0.91 (9H, t, *J* 8.0, Si(CH$_2$C*H*$_3$)$_3$), 0.97 (6H, t, *J* 6.7, NCH*Me*$_2$), 1.45 (9H, s, C*Me*$_3$), 2.20–2.33 (1H, m, C(5)*H*$_A$), 2.40–2.42 (1H, m, C(2)*H*$_2$), 2.33−2.47 (1H, m, C(5)*H*$_B$), 2.83 (1H, septet, *J* 6.7, NC*H*Me$_2$), 3.43 (1H, q, *J* 5.9, C(3)*H*), 3.61 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 3.78 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ph), 3.72–3.78 (1H, m, C(4)*H*), 5.00–5.05 (2H, m, C(7)*H*$_2$), 5.79 (1H, app ddt, *J* 17.2, 9.5, 7.0, C(6)*H*), 7.14−7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.2 (Si(*C*H$_2$CH$_3$)$_3$), 7.0 (Si(CH$_2$*C*H$_3$)$_3$), 19.2 (NCH*Me*$_A$Me$_B$), 20.9 (NCHMe$_A$*Me*$_B$), 28.1 (C*Me*$_3$), 35.2 (*C*(2)), 39.8 (*C*(5)), 49.6 (N*C*HMe$_2$), 50.3 (N*C*H$_2$Ph), 56.0 (*C*(3)), 74.2 (*C*(4)), 79.8 (*C*Me$_3$), 117.4 (*C*(7)), 126.4, 128.0, 128.2 (*o*,*m*,*p*-*Ph*), 134.6 (*C*(6)), 141.9 (*i*-*Ph*), 172.6 (*C*(1)); *m/z* (ESI^+) 462 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{48}NO_3Si^+$ ($[M+H]^+$) requires 462.3398; found 462.3395.

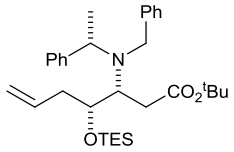
tert-Butyl (3*S*,4*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triethylsilyloxy)hept-6-enoate 250



BuLi (2.2 M in hexanes, 2.95 mL, 6.48 mmol) was added dropwise to a stirred solution of (*R*)-**197** (1.4 mL, 6.69 mmol, >99:1 er[19]) in THF (15 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **245** (1.30 g, 4.18 mmol, >99:1 dr [(*E*):(*Z*)], 96:4 er) in THF (15 mL) at −78 °C was added dropwise *via* cannula. The resultant reaction mixture was stirred at −78 °C for 2 h, then satd aq NH_4Cl (5 mL) was added. The resultant mixture was allowed to warm to rt then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (15 mL) and 10% aq citric acid (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 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 **250** in 96:4 dr. Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **250** as a colourless oil (1.40 g, 64%, >99:1 dr); $[\alpha]_D^{20}$ −27.4 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 2956, 2877 (C−H), 1727 (C=O), 1636 (C=C); δ_H (400 MHz, $CDCl_3$) 0.48 (6H, q, *J* 8.0, Si(CH_2CH$_3$)$_3$), 0.83 (9H, t, *J* 8.0, Si(CH$_2$CH_3)$_3$), 1.29 (3H, d, *J* 7.0, C(α)*Me*), 1.36 (9H, s, C*Me*$_3$), 1.65 (1H, dd, *J* 15.9, 2.3, C(2)H_A), 1.99−2.05 (1H, dd, *J* 15.9, 8.7, C(2)H_B), 2.30−2.40 (1H, m, C(5)H_A), 2.58 (1H, app dd, *J* 14.4, 7.7, C(5)H_B), 3.51 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.59−3.65 (3H, m, C(3)*H*, C(4)*H*, NCH$_A$$H_B$Ph), 3.69 (1H, q, *J* 7.0, C(α)*H*), 4.99−5.08 (2H, m, C(7)H_2), 5.78−5.91 (1H, m, C(6)*H*), 7.15−7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.0 (Si(*C*H$_2$CH$_3$)$_3$), 7.0 (Si(CH$_2$*C*H$_3$)$_3$), 19.6 (C(α)*Me*), 29.2 (C*Me*$_3$), 34.7 (*C*(2)), 38.8 (*C*(5)), 51.0 (N*C*H$_2$Ph), 55.6 (*C*(3)), 58.2 (*C*(α)), 73.5 (*C*(4)), 79.6 (*C*Me$_3$), 117.3 (*C*(7)), 126.7, 127.0, 128.0, 128.1, 128.3, 128.4 (*o,m,p-Ph*), 134.7 (*C*(6)), 141.5, 141.7 (*i-Ph*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 524 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{50}NO_3Si^+$ ([M+H]$^+$) requires 524.3554; found 524.3541.

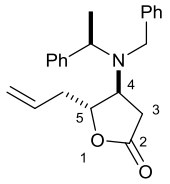
tert-Butyl (3*R*,4*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triethylsilyloxy)hept-6-enoate 251



BuLi (2.2 M in hexanes, 19.9 mL, 43.7 mmol) was added dropwise to a stirred solution of (*S*)-**197** (9.4 mL, 44.8 mmol, >99:1 er) in THF (35 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **245** (7.00 g, 22.4 mmol, >99:1 dr, 96:4 er) in THF (35 mL) at −78 °C was added dropwise *via* cannula. The resultant mixture was stirred at −78 °C for 2 h, then satd aq NH_4Cl (50 mL) was added. The resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL), H_2O (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **251** in 96:4 dr. Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **251** as a colourless

oil (8.30 g, 71%, >99:1 dr); $[\alpha]_D^{25}$ −7.2 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 2956, 2877 (C–H), 1725 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 0.45 (6H, q, *J* 7.8, Si(CH_2CH$_3$)$_3$), 0.79 (9H, t, *J* 7.8, Si(CH$_2$CH_3)$_3$), 1.25 (3H, d, *J* 7.1, C(α)*Me*), 1.33 (9H, s, C*Me*$_3$), 1.45–1.55 (1H, m, C(2)H_A) 2.33 (1H, dd, *J* 15.2, 10.2, C(5)H_A), 2.25−2.35 (1H, m, C(2)H_B), 2.80 (1H, app dt, *J* 15.2, 7.0, C(5)H_B), 3.28–3.30 (1H, m, C(3)*H*), 3.35 (1H, d, *J* 14.3, NCH_AH$_B$Ph), 3.69 (1H, q, *J* 7.1, C(α)*H*), 3.60−3.69 (1H, m, C(4)*H*), 4.23 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 4.99 (1H, d, *J* 10.2, C(7)H_A), 5.04 (1H, d, *J* 17.2, C(7)H_B), 5.67 (1H, app ddt, *J* 17.2, 10.2, 7.0, C(6)*H*), 7.10−7.27 (8H, m, *Ph*), 7.43 (2H, d, *J* 7.5, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.1 (Si(*C*H$_2$CH$_3$)$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 20.3 (C(α)*Me*), 28.1 (C*Me*$_3$), 33.4 (*C*(2)), 39.1 (*C*(5)), 52.9 (N*C*H$_2$Ph), 53.7 (*C*(3)), 58.0 (*C*(α)), 76.1 (*C*(4)), 79.9 (*C*Me$_3$), 116.6 (*C*(7)), 126.3, 127.0, 128.0, 128.1, 128.2, 128.6 (*o,m,p-Ph*), 136.0 (*C*(6)), 141.7, 142.3 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 524 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{49}NNaO_3Si^+$ ([M+Na]$^+$) requires 546.3374; found 546.3377.

(4*S*,5*R*,α*R*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-Allyl-dihydrofuran-2-one 252

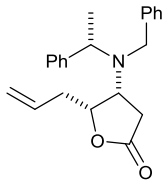


Method A: TBAF (1.0 M in THF, 2.68 mL, 2.68 mmol) was added to a stirred solution of **250** (1.40 g, 2.68 mmol, >99:1 dr) at rt. The reaction mixture was stirred at rt for 16 h, satd aq $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred at rt for 10 min. The reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo* to give **252** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 5:1) gave **252** as a white solid (380 mg, 70%, >99:1 dr); mp 128−130 °C; $[\alpha]_D^{20}$ +160.5 (*c* 1.2 in $CHCl_3$); ν_{max} (ATR) 2960, 2912 (C–H), 1777 (C=O) 1645 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 7.0, C(α)*Me*), 1.37 (1H, dd, *J* 18.3, 8.7, C(3)H_A), 2.08 (1H, dd, *J* 18.3, 7.7, C(3)H_B), 2.29−2.39 (1H, m, C(1')H_A), 2.51−2.60 (1H, m, C(1')H_B), 3.53−3.69 (3H, m, C(4)*H*, NCH_2Ph), 3.73 (1H, q, *J* 7.0, C(α)*H*), 4.26 (1H, app q, *J* 6.4, C(5)*H*), 5.06−5.15 (2H, m, C(3')H_2), 5.68−5.80 (1H, m, C(2')*H*),

7.14−7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.0 (C(α)*Me*), 29.5 (*C*(3)), 37.6 (*C*(1')), 50.6 (N*C*H_2Ph), 57.4 (*C*(4)), 58.0 (*C*(α)), 82.6 (*C*(5)), 119.1 (*C*(3')), 127.3, 127.6, 127.7, 128.0, 128.7, 128.7 (*o,m,p-Ph*), 132.4 (*C*(2')), 139.6, 141.3 (*i-Ph*), 175.8 (*C*(2)); *m/z* (ESI^+) 336 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{26}NO_2^+$ ($[M+H]^+$) requires 336.1958; found 336.1952.

Method B: HF (70% in py, 250 μL, 8.60 mmol) was added to a stirred solution of **250** (150 mg, 0.29 mmol, >99:1 dr) in THF (2 mL) at 0 °C and the resultant solution was allowed to warm to rt over 18 h. Satd aq $NaHCO_3$ was added until pH > 7 and the resultant mixture was stirred at rt for 30 min, then extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **252** as a white solid (30 mg, 30%, >99:1 dr);

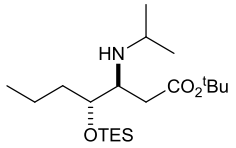
(4*R*,5*R*,α*S*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-allyl-dihydrofuran-2-one 253



TBAF (1.0 M in THF, 4.88 mL, 4.88 mmol) was added to a stirred solution of **251** (1.70 g, 3.25 mmol, >99:1 dr) at rt. The reaction mixture was stirred at rt for 48 h, then satd aq $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred at rt for 10 min. The reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo* to give **253** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 5:1) gave **253** as a white solid (880 mg, 81%, >99:1 dr); mp 153−155 °C; $[\alpha]_D^{25}$ +219 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 3020, 2966 (C–H), 1781 (C=O), 1645 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.1, C(α)*Me*), 1.66 (1H, dd, *J* 18.2, 3.8, C(3)H_A), 2.05 (1H, dd, *J* 18.2, 8.0, C(3)H_B), 2.47−2.55 (1H, m, C(1')H_A), 2.64−2.71 (1H, m, C(1')H_B), 3.59 (1H, d, *J* 17.4, NC$H_A$$H_B$Ph), 3.63 (1H, d, *J* 17.4, NC$H_A$$H_B$Ph), 3.79 (1H, q, *J* 7.1, C(α)*H*), 3.90 (1H, ddd, *J* 8.0, 6.4, 3.8, C(4)*H*), 4.50 (1H, app dt, *J* 9.0, 5.6, C(5)*H*), 5.10 (1H, dd, *J* 10.2, 1.5, C(3')H_A), 5.16 (1H, dd, *J* 17.2, 1.5, C(3')H_B), 5.90 (1H, ddt, *J* 17.2, 10.2, 6.8, C(2')*H*), 7.13−7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1 (C(α)*Me*), 32.1 (*C*(3)), 33.9 (*C*(1')), 51.9

(N*C*H$_2$Ph), 55.0 (*C*(4)), 56.3 (*C*(α)), 84.4 (*C*(5)), 118.1 (*C*(3')), 127.3, 127.7, 127.7, 127.9, 128.5, 128.8 (*o,m,p-Ph*), 133.8 (*C*(2')), 138.9, 140.4 (*i-Ph*), 176.4 (*C*(2)); *m/z* (ESI$^+$) 336 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{25}NNaO_2^+$ ([M+Na]$^+$) requires 358.1778; found 358.1780.

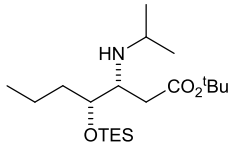
***tert*-Butyl (3*S*,4*R*)-3-(*N*-isopropylamino)-4-(triethylsilyloxy)heptanoate 254**



Method A: Pd(OH)$_2$/C (50 mg, 50% w/w) was added to a stirred solution of **250** (100 mg, 0.19 mmol, >99:1 dr) in degassed MeOH (2 mL) and acetone (0.2 mL) at rt under nitrogen. The resultant solution saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm). After 24 h, the reaction mixture was filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give **254** as a pale yellow oil (43 mg, 61%, >99:1 dr); $[\alpha]_D^{20}$ −3.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2876, 2935, 2958 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 0.60 (6H, q, *J* 8.0, Si(C*H*$_2$CH$_3$)$_3$), 0.90 (3H, t, *J* 6.9, C(7)*H*$_3$), 0.95 (9H, t, *J* 8.0, Si(CH$_2$C*H*$_3$)$_3$), 1.0 (3H, d, *J* 6.2, NCH*Me*$_A$Me$_B$), 1.01 (3H, d, *J* 6.2, NCHMe$_A$*Me*$_B$), 1.21−1.50 (4H, m, C(5)*H*$_2$, C(6)*H*$_2$), 1.44 (9H, s, C*Me*$_3$), 2.19 (1H, dd, *J* 15.0, 7.8, C(2)*H*$_A$), 2.33 (1H, dd, *J* 15.0, 5.2, C(2)*H*$_B$), 2.85 (1H, septet, *J* 6.2, NC*H*Me$_2$), 3.05 (1H, ddd, *J* 7.8, 5.2, 2.7 C(3)*H*), 3.75 (1H, td, *J* 6.0, 2.7, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 5.2 (Si(*C*H$_2$CH$_3$)$_3$), 7.0 (Si(CH$_2$*C*H$_3$)$_3$), 14.2 (*C*(7)), 19.1 (*C*(6)), 23.2, 23.4 (NCH*Me*$_2$), 28.1 ((C*Me*$_3$)), 36.0 (*C*(5)), 37.1 (*C*(2)), 45.4 (N*C*HMe$_2$), 55.8 (*C*(3)), 73.5 (*C*(4)), 80.0 ((*C*Me$_3$)), 172.5 (*C*(1)); *m/z* (ESI$^+$) 374 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{44}NO_3Si^+$ ([M+H]$^+$) requires 374.3085; found 374.3085.

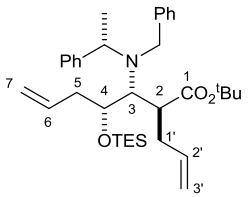
Method B: Pd(OH)$_2$/C (40 mg, 40% w/w) was added to a stirred solution of an 85:15 mixture of **248** and **249** (100 mg, 0.21 mmol) in degassed MeOH (1.5 mL) at rt under N_2. The resultant solution was stirred under an atmosphere of H_2 (1 atm). After 24 h, the reaction mixture was filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give an 85:15 mixture of **254** and **255** as a pale yellow oil (80 mg, quant).

tert-Butyl (_R_,_R_)-3-(_N_-isopropylamino)-4-(triethylsilyloxy)heptanoate 255



$Pd(OH)_2/C$ (33 mg, 50% w/w) was added to a stirred solution of **251** (66 mg, 0.13 mmol, >99:1 dr) in degassed MeOH (1.5 mL) and acetone (0.15 mL) at rt under nitrogen. The resultant solution saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm). After 24 h, the reaction mixture was filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give **255** as a pale yellow oil (40 mg, 82%, >99:1dr); $[\alpha]_D^{20}$ +6.1 (*c* 0.9 in $CHCl_3$); ν_{max} (ATR) 2876, 2957 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.61 (6H, q, *J* 8.0, $Si(CH_2CH_3)_3$), 0.90 (3H, t, *J* 7.1, C(7)H_3), 0.96 (9H, t, *J* 8.0, $Si(CH_2CH_3)_3$), 1.00 (3H, d, *J* 6.2, $NCHMe_AMe_B$), 1.03 (3H, d, *J* 6.2, $NCHMe_AMe_B$), 1.17−1.36 (2H, m, C(5)H_A, C(6)H_A), 1.45 (9H, s, CMe_3), 1.35−1.46 (1H, m, C(6)H_A), 1.53−1.64 (1H, m, C(5)H_B), 2.15 (1H, dd, *J* 14.8, 7.8, C(2)H_A), 2.50 (1H, dd, *J* 14.8, 5.2, C(2)H_B), 2.84 (1H, septet, *J* 6.2, $NCHMe_2$), 3.05 (1H, ddd, *J* 8.0, 4.9, 3.4 C(3)*H*), 3.65−3.70 (1H, m, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 5.1 ($Si(CH_2CH_3)_3$), 6.9 ($Si(CH_2CH_3)_3$), 14.2 (*C*(7)), 19.4 (*C*(6)), 23.4, 23.5 ($NCHMe_2$), 28.0 ((CMe_3)), 34.3 (*C*(5)), 37.5 (*C*(2)), 46.0 ($NCHMe_2$), 55.9 (*C*(3)), 73.6 (*C*(4)), 80.1 ((CMe_3)), 172.7 (*C*(1)); *m/z* (ESI^+) 374 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{44}NO_3Si^+$ ($[M+H]^+$) requires 374.3085; found 374.3079.

tert-Butyl (2_S_,3_R_,4_R_,α_S_)-2-allyl-3-[_N_-benzyl-_N_-(α-methylbenzyl)amino]-4-(triethylsilyloxy) hept-6-enoate 257



Method A: BuLi (2.2 M in hexanes, 2.60 mL, 5.74 mmol) was added dropwise to a stirred solution of $^iPr_2NH$ (0.94 mL, 6.70 mmol) in THF (15 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. A solution of **251** (1.00 g, 1.91 mmol, >99:1 dr) in THF (15 mL) at 0 °C was then added. The resultant mixture was stirred at 0 °C for 1 h, then allyl bromide (0.50

mL, 5.74 mmol) was added and the resultant mixture was allowed to warm to rt over 2 h. Satd aq NH_4Cl (15 mL) was then added and the reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (15 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **257** in 96:4 dr. Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **257** as a colourless oil (370 mg, 93%, 96:4 dr); $[\alpha]_D^{25}$ −31.3 (*c* 2.2 in $CHCl_3$); ν_{max} (ATR) 2977, 2955, 2912, 2876 (C−H), 1723 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 0.40 (6H, q, *J* 8.0, $Si(CH_2CH_3)_3$), 0.78 (9H, t, *J* 8.0, $Si(CH_2CH_3)_3$), 1.07 (3H, d, *J* 7.0, C(α)*Me*), 1.42 (9H, s, CMe_3), 2.06 (1H, ddd, *J* 12.7, 7.5, 5.0, C(5)H_A), 2.15−2.33 (2H, m, C(1')H_2), 2.49 (1H, app dt, *J* 7.5, 6.3, C(5)H_B), 2.75−2.85 (1H, m, C(2)*H*), 2.88 (1H, dd, *J* 7.9, 2.1, C(3)*H*), 3.76 (1H, ddd, *J* 7.5, 5.0, 2.1, C(4)*H*), 3.86 (1H, d, *J* 15.4, NCH_AH_BPh), 4.12 (1H, q, *J* 6.9, C(α)*H*), 4.45 (1H, d, *J* 15.4, NCH_AH_BPh), 4.65−4.74 (2H, m, C(3')H_2), 4.84−4.99 (3H, m, C(6)*H*, C(7)H_2), 5.63 (1H, ddt, *J* 17.2, 7.9, 6.3, C(2')*H*), 7.07−7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.3 ($Si(CH_2CH_3)_3$), 7.0 ($Si(CH_2CH_3)_3$), 22.1 (C(α)*Me*), 28.2 (CMe_3), 35.6 (*C*(1')), 39.2 (*C*(5)), 46.6 (*C*(2)), 52.8 (NCH_2Ph), 61.3 (*C*(α)), 61.9 (*C*(3)), 75.0 (*C*(4)), 80.7 (CMe_3), 116.5, 116.5 (*C*(7), *C*(3')), 125.8, 126.7, 127.7, 128.0, 128.1, 128.5 (*o,m,p-Ph*), 135.4, 135.6 (*C*(6), *C*(2')), 144.4, 146.2 (*i-Ph*), 174.8 (*C*(1)); *m/z* $(ESI)^+$ 564 ($[M+H]^+$,100%); HRMS (ESI^+) $C_{35}H_{54}NO_3Si^+$ ($[M+H]^+$) requires 564.3867; found 564.3858.

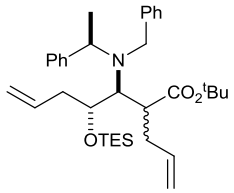
Method B: BuLi (2.2 M in hexanes, 275 μL, 0.61 mmol) was added dropwise *via* syringe to a stirred solution of (*S*)-**197** (135 μL, 0.64 mmol, >99:1 er) in THF (10 mL) at −78 °C. After stirring for 30 min a solution of **245** (100 mg, 0.32 mmol, >99:1 dr) in THF (10 mL) at −78 °C was added dropwise *via* cannula. The reaction mixture was left to stir for 2 h at −78 °C, before freshly distilled allyl bromide (55 μL, 0.64 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h, then concentrated *in vacuo*. The residue was 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 × 20 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 79:21 mixture of **251** and **257** and **258** (*anti*-**257**:*syn*-**258**, 71:29). Data for mixture *m/z* $(ESI)^+$ 564 ($[M+H]^+$, 100%); data for *syn*-**258** [selected peaks]; δ_H (400 MHz, $CDCl_3$) 0.54 (6H, q, *J* 7.9,

Si(CH_2CH$_3$)$_3$), 1.33 (3H, d, *J* 7.3, C(α)*Me*), 1.50 (9H, s, C*Me*$_3$), 3.01 (1H, app d, *J* 10.7, C(3)*H*), 3.53 (1H, app dd, *J* 8.2, 4.0, C(4)*H*), 4.34 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 5.80–6.00 (1H, m, C(2')*H*).

Method C: BuLi (2.2 M in hexanes, 275 μL, 0.61 mmol) was added dropwise *via* syringe to a stirred solution of (*S*)-**197** (135 μL, 0.64 mmol, >99:1 er) in THF (10 mL) at −78 °C. After stirring for 30 min a solution of **245** (100 mg, 0.32 mmol, >99:1 dr) in THF (10 mL) at −78 °C was added dropwise *via* cannula. The reaction mixture was left to stir for 2 h at −78 °C, before the addition of 12-crown-4 (100 μL, 0.61 mmol). The reaction mixture was stirred at −78 °C for 1 h before allyl bromide (55 μL, 0.64 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h, then concentrated *in vacuo*. The residue was 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 × 20 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 11:89 mixture of **251** and **257** and **258** (*anti*-**257**:*syn*-**258**, 47:53).

Method D: BuLi (2.2 M in hexanes, 275 μL, 0.61 mmol) was added dropwise *via* syringe to a stirred solution of (*S*)-**197** (135 μL, 0.64 mmol, >99:1 er) in THF (10 mL) at −78 °C. After stirring for 30 min a solution of **245** (100 mg, 0.32 mmol, >99:1 dr) in THF (10 mL) at −78 °C was added dropwise *via* cannula. The reaction mixture was left to stir for 2 h at −78 °C, before the addition of DMPU (74 μL, 0.61 mmol). The reaction mixture was stirred at −78 °C for 1 h before allyl bromide (55 μL, 0.64 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h, then concentrated *in vacuo*. The residue was 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 × 20 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 37:63 mixture of **251** and **257** and **258** (*anti*-**257**:*syn*-**258**, 70:30).

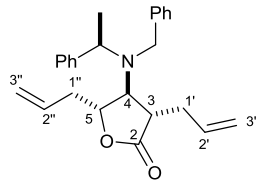
Attempted synthesis of *tert*-butyl (2*R*,3*S*,4*R*,α*R*)- or (2*S*,3*S*,4*R*,α*R*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triethylsilyloxy) hept-6-enoate 259



Method A: BuLi (2.2 M in hexanes, 225 μL, 0.49 mmol) was added dropwise *via* syringe to a stirred solution of (*R*)-**197** (105 μL, 0.50 mmol, >99:1 er) in THF (1 mL) at −78 °C. After stirring for 30 min a solution of **245** (100 mg, 0.32 mmol, >99:1 dr) in THF (1 mL) at −78 °C was added dropwise *via* cannula. The reaction mixture was left to stir for 2 h at −78 °C, before freshly distilled allyl bromide (55 μL, 0.64 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h, then concentrated *in vacuo*. The residue was 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 $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give a complex mixture containing **250** as the major component (150 mg, 80% purity).

Method B: BuLi (2.2 M in hexanes, 425 μL, 0.93 mmol) was added dropwise to a stirred solution of $^{i}Pr_2NH$ (135 μL, 0.96 mmol) in THF (1 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. A solution of **250** (100 mg, 0.19 mmol, >99:1 dr) in THF (2 mL) at 0 °C was then added. The resultant mixture was stirred at 0 °C for 1 h, then allyl bromide (85 μL, 0.96 mmol) was added and the resultant mixture was allowed to warm to rt over 2 h. Satd aq NH_4Cl (3 mL) was then added and the reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give a complex mixture of products containing **250** as the major component (200 mg, 60% purity).

(3*R*,4*S*,5*R*,α*R*)-3,5-Diallyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2-one 265

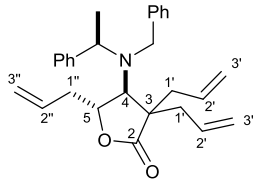


Step 1: BuLi (2.2 M in hexanes, 0.39 mL, 0.87 mmol) was added dropwise to a stirred solution of $^{i}Pr_2NH$ (125 μL mL, 0.90 mmol) in THF (3 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. The resultant solution was then added to a suspension of **252** (100 mg, 0.30 mmol, >99:1 dr) in THF (2 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 1 h, then allyl bromide (51 μL, 0.60 mmol) was added and the resultant mixture was then allowed to warm to rt over 2 h. Satd aq NH_4Cl (3 mL) was then added and the reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 75:25 mixture of **265** and **266**. Purification *via* flash column chromatography (eluent 30−40 °C petrol/EtOAc, 20:1) gave a 76:24 mixture of **265** and **266** as a colourless oil (70 mg, 63%). Selected data for **266**: δ_H (400 MHz, $CDCl_3$) 1.25 (3 H, d, *J*, 7.0, C(α)*Me*), 3.35 (1H, d, *J* 13.7 NCH_AH_BPh), 4.03 (1H, q, *J* 7.0, C(α)*H*), 5.87–5.48 (2H, m, C(2')*H*, C(5')*H*).

Step 2: KO^{t}Bu (18 mg, 0.16 mmol) was added to a stirred solution of a 74:26 mixture of **265** and **266** (54 mg, 0.16 mmol) in THF (3 mL). The resultant solution was stirred at rt for 16 h then satd aq NH_4Cl (3 mL) was added. The reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give **265** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc 10:1) gave **265** as a colourless oil (50 mg, 93%, >99:1 dr); $[\alpha]_D^{20}$ +24.4 (*c* 1.6 in $CHCl_3$); ν_{max} (ATR) 3063, 3029, 2977, 2933 (C−H), 1770 (C=O), 1642 (C=C); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.9, C(α)*Me*), 2.06−2.30 (3H, m, C(1')H_2, C(1")H_A), 2.38−2.46 (1H, m, C(1")H_B), 2.67 (1H, app q, *J* 6.0, C(3)*H*), 3.21 (1H, app t, *J* 6.3, C(4)*H*), 3.71−3.82 (2H, m, NCH_2Ph), 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.27 (1H, ddd, *J* 7.4, 6.0, 4.6, C(5)*H*), 4.76 (1H, dd, *J* 17.0,

1.2, C(3')H_A), 4.88 (1H, dd, *J* 10.5, 1.2, C(3')H_B), 4.98 (1H, dd, *J* 17.1, 1.5, C(3")H_A), 5.08 (1H, app d, *J* 10.3 C(3")H_B), 5.45 (1H, ddt, *J* 17.0, 10.5, 0.9, C(2')*H*), 5.66 (1H, ddt, *J* 17.1, 10.3, 6.9, C(2")*H*), 7.16−7.29 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8 (C(α)*Me*), 33.8 (*C*(1')), 38.4 (*C*(1")), 42.9 (*C*(3)), 51.1 (N*C*H_2Ph), 59.3 (*C*(α)), 62.8 (*C*(4)), 81.0 (*C*(5)), 118.5 (*C*(3')), 118.8 (*C*(3")), 127.2, 127.4, 127.7, 127.9, 128.5, 128.5 (*o,m,p-Ph*), 132.7 (*C*(2")), 133.9 (*C*(2')), 140.7, 144.0 (*i-Ph*), 177.4 (*C*(2)); *m/z* (ESI^+) 376 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{26}NO_2^+$ ($[M+H]^+$) requires 376.2271; found 376.2264.

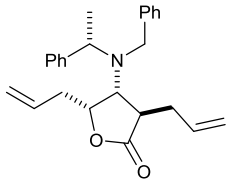
(4*S*,5*R*,α*R*)-3,3,5-Triallyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2-one 267



Step 1: BuLi (2.2 M in hexanes, 0.39 mL, 0.87 mmol) was added dropwise to a stirred solution of $^iPr_2NH$ (125 μL, 0.90 mmol) in THF (3 mL) at 0 °C and stirred for 30 min at 0 °C. The resultant solution was then added to a suspension of **252** (100 mg, 0.30 mmol, >99:1 dr) in THF (2 mL) at 0 °C. The reaction mixture was left to stir for 1 h, before the addition of allyl bromide (128 μL, 1.5 mmol) and the resultant mixture was allowed to warm to rt over 2 h. Satd aq NH_4Cl (3 mL) was added and THF was evaporated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 70:5:25 mixture of **265**, **266** and **267**, respectively. Purification *via* flash column chromatography (eluent 30−40 °C petrol/EtOAc, 20:1) gave **267** as a colourless oil (20 mg, 16%, >99:1 dr); $[\alpha]_D^{20}$ +10.2 (*c* 0.5 in $CHCl_3$); ν_{max}(ATR) 3076, 3029, (C–H), 1763 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 7.0, C(α)*Me*), 2.03 (2H, dd, *J* 7.0, 3.1 2 × C(1')H_A), 2.23−2.58 (4H, m, 2 × C(1')H_B, C(1")H_2), 3.31 (1H, d, *J* 4.6, C(3)*H*), 3.76 (2H, d, *J* 14.2, NCH_AH_BPh), 3.88 (1H, d, *J* 14.2, NCH_AH_BPh), 4.00 (1H, q, *J* 7.0, C(α)*H*), 4.57 (1H, dd, *J* 9.2, 4.3, C(5)*H*), 4.67 (1H, d, *J* 17.1 C(3")H_A), 4.73 (1H, d, *J* 8.5, C(3")H_B), 4.89–5.20 (5H, m, C(2")H, 2 × C(3')H_2), 5.77−5.95 (2H, m, 2 × C(2')*H*), 7.14−7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.3 (C(α)*Me*), 35.6 (*C*(1")),

39.2, 39.44 (2 × *C*(1')), 49.0 (N*C*H_2Ph), 51.7 (*C*(α)), 56.6 (*C*(4)), 63.0 (*C*(5)), 78.2 (*C*(3)), 118.3, 118.3, 119.3 (2 × *C*(3'), *C*(3")), 127.3, 127.5, 128.2, 128.5, 128.7 (*o,m,p-Ph*), 131.9 (*C*(2")), 133.8, 133.5 (2 × *C*(2')), 139.1 142.8 (*i-Ph*), 179.2 (*C*(2)). *m/z* (ESI^+) 438 ($[M+Na]^+$, 100%), 416 ($[M+H]^+$, 31%); HRMS (ESI^+) $C_{22}H_{26}NO_2^+$ ($[M+H]^+$) requires 416.2584; found 416.2585. Further elution gave a 90:10 mixture of **265** and **266** (59 mg, 52%).

(3*R*,4*R*,5*R*,α*S*)-3,5-Diallyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2-one 268

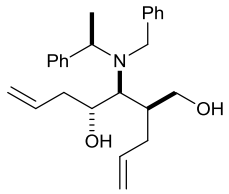


Step 1: BuLi (2.2 M in hexanes, 1.75 mL, 3.84 mmol) was added dropwise to a stirred solution of $^iPr_2NH$ (630 μL, 4.48 mmol) in THF (4.5 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. The resultant solution was then added to a suspension of **253** (430 mg, 1.28 mmol, >99:1 dr) in THF (9 mL) at 0 °C. The reaction mixture was left to stir at 0 °C for 1 h then allyl bromide (220 μL, 2.56 mmol) was added and the resultant mixture was allowed to warm to rt over 2 h. Satd aq NH_4Cl (5 mL) was then added and the reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give an 85:15 mixture of **268** and **269** (400 mg).

Step 2: KHMDS (0.7 M in PhMe, 760 μL, 0.53 mmol) was added to ^tBuOH (204 μL, 2.14 mmol) in THF (10 mL) and stirred at rt for 15 min. The resultant solution was added to a stirred solution of an 85:15 mixture of **268** and **269** (400 mg, 1.28 mmol) in THF (10 mL). The resultant solution was left to stir at rt for 24 h then satd aq NH_4Cl (5 mL) was added and the reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **268** in >95:5 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc 20:1) gave **268** as a colourless oil (250 mg, 52%, >99:1 dr); $[\alpha]_D^{25}$ +42.6 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3062, 2979 (C−H), 1764 (C=O), 1642

(C=C); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 7.1, C(α)*Me*), 1.92−2.00 (1H, m, C(1')H_A), 2.04−2.12 (1H, m, C(3)*H*, C(1')H_B), 2.48−2.65 (2H, m, C(1'')H_2), 3.50 (1H, dd, *J* 6.0, 1.5, C(4)*H*), 3.78 (2H, s, NCH_2Ph), 3.81 (1H, q, *J* 7.1, C(α)*H*), 4.45 (1H, td, *J* 8.8, 6.0, C(5)*H*), 4.90 (1H, d, *J* 17.2, C(3')H_A), 4.94 (1H, d, *J* 10.2, C(3')H_B), 5.09 (1H, d, *J* 10.2, C(3'')H_A), 5.14 (1H, d, *J* 17.2, C(3'')H_B), 5.47 (1H, app ddt, *J* 17.1, 10.2, 7.0, C(2')*H*), 5.88 (1H, app ddt, *J* 17.1, 10.2, 6.8, C(2'')*H*), 7.15−7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.3 (C(α)*Me*), 34.2 (*C*(1')), 34.4 (*C*(1'')), 42.6 (*C*(3)), 52.2 (N*C*H_2Ph), 56.9 (*C*(α)), 59.9 (*C*(4)), 83.4 (*C*(5)), 117.9 (*C*(3'')), 118.4 (*C*(3')), 127.3, 127.7, 127.8, 127.8, 127.6, 128.8 (*o*,*m*,*p*-*Ph*), 133.6 (*C*(2')), 134.1 (*C*(2'')), 139.2, 141.4 (*i*-*Ph*), 178.1 (*C*(2)); *m/z* (ESI^+) 376 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{30}NO_2^+$ ($[M+H]^+$) requires 376.2271; found 376.2271.

(2*S*,3*S*,4*R*,α*R*)-2-Allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-ene-1,4-diol 270



Method A: $LiAlH_4$ (1.0 M in THF, 1.5 mL, 1.50 mmol) was added to a stirred solution of **265** (140 mg, 0.37 mmol, >99:1 dr) in THF (3 mL) at 0 °C. The resultant solution was allowed to warm to rt over 2 h, 2.0 M aq NaOH (0.75 mL, 1.5 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **270** as a colourless oil (90 mg, 64%, >99:1 dr); $[\alpha]_D^{20}$ +34.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3268 (O–H) 2973 (C−H), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.28 (1H, d, *J* 6.9, C(α)*Me*), 1.56–1.68 (1H, m, C(2)*H*), 1.76–1.88 (1H, m, C(1')H_A), 2.13–2.28 (2H, m, C(1')H_B, C(5)H_A), 2.53–2.63 (1H, m, C(5)H_B), 2.61 (1H, app t, *J* 5.0, C(3)*H*), 2.79 (1H, br s, O*H*), 3.34 (1H, dd, *J* 11.4, 6.5, C(1)H_A), 3.62 (1H, app d, *J* 11.4, C(1)H_B), 3.82 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.88–4.01 (2H, m, C(4)*H*, C(α)*H*), 3.95 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 4.82 (2H, d, *J* 14.0, C(3')H_2), 5.02–5.05 (1H, m, C(7)H_A), 5.06–5.10 (1H, m, C(7)H_B), 5.36 (1H, dddd, *J* 17.7, 14.2, 8.5, 5.6, C(2')*H*), 5.71–5.87 (1H, m, C(6)*H*), 7.12–7.33 (10H, m, *Ph*); δ_C (100 MHz,

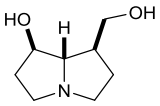
$CDCl_3$) 17.4 (C(α)*Me*), 35.5 (*C*(1')), 40.6 (*C*(2)), 41.2 (*C*(5)), 51.7 (NCH_2Ph), 58.0 (*C*(α)), 62.3 (*C*(1)), 63.0 (*C*(3)), 71.5 (*C*(4)), 115.9, 118.0 (*C*(7), *C*(3')), 126.8, 127.0, 128.1, 128.2 128.4, 128.6 (*o,m,p-Ph*), 136.0, 137.8 (*C*(6), *C*(2')), 141.4, 143.9 (*i-Ph*); *m/z* (ESI^+) 380 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{34}NO_2^+$ ($[M+H]^+$) requires 380.2584; found 380.2574.

Method B: Step 1: BuLi (2.2 M in hexanes, 2.5 mL, 5.40 mmol) was added dropwise to a stirred solution of $^iPr_2NH$ (885 μL, 6.30 mmol) in THF (9 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. The resultant solution was then added to a suspension of **252** (600 mg, 1.80 mmol, >99:1 dr) in THF (15 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 1 h, then allyl bromide (315 μL, 3.60 mmol) was added and the resultant mixture was then allowed to warm to rt over 2 h. Satd aq NH_4Cl (5 mL) was then added and the reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a 75:25 mixture of **265** and **266** (700 mg).

Step 2: KO^tBu (202 mg, 1.80 mmol) was added to a stirred solution of a 75:25 mixture of **265** and **266** (700 mg, 1.8 mmol) in THF (25 mL). The resultant solution was stirred at rt for 16 h then satd aq NH_4Cl (10 mL) was added. The reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **265** in >95:5 dr (725 mg).

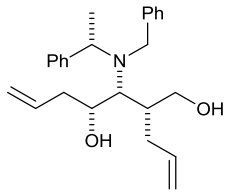
Step 3: $LiAlH_4$ (1.0 M in THF, 7.2 mL, 7.20 mmol) was added to a stirred solution of **265** (725 mg, 1.80 mmol, >95:5 dr) in THF (10 mL) at 0 °C. The resultant solution was allowed to warm to rt over 2 h, 2.0 M aq NaOH (3.6 mL, 3.60 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **270** as a colourless oil (390 mg, 57%, >99:1 dr);

(1*S*,7*R*,7a*S*)-1-Hydroxymethyl-7-hydroxyhexahydro-1*H*-pyrrolizine [(–)-hastanecine] 129



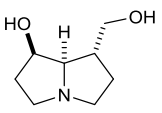
Amino diol **270** (380 mg, 1.00 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3mL), then dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 1.00 g, 3.00 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a volume of 3 mL, then AcOH (0.3 mL) and $Pd(OH)_2/C$ (100 mg, 25% w/w) were added. The resultant solution was degassed with N_2 and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo and coevaporated with HCl (2.0 M in Et_2O, 3 mL). Purification *via* ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **129** as a white solid (129 mg, 82% from **270**, >99:1 dr); mp 108–109 °C; $[\alpha]_D^{20}$ −8.3 (*c* 0.9 in EtOH); ν_{max} (ATR) 3290 (O−H); δ_H (400 MHz, MeOH-d_4) 1.40−1.55 (1H, m, C(2)H_A), 1.58−1.68 (1H, m, C(6)H_A), 1.75−2.00 (3H, m, C(1)*H*, C(2)H_B, C(6)H_B), 2.46 (1H, dt, *J* 10.1, 5.6, C(3)H_A), 2.63 (1H, ddd, *J* 11.2, 6.9, 4.1, C(5)H_A), 2.90 (1H, dd, *J* 7.5, 2.0, C(7a)*H*), 2.98−3.10 (2H, m, C(3)H_B, C(5)H_B), 3.45−3.55 (2H, m, C(1')H_2), 3.96−4.01 (1H, m, C(7)*H*); δ_C (100 MHz, MeOH-d_4) 29.2 (*C*(2)), 32.0 (*C*(6)), 46.1 (*C*(1)), 51.7 (*C*(5)), 54.1 (*C*(3)), 63.5 (*C*(1')), 75.8 (*C*(7a)), 75.9 (*C*(7)); δ_H (400 MHz, $CDCl_3$) 1.60−1.76 (1H, m, C(2)H_A), 1.81−2.01 (3H, m, C(1)*H*, C(2)H_B, C(6)H_A), 2.06 (1H, dq, *J* 12.6, 6.4, C(6)H_B), 2.51 (1H, td, *J* 10.1, 5.6, C(3)H_A), 2.65 (1H, dt, *J* 10.9, 6.4, C(5)H_A), 3.09–3.25 (3H, m, C(3)H_B, C(5)H_B, C(7a)*H*), 3.54 (1H, dd, *J* 10.7, 7.9, C(1')H_A), 3.80 (1H, dd, *J* 10.7, 4.2, C(1')H_B), 4.05−4.13 (1H, m, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 30.8 (*C*(2)), 33.5 (*C*(6)), 47.6 (*C*(1)), 53.3 (*C*(5)), 55.6 (*C*(3)), 65.5 (*C*(1')), 77.3 (*C*(7a)), 77.5 (*C*(7)); *m/z* (ESI$^+$) 158 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_2^+$ ([M+H]$^+$) requires 158.1176; found 158.1176.

(2*R*,3*R*,4*R*,α*S*)-2-Allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-en-1,4-diol 273



$LiAlH_4$ (2.4 M in THF, 3.2 mL, 7.68 mmol) was added to a stirred solution of **268** (700 mg, 1.92 mmol, >99:1 dr) in THF (10 mL) at 0 °C. The resultant solution was allowed to warm to rt over 2 h, 2.0 M aq NaOH (3.8 mL, 7.6 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O, 4:1) gave **273** as a colourless oil (570 mg, 80%, >99:1 dr); $[\alpha]_D^{20}$ −31.2 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 3327 (O−H), 3063, 2974, 2930 (C−H), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 7.0, C(α)*Me*), 1.47 (1H, app tt, *J* 9.1, 4.4, C(2)*H*), 1.87−2.00 (2H, m, C(5)H_2), 2.26−2.36 (2H, m, C(1')H_2), 2.73 (1H, m, C(3)*H*), 3.35 (1H, br s O*H*), 3.35 (1H, dd, *J* 11.7, 4.4, C(1)H_A), 3.59 (1H, dd, *J* 11.7, 4.4, C(1)H_B), 3.78 (1H, app q, *J* 5.8, C(4)*H*), 3.86 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 4.02 (1H, q, *J* 7.0, C(α)*H*), 4.20 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 4.84–4.88 (2H, m, C(7)H_2), 5.07 (1H, m, C(3')H_A), 5.08−5.13 (1H, m, C(3')H_B), 5.30−5.43 (1H, m, C(6)*H*), 5.08−5.13 (1H, m, C(2')*H*), 7.15−7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(α)*Me*), 36.3 (*C*(5)), 39.8 (*C*(1')), 40.8 (*C*(2)), 52.6 (N*C*H_2Ph), 58.4 (*C*(α)), 62.7 (*C*(1)), 62.8 (*C*(3)), 69.7 (*C*(4)), 116.3 (*C*(7)), 117.7 *C*(3')), 126.9, 127.2, 128.0, 128.2, 128.4, 128.5, 128.6 (*o*,*m*,*p*-*Ph*), 135.7 (*C*(2')), 137.6 (*C*(6)), 141.1, 143.6 (*i*-*Ph*); *m/z* (ESI^+) 380 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{34}NO_2^+$ ($[M+H]^+$) requires 380.2584; found 380.2581.

(*R*,*R*,*R*)-1-Hydroxymethyl-7-hydroxyhexahydro-1*H*-pyrrolizine [(−)-turneforcidine] 130



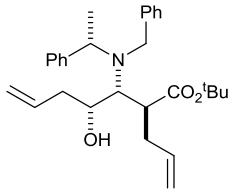
Method A: Aminodiol **273** (500 mg, 1.32 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3mL) then dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution

until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 1.30 g, 3.96 mmol) was added and the reaction mixture was allowed to warm to rt and stirred at rt for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a volume of 3 mL, then AcOH (0.15 mL) and $Pd(OH)_2/C$ (400 mg, 40% w/w) were added. The resultant solution was degassed with N_2 and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification *via* column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 6:4:1) gave a complex mixture of compounds.

Method B: **273** (230 mg, 0.60 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3mL), then dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 600 mg, 1.80 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for at rt for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a volume of 3 mL then AcOH (0.15 mL) and $Pd(OH)_2/C$ (92 mg, 40% w/w) were added. The resultant solution was degassed with N_2 and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) at rt for 48 h then heated at 50 °C for further 72 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification *via* column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 6:4:1) gave **130** as a white solid (40 mg, 42%, >99:1 dr); mp 110–115 °C; $[\alpha]_D^{20}$ −10.0 (*c* 0.8 in MeOH); ν_{max} (ATR) 3391 (O−H), 2967, 2934 (C−H); ν_{max} (ATR) 3391 (O−H), 2967, 2934 (C−H); δ_H (400 MHz, MeOH-d_4) 1.66 (1H, dtd, *J* 12.4, 9.3, 6.8, C(2)H_A), 1.93−1.99 (2H, m, C(6)H_2), 2.07 (1H, dtd, *J* 12.4, 6.8, 3.0, C(2)H_B), 2.46−2.60 (2H, m, C(1)*H*, C(3)H_A), 2.68 (1H, q, *J* 8.9, C(5)H_A), 2.97−3.08 (2H, m, C(3)H_B, C(5)H_B), 3.14 (1H, dd, *J* 6.9, 4.6, C(7a)*H*), 3.49 (1H, dd, *J* 10.6, 7.1, C(1')H_A), 3.54 (1H, dd, *J* 10.6, 6.6, C(1')H_B), 4.14 (1H, app q, *J* 3.7, C(7)*H*); δ_C (100 MHz, MeOH-d_4) 32.6 (*C*(2)), 37.6 (*C*(6)), 40.9 (*C*(1)), 52.9 (*C*(3)), 56.4 (*C*(5)), 65.8 (*C*(1')), 72.1 (*C*(7)), 73.8 (*C*(7a)); δ_H (400 MHz, $CDCl_3$) 1.60−1.72 (1H, m, C(2)H_A), 1.83−2.14 (3H, m, C(2)H_B, C(6)H_2), 2.46−2.57 (1H, m, C(1)*H*), 2.62

(1H, td, *J* 10.3, 6.2, C(3)H_A), 2.70 (1H, td, *J* 9.5, 6.4, C(5)H_A), 3.07 (1H, ddd, *J* 10.3, 6.9, 4.1, C(3)H_B), 3.23 (1H, ddd, *J* 9.4, 7.4, 1.8, C(5)H_B), 3.38 (1H, dd, *J* 8.3, 5.4, C(7a)*H*), 3.49 (1H, app t, *J* 9.8, C(1')H_A), 3.87 (1H, dd, *J* 9.8, 4.6, C(1')H_B), 4.37 (1H, dd, *J* 9.2, 5.4, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 31.0 (*C*(2)), 35.7 (*C*(6)), 40.0 (*C*(1)), 52.1 (*C*(3)), 55.0 (*C*(5)), 65.4 (*C*(1')), 71.5 (*C*(7)), 74.3 (*C*(7a)); *m/z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1176.

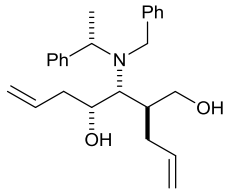
tert-Butyl (2*S*,3*R*,4*R*,α*S*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-hydroxyhept-6-enoate 275



HF (70% in py, 1.45 mL, 53.3 mmol) was added to a stirred solution of **257** (1.00 g, 1.78 mmol, 96:4 dr) in THF (10 mL) at 0 °C and the resultant solution was allowed to warm to rt over 18 h. Satd aq $NaHCO_3$ was added until pH > 7 and the resultant mixture was stirred at rt for 30 min, then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **275** as a colorless oil (760 mg, 92%, 96:4 dr); $[\alpha]_D^{25}$ −13.3 (*c* 1.3 in $CHCl_3$); ν_{max} (ATR) 3375 (O−H), 2977 (C−H), 1722 (C=O), 1641 (C=C); δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.50 (9H, s, CMe_3), 2.00−2.11 (1H, m, C(5)H_A), 2.22−2.33 (2H, m, C(5)H_B, C(1')H_A), 2.39 (1H, ddd, *J* 14.3, 10.9, 6.9, C(1')H_B), 2.52 (1H, dt, *J* 10.9, 2.6, C(2)*H*), 3.36 (1H, dd, *J* 8.0, 2.6, C(3)*H*), 3.67 (1H, app t, *J* 7.8, C(4)*H*), 3.74 (1H, d, *J* 14.3, NCH_AH_BPh), 3.94 (1H, br s, O*H*), 4.10 (1H, d, *J* 14.3, NCH_AH_BPh), 4.13 (1H, q, *J* 6.9, C(α)*H*), 4.95 (1H, app d, *J* 7.1, C(3')H_A), 4.98 (1H, app s, C(3')H_B), 5.05 (1H, d, *J* 10.2, C(7)H_A), 5.09 (1H, dd, *J* 17.0, 1.6, C(7)H_B), 5.67 (1H, ddt, *J* 16.8, 10.5, 6.5, C(2')*H*), 5.83 (1H, app ddt, *J* 17.0, 10.2, 7.0, C(6)*H*), 7.24−7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.7 (C(α)*Me*), 27.1 (CMe_3), 31.5 (*C*(1')), 38.1 (*C*(5)), 44.2 (*C*(2)), 50.2 (N*C*H_2Ph), 58.7 (*C*(α)), 61.6 (*C*(3)), 67.0 (*C*(4)), 80.1 (*C*Me_3), 115.0 (*C*(3')), 115.8 (*C*(7)), 125.9, 126.3, 127.1, 127.3, 127.5, 127.8 (*o,m,p-Ph*), 134.5

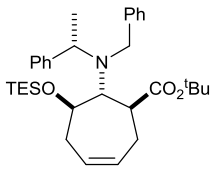
(*C*(6)), 135.2 (*C*(2')), 139.5, 141.9 (*i-Ph*), 172.7 (*C*(1)); *m/z* (ESI)$^+$ 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_3^+$ ([M+H]$^+$) requires 450.3003; found 450.2999.

(2*S*,3*R*,4*R*,α*S*)-2-Allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-ene-1,4-diol 276



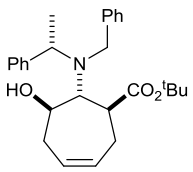
$LiAlH_4$ (2.4 M in THF, 2.6 mL, 6.24 mmol) was added to a stirred solution of **275** (700 mg, 1.56 mmol, 96:4 dr) in THF (7 mL) at –78 °C. The resultant solution was allowed to warm to rt and stirred for 16 h, 2.0 M aq NaOH (3.15 mL, 6.3 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **276** as a colourless oil (530 mg, 91%, 95:5 dr); (530 mg, 91%, 96:4 dr); $[\alpha]_D^{25}$ −49.2 (*c* 1.3 in $CHCl_3$); ν_{max} (ATR) 3405 (O–H), 3062, 2975, 2934 (C−H) 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 7.0, C(α)*Me*), 1.55−1.66 (1H, m, C(2)*H*), 1.75−1.86 (1H, m, C(1')H_A), 1.97−2.09 (1H, m, C(5)H_A), 2.21−2.36 (2H, m, C(5)H_B, C(1')H_B), 2.81 (1H, dd, *J* 7.5, 3.4, C(3)*H*), 3.12−3.23 (1H, m, C(1)H_A), 3.23 (1H, dd, *J* 10.5, 5.0, C(1)H_B), 3.69 (1H, app td, *J* 8.0, 2.5, C(4)*H*), 3.75 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 3.80 (1H, br s, O*H*), 3.98 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 4.01 (1H, q, *J* 7.0, C(α)*H*), 4.86−4.95 (2H, m, C(3')H_2), 5.00−5.09 (2H, m, C(7)H_2), 5.55−5.66 (1H, m, C(2')*H*), 5.76−5.88 (1H, m, C(6)*H*), 7.17−7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.9 (C(α)*Me*), 33.3 (*C*(1')), 39.2 (*C*(5)), 40.0 (*C*(2)), 51.4 (N*C*H$_2$Ph), 58.0 (*C*(α)), 61.5 (*C*(3)), 65.8 (*C*(1)), 67.8 (*C*(4)), 115.9 (*C*(3')), 117.2 (*C*(7)), 127.1, 127.3, 128.0, 128.4, 128.6, 128.7 (*o,m,p-Ph*), 135.6 (*C*(2')), 137.4 (*C*(6)), 140.1, 143.2 (*i-Ph*); *m/z* (ESI$^+$) 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_2^+$ ([M+H]$^+$) requires 380.2584; found 380.2580.

tert-Butyl (1*S*,6*R*,7*R*,α*S*)-6-(triethylsilyloxy)-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino] cyclohept-3-ene-1-carboxylate 279



Grubbs I catalyst (102 mg, 0.12 mmol) was added to a stirred solution of **257** (350 mg, 0.62 mmol, 96:4 dr) in degassed CH_2Cl_2 (35 mL) at 35 °C. The resultant mixture was stirred at 35 °C for 16 h then allowed to cool to rt and concentrated *in vacuo*. Purification *via* column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **279** as a colourless oil (310 mg, 93%, >99:1 dr); $[\alpha]_D^{25}$ –8.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2955, 2876 (C–H), 1726 (C=O), 1656 (C=C); δ_H (400 MHz, $CDCl_3$) 0.72 (6H, q, *J* 8.0, Si(CH_2CH$_3$)$_3$), 1.05 (9H, t, *J* 8.0, Si(CH$_2$CH_3)$_3$), 1.48 (9H, s, CMe_3), 1.46 (3H, m, C(α)*Me*), 2.09 (1H, dd, *J* 15.0, 6.6, C(2)H_A), 2.37–2.55 (4H, m, C(1)*H*, C(2)H_B, C(5)H_2), 3.72 (1H, d, *J* 14.5, NCH_AH$_B$Ph), 3.80 (1H, dd, *J* 8.2, 6.6, C(7)*H*), 3.88 (1H, d, *J* 14.5, NCH$_A$$H_B$Ph), 4.05 (1H, q, *J* 6.9, C(α)*H*), 4.17–4.25 (1H, m, C(6)*H*), 5.50–5.58 (1H, m, C(4)*H*), 5.63–5.71 (1H, m, C(3)*H*), 7.07–7.29 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.6 (Si(*C*H$_2$CH$_3$)$_3$), 7.1 (Si(CH$_2$*C*H$_3$)$_3$), 20.1 (C(α)*Me*), 28.1 (C*Me*$_3$), 28.9 (*C*(2)), 35.3 (*C*(5)), 48.9 (*C*(1)), 52.3 (N*C*H$_2$Ph), 61.5 (*C*(α)), 64.8 (*C*(7)), 71.9 (*C*(6)), 79.7 (*C*Me$_3$), 126.8 (*C*(4)), 126.2, 126.2, 127.5, 127.6, 128.0, 128.9 (*o*,*m*,*p*-*Ph*), 129.6 (*C*(3)), 141.5, 145.9 (*i*-*Ph*), 174.1 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 536 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{50}NO_3Si^+$ ([M+H]$^+$) requires 536.3554; found 536.3551.

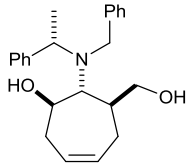
tert-Butyl (1*S*,6*R*,7*R*,α*S*)-6-hydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-hydroxylcyclohept-3-en-1-carboxylate 280



HF (70% in py, 0.33 mL, 11.4 mmol) was added to a stirred solution of **279** (200 mg, 0.38 mmol) in THF (3 mL) at 0 °C and the resultant solution was allowed to warm to rt then stirred at rt for

18 h. Satd aq $NaHCO_3$ was added until pH > 7 and the resultant mixture was stirred at rt for 30 min, then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **280** as a white solid (167 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ −55.7 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3443 (O−H), 2930, 2974, 3026 (C−H), 1724 (C=O), 1656 (C=C); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 1.42 (3H, d, *J* 7.2, C(α)*Me*), 2.08−2.15 (1H, m, C(1)*H*), 2.23−2.58 (4H, m, C(2)H_2, C(5)H_2), 3.53 (1H, d, *J* 13.9, NCH_AH$_B$Ph), 3.88 (1H, q, *J* 7.2, C(α)*H*), 3.84−3.95 (2H, m, C(6)*H*, C(7)*H*), 3.95 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 4.01 (1H, br s, O*H*), 5.37 (1H, m, C(3)*H*), 5.55 (1H, app ddt, *J* 11.1, 6.5, 2.0, C(4)*H*), 7.20−7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 28.0 (C*Me*$_3$), 27.8 (*C*(2)), 34.4 (*C*(5)), 43.5 (*C*(1)), 49.5 (N*C*H$_2$Ph), 56.7 (*C*(α)), 59.7 (*C*(7)), 66.9 (*C*(6)), 80.3 (*C*Me$_3$), 126.4 (*C*(3)), 128.6 (*C*(4)), 127.2, 127.3, 128.0, 128.4, 128.7, 128.7 (*o,m,p-Ph*), 139.6, 140.7 (*i-Ph*), 173.2 (*C*O$_2$^{t}Bu); *m/z* (ESI)$^+$ 422 ([M+H]$^+$,100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_3^+$ ([M+H]$^+$) requires 422.2690; found 422.2687.

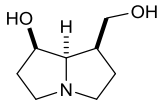
(1*S*,6*R*,7*R*,α*S*)-1-hydroxymethyl-6-hydroxy-7-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-cyclohept-3-ene 281



$LiAlH_4$ (2.4 M in THF, 0.67 mL, 1.6 mmol) was added to a stirred solution of **280** (165 mg, 0.39 mmol, >99:1 dr) in THF (2 mL) at –78 °C. The resultant solution was allowed to warm to rt and stirred at rt for 18 h, 2.0 M aq NaOH (0.8 mL, 1.6 mmol) was then added and the reaction mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **281** as a colourless oil (140 mg, 95%, >99:1 dr). $[\alpha]_D^{25}$ −68.5 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3415 (O−H), 3025, 2969, 2915 (C–H), 1660 (C=C); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.0, C(α)*Me*), 1.63 (1H, br s, O*H*), 1.77–1.86 (1H, m, C(1)*H*), 1.77–1.86 (1H, m, C(5)H_A), 2.08–2.28 (2H, m, C(2)H_2), 2.43 (1H, dd, *J* 9.0, 2.6, C(7)*H*), 2.48

(1H, dd, *J* 17.6, 6.3, C(5)H_B), 3.16 (1H, dd, *J* 10.5, 5.5, C(1')H_A), 3.30 (1H, m, C(1')H_B), 3.72 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 3.77 (1H, br s, O*H*), 3.81–3.89 (1H, m, C(6)*H*), 3.96 (1H, q, *J* 7.0, C(α)*H*), 3.99 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 5.39–5.47 (1H, m, C(3)*H*), 5.47–5.55 (1H, m, C(4)*H*), 7.18–7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.7 (C(α)*Me*), 26.9 (*C*(2)), 34.9 (*C*(5)), 38.5 (*C*(1)), 50.2 (N*C*H$_2$Ph), 60.0 (*C*(α)), 65.3 (*C*(1')), 65.6 (*C*(7)), 67.7 (*C*(6)), 127.0 (*C*(3)), 127.4 (*C*(4)), 126.8, 127.1, 127.9, 128.4, 128.5, 128.6 (*o,m,p-Ph*), 140.6, 143.3 (*i-Ph*); *m/z* (ESI$^+$) 352 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{30}NO_2^+$ ([M+H]$^+$) requires 352.2271; found 352.2268.

(1*S*,7*R*,7a*R*)-1-Hydroxymethyl-7-hydroxy-hexahydro-1*H*-pyrrolizine [(–)-platynecine] 131



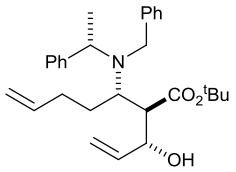
Method A: aminodiol **273** (200 mg, 0.53 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 2 mL), then dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 550 mg, 1.59 mmol) was added and the reaction mixture was allowed to warm to rt and stirred at rt for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a volume of 3 mL, then AcOH (0.15 mL) and $Pd(OH)_2$/C (76 mg, 40% w/w) were added. The resultant solution was degassed with N_2 and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to give a complex mixture of products.

Method B: aminodiol **281** (170 mg, 0.48 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 2 mL), then dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 480 mg, 1.44 mmol) was added and the reaction mixture was allowed to warm to rt and stirred at rt for 3 h. The reaction mixture was then filtered through a

short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a volume of 3 mL, then AcOH (0.15 mL) and $Pd(OH)_2/C$ (76 mg, 40% w/w) were added. The resultant solution was degassed with N_2 and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification *via* column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 6:4:1) gave **131** as a white solid (39 mg, 51%, >99:1 dr); mp 140–142 °C; $[\alpha]_D^{20}$ −58.8 (*c* 0.85 in EtOH); $[\alpha]_D^{20}$ −55.0 (*c* 0.2 in $CHCl_3$); ν_{max} (ATR) 3334 (O−H); δ_H (400 MHz, MeOH-d_4) 1.78 (1H, app dtd, *J* 11.8, 7.2, 2.3, C(2)H_A), 1.89−1.96 (2H, m, C(6)H_2), 1.99−2.11 (1H, m, C(2)H_B), 2.42−2.57 (1H, m, C(1)*H*), 2.85−3.00 (2H, m, C(3)H_A, C(5)H_A), 3.20 (1H, app td, *J* 10.5, 7.2, C(3)H_B), 3.33−3.38 (1H, m, C(5)H_B), 3.43 (1H, dd, *J* 8.1, 3.2, C(7a)*H*), 3.90−4.00 (2H, m, C(1')H_2), 4.30 (1H, app q, *J* 2.7, C(7)*H*); δ_C (100 MHz, MeOH-d_4) 29.0 (*C*(2)), 37.4 (*C*(6)), 45.0 (*C*(1)), 55.1 (*C*(5)), 56.7 (*C*(3)), 61.6 (*C*(1')), 73.0 (*C*(7)), 73.2 (*C*(7a)); δ_H (400 MHz, $CDCl_3$) 1.65−1.76 (1H, m, C(2)H_A), 1.88−2.07 (2H, m, C(6)H_2), 2.17 (1H, tt, *J* 11.0, 9.3, C(2)H_B), 2.45–2.55 (1H, m, C(1)*H*), 2.85 (1H, dt, *J* 8.9, 1.8, C(3)H_A), 2.91–3.00 (1H, m, C(5)H_A), 3.24 (1H, app q, *J* 8.9, C(3)H_B), 3.30–3.43 (2H, m, C(5)H_B, C(7a)*H*), 3.91 (1H, dd, *J* 11.2, 2.1, C(1')H_A), 3.93 (1H, dd, *J* 11.2, 4.7, C(1')H_B), 4.25–4.32 (1H, m, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 27.0 (*C*(2)), 36.0 (*C*(6)), 42.2 (*C*(1)), 53.8 (*C*(3)), 55.3 (*C*(5)), 60.0 (*C*(1')), 72.0 (*C*(7)), 72.8 (*C*(7a)); *m/z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1175.

5.4. Experimental data for Chapter 4

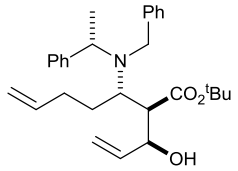
tert-Butyl (2*R*,3*S*,*αS*,1'*R*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino] hept-6-enoate 293



BuLi (2.2 M in hexanes, 390 μL, 0.85 mmol) was added dropwise *via* syringe to a stirred solution of (*S*)-**197** (185 μL, 0.88 mmol) in THF (3 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **181** (100 mg, 0.55 mmol, >99:1 dr) in THF (3 mL) at −78 °C was added dropwise via cannula. The resultant reaction mixture was stirred at −78 °C for 2 h, before the addition of $TiCl(O^iPr)_3$ (395 μL, 1.65 mmol). The resultant mixture was stirred for 1 h at −78 °C, then acrolein (515 μL, 7.75 mmol) was added and the reaction mixture was allowed to warm to 0 °C over 2 h. Satd aq NH_4Cl (2 mL) was then added, the reaction mixture was concentrated *in vacuo* and 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 (3 × 10 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 49:15:23:13 mixture of **293**, **294**, **295** and **296**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 increased to 10:1) gave **293** as a colourless oil (55 mg, 22%, >99:1 dr); $[\alpha]_D^{25}$ +14.3 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3522 (O−H), 2976 (C−H), 1701 (C=O), 1634 (C=C); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.9, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 1.45−1.55 (1H, m, C(4)H_A), 1.65−1.76 (1H, m, C(4)H_B), 2.03−2.15 (2H, m, C(5)H_2), 2.43 (1H, dd, *J* 8.5, 2.2, C(2)*H*), 3.25−3.32 (1H, m, C(3)*H*), 3.72 (1H, d, *J* 14.5, NCH_AH$_B$Ph), 3.87−3.93 (2H, m, C(α)*H*, C(1')*H*), 3.94 (1H, d, *J* 14.5, NCH$_A$$H_B$Ph), 4.85−5.00 (3H, m, C(3')H_A, C(7)H_2), 5.10−5.15 (1H, m, C(3')H_B), 5.56−5.75 (2H, m, C(2')*H*, C(6)*H*), 7.10−7.40 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 28.3 (C*Me*$_3$), 29.9 (*C*(4)), 32.0 (*C*(5)), 50.8 (N*C*H$_2$Ph), 54.3 (*C*(2)), 57.3 (*C*(3)), 59.1 (*C*(α)), 70.8 (*C*(1')), 81.8 (*C*Me$_3$), 114.6, 114.7 (*C*(7), *C*(3')), 126.7, 126.9, 127.9, 128.1, 128.4, 128.9 (*o,m,p-Ph*), 138.5, 138.8 (*C*(6), *C*(2')), 141.3, 143.7 (*i-Ph*), 173.4 (*C*(1)); *m/z* $(ESI)^+$

450 ($[M+H]^+$,100%); HRMS (ESI^+) $C_{29}H_{40}NO_3^+$ ($[M+H]^+$) requires 450.3003; found 450.3003. Further elution gave a 28:21:33:18 mixture of **293**, **294**, **295** and **296**, respectively (120 mg, 48%, 28:21:33:18 dr).

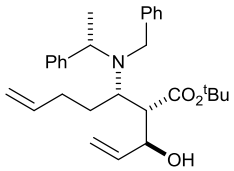
tert-Butyl (2*R*,3*S*,α*S*,1'*S*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino] hept-6-enoate 294



BuLi (2.2 M in hexanes, 4.5 mL, 9.90 mmol) was added to a stirred solution of $^iPr_2NH$ (1.62 mL, 11.6 mmol) in THF (10 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **182** (1.30 g, 3.30 mmol, >99:1 dr) in THF (10 mL) at 0 °C was added dropwise. The reaction mixture was left to stir at 0 °C for 1 h then cooled to −78 °C and $B(OMe)_3$ (4.5 mL, 13.2 mmol) was added. The reaction mixture was left to stir at −78 °C for 1 h then acrolein (1.1 mL, 16.5 mmol) was added and the reaction mixture was allowed to warm to 0 °C over 2 h. Satd aq NH_4Cl (5 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed sequentially with H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a 10:33:31:36 mixture of **293**, **294**, **295** and **296**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 increased to 10:1) gave **293** (30 mg, 3%, >99:1 dr), a 80:20 mixture of **294** and **293**, respectively (100 mg, 10%, 80:20 dr) and **294** (210 mg, 14%, >99:1 dr); $[\alpha]_D^{25}$ −38.5 (*c* 1.4 in $CHCl_3$); ν_{max} (ATR) 3427 (O−H), 2976 (C−H), 1721 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 7.0, C(α)*Me*), 1.70−1.90 (2H, m, C(4)*H*$_2$), 1.90−2.02 (1H, m, C(5)*H*$_A$), 2.10−2.22 (1H, m, C(5)*H*$_B$), 2.24 (1H, dd, *J* 9.8, 4.4, C(2)*H*), 3.13 (1H, dt, *J* 9.8, 3.9, C(3)*H*), 3.59 (1H, d, *J* 13.7, NC*H*$_A$H$_B$Ph), 3.90 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ph), 3.99 (1H, q, *J* 7.0, C(α)*H*), 4.15−4.27 (1H, m, C(1')*H*), 4.93−5.04 (3H, m, C(3')*H*$_A$, C(7)*H*$_2$), 5.12 (1H, app dt, *J* 17.0, 1.6, C(3')*H*$_B$), 5.69 (1H, ddd, *J* 17.0, 10.6, 5.6, C(2')*H*), 5.79 (1H, ddt, *J* 17.0, 10.2, 6.7, C(6)*H*), 7.15−7.32 (8H, m, *Ph*), 7.40−7.46 (2H, d, *J* 7.3, *Ph*); δ_C (100

MHz, $CDCl_3$) 12.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 29.3 (*C*(4)), 31.7 (*C*(5)), 51.2 (N*C*H$_2$Ph), 54.0 (*C*(2)), 54.7 (*C*(3)), 56.7 (*C*(α)), 70.1 (*C*(1')), 80.9 (*C*Me$_3$), 115.6, 115.1 (*C*(7), *C*(3')), 127.0, 127.3, 128.3, 128.3, 128.5, 129.4 (*o*,*m*,*p*-*Ph*), 138.2 (*C*(6)), 138.7 (*C*(2')), 140.9, 143.9 (*i*-*Ph*), 172.0 (*C*(1)); *m/z* (ESI)$^+$ 450 ([M+H]$^+$,100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_3^+$ ([M+H]$^+$) requires 450.3003; found 450.2996. Further elution gave a 78:22 mixture of **295** and **294**, respectively (280 mg, 19%, 78:22 dr), a 91:9 mixture of **295** and **296**, respectively (200 mg, 20%, 54:64 dr).

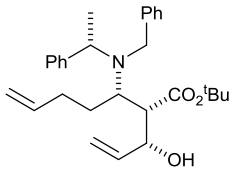
tert-Butyl (*S*,*S*,*S*,*S*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino] hept-6-enoate 295



BuLi (2.2 M in hexanes, 1.67 mL, 3.67 mmol) was added to a stirred solution of TMP (645 μL, 3.81 mmol) in THF (10 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **182** (500 mg, 1.20 mmol, >99:1 dr) in THF (10 mL) at 0 °C was added dropwise. The reaction mixture was left to stir at 0 °C for 1 h then cooled to −78 °C and acrolein (470 μL, 6.35 mmol) was added and the reaction mixture was allowed to warm to rt over 3 h. Satd aq NH_4Cl (5 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue was then partitioned between CH_2Cl_2 (20 mL) and satd aq NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 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 5:1:72:22 mixture of **293**, **294**, **295** and **296**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 increased to 10:1) gave a 85:15 mixture of **293** and **294**, respectively (25 mg, 5%, 85:15 dr), a 14:86 mixture of **294** and **295**, respectively (37 mg, 7%, 14:86 dr) and **295** as a colourless oil (260 mg, 49%, >99:1 dr); $[\alpha]_D^{20}$ −16.4 (*c* 0.55 in $CHCl_3$); ν_{max} (ATR) 3484 (O−H), 2976, 2934 (C−H), 1697 (C=O), 1640 (C=C); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.33−1.42 (1H, m, C(4)*H*$_A$), 1.60−1.70 (1H, m, C(4)*H*$_B$), 1.79−1.88 (1H, m, C(5)*H*$_A$), 2.04−2.15 (1H, m, C(5)*H*$_B$), 2.25 (1H, dd, *J* 8.5, 3.2, C(2)*H*), 3.14 (1H, app d, *J* 14.8, O*H*), 3.24 (1H, dt, *J* 8.5, 4.4, C(3)*H*),

3.75 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph),3.94 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ph), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.15−4.23 (1H, m, C(1')*H*), 4.80−4.90 (2H, m, C(7)*H*$_2$) 4.92 (1H, ap dt, *J* 10.8, 1.5, C(3')*H*$_A$), 5.05 (1H, app dt, *J* 17.3, 1.5, C(3')*H*$_B$), 5.42 (1H, ddd, *J* 17.3, 10.8, 4.4, C(2')*H*), 5.63 (1H, ddt, *J* 17.0, 10.4, 6.6, C(6)*H*), 7.10−7.30 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 30.4 (*C*(4)), 31.7 (*C*(5)), 50.6 (N*C*H$_2$Ph), 53.9 (*C*(2)), 57.4 (*C*(3)), 59.9 (*C*(α)), 71.2 (*C*(1')), 81.7 (*C*Me$_3$), 114.3, 114.3 (*C*(7), *C*(3')), 126.7, 126.9, 127.0, 127.8, 128.1, 128.3 (*o,m,p-Ph*), 139.1 (*C*(6)), 138.7 (*C*(2')), 142.0, 145.0 (*i-Ph*), 173.9 (*C*(1)); *m/z* $(ESI)^+$ 450 ($[M+H]^+$,100%); HRMS (ESI^+) $C_{29}H_{40}NO_3^+$ ($[M+H]^+$) requires 450.3003; found 450.3005. Further elution gave a 20:80 mixture of **295** and **296**, respectively (60 mg, 12%, 20: 80 dr).

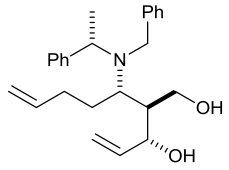
tert-Butyl (2*S*,3*S*,α*S*,1'*R*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino] hept-6-enoate 296



BuLi (2.2 M in hexanes, 260 μL, 0.57 mmol) was added dropwise via syringe to a stirred solution of (*S*)-**197** (125 μL, 0.54 mmol) in THF (2 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **181** (100 mg, 0.54 mmol, >99:1 dr) in THF (7 mL) at −78 °C was added dropwise via cannula. The resultant reaction mixture was stirred at −78 °C for 2 h, then acrolein (75 μL, 1.08 mmol) was added and the reaction mixture was allowed to warm to rt over 3 h. Satd aq NH_4Cl (1 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (5 mL) and 10% aq citric acid solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give a 12:7:28:53 mixture of **293**, **294**, **295** and **296**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 increased to 10:1) gave a 29:24:40:7 mixture of **293**, **294**, **295** and **296**, respectively (85 mg, 38%, 29:24:40:7 dr). Further elution gave **296** as a pale yellow oil (100 mg, 41%, >99:1 dr); $[\alpha]_D^{20}$ +3.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O−H), 2976 (C−H), 1720 (C=O), 1640 (C=C); δ_H (500 MHz, $CDCl_3$)

1.30 (9H, s, C*Me*$_3$), 1.36 (3H, d, *J* 7.0, C(α)*Me*), 1.45−1.54 (1H, m, C(4)H_A), 1.75−1.85 (1H, m, C(4)H_B), 2.05−2.25 (2H, m, C(5)H_2), 2.41 (1H, t, *J* 8.2, C(2)*H*), 3.35 (1H, dt, *J* 8.2, 4.4, C(3)*H*), 3.56 (1H, t, *J* 8.2, C(1')*H*), 3.72 (1H, t, *J* 13.5, NCH_AH$_B$Ph), 3.84 (1H, d, *J* 13.5, NCH$_A$$H_B$Ph), 3.93 (1H, q, *J* 7.0, C(α)*H*), 4.89−5.06 (4H, m, C(7)H_2, C(3')H_2), 5.57 (1H, ddd, *J* 17.3, 10.4, 8.2, C(2')*H*), 5.72 (1H, ddt, *J* 16.9, 10.2, 6.5, C(6)*H*), 6.34 (1H, br s, O*H*), 7.12−7.35 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.9 (C(α)*Me*), 28.4 (C*Me*$_3$), 30.0 (*C*(4)), 32.3 (*C*(5)), 51.1 (N*C*H$_2$Ph), 54.7 (*C*(2)), 58.4 (*C*(α)), 58.7 (*C*(3)), 75.5 (*C*(1')), 81.2 (*C*Me$_3$), 114.8 (*C*(7)), 116.8 (*C*(3')), 127.3, 127.4, 128.3, 128.5, 128.6, 129.4 (*o,m,p-Ph*), 137.6 (*C*(2')), 138.3 (*C*(6)), 138.9, 142.3 (*i-Ph*), 171.4 (*C*(1)); *m/z* (ESI)$^+$ 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_3^+$ ([M+H]$^+$) requires 450.3003; found 450.3000.

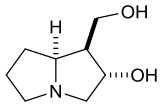
(2*S*,3*S*,α*S*,1'*R*)-1-Hydroxy-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl) amino] hept-6-enoate 298



$LiAlH_4$ (1.0 M in THF, 1.5 mL, 1.50 mmol) was added to a stirred solution of **239** (170 mg, 0.38 mmol, >99:1 dr) in THF (5 mL) at –78 °C. The resultant solution was allowed to warm to rt over 16 h, 2.0 M aq NaOH (0.75 mL, 1.5 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **298** as a colourless oil (101 mg, 70%, >99:1 dr); $[\alpha]_D^{20}$ +14.4 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 3350 (O–H) 2972, 2933 (C−H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29–1.34 (1H, m, C(2)*H*), 1.38 (1H, d, *J* 7.0, C(α)*Me*), 1.60–1.73 (1H, m, C(4)H_A), 1.82–1.92 (1H, m, C(4)H_B), 2.06–2.18 (1H, m, C(5)H_A), 2.21–2.34 (1H, m, C(5)H_B), 3.07 (1H, dt, *J* 8.5, 2.0, C(3)*H*), 3.61 (1H, dd, *J* 11.8, 2.6, C(1)H_A), 3.65 (1H, d, *J* 13.6, NCH_AH$_B$Ph), 3.74 (1H, app s, C(1')*H*), 3.86–3.97 (3H, m, C(1)H_B, C(α)*H*, NCH$_A$$H_B$Ph), 4.95 (1H, app d, *J* 10.2, C(3')H_A), 4.98–5.05 (2H, m, C(7)H_2), 5.18 (1H, app d, *J* 17.2, C(3')H_B), 5.60 (1H, ddd, *J* 17.2, 10.2, 4.0,

C(2')*H*), 5.81 (1H, ddt, *J* 16.9, 10.2, 6.7, C(6)*H*), 7.11−7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.4 (C(α)*Me*), 29.7 (*C*(4)), 32.2 (*C*(5)), 46.6 (*C*(2)), 51.2 (N*C*H_2Ph), 54.6 (*C*(3)), 56.5 (*C*(α)), 60.2 (*C*(1)), 73.6 (*C*(1')), 113.8, 115.0 (*C*(7), (*C*(3')), 127.3, 127.4, 128.4, 128.5, 128.7, 129.3 (*o*,*m*,*p*-*Ph*), 138.5, 140.7 (*C*(6), *C*(2')), 140.1, 143.3 (*i*-*Ph*); *m/z* (ESI^+) 380 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{33}NO_2Na^+$ ($[M+Na]^+$) requires 402.2404; found 402.2402.

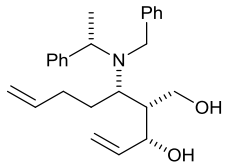
(*S*,*S*,*S*)-1-(hydroxymethyl)hexahydro-1H-pyrrolizin-2-ol [(–)-1-*epi*-macronecine] 300



298 (790 mg, 2.08 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 4 mL), then dissolved in CH_2Cl_2 (20 mL) and MeOH (20 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 2.08 g, 6.24 mmol) was added and the reaction mixture was cooled to rt and stirred for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to 3 mL of the solvent, then AcOH (0.15 mL) and $Pd(OH)_2$/C (200 mg, 25% w/w) were added. The resultant solution was degassed with N_2 and saturated with H_2 and then stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **300** as a white solid (224 mg, 69%, >99:1 dr); mp 90−91 °C; $[\alpha]_D^{20}$ −96 (*c* 0.12 in EtOH); ν_{max} (ATR) 3312 (O−H); δ_H (400 MHz, MeOH-d_4) 1.42−1.55 (1H, m, C(7)H_A), 1.55−1.69 (1H, m, C(6)H_A), 1.70−1.86 (2H, m, C(6)H_B, C(7)H_B), 2.19 (1H, app dq, *J* 7.6, 5.8, C(1)*H*), 2.45 (1H, td, *J* 10.0, 6.3, C(5)H_A), 2.70−2.85 (2H, m, C(3)H_2), 3.02 (1H, ddd, *J* 10.0, 7.0, 3.6, C(5)H_B), 3.50−3.61 (2H, m, C(7a)*H*, C(1')H_A), 3.69 (1H, dd, *J* 10.9, 5.8, C(1')H_B), 3.94 (1H, app q, *J* 7.6, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 25.9 (*C*(7)), 26.2 (*C*(6)), 50.7 (*C*(1)), 55.5 (*C*(5)), 60.4 (*C*(3)), 60.5 (*C*(1')), 65.5 (*C*(7a)), 71.2 (*C*(2)); δ_H (400 MHz, $CDCl_3$) 1.33−1.48 (1H, m,

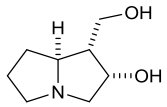
C(6)H_A), 1.64−1.79 (2H, m, C(6)H_B, C(7)H_A), 1.81−1.94 (2H, m, C(7)H_B), 2.37 (1H, app q, *J* 7.0, C(1)*H*), 2.46−2.65 (1H, m, C(3)H_A), 2.84 (1H, app dd, *J* 11.4, 6.8, C(5)H_A), 2.93 (1H, app dd, *J* 11.4, 6.3, C(5)H_B), 3.10 (1H, ddd, *J* 10.8, 7.1, 3.9, C(3)H_B), 3.55−3.63 (1H, m, C(7a)*H*), 3.76 (2H, app d, *J* 7.3, C(1')H_2), 4.13 (1H, app q, *J* 7.0, C(2)*H*); *m/z* (ESI$^+$) 158 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_2^+$ ([M+H]$^+$) requires 158.1176; found 158.1172.

(2*R*,3*S*,*αS*,1'*R*)-1-Hydroxy-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(*α*-methylbenzyl) amino] hept-6-enoate 301



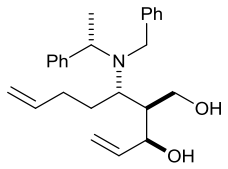
$LiAlH_4$ (1.0 M in THF, 2.7 mL, 2.70 mmol) was added to a stirred solution of **296** (300 mg, 0.67 mmol, >99:1 dr) in THF (15 mL) at –78 °C. The resultant solution was allowed to warm to rt over 16 h, 2.0 M aq NaOH (1.35 mL, 2.7 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **301** as a colourless oil (235 mg, 93%, >99:1 dr); $[\alpha]_D^{20}$ +6.9 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3330 (O–H) 2966 (C−H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.37–1.49 (1H, m, C(4)H_A), 1.62–1.73 (1H, m, C(4)H_B), 1.81–1.90 (1H, m, C(2)*H*), 1.96–2.07 (1H, m, C(5)H_A), 2.07–2.18 (1H, m, C(5)H_B), 2.00–2.40 (2H, br s, O*H*), 2.77 (1H, dt, *J* 7.0, 4.5, C(3)*H*), 3.44 (1H, dd, *J* 11.1, 7.0, C(1)H_A), 3.53 (1H, dd, *J* 11.1, 3.5, C(1)H_B), 3.73 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.87 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.93 (1H, q, *J* 6.9, C(α)*H*), 4.09 (1H, t, *J* 6.1, C(1')*H*), 4.88–5.02 (4H, m, C(7)H_2, C(3')H_2), 5.44 (1H, ddd, *J* 16.9, 10.4, 6.1, C(2')*H*), 5.71 (1H, ddt, *J* 16.9, 10.2, 6.7, C(6)*H*), 7.11–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 29.4 (*C*(4)), 32.5 (*C*(5)), 47.4 (*C*(2)), 50.9 (N*C*H_2Ph), 56.9 (*C*(3)), 58.5 (*C*(α)), 61.8 (*C*(1)), 75.3 (*C*(1')), 114.8, 115.8 (*C*(7), (*C*(3')), 127.0, 127.2, 128.2, 128.4, 128.4, 129.0 (*o,m,p-Ph*), 138.4, 138.5 (*C*(6), *C*(2')), 140.6, 143.6 (*i-Ph*); *m/z* (ESI$^+$) 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{33}NNaO_2^+$ ([M+Na]$^+$) requires 402.2404; found 402.2407.

(1*R*,2*S*,7a*S*)-1-(Hydroxymethyl)hexahydro-1H-pyrrolizin-2-ol [(–)-macronecine] 105



301 (330 mg, 0.87 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3mL), then dissolved in CH_2Cl_2 (20 mL) and MeOH (20 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 870 mg, 2.6 mmol) was added and the reaction mixture was cooled to rt and stirred for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to 3 mL of the solvent, then AcOH (0.25 mL) and $Pd(OH)_2/C$ (50 mg, 0.36 mmol) were added. The resultant solution was degassed with N_2 and saturated with H_2 and then stirred under an atmosphere of H_2 (5 atm) at rt for 36 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **105** as a white solid (82 mg, 60%, >99:1 dr); mp 120−123 °C; $[\alpha]_D^{20}$ −40.0 (*c* 0.6 in EtOH); ν_{max} (ATR) 3302 (O−H); δ_H (400 MHz, MeOH-d_4) 1.64−1.73 (1H, m, C(7)H_A), 1.78−2.07 (4H, m, C(1)*H*, C(6)H_2, C(7)H_B), 2.63 (1H, dt, *J* 10.8, 6.2, C(5)H_A), 2.77 (1H, dd, *J* 11.1, 3.6, C(3)H_A), 2.98 (1H, dt, *J* 10.8, 6.2, C(5)H_B), 3.19 (1H, app d, *J* 11.1, C(3)H_B), 3.47 (1H, ddd, *J* 9.3, 7.6, 5.0, C(7a)*H*), 3.67 (1H, dd, *J* 10.8, 6.2, C(1')H_A), 3.85 (1H, dd, *J* 10.8, 7.4, C(1')H_B), 4.46 (1H, t, *J* 3.6, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 25.1 (*C*(7)), 30.9 (*C*(6)), 52.5 (*C*(1)), 54.6 (*C*(5)), 59.8 (*C*(1')), 62.8 (*C*(3)), 65.6 (*C*(7a)), 73.7 (*C*(2)); δ_H (400 MHz, $CDCl_3$) 1.55 (1H, app dq, *J* 11.9, 6.1, C(7)H_A), 1.78−1.90 (3H, m, C(6)H_2, C(7)H_B), 1.92−2.05 (1H, m, C(1)*H*), 2.56−2.65 (1H, m, C(5)H_A), 2.71 (1H, dd, *J* 11.0, 3.7, C(3)H_A), 3.01 (1H, dt, *J* 11.0, 6.6, C(5)H_B), 3.23 (1H, app d, *J* 11.0, C(3)H_B), 3.56−3.65 (1H, m, C(7a)*H*), 3.80−3.92 (2H, m, C(1')H_2), 4.51 (1H, app t, *J* 3.7, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 25.5 (*C*(6)), 31.2 (*C*(7)), 52.4 (*C*(1)), 54.9 (*C*(5)), 60.9 (*C*(1')), 62.9 (*C*(3)), 64.2 (*C*(7a)), 75.6 (*C*(2)); *m/z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1173.

(*S*,*S*,*S*,*S*)-1-Hydroxy-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino] hept-6-enoate 303

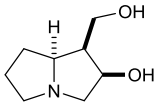


Method A: $LiAlH_4$ (2.4 M in THF, 100 μL, 0.23 mmol) was added to a stirred solution of **294** (26 mg, 0.058 mmol, >99:1 dr) in THF (0.5 mL) at –78 °C. The resultant solution was allowed to warm to rt over 16 h, 2.0 M aq NaOH (115 μL, 0.23 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **304** as a colourless oil (19 mg, 86%, >99:1 dr); $[\alpha]_D^{20}$ +12.2 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3351 (O–H) 3063, 3028, 2974 (C−H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.26 (1H, d, *J* 7.0, C(α)*Me*), 1.48–1.68 (3H, m, C(2)*H*, C(4)H_2), 1.90–2.11 (2H, m, C(5)H_2), 3.14 (1H, dt, *J* 9.3, 3.8, C(3)*H*), 3.66−3.72 (2H, m, C(1)H_A, NC$H_A$$H_B$Ph), 3.82 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.85 (1H, dd, *J* 10.8, 6.9, C(1)H_B), 3.92 (1H, q, *J* 7.0, C(α)*H*), 3.98 (1H, t, *J* 4.9, C(1')*H*), 4.90–4.99 (3H, m, C(7)H_2, C(3')H_A), 5.06 (1H, app d, *J* 16.8, C(3')H_B), 5.43 (1H, ddd, *J* 16.8, 10.5, 5.5, C(2')*H*), 5.70 (1H, ddt, *J* 17.0, 10.1, 6.7, C(6)*H*), 7.12–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 28.8 (*C*(4)), 32.0 (*C*(5)), 47.7 (*C*(2)), 51.6 (N*C*H_2Ph), 56.6 (*C*(3)), 59.0 (*C*(α)), 60.9 (*C*(1)), 73.1 (*C*(1')), 115.0, 115.3 (*C*(7), (*C*(3')), 127.3, 127.5, 128.2, 128.6, 128.7, 129.0 (*o*,*m*,*p*-*Ph*), 138.0, 140.1 (*C*(6), *C*(2')), 139.8, 142.4 (*i*-*Ph*); *m/z* (ESI^+) 380 ($[M+H]^+$, 100%), 402 ($[M+Na]^+$, 4%); HRMS (ESI^+) $C_{25}H_{34}NO_2^+$ ($[M+H]^+$) requires 380.2584; found 380.2583.

Method B: $LiAlH_4$ (1.0 M in THF, 6.3 mL, 6.30 mmol) was added to a stirred solution of **294** and **295** (700 mg, 1.56 mmol, 55:45 dr) in THF (10 mL) at –78 °C. The resultant solution was allowed to warm to rt over 16 h, 2.0 M aq NaOH (3.1 mL, 6.24 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column

chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **304** as a colourless oil (280 mg, 47%, >99:1 dr). Further elution gave **303** as a colourless oil (300 mg, 51%, >99:1 dr).

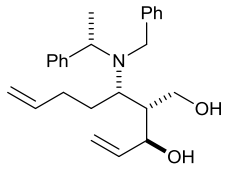
(1*S*,2*R*,7a*S*)-1-(Hydroxymethyl)hexahydro-1H-pyrrolizin-2-ol [(–)-petasinecine] 106



303 (380 mg, 1.00 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3mL), then dissolved in CH_2Cl_2 (20 mL) and MeOH (20 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 1.00 g, 3.00 mmol) was added and the reaction mixture was cooled to rt and stirred for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to 3 mL of the solvent, then AcOH (0.10 mL) and $Pd(OH)_2/C$ (100 mg, 25% w/w) were added. The resultant solution was degassed with N_2 and saturated with H_2 and then stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **106** as a white solid (89 mg, 57%, >99:1 dr); mp 128−130 °C; $[\alpha]_D^{20}$ −26.0 (*c* 0.8 in EtOH); ν_{max} (ATR) 3341 (O−H); δ_H (400 MHz, MeOH-d_4) 1.61−1.73 (1H, m, C(6)H_A), 1.75−1.83 (1H, m, C(7)H_A), 1.93−2.08 (2H, m, C(6)H_B, C(7)H_B), 2.25−2.35 (1H, m, C(1)*H*), 2.90 (1H, d, *J* 12.7, C(3)H_A), 2.90−3.00 (1H, m, C(5)H_A), 3.19 (1H, dd, *J* 12.7, 3.7, C(3)H_B), 3.32 (1H, app t, *J* 7.9, C(5)H_B), 3.68 (1H, dd, *J* 11.0, 7.5, C(1')H_A), 3.75−3.90 (1H, m, C(7a)*H*), 3.83 (1H, dd, *J* 11.0, 7.3, C(1')H_B), 4.27 (1H, app t, *J* 3.7, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 26.3 (*C*(6)), 27.1 (*C*(7)), 49.1 (*C*(1)), 56.6 (*C*(5)), 57.8 (*C*(1')), 61.4 (*C*(3)), 67.4 (*C*(7a)), 72.5 (*C*(2)); δ_H (400 MHz, $CDCl_3$) 1.62−1.89 (3H, m, C(6)H_2, C(7)H_A), 1.93−2.02 (1H, m, C(7)H_B), 2.34−2.43 (1H, m, C(1)*H*), 2.69−2.82 (2H, m, C(3)H_A, C(5)H_A), 3.09−3.17 (1H, m, C(3)H_B), 3.24 (1H, app dd, *J* 11.7, 5.0, C(5)H_B), 3.45−3.53 (1H, m, C(7a)*H*), 3.82 (1H, dd, *J* 10.8, 5.0,

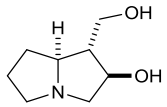
C(1')H_A), 3.94 (1H, dd, *J* 10.8, 9.3, C(1')H_B), 4.47−4.54 (1H, m, C(2)*H*); *m/z* (ESI$^+$) 158 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{15}NO^+$ ([M+H]$^+$) requires 158.1176; found 158.1179.

(2*R*,3*S*,*αS*,1'*S*)-1-Hydroxy-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl) amino] hept-6-enoate 304



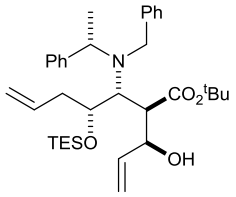
$LiAlH_4$ (1.0 M in THF, 2.8 mL, 2.80 mmol) was added to a stirred solution of **295** (310 mg, 0.69 mmol, >99:1 dr) in THF (10 mL) at –78 °C. The resultant solution was allowed to warm to rt over 16 h, 2.0 M aq NaOH (1.4 mL, 2.8 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **304** as a colourless oil (255 mg, 98%, >99:1 dr); $[\alpha]_D^{20}$ –23.2 (*c* 0.35 in $CHCl_3$); ν_{max} (ATR) 3342 (O–H) 2973, 2933 (C−H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.25 (1H, dd, *J* 9.3, 1.8, C(2)*H*), 1.38 (1H, d, *J* 7.0, C(α)*Me*), 1.48–1.61 (1H, m, C(4)H_A), 1.81–1.92 (1H, m, C(4)H_B), 2.11–2.36 (2H, m, C(5)H_2), 3.03 (1H, ddd, *J* 10.0, 7.7, 3.1, C(3)*H*), 3.30 (1H, dd, *J* 11.9, 2.8, C(1)H_A), 3.70–3.75 (1H, m, C(1)H_B), 3.72 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.84 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.93 (1H, q, *J* 7.0, C(α)*H*), 4.66 (1H, app s, C(1')*H*), 4.90–5.06 (3H, m, C(7)H_2, C(3')H_A), 5.14 (1H, app dt, *J* 17.2, 1.8, C(3')H_B), 5.60 (1H, ddd, *J* 18.3, 11.9, 4.3, C(2')*H*), 5.82 (1H, ddt, *J* 17.0, 10.2, 6.6, C(6)*H*), 7.13–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 30.3 (*C*(4)), 32.3 (*C*(5)), 47.3 (*C*(2)), 51.2 (N*C*H_2Ph), 52.9 (*C*(3)), 56.7 (*C*(α)), 60.5 (*C*(1)), 72.5 (*C*(1')), 114.2, 114.7 (*C*(7), (*C*(3')), 127.2, 127.2, 128.3, 128.4, 128.6, 129.2 (*o*,*m*,*p*-*Ph*), 138.9, 140.0 (*C*(6), *C*(2')), 140.7, 144.3 (*i*-*Ph*); *m/z* (ESI$^+$) 380 ([M+H]$^+$, 100%), 402 ([M+Na]$^+$, 5%); HRMS (ESI$^+$) $C_{25}H_{34}NO_2^+$ ([M+H]$^+$) requires 380.2584; found 380.2581.

(1*R*,2*R*,7a*S*)-1-(Hydroxymethyl)hexahydro-1H-pyrrolizin-2-ol [(+)-1-*epi*-petasinecine] 305



304 (310 mg, 0.82 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3mL), then dissolved in CH_2Cl_2 (20 mL) and MeOH (20 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 820 mg, 2.4 mmol) was added and the reaction mixture was cooled to rt and stirred for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to 3 mL of the solvent, then AcOH (0.3 mL) and $Pd(OH)_2/C$ (63 mg, 25% w/w) were added. The resultant solution was degassed with N_2 and saturated with H_2 and then stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **305** as a white solid (62 mg, 48%, >99:1 dr); mp 98−100 °C; $[\alpha]_D^{20}$ +25.0 (*c* 0.3 in EtOH); ν_{max} (ATR) 3311 (O−H); δ_H (400 MHz, MeOH-d_4) 1.60−1.75 (3H, m, C(1)*H*, C(6)H_A, C(7)H_A), 1.85−1.97 (2H, m, C(6)H_B, C(7)H_B), 2.42 (1H, dd, *J* 9.8, 8.1, C(3)H_A), 2.61−2.70 (1H, m, C(5)H_A), 2.81−2.89 (1H, m, C(5)H_B), 3.14 (1H, dd, *J* 9.8, 6.1, C(3)H_B), 3.16−3.20 (1H, m, C(7a)*H*), 3.47 (1H, dd, *J* 11.1, 7.1, C(1')H_A), 3.64 (1H, dd, *J* 11.1, 4.7, C(1')H_B), 3.96 (1H, dt, *J* 8.1, 6.1, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 24.9, 31.9 (*C*(6), *C*(7)), 54.7 (*C*(5)), 55.0 (*C*(1)), 60.5 (*C*(3)), 61.6 (*C*(1')), 66.1 (*C*(7a)), 73.2 (*C*(2)); δ_H (400 MHz, $CDCl_3$) 1.58−1.71 (1H, m, C(6)H_A), 1.72−1.89 (2H, m, C(6)H_B, C(7)H_A), 1.89−2.03 (2H, m, C(1)*H*, C(7)H_B), 2.54 (1H, app t, *J* 9.1, C(3)H_A), 2.69−2.77 (1H, m, C(5)H_A), 2.97−3.05 (1H, m, C(3)H_B), 3.26−3.34 (1H, m, C(5)H_B), 3.42 (1H, dd, *J* 9.8, 5.6, C(7a)*H*), 3.72 (1H, dd, *J* 10.7, 6.9, C(1')H_A), 3.87 (1H, dd, *J* 10.7, 4.5, C(1')H_B), 4.30−4.38 (1H, m, C(2)*H*); *m/z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1174.

tert-Butyl (α*S*,2*R*,3*R*,4*R*)-3-[*N*-benzyl-*N*-(α-methyl-benzyl)amino]-2-((S)-1-hydroxyallyl)-4-((triethylsilyl)oxy)hept-6-enoate 306



Method A: BuLi (2.2 M in hexanes, 2.60 mL, 5.64 mmol) was added to a stirred solution of TMP (970 μL, 5.74 mmol) in THF (9 mL) at 0 °C. After stirring for 30 min a solution of **251** (600 mg, 1.15 mmol, >99:1 dr) in THF (9 mL) at 0 °C was added dropwise via cannula. The reaction mixture was stirred at 0 °C for 1 h then cooled to −78 °C, then acrolein (385 μL, 5.74 mmol) was added and the reaction mixture was allowed to warm to 0 °C over 3 h. Satd aq NH_4Cl (5 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (20 mL) and satd aq NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 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 **306** in >95:5 dr. Purification via flash column chromatography gave **306** as a colourless oil (666 mg, 96%, >99:1 dr); $[\alpha]_D^{25}$ +40.0 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3373 (O−H), 2877, 2956 (C−H), 1721 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 0.29 (6H, q, *J* 8.0, Si(C*H*$_2$CH$_3$)$_3$), 0.77 (9H, t, *J* 8.0, Si(CH$_2$C*H*$_3$)$_3$), 0.97 (3H, d, *J* 7.0, C(α)*Me*), 1.45 (9H, s, C*Me*$_3$), 2.24−2.38 (2H, m, C(5)*H*$_2$), 2.87 (1H, dd, *J* 9.3, 8.1, C(2)*H*), 3.28 (1H, dd, *J* 9.3, 3.8, C(3)*H*), 2.80−2.86 (1H, m, C(4)*H*), 4.00 (1H, d, *J* 16.7, NC*H*$_A$H$_B$Ph), 4.10−4.21 (3H, m, NCH$_A$*H*$_B$Ph, C(α)*H*, C(1')*H*), 4.71 (1H, br s, O*H*), 4.81−4.91 (2H, m, C(7)*H*$_2$), 5.08 (1H, m, C(3')*H*$_A$), 5.22 (1H, app d, *J* 17.0, C(3')*H*$_B$), 5.40−5.57 (1H, m, C(6)*H*), 5.82 (1H, ddd, *J* 17.0, 10.2, 7.0, C(2')*H*), 7.10−7.17 (2H, m, *p-Ph*), 7.24 (4H, app q, *J* 7.5, *m-Ph*), 7.38 (2H, d, *J* 7.5, *o-Ph*), 7.40 (2H, d, *J* 7.5, *o-Ph*); δ_C (100 MHz, $CDCl_3$) 4.5 (Si(*C*H$_2$CH$_3$)$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 22.7 (C(α)*Me*), 28.3 (C*Me*$_3$), 37.1 (*C*(5)), 52.1 (NCH$_2$Ph), 53.7 (*C*(2)), 63.2 (*C*(α)), 63.5 (*C*(3)), 73.6 (*C*Me$_3$), 76.8 (*C*(1')), 81.4 (*C*(4)), 117.3, 117.4 (*C*(7), *C*(3')), 126.3, 126.9, 127.3, 128.1, 128.2, 128.5 (*o,m,p-Ph*), 135.3 (*C*(6)), 137.6 (*C*(2')), 144.1, 146.5 (*i-Ph*), 172.4 (*C*(1)); *m/z* (ESI)$^+$ 580 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{54}NO_4Si^+$ ([M+H]$^+$) requires 580.3814; found 580.3817.

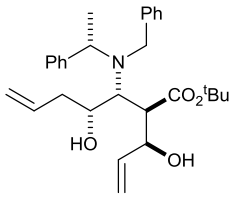
Method B: BuLi (2.2 M in hexanes, 285 μL, 0.62 mmol) was added dropwise via syringe to a stirred solution of (*S*)-**197** (135 mg, 0.64 mmol) in THF (2 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of (*R*)-**245** (100 mg, 0.32 mmol, >99:1 dr) in THF (2 mL) at −78 °C was added dropwise via cannula. The reaction mixture was stirred at −78 °C for 2 h, then acrolein (65 μL, 0.96 mmol) was added and the resultant mixture was allowed to warm to 0 °C over 3 h. Satd aq NH_4Cl (3 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (5 mL) and 10% aq citric acid solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL), H_2O (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give 80:20 mixture of **306** and other isomers, respectively.

Method C: BuLi (2.2 M in hexanes, 425 μL, 0.93 mmol) was added to a stirred solution of TMP (160 μL, 0.95 mmol) in THF (1.5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **251** (100 mg, 0.20 mmol, >99:1 dr) in THF (1.5 mL) at 0 °C was added dropwise. The reaction mixture was stirred at 0 °C for 1 h then cooled to −78 °C and $B(OMe)_3$ (105 μL, 0.95 mmol) was added. The resultant mixture was stirred for 30 min, then acrolein (65 μL, 0.95 mmol) was added and the reaction mixture was allowed to warm to 0 °C over 3 h. Satd aq NH_4Cl (3 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (5 mL) and satd aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 30:54:16 mixture of **251**, **306** and other isomers, respectively.

Method D: BuLi (2.2 M in hexanes, 260 μL, 0.57 mmol) was added to a stirred solution of TMP (115 μL, 0.70 mmol) in THF (1.5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **251** (100 mg, 0.20 mmol, >99:1 dr) in THF (1.5 mL) at 0 °C was added dropwise. The reaction mixture was stirred at 0 °C for 1 h then cooled to −78 °C and $TiCl(O^iPr)_3$ (105 μL, 0.95 mmol) was added. The resultant mixture was stirred for 30 min, then acrolein (65 μL, 0.95 mmol) was added and the reaction mixture was allowed to warm to 0 °C over 3 h. Satd aq NH_4Cl (3 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue

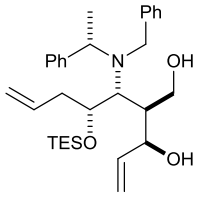
was partitioned between CH_2Cl_2 (5 mL) and satd aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed sequentially with H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 5:65:30 mixture of **251**, **306** and other isomers, respectively.

tert-Butyl (2*R*,3*R*,4*R*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-hydroxy hept-6-enoate 309



HF (70% in py, 1.5 mL, 52.8 mmol) was added to a stirred solution of **306** (1.02 g, 1.76 mmol) in THF (10 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. Satd aq $NaHCO_3$ was added until pH > 7 and the resultant mixture was stirred at rt for 30 min, then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **309** as a white solid (740 mg, 90%, >99:1 dr); mp 90−92 °C; $[\alpha]_D^{25}$ +14.1 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 3360 (O−H), 3064, 2918, 2978 (C−H), 1722 (C=O), 1640 (C=C); δ_H (500 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.35 (9H, s, C*Me*$_3$), 2.15−2.31 (2H, m, C(5)*H*$_2$), 2.67 (1H, dd, *J* 7.3, 4.8, C(2)*H*), 2.85 (2H, br s, 2 × O*H*), 3.26 (1H, app t, *J* 4.8, C(3)*H*), 3.90 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.85−3.92 (1H, m, C(4)*H*), 4.15 (1H, q, *J* 6.9, C(α)*H*), 4.21 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.29 (1H, app t, *J* 7.3, C(1')*H*), 4.99–5.03 (1H, m, C(7)*H*$_A$), 5.02–5.06 (1H, m, C(7)*H*$_B$), 5.07 (1H, app d, *J* 10.5, C(3')*H*$_A$), 5.20 (1H, app d, *J* 17.2, C(3')*H*$_B$), 5.60−5.72 (1H, m, C(6)*H*), 5.80 (1H, ddd, *J* 17.2, 10.5, 7.3, C(2')*H*), 7.10−7.36 (10H, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 28.1 (C*Me*$_3$), 39.9 (*C*(5)), 52.2 (N*C*H$_2$Ph), 53.4 (*C*(2)), 60.7 (*C*(4)), 61.8 (*C*(3)), 70.9 (*C*(α)), 72.1 (*C*(1')), 81.5 (*C*Me$_3$), 117.1 (*C*(3')), 117.9 (*C*(7), 126.6, 127.0, 128.2, 128.2, 128.3, 128.4 (*o*,*m*,*p*-*Ph*), 135.3 (*C*(6)), 138.1 (*C*(2')), 142.1, 144.7 (*i*-*Ph*), 172.3 (*C*(1)); *m/z* (ESI^+) 466 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{40}NO_3^+$ ($[M+H]^+$) requires 466.2952; found 466.2947.

(2*S*,3*R*,4*R* 1'*S*,α*S*)-2-(1'-hydroxyprop-2'-en-1'-yl)- 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triethylsilyloxy)-hept-6-en-1-ol 310



Method A: DIBAL-H (1.0 M in THF, 0.85 mL, 0.85 mmol) was added to a stirred solution of **306** (100 mg, 0.17 mmol, >99:1 dr) in THF (0.2 mL) at 0 °C. The resultant solution was allowed to warm to rt over 16 h then MeOH (1mL) was added. Satd aq Rochelle salt (0.2 mL) was added and the resultant mixture was stirred at rt for 16 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography gave **310** as a colourless oil (23 mg, 27%, 75% purity, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 0.68 (6H, q, *J* 7.9, Si(CH_2CH$_3$)$_3$), 1.01 (9H, t, *J* 7.9, Si(CH$_2$CH_3)$_3$), 1.47 (3H, d, *J* 6.9, C(α)*Me*), 2.33−2.48 (2H, m, C(2)*H*, C(5)H_A), 2.59−2.70 (1H, m, C(5)H_B), 2.99 (1H, dd, *J* 8.8, 3.1, C(3)*H*), 2.03−2.15 (2H, m, C(1)H_2), 4.10 (2H, s, NCH_2Ph), 4.15−4.20 (1H, m, C(4)*H*), 4.28 (1H, q, *J* 6.9, C(α)*H*), 4.43 (1H, app br t, , *J* 4.8, C(1')*H*), 5.04–5.10 (2H, m, C(7)H_2), 5.20 (1H, app d, *J* 10.8, C(3')H_A), 5.34 (1H, app d, *J* 17.1, C(3')H_B), 5.58−5.70 (1H, m, C(6)*H*), 5.87 (1H, ddd, *J* 17.1, 10.8, 4.8, C(2')*H*), 7.17−7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.4 (Si(*C*H$_2$CH$_3$)$_3$), 7.1 (Si(CH$_2$*C*H$_3$)$_3$), 19.5 (C(α)*Me*), 39.4 (*C*(5)), 45.5 (*C*(2)), 53.1 (N*C*H$_2$Ph), 57.5 (*C*(3)), 59.6 (*C*(α)), 62.3 (*C*(1)), 73.7 (*C*(1')), 74.7 (*C*(4)), 115.9 (*C*(3')), 117.4 (*C*(7)), 126.6, 127.0, 128.0, 128.1, 128.2, 128.6 (*o,m,p-Ph*), 135.1 (*C*(6)), 138.4 (*C*(2')), 141.1, 144.6 (*i-Ph*); *m/z* (ESI)$^+$ 510 ([M+H]$^+$, 100%) 396 ([M−TES]$^+$, 4%); HRMS (ESI$^+$) $C_{31}H_{48}NO_3Si^+$ ([M+H]$^+$) requires 510.3398; found 510.3385.

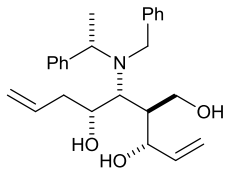
Method B: $LiAlH_4$ (1.0 M in THF, 0.69 mL, 0.69 mmol) was added to a stirred solution of **306** (100 mg, 0.17 mmol, >99:1 dr) in THF (1.0 mL) at −78 °C. The resultant solution was allowed to warm to rt over 16 h then 2.0 M aq NaOH (0.35 mL) was added and the resultant mixture was stirred at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C

petrol:EtOAc 4:1 increased to 1:1) gave **310** as a colourless oil (20 mg, 23%, 90% purity), further elution gave **311** (20 mg, 30%, 90% purity).

Method C: $LiAlH_4$ (1.0 M in THF, 0.17 mL, 0.17 mmol) was added to a stirred solution of **306** (100 mg, 0.17 mmol, >99:1 dr) in THF (1.0 mL) at –78 °C. The resultant solution was allowed to warm to rt over 16 h then 2.0 M aq NaOH (0.09 mL) was added and the resultant mixture was left stirred at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol:EtOAc 4:1 increased to 1:1) gave **309** as a colourless oil (22 mg, 28%, >99:1 dr), further elution gave **310** (32 mg, 37%, 90% purity).

Method D: DIBAL-H (1.0 M in THF, 0.85 mL, 0.85 mmol) was added to a stirred solution of **306** (100 mg, 0.17 mmol, >99:1 dr) in THF (0.2 mL) at 0 °C. The resultant solution was allowed to warm to rt over 16 h then MeOH (1mL) was added. Satd aq Rochelle salt (0.2 mL) was then added and the resultant mixture was stirred at rt for 16 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo* to give the crude reaction mixture (90 mg). Purification via flash column chromatography gave **310** as a colourless oil (23 mg, 27%, 80% purity, >99:1 dr).

(2*S*,3*R*,4*R* 1'*S*,α*S*)-2-(1'-hydroxyprop-2'-en-1'-yl)- 3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-hept-6-ene-1,4-diol 311



Method A: Step 1: TFA (3 mL) was added dropwise to a stirred solution of **306** (600 mg, 0.86 mmol, >99:1 dr) in CH_2Cl_2 (3 mL) at 0 °C. The resultant solution was allowed to warm to rt over 16 h then satd aq $NaHCO_3$ (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **312** as a light yellow oil which was used in the next step without further purification (600 mg, >95:5 dr); selected data for **312**: δ_H (400 MHz, $CDCl_3$)

0.65 (6H, q, *J* 8.0, Si(C*H*$_2$CH$_3$)$_3$), 0.94 (9H, t, *J* 8.0, Si(CH$_2$C*H*$_3$)$_3$), 1.48 (3H, d, *J* 6.9, C(α)*Me*), 2.49−2.66 (2H, m, C(5)*H*$_2$), 2.94 (1H, dd, *J* 10.4, 4.3, C(2)*H*), 3.48 (1H, dd, *J* 10.4, 2.2, C(3)*H*), 3.83 (1H, d, *J* 13.9, C*H*$_A$H$_B$Ph), 4.18−4.24 (1H, m, C(4)*H*), 4.24−4.36 (2H, m, C(α)*H*, C(1')*H*), 4.45 (1H, d, *J* 13.9, CH$_A$*H*$_B$Ph), 5.05 (1H, d, *J* 10.4, C(3')*H*$_A$), 5.17 (3H, m, C(7)*H*$_2$, C(3')*H*$_B$), 5.62−5.85 (2H, m, C(6)*H*, C(2')*H*), 7.05−7.25 (10H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 5.5 (Si(*C*H$_2$CH$_3$)$_3$), 7.1 (Si(CH$_2$*C*H$_3$)$_3$), 18.3 (C(α)*Me*), 39.4 (*C*(5)), 46.6 (*C*(2)), 52.8 (N*C*H$_2$Ph), 61.4 (*C*(3)), 62.3 (*C*(α)), 72.4 (*C*(4)), 73.1 (*C*(1')), 118.1 *C*(3')), 119.1 (*C*(7)), 128.1, 128.6, 128.7, 128.7, 128.8, 129.4 (*o,m,p-Ph*), 133.6 (*C*(2')), 134.9 (*i-Ph*), 137.1 (*C*(6)), 139.2 (*i-Ph*), 175.9 (*C*(1)); *m/z* (ESI)$^+$ 524 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{46}NO_4Si^+$ ([M+H]$^+$) requires 524.3190; found 524.3187.

Step 2: LiAlH$_4$ (2.4 M in THF, 1.7 mL, 4.16 mmol) was added to a stirred solution of **312** (600 mg, 1.04 mmol, >95:5 dr) in THF (5 mL) at 0 °C. The resultant solution was allowed to warm to rt and heated at 70 °C for 16 h. The reaction mixture was then allowed to cool to rt, then 2.0 M aq NaOH (2.1 mL, 4.20 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo* to give a **310** (460 mg).

Step 3: HF (70% in py, 760 μL, 27.0 mmol) was added to a stirred solution of the crude reaction mixture of **310** (460 mg) in THF (8 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. Satd aq NaHCO$_3$ was added until pH > 7 and the resultant mixture was stirred at rt for 30 min, then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **311** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **311** as a colourless oil (260 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ −9.9 (*c* 1.1 in CHCl$_3$); ν_{max} (ATR) 3359 (O−H), 2974 (C−H), 1701 (C=O), 1639 (C=C); δ_H (400 MHz, CDCl$_3$) 1.45 (3H, d, *J* 6.9, C(α)*Me*), 1.80−2.00 (1H, m, C(2)*H*), 2.30−2.40 (2H, m, C(5)*H*$_2$), 3.00 (1H, dd, *J* 6.6, 4.9, C(3)*H*), 3.44 (1H, dd, *J* 11.1, 3.9, C(1)*H*$_A$), 3.55 (1H, dd, *J* 11.1, 6.6, C(1)*H*$_B$), 3.93−3.98 (1H, m, C(4)*H*), 4.00 (1H, d, *J* 14.4, NC*H*$_A$H$_B$Ph), 4.05 (1H, d, *J* 14.4, NCH$_A$*H*$_B$Ph), 4.16 (1H, app t, *J* 5.7, C(1')*H*), 4.22 (1H, q, *J* 6.9, C(α)*H*), 5.08−5.16 (3H, m, C(3')*H*$_A$, C(7)*H*$_2$), 5.19−5.25 (1H, m, C(3')*H*$_B$), 5.74−5.90 (2H, m, C(2')*H*, C(6)*H*), 7.17−7.33 (10H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 18.2 (C(α)*Me*), 39.8 (*C*(5)), 46.0 (*C*(2)), 52.2 (N*C*H$_2$Ph),

58.5 (*C*(α)), 59.9 (*C*(3)), 62.1(*C*(1)), 71.0 (*C*(4)), 73.5 (*C*(1')), 116.1, 117.9 (*C*(7), *C*(3')), 127.0, 127.1, 128.0, 128.3, 128.4, 129.0 (*o,m,p-Ph*), 135.3 (*C*(2')), 139.1 (*C*(6)), 140.3, 144.0 (*i-Ph*); *m/z* (ESI)$^+$ 396 ([M+H]$^+$,100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_3^+$ ([M+H]$^+$) requires 396.2533; found 396.2525.

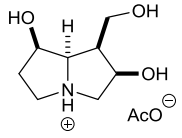
Method B: $LiAlH_4$ (1.0 M in THF, 4.3 mL, 4.30 mmol) was added to a stirred solution of **309** (500 mg, 1.08 mmol, >99:1 dr) in THF (5 mL) at −78 °C. The resultant solution was allowed to warm to rt over 48 h then 2.0 M aq NaOH (2.2 mL) was added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo* to give the crude reaction mixture. Purification via flash column chromatography gave **311** as a colourless oil (196 mg, 81%, 70% purity).

Method C: DIBAL-H (1.0 M in THF, 2.2 mL, 2.20 mmol) was added to a stirred solution of **309** (100 mg, 0.22 mmol, >99:1 dr) in THF (0.2 mL) at 0 °C. The resultant solution was allowed to warm to rt over 16 then heated to 35 °C for further 24 h then MeOH (1mL) was added. Satd aq Rochelle salt (0.2 mL) was then added and the resultant mixture was stirred at rt for 16 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo* to give a complex mixture of products.

Method D: *Step 1:* DIBAL-H (1.0 M in THF, 0.85 mL, 0.85 mmol) was added to a stirred solution of **306** (100 mg, 0.17 mmol, >99:1 dr) in THF (0.2 mL) at 0 °C. The resultant solution was allowed to warm to rt over 16 h then MeOH (1mL) was added. Satd aq Rochelle's salt (0.2 mL) was then added and the resultant mixture was left to stir at rt for 16 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo* to give the crude reaction mixture (90 mg).

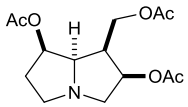
Step 2: HF (70% in py, 130 μL, 5.1 mmol) was added to a stirred solution of the crude mixture of **310** (90 mg) in THF (1 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. Satd aq $NaHCO_3$ was added until pH > 7 and the resultant mixture was stirred at rt for 30 min, then extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **311** (40 mg, 70% purity).

(1*R*,2*S*,7*R*,7a*R*)-1-Hydroxymethyl-2,7-dihydroxy-hexahydro-1*H*-pyrrolizinium acetate 149·HOAc



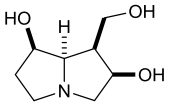
311 (250 mg, 0.63 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3 mL), then dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant solution was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 630 g, 1.90 mmol) was added and the reaction mixture was cooled to rt and stirred for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to 3 mL of the solvent, then AcOH (0.3 mL) and $Pd(OH)_2/C$ (100 mg, 40% w/w) were added. The resultant solution was degassed with N_2 and saturated with H_2 and then stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 6:4:1) gave **149**·HOAc as a white solid (90 mg, 65%, >99:1 dr); mp 212–214 °C; $[\alpha]_D^{20}$ +112.0 (*c* 0.2 in MeOH); ν_{max} (ATR) 3274 (O−H), 1572 (C=O); δ_H (400 MHz, D_2O) 1.84 (1H, s, OCO*Me*), 1.07−2.14 (2H, m, C(6)H_2), 2.71−2.83 (1H, m, C(1)*H*), 3.30−3.40 (2H, m, C(3)H_A, C(5)H_A), 3.73 (1H, dd, *J* 13.7, 4.9, C(3)H_B), 3.89 (1H, dd, *J* 11.4, 6.7, C(1')H_A), 3.92 (1H, app dd, *J* 11.9, 6.4, C(5)H_B), 4.01 (1H, dd, *J* 11.4, 8.2, C(1')H_B), 4.33 (1H, dd, *J* 9.8, 3.5, C(7a)*H*), 4.48 (1H, t, *J* 4.7, C(2)*H*), 4.53 (1H, t, *J* 3.5, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 23.2 (CO_2*Me*), 35.8 (*C*(6)), 46.8 (*C*(1)), 55.1 (*C*(5)), 55.9 (*C*(1')), 62.2 (*C*(3)), 69.6 (*C*(7a)), 70.4, 72.9 (*C*(2), *C*(7)); *m/z* (ESI^+) 174 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_3^+$ ($[M+H]^+$) requires 174.1125; found 174.1124.

(1*R*,2*S*,7*R*,7a*R*)-1-(Acetoxymethyl)hexahydro-1H-pyrrolizine-2,7-diyl diacetate 313



Ac_2O (375 μL, 4.00 mmol) and DMAP (10 mg, 0.08 mmol) were added to a stirred solution of **149**·HOAc (70 mg) in py (0.6 mL) and the resultant solution was stirred at rt for 16 h. Satd aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with H_2O (3 × 5 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via column chromatography (eluent 30–40 °C petrol:EtOAc 2:1) gave **313** as a colourless oil (92 mg, 77%, >99:1 dr); $[\alpha]_D^{20}$ −22.0 (*c* 0.6 in $CHCl_3$); ν_{max} (ATR) 1734 (C=O); δ_H (400 MHz, $CDCl_3$) 2.03 (3H, s, OCO*Me*$_A$), 2.07 (3H, s, OCO*Me*$_B$), 2.10 (3H, s, OCO*Me*$_C$), 2.01−2.16 (2H, m, C(6)*H*$_2$), 2.80−2.95 (3H, m, C(1)*H*, C(3)*H*$_A$, C(5)*H*$_A$), 3.12−3.19 (1H, m, C(5)*H*$_B$), 3.44 (1H, dd, *J* 12.0, 6.0, C(3)*H*$_B$), 3.63 (1H, dd, *J* 9.2, 4.0, C(7a)*H*), 4.20 (1H, dd, *J* 11.0, 7.3, C(1')*H*$_A$), 4.38 (1H, dd, *J* 11.0, 8.5, C(1')*H*$_B$), 5.22 (1H, app t, *J* 4.0, C(7)*H*), 5.36 (1H, td, *J* 6.0, 3.4, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 20.8 (CO*Me*$_A$), 21.1 (CO*Me*$_B$), 21.6 (CO*Me*$_C$), 34.9 (*C*(6)), 42.1 (*C*(1)), 52.4 (*C*(5)), 60.1 (*C*(1')), 60.6 (*C*(3)), 68.6 (*C*(7a)), 74.7 (*C*(2)), 75.0 (*C*(7)), 169.9, 170.4, 170.9 (*C*OMe$_A$, *C*OMe$_B$, *C*OMe$_C$); *m/z* (ESI^+) 300 ($[M+H]^+$, 100%), 322 ($[M+Na]^+$, 13%); HRMS (ESI^+) $C_{14}H_{22}NO_6^+$ ($[M+H]^+$) requires 300.1442; found 300.1442.

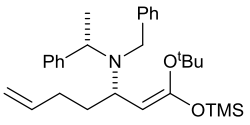
(1*R*,2*S*,7*R*,7a*R*)-1-Hydroxymethyl-7,2-dihydroxy-hexahydro-1*H*-pyrrolizine [(+)-2-*epi*-rosmarinecine] 149



K_2CO_3 (70 mg, 0.51 mmol) was added to a solution of **313** (50 mg, 0.17 mmol, >99:1 dr) in MeOH (1 mL). The resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 6:4:1) gave **149** as a white solid (30 mg, quant, >99:1 dr); mp 187–189 °C; $[\alpha]_D^{20}$ +18.3 (*c* 0.37 in EtOH); for **149**·HCl $[\alpha]_D^{20}$ –27.0 (*c*

0.3 in EtOH); {lit[20] **149**·HCl $[\alpha]_D^{20}$ −31.2 (*c* 1.3 in EtOH)}; ν_{max} (ATR) 3243 (O–H); δ_H (400 MHz, D_2O) 1.71−1.92 (2H, m, C(6)H_2), 2.40−2.50 (1H, m, C(1)*H*), 2.70−2.83 (2H, m, C(3)H_A, C(5)H_A), 3.08 (1H, dd, *J* 13.4, 4.0, C(3)H_B), 3.14−3.23 (1H, m, C(5)H_B), 3.49 (1H, dd, *J* 9.1, 3.6, C(7a)*H*), 3.81 (1H, dd, *J* 11.0, 6.3, C(1')H_A), 3.95 (1H, dd, *J* 11.0, 8.5, C(1')H_B), 4.13−4.21 (2H, m, C(2)*H*, C(7)*H*); δ_C (100 MHz, D_2O) 36.1 (*C*(6)), 47.1 (*C*(1)), 53.4 (*C*(5)), 57.0 (*C*(1')), 62.0 (*C*(3)), 69.8 (*C*(7a)), 70.6, 71.5 (*C*(2), *C*(7)); *m/z* (ESI^+) 174 ($[M+H]^+$, 100%), 196 ($[M+Na]^+$, 19%); HRMS (ESI^+) $C_8H_{16}NO_3^+$ ($[M+H]^+$) requires 174.1125; found 174.1125.

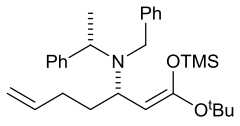
Trapping of (*E*)-198



Method A: BuLi (2.2 M in hexanes, 125 µL, 0.28 mmol) was added dropwise to a stirred solution of TMP (50 µL, 0.28 mmol) in THF (0.5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **182** (100 mg, 0.25 mmol) in THF (0.5 mL) at 0 °C was added. The resultant mixture was stirred at 0 °C for 1 h, then TMSCl (65 µL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give **323** [(*E*)-**323**:(*Z*)-**323** >95:5]. δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.18 (9H, s, OSiMe_3), 1.12 (9H, s, CMe_3), 1.11 (3H, d, *J* 7.1, C(α)*Me*), 3.37 (1H, dt, *J* 9.7, 7.3, C(3)*H*), 3.47 (1H, d, *J* 15.5, NC$H_A$$H_B$Ph), 3.73 (1H, d, *J* 9.7, C(2)*H*), 3.83−3.90 (2H, m, NC$H_A$$H_B$Ph, C(α)*H*), 4.75−4.90 (2H, m, C(7)H_2), 5.67 (1H, ddt, *J* 17.1, 10.3, 6.6, C(6)*H*), 7.10−7.49 (10H, m, *Ph*).

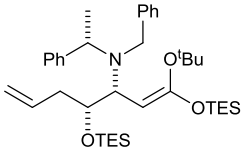
Method B: BuLi (2.2 M in hexanes, 125 µL, 0.28 mmol) was added dropwise to a stirred solution of iPr_2NH (40 µL, 0.28 mmol) in THF (0.5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **182** (100 mg, 0.25 mmol) in THF (0.5 mL) at 0 °C was added. The resultant mixture was stirred at 0 °C for 1 h, then TMSCl (65 µL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give a mixture containing **323** [(*E*)-**323**:(*Z*)-**323** >95:5] and **182**.

Trapping of (*Z*)-198



BuLi (2.2 M in hexanes, 125 μL, 0.27 mmol) was added dropwise to a stirred solution of (*S*)-**197** (55 μL, 0.27 mmol) in THF (0.5 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **181** (50 mg, 0.27 mmol) in THF (0.5 mL) at −78 °C was added. The resultant mixture was stirred at −78 °C for 2 h, then TMSCl (55 μL, 0.41 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give **323** [(*Z*)-**323**:(*E*)-**323** >95:5]. δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.01 (9H, s, OSi*Me*$_3$), 1.25 (9H, s, C*Me*$_3$), 1.28 (3H, d, *J* 6.7, C(α)*Me*), 3.30 (1H, dt, *J* 9.8, 7.2, C(3)*H*), 3.42 (1H, d, *J* 15.6, NC*H*$_A$H$_B$Ph), 3.77 (1H, d, *J* 9.8, C(2)*H*), 3.83 (1H, q, *J* 6.7, C(α)*H*), 3.87 (1H, d, *J* 15.6, NCH$_A$*H*$_B$Ph), 4.75 (1H, app ddt, *J* 10.2, 2.2, 1.5, C(7)*H*$_A$), 4.82 (1H, app dq, *J* 17.0, 1.5, C(7)*H*$_B$), 5.63 (1H, ddt, *J* 17.0, 10.2, 6.6, C(6)*H*), 7.05−7.43 (10H, m, *Ph*).

Trapping of (*E*)-256



BuLi (2.2 M in hexanes, 70 μL, 0.15 mmol) was added dropwise to a stirred solution of TMP (30 μL, 0.15 mmol) in THF (0.2 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **251** (70 mg, 0.13 mmol) in THF (0.2 mL) at 0 °C was added. The resultant mixture was stirred at 0 °C for 1 h, then TESCl (50 μL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give **324** [(*E*)-**324**:(*Z*)-**324** >95:5]. δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.54 (6H, q, *J* 8.0, C(4)OSi(C*H*$_2$CH$_3$)$_3$), 0.73 (6H, q, *J* 8.1, OSi(C*H*$_2$CH$_3$)$_3$), 0.89 (9H, t, *J* 8.0, C(4)OSi(C*H*$_2$CH$_3$)$_3$), 1.05 (9H, t, *J* 8.0, OSi(C*H*$_2$CH$_3$)$_3$), 1.16 (3H, C(α)*Me*), 1.26 (9H, s, C*Me*$_3$), 2.17 (1H, ddd, *J* 13.3, 8.2, 5.1, C(5)*H*$_A$), 2.74 (1H, quin, *J* 6.9, C(5)*H*$_B$), 3.39 (1H, dd, *J* 10.0, 2.7, C(3)*H*), 3.46 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ph), 3.59 (1H, ddd, *J* 7.7, 5.0, 2.7, C(4)*H*), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.12 (1H, d,

J 10.0, C(2)*H*), 4.77−4.86 (2H, m, C(7)H_2), 4.53 (1H, d, *J* 15.2, NCH_AH_BPh), 5.13−5.25 (1H, m, C(6)*H*), 7.15−7.55 (10H, m, *Ph*).

5.5. References and notes

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(3) 80% Aqueous tetrakis(hydroxymethyl)phosphonium chloride was evaporated to dryness. Dry tetrakis (hydroxymethyl)phosphonium chloride is extremely hygroscopic and was used immediately.

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(6) (*S*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine was assessed to be >99:1 er by 400MHz ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acetylmandelic acid in $CDCl_3$, and in comparison with that of an authentic racemic sample.

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(19) (*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine was assessed to be >99:1 er by 400MHz ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acetylmandelic acid in $CDCl_3$, and in comparison with that of an authentic racemic sample.

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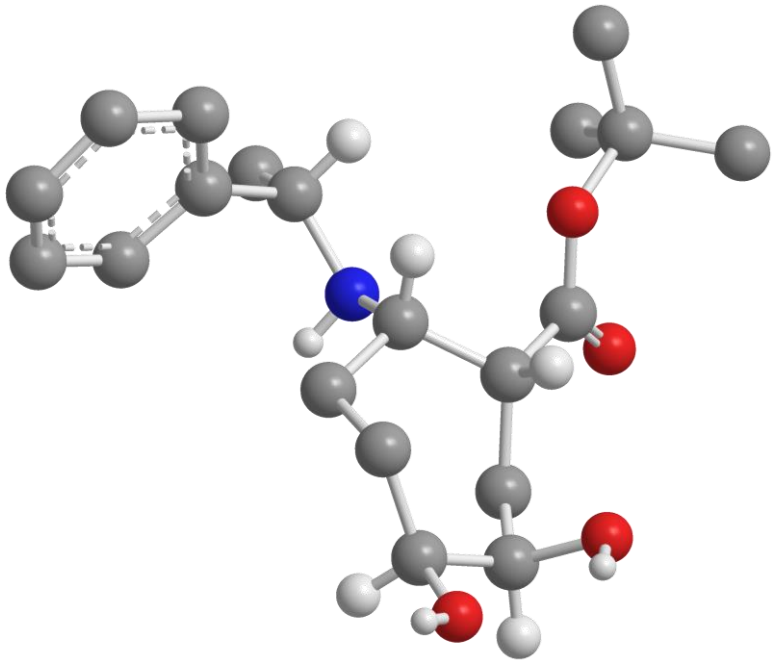
Appendix I: X-Ray crystal structure data for (1*S*,3*R*,4*S*,7*S*,α*S*)-210

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 210

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 **210** [$C_{20}H_{31}NO_4$]: M = 349.47, orthorhombic, space group $P\,2_12_12_1$, a = 7.9164(3) Å, b = 10.2293(3) Å, c = 24.0049(9) Å, V = 1943.90(12) Å^3, Z = 4, μ = 0.660 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.25 × 0.29 mm^3. A total of 4030 unique reflections were measured for 5 < θ < 77 and 3450 reflections were used in the refinement. The final parameters were wR_2 = 0.114 and R_1 = 0.046 [I>–3.0σ(I)], with Flack enantiopole = 0.0(2).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
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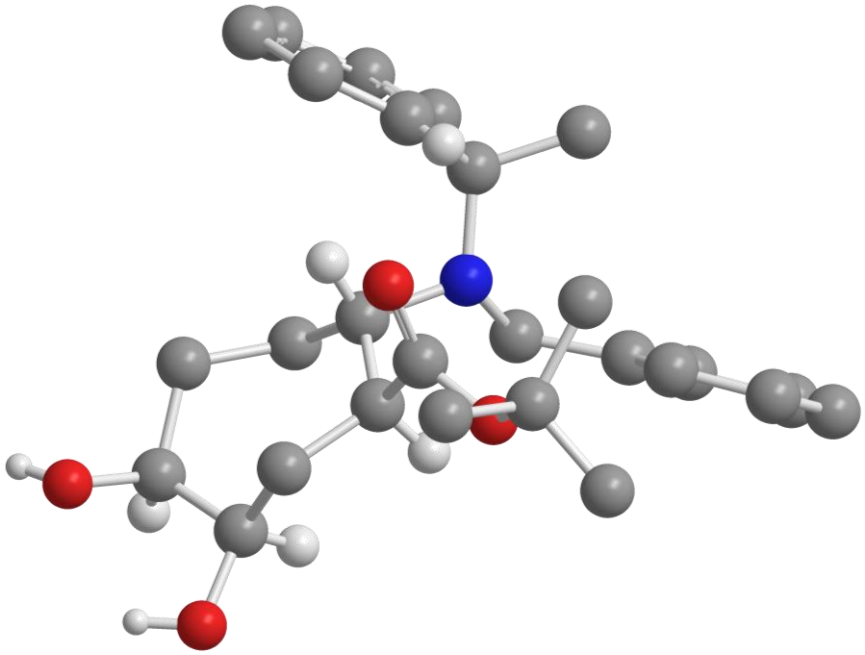
X-Ray crystal structure data for (1*S*,3*R*,4*S*,7*S*,α*S*)-211

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 211

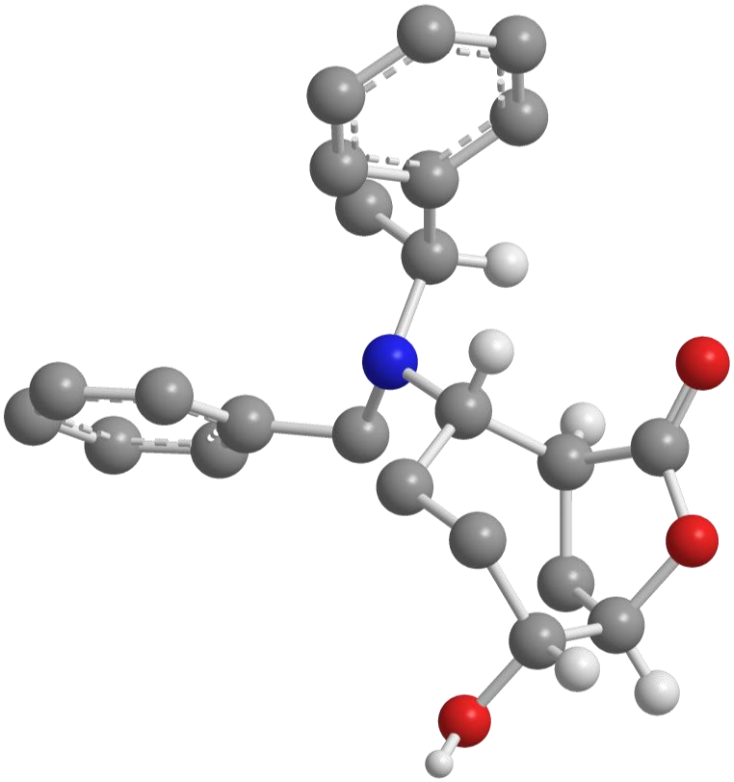
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[3]

X-ray crystal structure data for **211** [$C_{27}H_{37}NO_4$]: M = 439.59, monoclinic, space group $P\ 2_1$, a = 9.48977(14) Å, b = 10.47984(14) Å, c = 12.67854(19) Å, β = 102.2077(15)°, V = 1232.39(3) Å^3, Z = 2, μ = 0.623 mm^{-1}, colourless block, crystal dimensions = 0.25 × 0.26 × 0.29 mm^3. A total of 5059 unique reflections were measured for 4 < θ < 77 and 5042 reflections were used in the refinement. The final parameters were wR_2 = 0.090 and R_1 = 0.035 [I>–3.0σ(I)], with Flack enantiopole = 0.10(13).[4] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (1*S*,2*S*,5*R*,6*R*,α*S*)-227

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 227

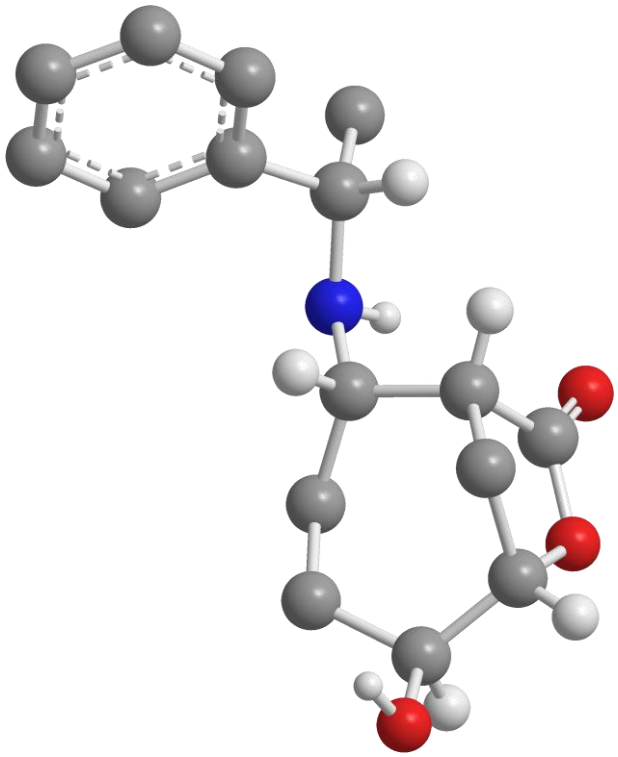
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[5]

X-ray crystal structure data for **227** [$C_{23}H_{27}NO_3$]: M = 365.47, orthorhombic, space group $P\,2_12_12_1$, a = 6.47260(10) Å, b = 11.0282(2) Å, c = 27.0933(5) Å, V = 1933.95(6) Å^3, Z = 4, μ = 0.082 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.22 × 0.24 mm^3. A total of 2476 unique reflections were measured for 5 < θ < 27 and 2061 reflections were used in the refinement. The final parameters were wR_2 = 0.086 and R_1 = 0.062 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[5] 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*,5*S*,6*S*,*αS*)-231

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 231

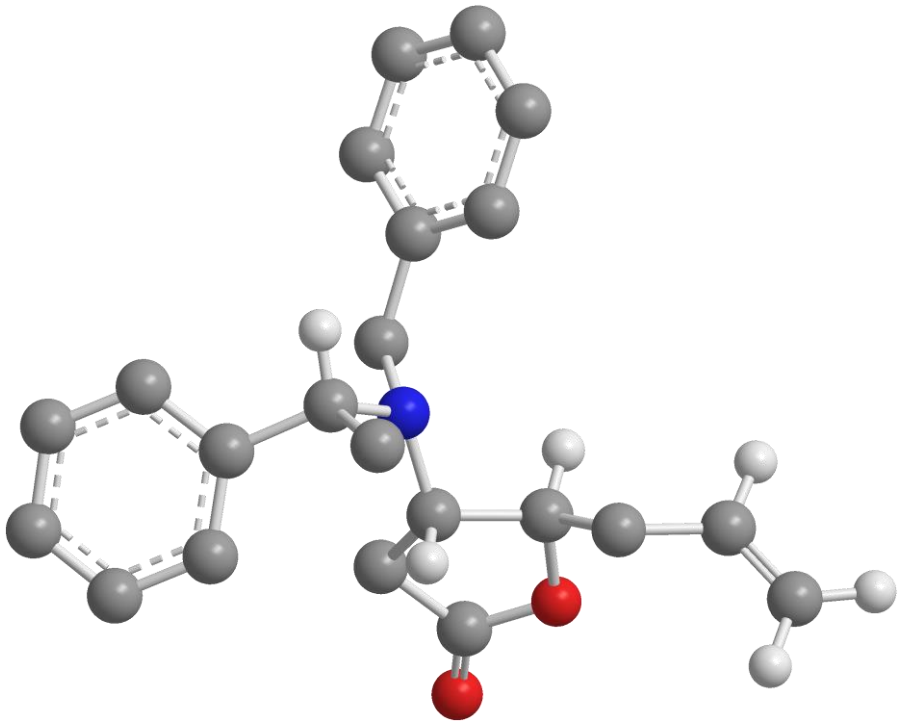
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[6]

X-ray crystal structure data for **231** [$C_{16}H_{21}NO_3$]: M = 275.35, monoclinic, space group $P\ 2_1$, a = 14.1092(4) Å, b = 6.8039(2) Å, c = 15.4968(5) Å, β = 100.147(3)°, V = 1464.39(8) Å^3, Z = 4, μ = 0.693 mm^{-1}, colourless plate, crystal dimensions = 0.08 × 0.20 × 0.25 mm^3. A total of 5798 unique reflections were measured for 3 < θ < 77 and 5777 reflections were used in the refinement. The final parameters were wR_2 = 0.094 and R_1 = 0.038 [I>–3.0σ(I)], with Flack enantiopole = 0.04(13).[7] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (4*S*,5*R*,α*R*)-252

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 252

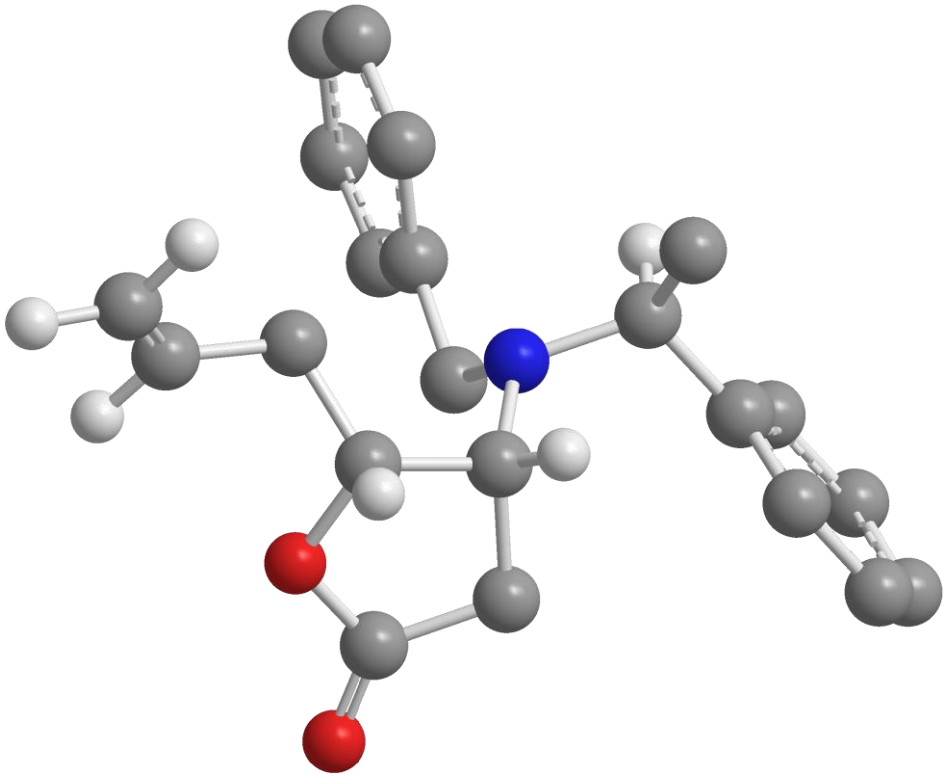
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[8]

X-ray crystal structure data for **252** [$C_{22}H_{25}NO_2$]: M = 335.45, monoclinic, space group $P\ 2_1$, a = 11.01499(18) Å, b = 7.24372(12) Å, c = 11.64962(19) Å, β = 98.1087(14)°, V = 920.22(3) Å^3, Z = 2, μ = 0.603 mm^{-1}, colourless prism, crystal dimensions = 0.10 × 0.11 × 0.26 mm^3. A total of 3631 unique reflections were measured for 4 < θ < 76 and 3188 reflections were used in the refinement. The final parameters were wR_2 = 0.109 and R_1 = 0.042 [I>–3.0σ(I)], with Flack enantiopole = –0.1(2).[9] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (4*R*,5*R*,α*S*)-253

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 253

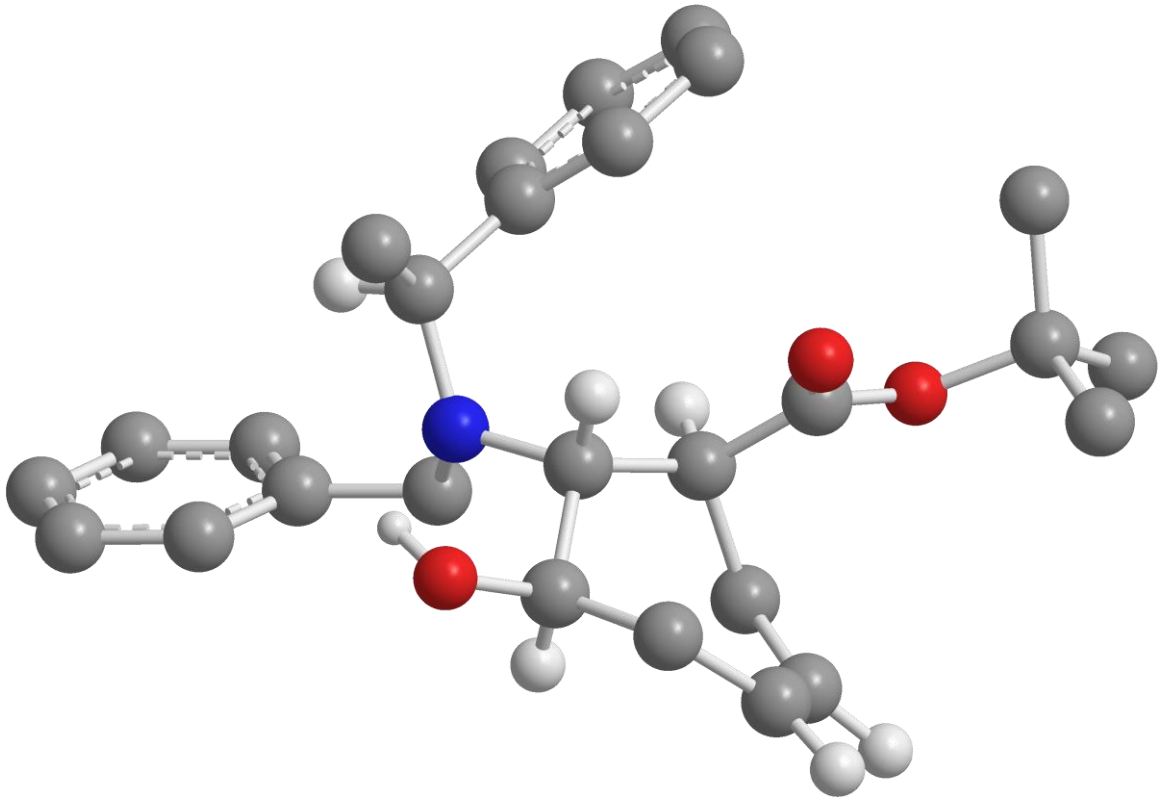
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[10]

X-ray crystal structure data for **253** [$C_{22}H_{25}NO_2$]: M = 335.45, monoclinic, space group $P\ 2_1$, a = 11.0132(3) Å, b = 7.5144(2) Å, c = 11.2730(4) Å, β = 95.7597(13)°, V = 928.22(5) Å^3, Z = 2, μ = 0.076 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.22 × 0.24 mm^3. A total of 2271 unique reflections were measured for 5 < θ < 27 and 2271 reflections were used in the refinement. The final parameters were wR_2 = 0.119 and R_1 = 0.068 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (1*R*,6*R*,7*R*,α*S*)-280

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 280

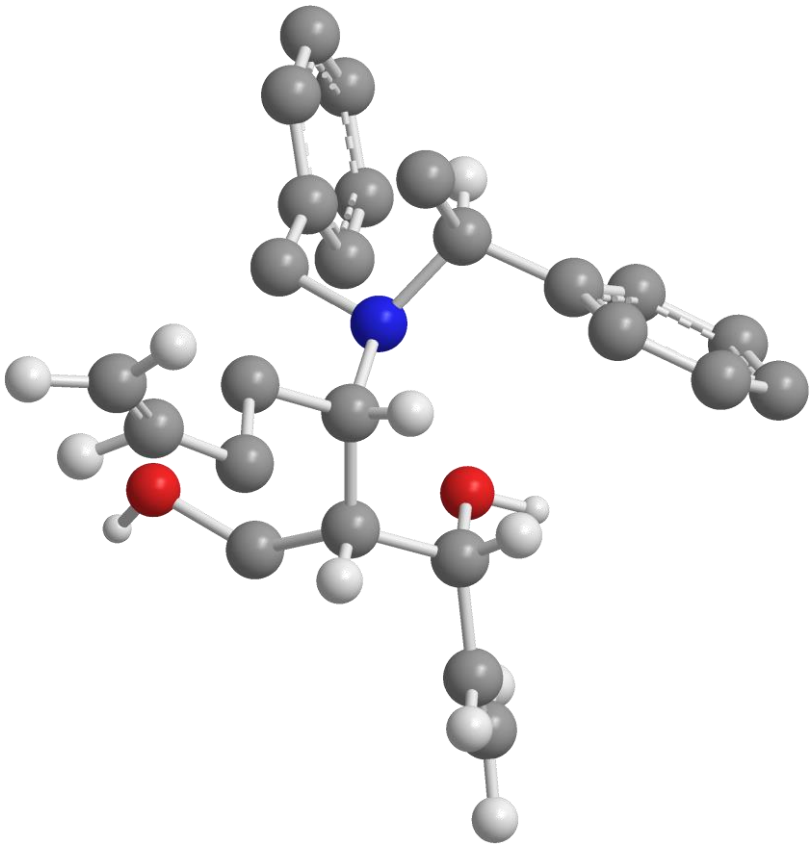
Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[11]

X-ray crystal structure data for **280** [$C_{27}H_{35}NO_3$]: M = 421.58, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 9.6285(2) Å, b = 12.0801(2) Å, c = 20.8333(4) Å, V = 2423.19(8) Å^3, Z = 4, μ = 0.074 mm^{-1}, colourless plate, crystal dimensions = 0.10 × 0.25 × 0.26 mm^3. A total of 3097 unique reflections were measured for $5 < \theta < 27$ and 2549 reflections were used in the refinement. The final parameters were wR_2 = 0.083 and R_1 = 0.042 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[11] 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*,1'*R*,α*S*)-298·HBF_4

(selected H atoms and the BF_4 counterion are omitted for clarity)



X-ray crystal structure determination for 298·HBF_4

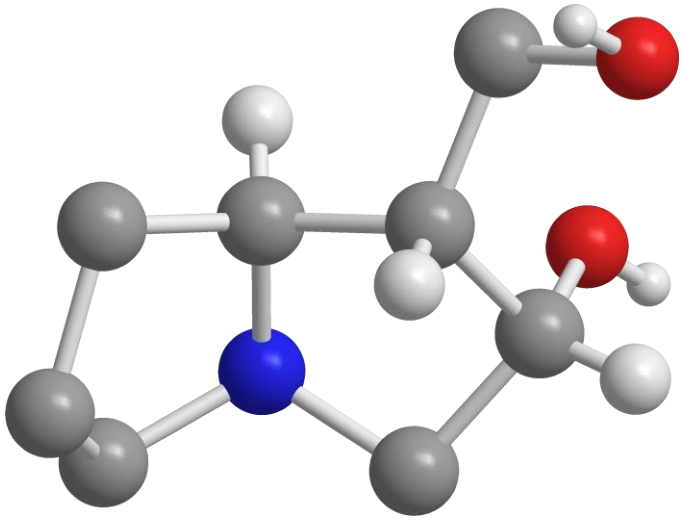
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[12]

X-ray crystal structure data for **298**· HBF_4 [$C_{25}H_{32}BF_4NO_2$]: M = 418.91, monoclinic, space group *C 2*, a = 14.9599(11) Å, b = 12.5400(8) Å, c = 13.7389(8) Å, β = 99.158(7)°, V = 2544.7(3) $Å^3$, Z = 4, μ = 0.64 mm^{-1}, colourless plate, crystal dimensions = 0.08 × 0.20 × 0.25 mm^3. A total of 5180 unique reflections were measured for 3 < θ < 76 and 5157 reflections were used in the refinement. The final parameters were wR_2 = 0.408 and R_1 = 0.146 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

[12] 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*,7a*S*)-105

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 105

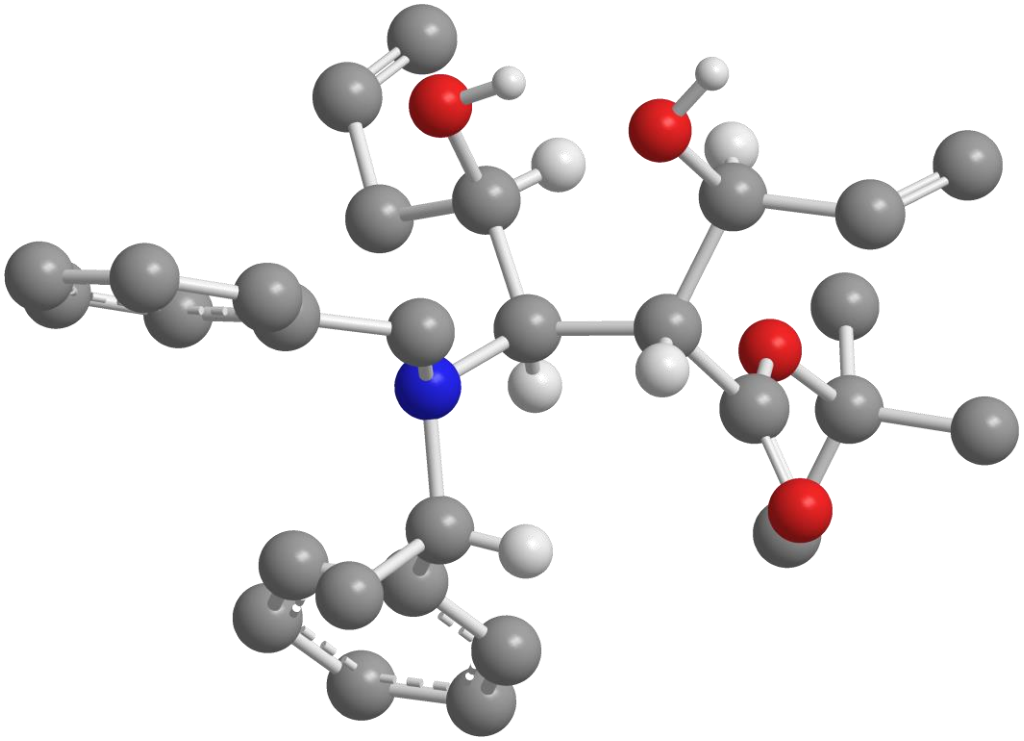
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[13]

X-ray crystal structure data for **105** [$C_8H_{15}NO_2$]: M = 314.43, monoclinic, space group $P\ 2_1$, a = 10.0504(4) Å, b = 7.1703(2) Å, c = 11.7523(4) Å, β = 93.315(3)°, V = 845.50(5) Å^3, Z = 4, μ = 0.714 mm^{-1}, colourless plate, crystal dimensions = 0.10 × 0.18 × 0.21 mm^3. A total of 3480 unique reflections were measured for 4 < θ < 77 and 2480 reflections were used in the refinement. The final parameters were wR_2 = 0.274 and R_1 = 0.098 [I>–3.0σ(I)], with Flack enantiopole = 0.2(8).[14] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (2*R*,3*R*,4*R*,1'*S*,α*S*)-309

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 309

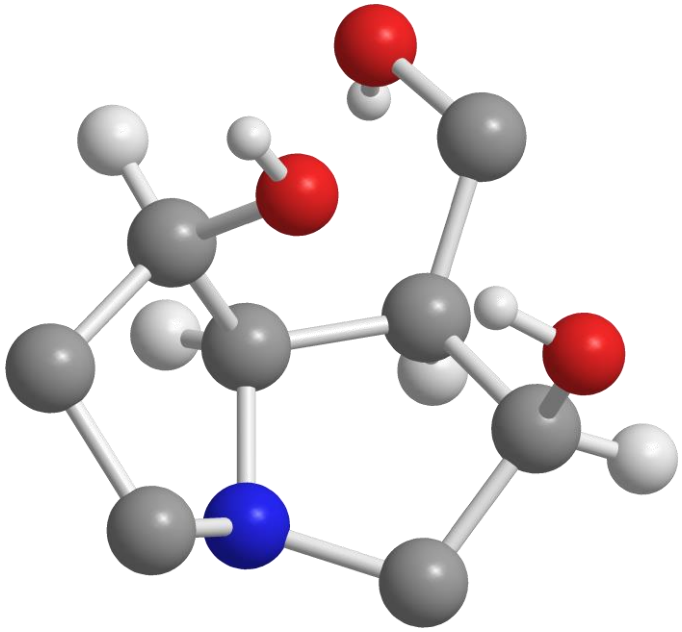
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[15]

X-ray crystal structure data for **309** [$C_{29}H_{39}NO_4$]: M = 464.63, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 10.09161(13) Å, b = 15.13155(19) Å, c = 17.4842(2) Å, V = 2669.86(6) Å^3, Z = 4, μ = 0.603 mm^{-1}, colourless block, crystal dimensions = 0.16 × 0.16 × 0.29 mm^3. A total of 5534 unique reflections were measured for 3 < θ < 76 and 5515 reflections were used in the refinement. The final parameters were wR_2 = 0.104 and R_1 = 0.041 [I>–3.0σ(I)], with Flack enantiopole = 0.15(17).[16] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

X-Ray crystal structure data for (1*S*,2*R*,7*R*,7a*S*)-149

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 149

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.[17]

X-ray crystal structure data for **149** [$C_8H_{15}NO_3$]: M = 173.21, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 7.8419(1) Å, b = 8.39517(8) Å, c = 12.30372(13) Å, V = 810.008(15) Å^3, Z = 4, μ = 0.896 mm^{-1}, colourless prism, crystal dimensions = 0.06 × 0.08 × 0.21 mm^3. A total of 1681 unique reflections were measured for $6 < \theta < 76$ and 1495 reflections were used in the refinement. The final parameters were wR_2 = 0.059 and R_1 = 0.023 [I>–3.0σ(I)], with Flack enantiopole = 0.06(16).[18] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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

Appendix II:

NMR data for (–)-hastanecine, (–)-turneforcidine and (–)-platynecine

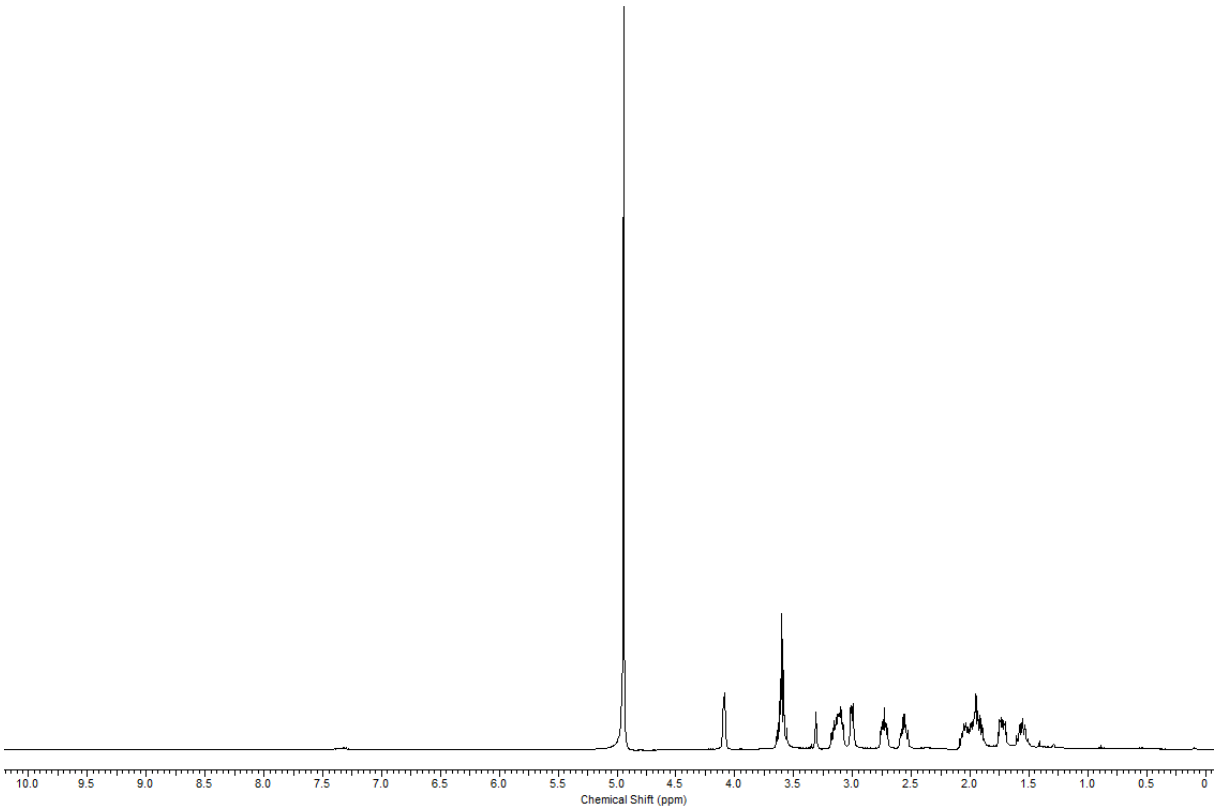


Figure 44. ^{1}H NMR spectrum (400 MHz) of (–)-hastanecine **129** in MeOH-d_4.

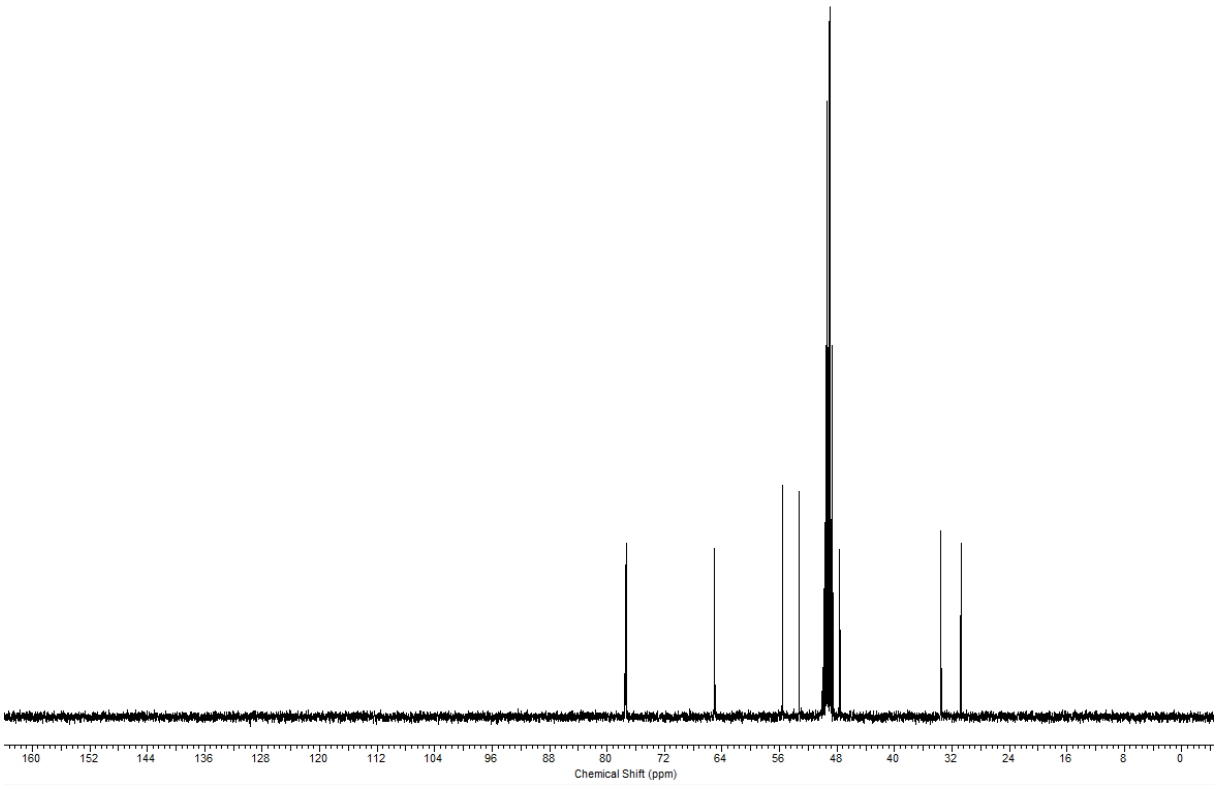


Figure 45. ^{13}C NMR spectrum (100 MHz) of (–)-hastanecine **129** in MeOH-d_4.

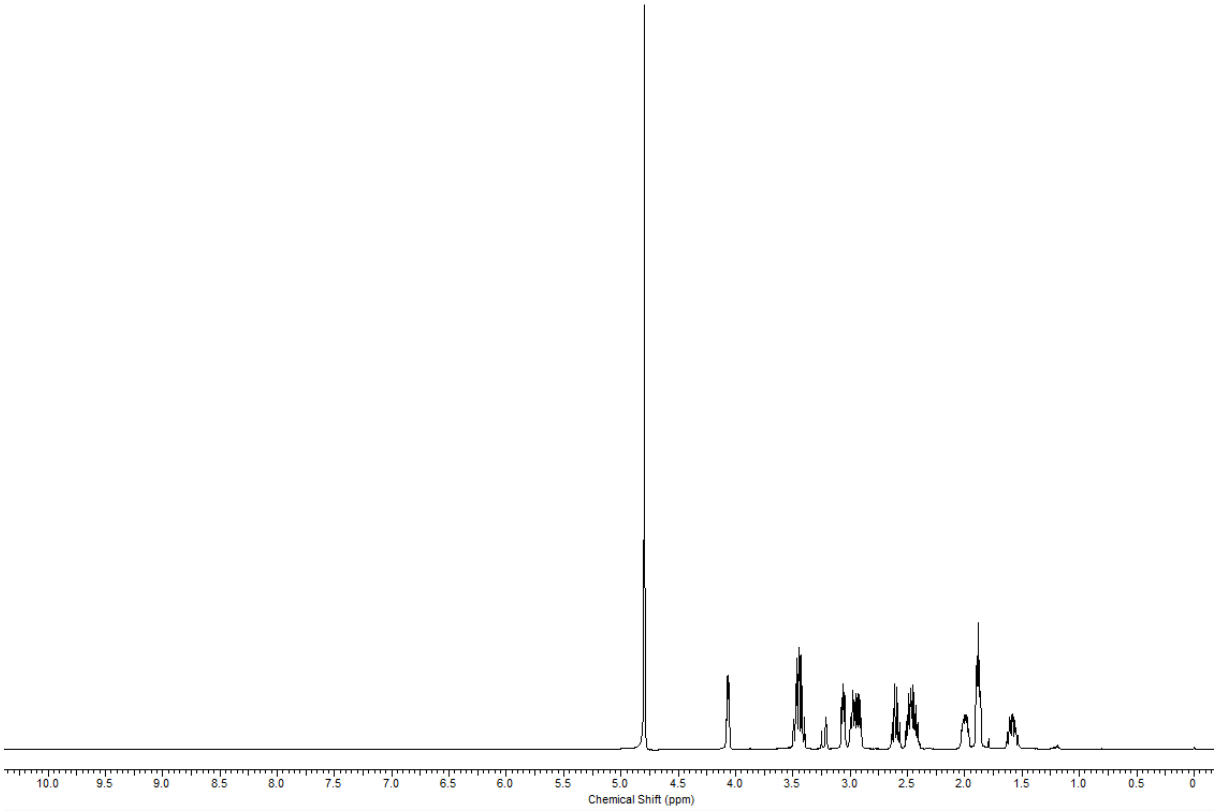


Figure 46. ^{1}H NMR spectrum (400 MHz) of (–)-turneforcidine **130** in MeOH-d_4.

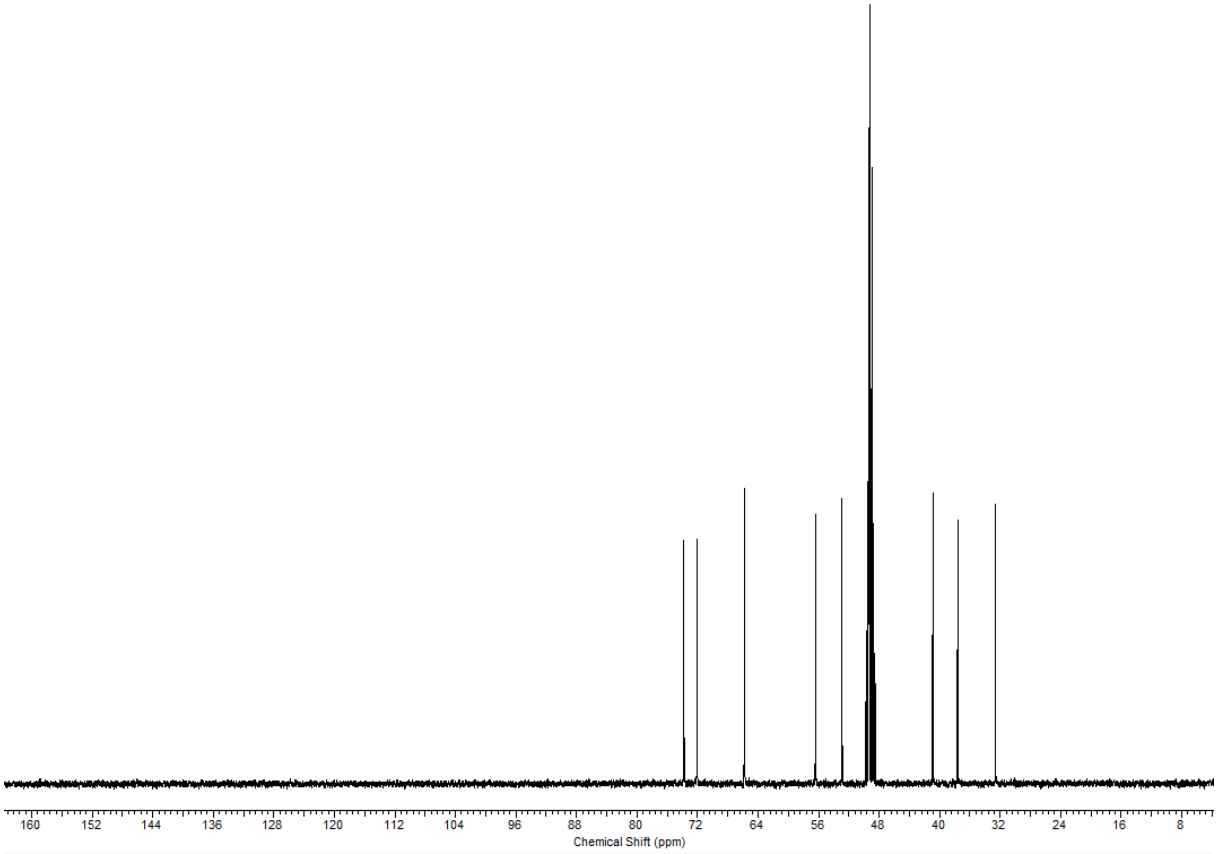


Figure 47. ^{13}C NMR spectrum (100 MHz) of (–)-turneforcidine **130** in MeOH-d_4.

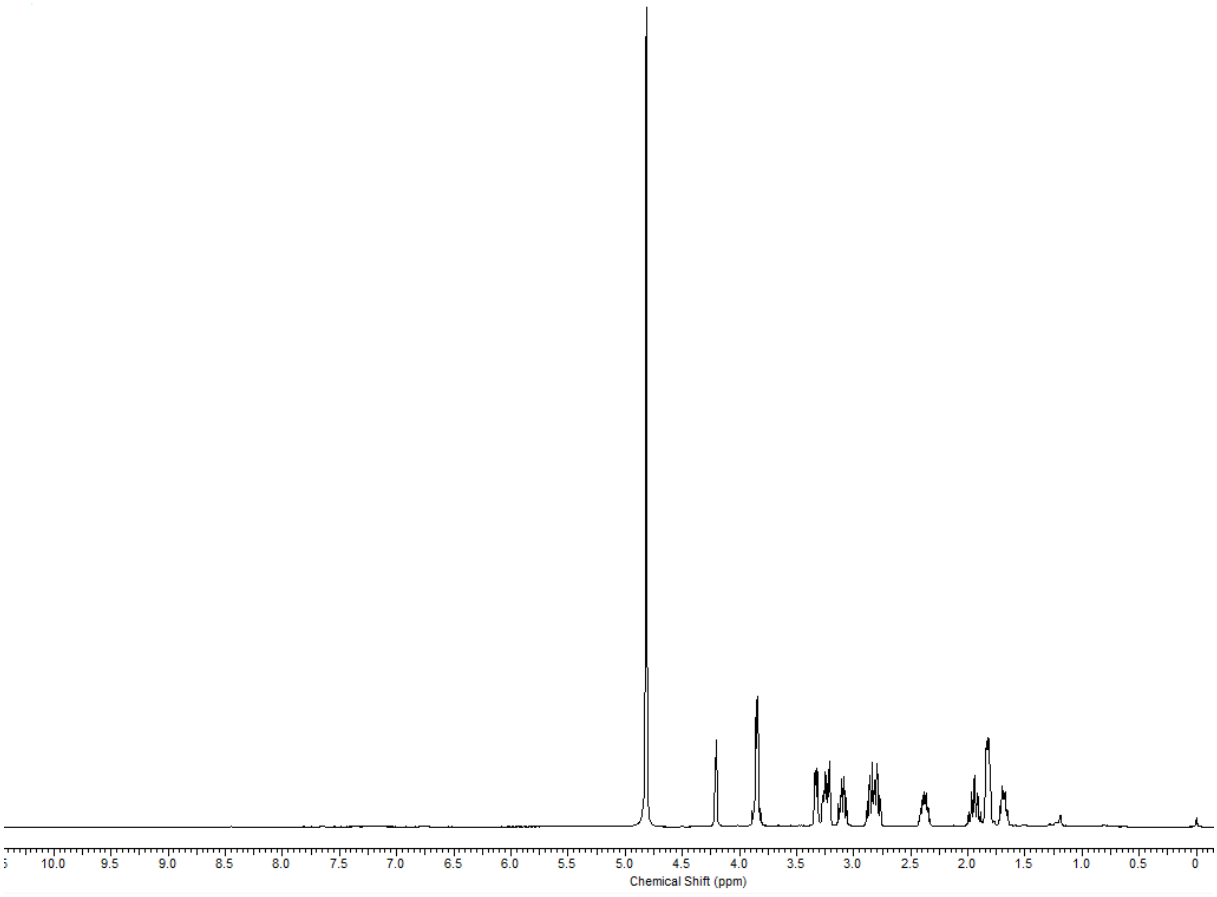


Figure 48. ^{1}H NMR spectrum (400 MHz) of (–)-platynecine **131** in MeOH-d_4.

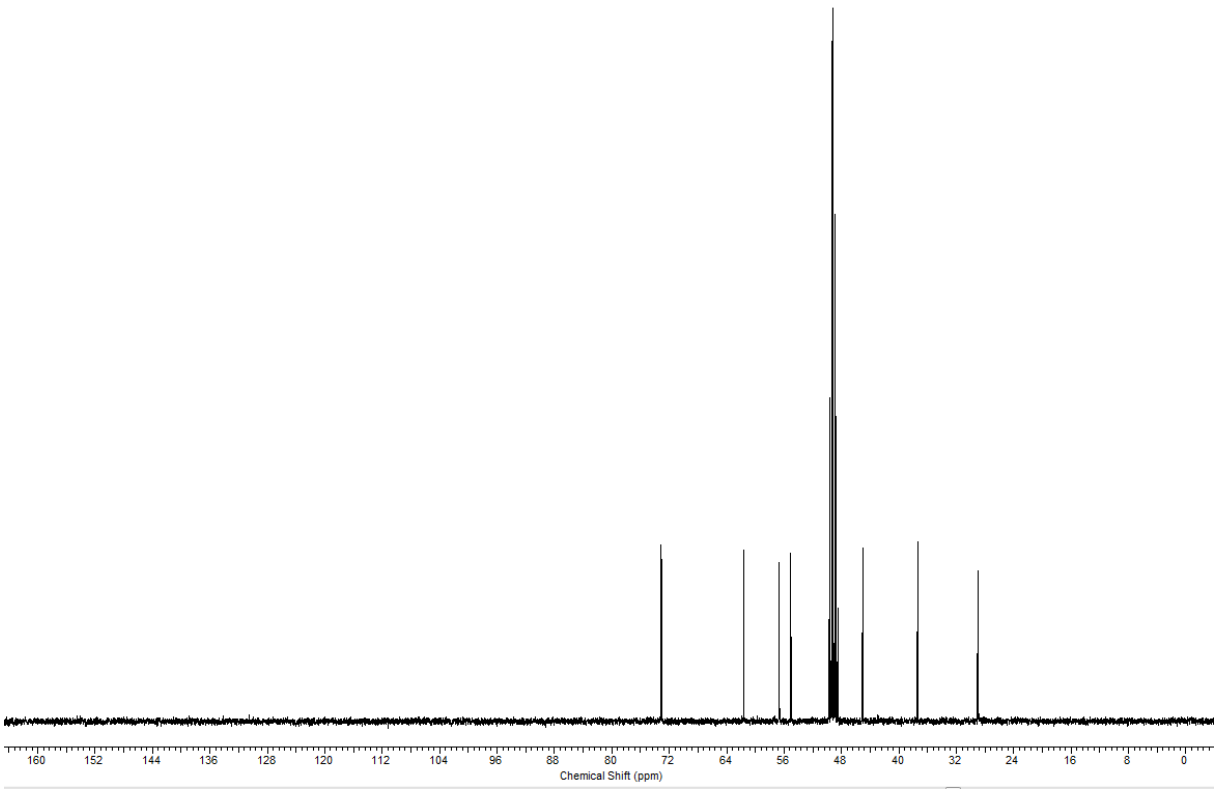


Figure 49. ^{13}C NMR spectrum (100 MHz) of (–)-platynecine **131** in MeOH-d_4.

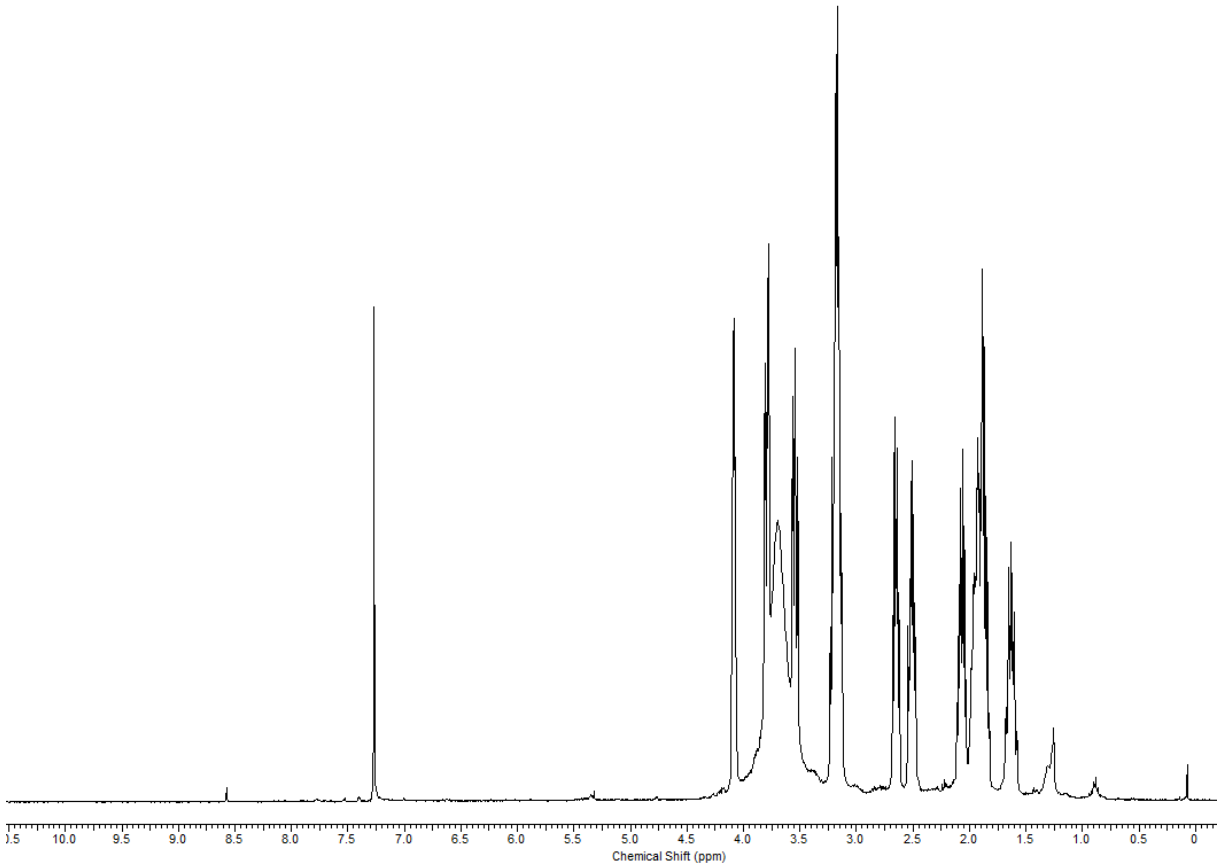


Figure 50. ^{1}H NMR spectrum (400 MHz) of (–)-hastanecine**129** in $CDCl_3$.

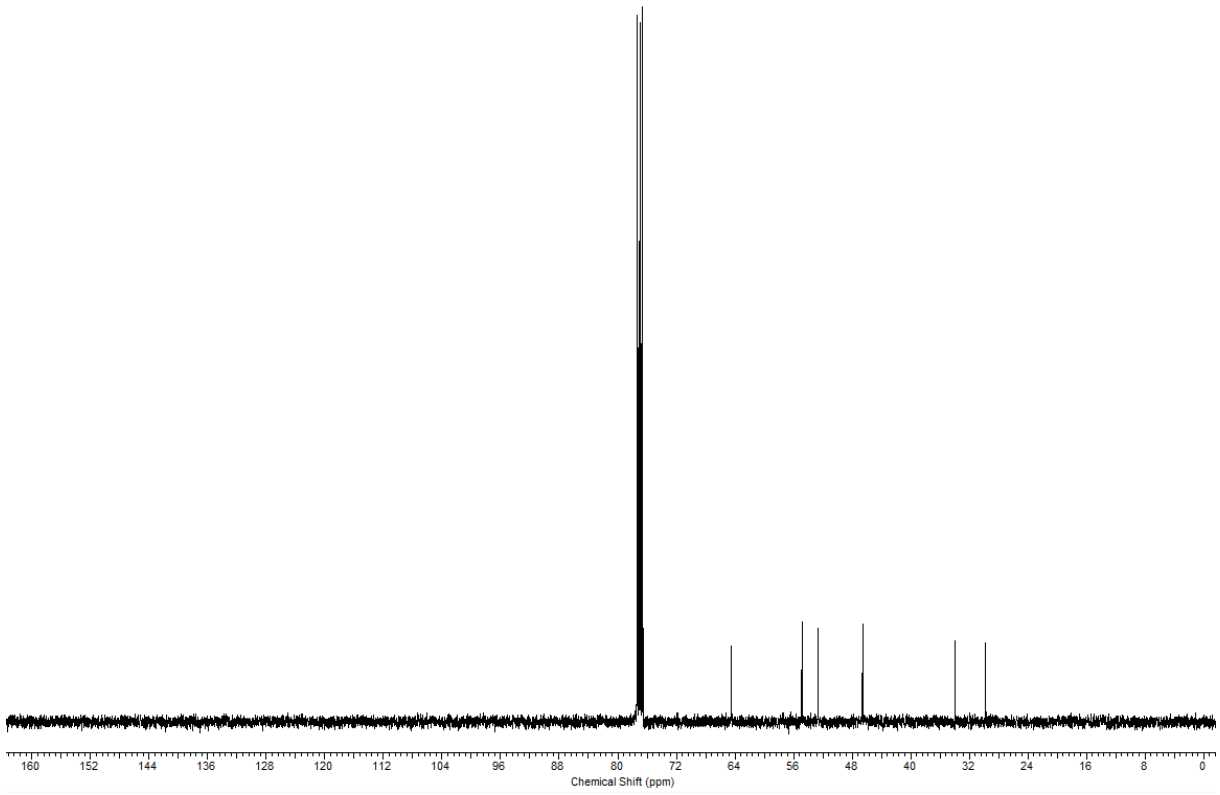


Figure 51. ^{13}C NMR spectrum (100 MHz) of (–)-hastanecine **129** in $CDCl_3$.

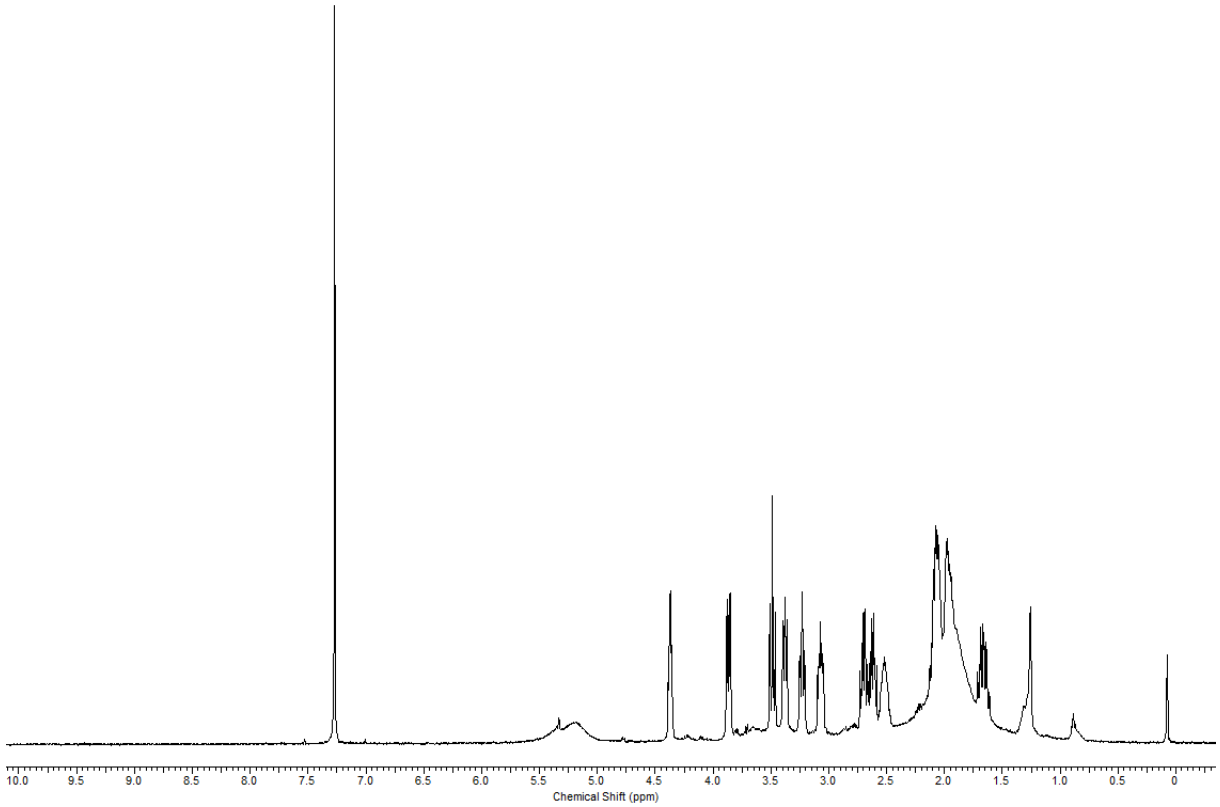


Figure 52. ^{1}H NMR spectrum (400 MHz) of (–)-turneforcidine **130** in $CDCl_3$.

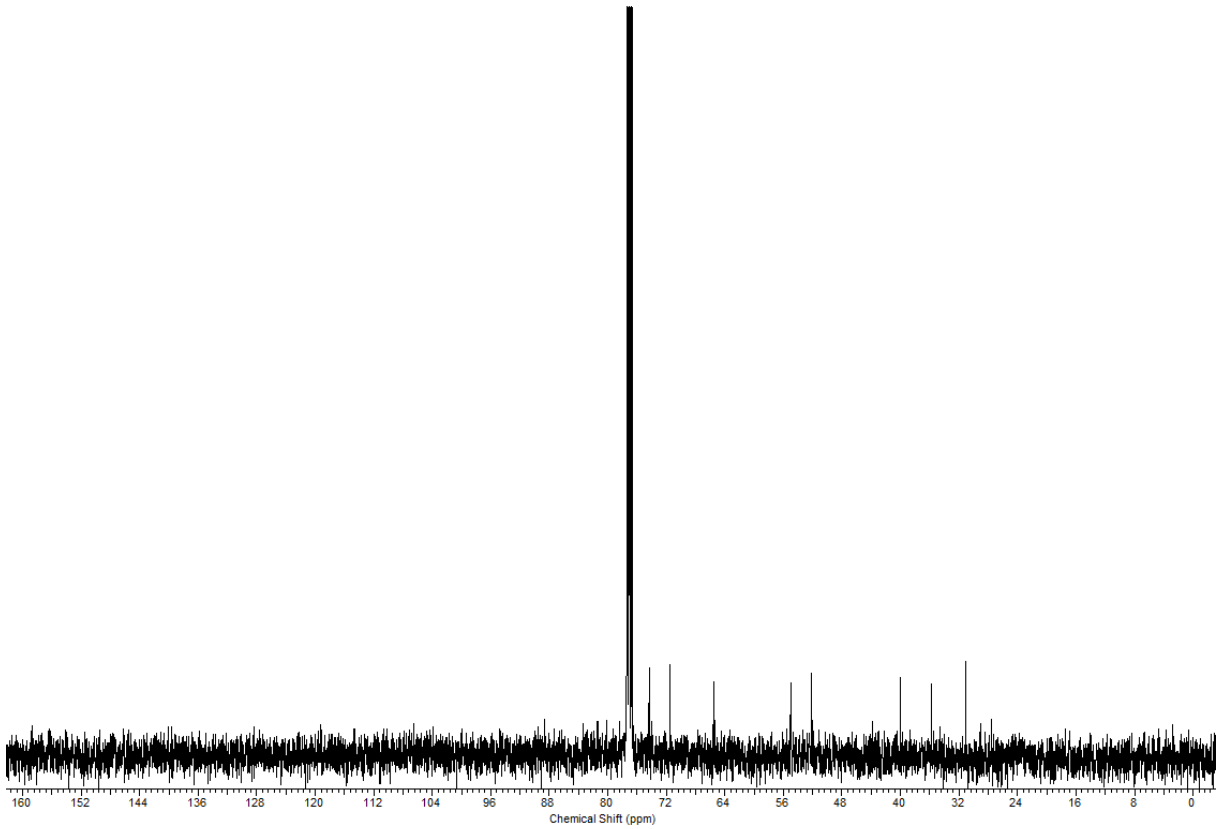


Figure 53. ^{13}C NMR spectrum (100 MHz) of (–)-turneforcidine **130** in $CDCl_3$.

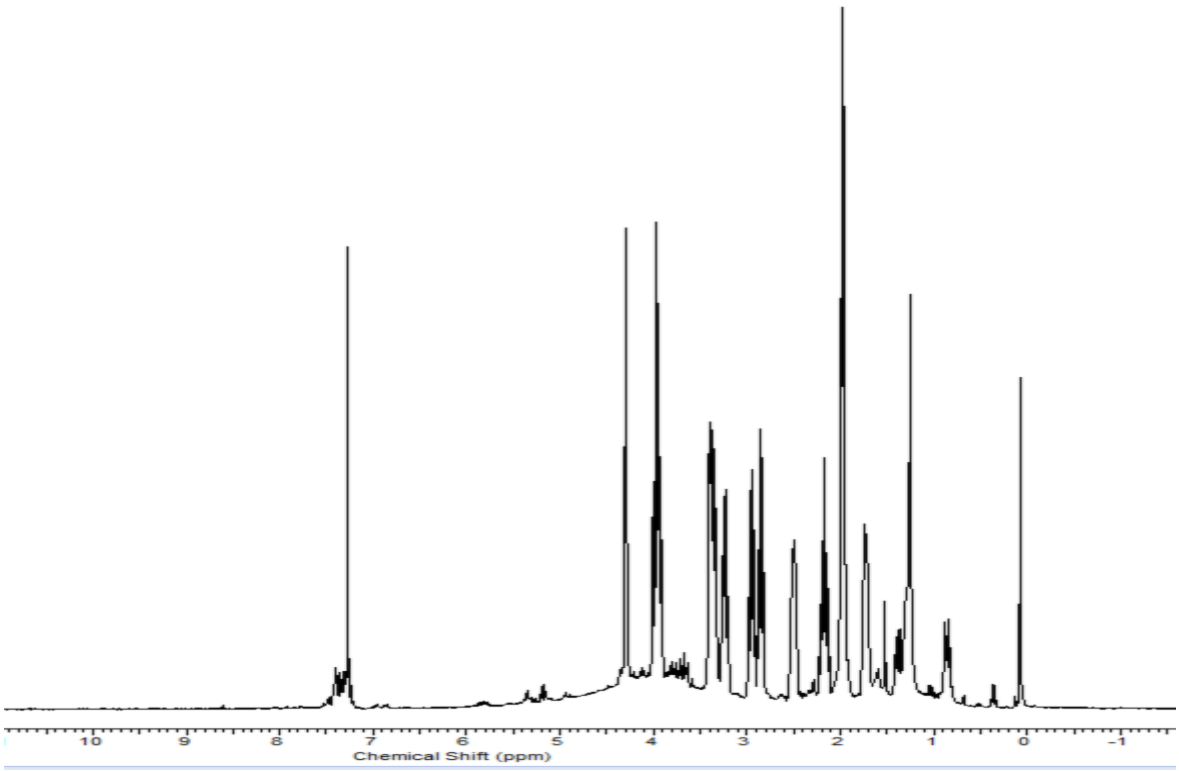


Figure 54. ^{1}H NMR spectrum (400 MHz) of (–)-platynecine **131** in $CDCl_3$.

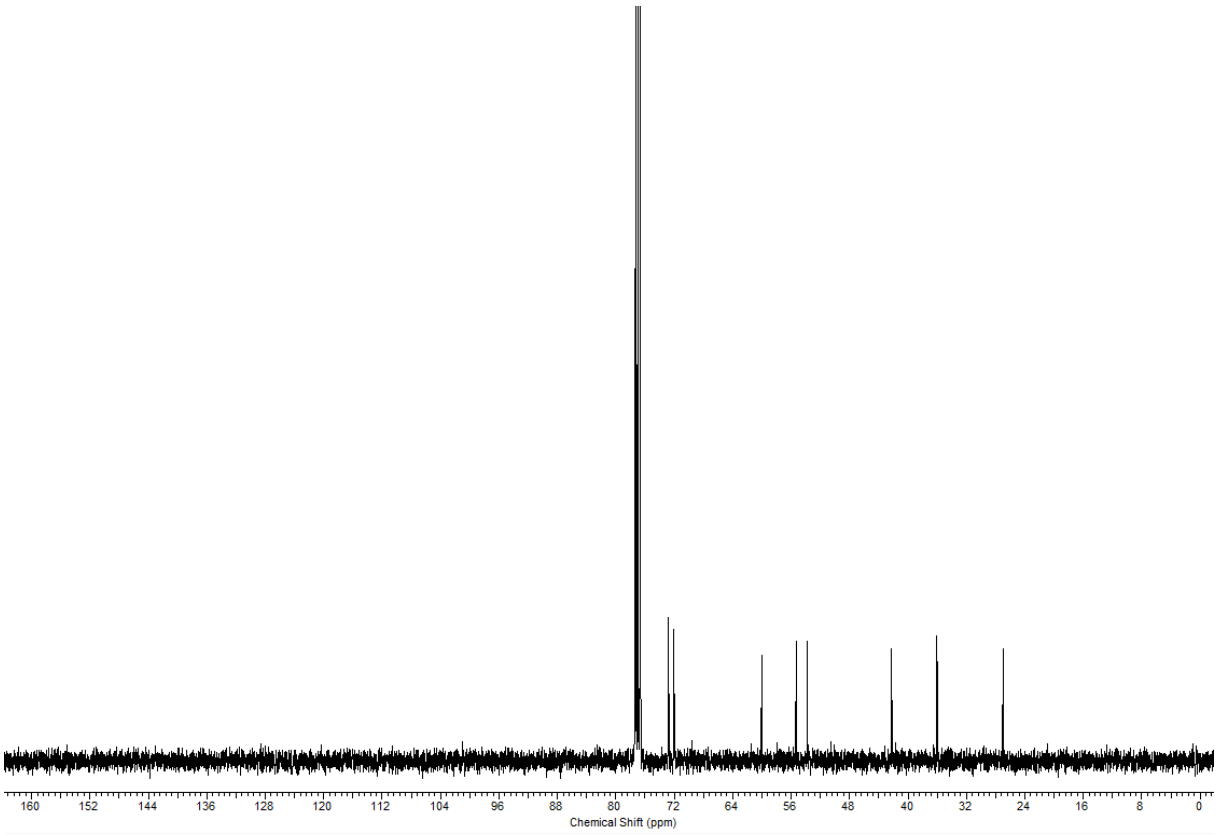


Figure 55. ^{13}C NMR spectrum (100 MHz) of (–)-platynecine **131** in $CDCl_3$.

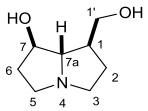
^{1}H NMR data for (–)-hastanecine 129 							
	MeOH-d_4		**$CDCl_3$**				
H	**This study** (400 MHz)	**Denmark[1]** (500 MHz)	**This study** (400 MHz)	**Mulzer[2]** (270 MHz)	**Pilli[3]** data for (+)-**129**	**Hart[4]** (200 MHz)	**Niwa[5]** data for (±)-**129** (270 MHz)
C(1)*H*	1.75−2.00 m	1.87−2.06 m	1.81–2.01 m	1.80–2.15 m	2.09 m	2.05–2.22 m	2.10 m
C(2)H_A	1.40−1.55 m	1.50 −1.58 m	1.60–1.76 m	1.70 m	1.60–1.76 m	1.58–1.80 m	1.63 m
C(2)H_B	1.75−2.00 m	1.87−2.06 m	1.81–2.01 m	1.80–2.15 m	1.84–2.02 m	1.86–2.05 m	1.86–2.03 m
C(3)H_A	2.46 dt (*J* 10.1, 5.6)	2.53 dt (*J* 10.2, 5.5)	2.51 td (*J* 10.1, 5.6)	2.56 dt (*J* 9.5, 5.0)	2.56–2.61 m	2.45–2.58 m	2.52 dt (*J* 10.6, 5.6)
C(3)H_B	2.98−3.10 m	3.04−3.30 m	3.09–3.25 m	3.20–3.40 m	3.21–3.41 m	3.19–3.35 m	2.64 dt (*J* 10.6, 6.6)
C(5)H_A	2.63 ddd (*J* 11.2, 6.9, 4.1)	2.70 ddd (*J* 11.2, 6.9, 4.2)	2.65 dt (*J* 10.9, 6.4)	2.70 ddd (*J* 11.0, 6.0, 4.0)	2.64–2.76 m	2.60–2.75 m	3.11–3.26 m
C(5)H_B	2.98−3.10 m	3.04−3.30 m	3.09–3.25 m	3.20–3.40 m	3.21–3.41 m	3.19–3.35 m	3.11–3.26 m
C(6)H_A	1.58−1.68 m	1.67−1.73 m	1.81–2.01 m	1.80–2.15 m	1.84–2.02 m	1.86–2.05 m	1.86–2.03 m
C(6)H_B	1.75−2.00 m	1.87−2.06 m	2.06 dq (*J* 12.6, 6.4)	1.80–2.15 m	1.84–2.02 m	2.05–2.22 m	1.86–2.03 m
C(7)*H*	3.96−4.01 m	4.06 dt (*J* 4.9, 2.7)	4.05-4.13 m	4.15 m	4.14 dd (*J* 8.5, 5.0)	4.08–4.17 m	4.07 dt (*J* 5.9, 4.3)
C(7a)*H*	2.90 dd (*J* 7.5, 2.0)	2.96 dd (*J* 7.5, 2.5)	3.09–3.25 m	3.20–3.40 m	3.21–3.41 m	3.19–3.35 m	3.11–3.26 m
C(1')H_2	3.45−3.55 m	3.54−3.63 m	3.54 dd (*J* 10.7, 7.9) 3.80 dd (*J* 10.6, 4.2)	3.60 dd (*J* 10.5, 7.0) 3.80 dd (*J* 10.5)	3.82 dd (*J* 10.6, 4.0) 3.56 dd (*J* 10.6, 7.5)	3.59 dd (*J* 10.6, 7.6) 3.86 dd (*J* 10.8, 4.2)	3.53 dd (*J* 10.2, 8.3) 3.81 dd (*J* 10.2, 4.6)

Table 17. Comparison of ^{1}H NMR spectroscopic data in $CDCl_3$ for hastanecine **129** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

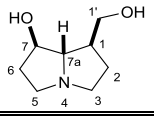
^{13}C NMR data for (–)-hastanecine 129 							
	MeOH-d_4					**$CDCl_3$**	
C	**This study** (100 MHz)	**Denmark[1]** (125 MHz)	**Mulzer[2]** (63 MHz)	**Pilli[3]** data for (+)-**129**	**Hartmann[6]** (63 MHz)	**This study** (100 MHz)	**Pilli[3]** data for (+)-**129**
C(1)	47.6	47.77	47.8	46.5	47.7	46.5	46.3
C(2)	30.8	30.87	30.8	29.9	30.9	29.8	29.7
C(3)	55.6	55.36	55.4	55.8	55.3	54.8	54.9
C(5)	53.3	53.00	53.1	53.4	53.0	52.6	52.7
C(6)	33.5	33.50	33.5	33.0	33.5	33.9	33.8
C(7)	77.5	77.82	77.8	78.3	77.9	76.8	77.2
C(7a)	77.3	76.79	76.8	75.9	76.6	76.6	76.8
C(1')	65.5	65.27	65.3	63.7	65.3	64.5	64.3

Table 18. Comparison of ^{13}C NMR spectroscopic data for hastanecine **129** [chemical shifts (δ_C) are reported in ppm].

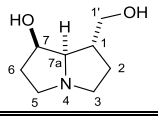
^{1}H NMR data for turneforcidine 130 								
	MeOH-d_4			**$CDCl_3$**				
H	**This study** (400 MHz)	**Wee**[7] (300 MHz)	**Hartmann**[6] (400 MHz)	**This study** (400 MHz)	**West**[8] (500 MHz)	**Livinghouse**[9] (300 MHz)	**Niwa**[10] (270 MHz)	**Knight**[11] (400 MHz)[a]
C(1)*H*	2.46−2.60 m	2.48−2.66 m	2.53	2.46−2.57 m	2.61 ddd (*J* 10.3, 10.3, 6.0)	2.42−2.72 m	2.43−2.74 m	2.70−2.90 m
C(2)H_A	1.66 dtd (*J* 12.4, 9.3, 6.8)	1.66 dddd (*J* 12.2, 12.2, 9.7, 6.8)	1.68	1.60−1.72 m	1.60 dddd (*J* 12.1, 10.6, 10.6, 7.3)	1.59 m	1.55−1.71 m	1.85−2.05 m
C(2)H_B	2.07 dtd (*J* 12.4, 6.8, 3.0)	2.09 dddd (*J* 12.6, 6.6, 6.6, 3.3)	2.10	1.83−2.14 m	2.03 m	1.86−2.07 m	1.55−1.71 m	2.05−2.40 m
C(3)H_A	2.46−2.60 m	2.48−2.66 m	2.58	2.62 td (*J* 10.3, 6.2)	2.49 m	2.42−2.72 m	2.43−2.74 m	3.00−3.15 m
C(3)H_B	2.97−3.08 m	3.03−3.16 m	3.08	3.07 ddd (*J* 10.3, 6.9, 4.1)	3.03 ddd (*J* 10.4, 6.9, 5.0)	3.00 m	3.06 m	3.15−3.40 m
C(5)H_A	2.68 q (*J* 8.9)	2.73 q (*J* 9.1)	2.70	2.70 td (*J* 9.5, 6.4)	2.68 ddd (*J* 10.2, 8.5, 6.5)	2.42−2.72 m	2.43−2.74 m	3.15−3.40 m
C(5)H_B	2.97−3.08 m	3.03−3.16 m	3.03	3.23 ddd (*J* 9.5, 7.4, 1.8)	3.20 ddd (*J* 9.6, 7.3, 2.2)	3.20 m	3.21 m	3.15−3.40 m
C(6)H_A	1.93−1.99 m	1.85−2.20 m	2.00	1.83−2.14 m	1.92 m	1.86−2.07 m	1.88−2.11 m	2.05−2.40 m
C(6)H_B	1.93−1.99 m	1.85−2.20 m	1.99	1.83−2.14 m	2.03 m	1.86−2.07 m	1.88−2.11 m	2.05−2.40 m
C(7)*H*	4.14 q (*J* 3.7)	4.17 q (*J* 3.3)	4.18	4.37 dd (*J* 9.2, 5.4)	4.32 dd (*J* 10.0, 5.6)	4.30 dd (*J* 7.5, 5.1)	4.34 dd (*J* 10.0, 5.6)	4.30−4.40 m
C(7a)*H*	3.14 dd (*J* 6.9, 4.6)	3.21 dd (*J* 6.6, 4.5)	3.16	3.38 dd (*J* 8.3, 5.4)	3.32 dd (*J* 8.3, 5.6)	3.37 m	3.32 dd (*J* 8.2, 5.6)	3.50−3.85 m
C(1')H_A	3.49 dd (*J* 10.6, 7.1)	3.51 dd (*J* 10.5, 7.2)	3.53	3.49 t (*J* 9.8)	3.41 dd (*J* 9.8, 9.8)	3.37 m	3.56 dd (*J* 10.5, 6.6)	3.50−3.85 m
C(1')H_B	3.14 dd (*J* 10.6, 6.6)	3.56 dd (*J* 10.5, 6.6)	3.57	3.87 dd (*J* 9.8, 4.6)	3.80 dd (*J* 10.0, 4.5)	3.76 dd (*J* 10.2, 4.8)	3.85 dd (*J* 9.9, 4.6)	3.50−3.85 m

Table 19. Comparison of ^{1}H NMR data in MeOH-d_4 and $CDCl_3$ for **(−)**-turneforcidine **130** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz]; [a][an additional signal was reported at 3.90−4.10 ppm]

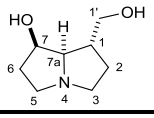
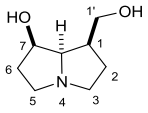
^{13}C NMR data for (−)-turneforcidine 130 							
	MeOH-d_4			**$CDCl_3$**			
C	**This study** (100 MHz)	**Wee**[7] (100 MHz)	**Hartmann**[6] (100 MHz)	**This study** (100 MHz)	**West**[8] (125 MHz)	**Livinghouse**[9] (75 MHz)	**Knight**[11] (100 MHz)
C(1)	40.9	40.7	40.8	40.0	40.5	40.2	40.4
C(2)	32.6	32.4	32.6	31.0	31.0	30.8	31.1
C(3)	52.9	52.8	52.8	52.1	52.3	52.1	53.5
C(5)	56.4	56.3	56.2	55.0	55.2	55.0	56.3
C(6)	37.6	37.4	37.5	35.7	35.4	35.3	37.0
C(7)	72.1	71.8	72.0	71.5	71.5	71.2	70.7
C(7a)	73.8	73.9	73.7	74.3	74.3	74.2	75.7
C(1')	65.8	65.5	65.6	65.4	65.3	64.9	63.7

Table 20. Comparison of ^{13}C NMR spectroscopic data in MeOH-d_4 and $CDCl_3$ for **(−)**-turneforcidine **130** [Chemical shifts (δ_C) are reported in ppm].

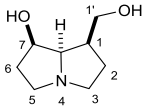
^{1}H NMR data for platynecine 131 in MeOH-d_4



H	**This study** (400 MHz)	**Denmark**[12] (500 MHz)	**West**[8] (500 MHz)	**Donohoe**[13] (500 MHz)	**Hartmann**[6] (400 MHz)	**Yu**[14] data for (±)-**131** (500 MHz)	**Niwa**[5] data for (±)-**131** (270 MHz)
C(1)*H*	2.42−2.57 m	2.49 m	2.47 m	2.26–2.40 m	2.45 m	2.39–2.45 m	2.10 m
C(2)H_A	1.78 dtd (*J* 11.8, 7.2, 2.3)	1.71 dtd (*J* 11.9, 7.4, 3.0)	1.77 dddd (*J* 9.6, 7.1, 7.1, 2.5)	1.54–2.00 m	1.74 m	1.68–1.74 m	1.63 m
C(2)H_B	1.99−2.11 m	2.08 tt (*J* 11.7, 8.7)	2.91 m	1.54–2.00 m	1.98 m	1.94–2.02 m	1.86–2.03 m
C(3)H_A	2.85−3.00 m	2.80 ddd (*J* 10.4, 9, 2.9)	2.87 ddd (*J* 11.3, 9.1, 2.5)	2.62–2.82 m	2.79 m	2.75–2.81 m	2.52 dt (*J* 10.6, 5.6)
C(3)H_B	3.20 td (*J* 10.5, 7.2)	3.14 td (*J* 9.6, 7.8)	3.17 ddd (*J* 10.7, 10.7, 7.1)	2.62–2.82 m	3.10 m	3.18–3.22 m	2.64 dt (*J* 10.6, 6.6)
C(5)H_A	2.85−3.00 m	2.89 m	2.93 ddd (*J* 11.3, 11.3, 7.1)	2.95–3.24 m	2.86 m	2.83–2.87 m	3.11–3.26 m
C(5)H_B	3.33−3.38 m	3.22 m	3.31 m	2.95–3.24 m	3.23 m	3.06–3.11 m	3.11–3.26 m
C(6)H_A	1.89−1.96 m	1.90 m	1.91 m	1.54–2.00 m	1.88 m	1.84–1.89 m	1.86–2.03 m
C(6)H_B	1.89−1.96 m	1.90 m	2.03 m	1.54–2.00 m	1.90 m	1.84–1.89 m	1.86–2.03 m
C(7)*H*	4.30 q (*J* 2.7)	4.25 q (*J* 2.3)	4.29 m	4.13–4.17 m	4.25 m	4.23 m	4.07 dt (*J* 5.9, 4.3)
C(7a)*H*	3.43 dd (*J* 8.1, 3.2)	3.26 dd (*J* 7.6, 2.5)	3.38 dd (*J* 8.0, 3.3)	2.95–3.24 m	3.29 m	3.26 dd (*J* 8.0, 3.2)	3.11–3.26 m
C(1')H_2	3.90−4.00 m	4.00 m	3.95 dddd (*J* 11.0, 11.0, 11.0, 5.9)	3.84 d (*J* 5.5)	3.94 m 3.93 m	3.93 d (*J* 5.2)	3.53 dd (*J* 10.2, 8.3) 3.81 dd (*J* 10.2, 4.6)

Table 21. Comparison of ^{1}H NMR spectroscopic data in MeOH-d_4 for platynecine **131** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

^{13}C NMR data for platynecine 131 in MeOD-d_4



C	**This study** (100 MHz)	**Denmark**[12] (125 MHz)	**West**[8] (125 MHz)	**Hartmann**[6] (100 MHz)	**Yu**[14] data for (±)-**131** (75 MHz)	**Fleet**[15] (75 MHz)	**Donnohoe**[13] (75 MHz)
C(1)	45.0	45.1	45.1	45.0	45.0	44.94	43.55
C(2)	29.0	28.9	29.0	28.9	28.8	28.85	27.40
C(3)	56.7	54.8	56.7	56.5	54.8	54.81	53.36
C(5)	55.1	56.6	55.1	54.8	56.5	56.56	55.09
C(6)	37.4	37.3	37.4	37.3	37.3	37.27	35.84
C(7)	73.0	72.6	73.1	72.6	72.6	72.90	71.25
C(7a)	73.2	73.2	72.9	73.2	73.1	73.05	71.58
C(1')	61.6	61.73	61.7	61.6	61.6	61.61	60.17

Table 22. Comparison of ^{13}C NMR spectroscopic data for platynecine **131** in MeOD- d_4 [chemical shifts (δ_C) are reported in ppm].

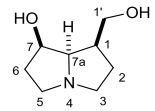
^{1}H NMR data for platynecine 131 in $CDCl_3$ 					
H	**This study** (400 MHz)	**Robins**[16] (200 MHz)	**Glasnov**[17] (300 MHz)	**Correia**[18] data for (±)-**131** (300 MHz)	**Niwa**[5] data for (±)-**131** (270 MHz)
C(1)*H*	2.45-2.55 m	2.41 m	2.64–2.89 m	2.23 m	2.40–2.70 m
C(2)H_A	1.65-1.76 m	1.56−2.24 m	1.50–1.69 m	1.56–1.65 m	1.60–1.70 m
C(2)H_B	2.17 tt (*J* 11.0, 9.3)	1.56−2.24 m	1.78–1.95 m	1.56–1.65 m	1.60–1.70 m
C(3)H_A	2.85 dt (*J* 8.9, 1.8)	2.69−3.00 m	2.64–2.89 m	2.53–2.62 m	2.40–2.70 m
C(3)H_B	3.24 q (*J* 8.9)	2.69−3.00 m	2.64–2.89 m	2.53–2.62 m	2.40–2.70 m
C(5)H_A	2.91-3.00 m	3.20 m	2.96–3.38 m	3.00 m	3.20 m
C(5)H_B	3.30-3.43 m	3.20 m	2.96–3.38 m	3.08 dd (*J* 8.0, 3.4)	3.30 dd (*J* 8.2, 3.0)
C(6)H_A	1.88-2.07 m	1.56−2.24 m	1.78–1.95 m	1.67–1.72 m	1.90–2.01 m
C(6)H_B	1.88-2.07 m	1.56−2.24 m	2.01–2.15 m	1.67–1.72 m	1.90–2.01 m
C(7)*H*	4.25-4.32 m	4.21 m	4.07–4.27 m	4.10 q (*J* 2.1)	4.18 ddd (*J* 4.2, 4.0, 3.5)
C(7a)*H*	3.30-3.43 m	3.04 m	2.96–3.38 m	2.84 m	3.00 m
C(1')H_2	3.93 dd (*J* 11.2, 4.7) 3.91 dd (*J* 11.2, 2.1)	3.81 dd (*J* 11.2, 4.2) 3.91 dd (*J* 11.2, 2.6)	3.59–3.91 m	3.74 m	3.90–4.00 m

Table 23. Comparison of ^{1}H NMR spectroscopic data in $CDCl_3$ for platynecine **131** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

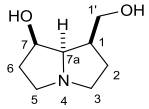
^{13}C NMR data for platynecine 131 in $CDCl_3$ 				
C	**This study** (100 MHz)	**Robins**[16] (25 MHz)	**Correia**[18] data for (±)-**131** (75 MHz)	**Glasnov**[17] (75 MHz)
C(1)	42.2	43.9	42.7	42.73
C(2)	27.0	28.6	27.3	27.16
C(3)	53.8	53.7	52.5	54.12
C(5)	55.3	55.3	54.0	55.59
C(6)	36.0	36.5	35.3	36.14
C(7)	72.0	71.8	69.8	72.22
C(7a)	72.8	73.1	71.8	72.95
C(1')	60.0	61.6	60.3	59.94

Table 24. Comparison of ^{13}C NMR spectroscopic data for platynecine **131** in $CDCl_3$ [chemical shifts (δ_C) are reported in ppm].

NMR data for (–)-macronecine, (–)-1-*epi*-macronecine, (–)-petasinecine and (+)-1-*epi*-petasinecine

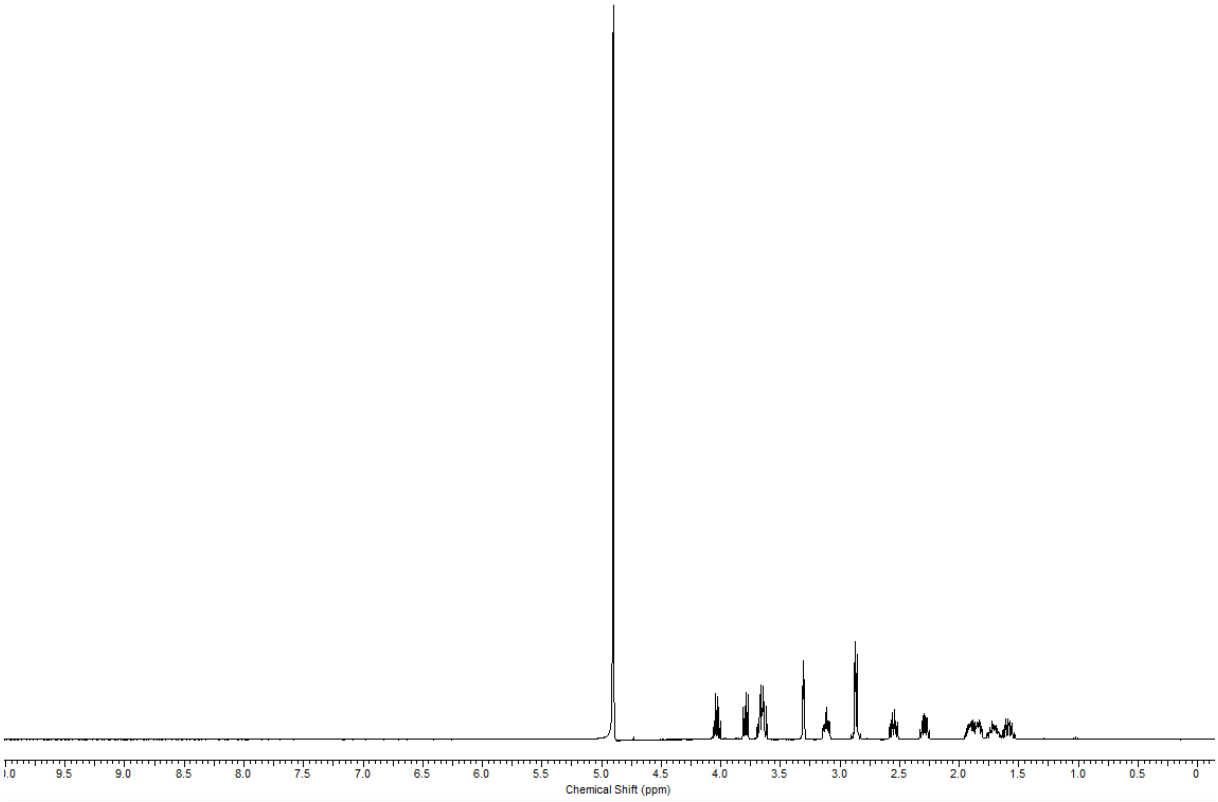


Figure 56. ^{1}H NMR spectrum (400 MHz) of (–)-1-*epi*-macronecine **300** in MeOH-d_4

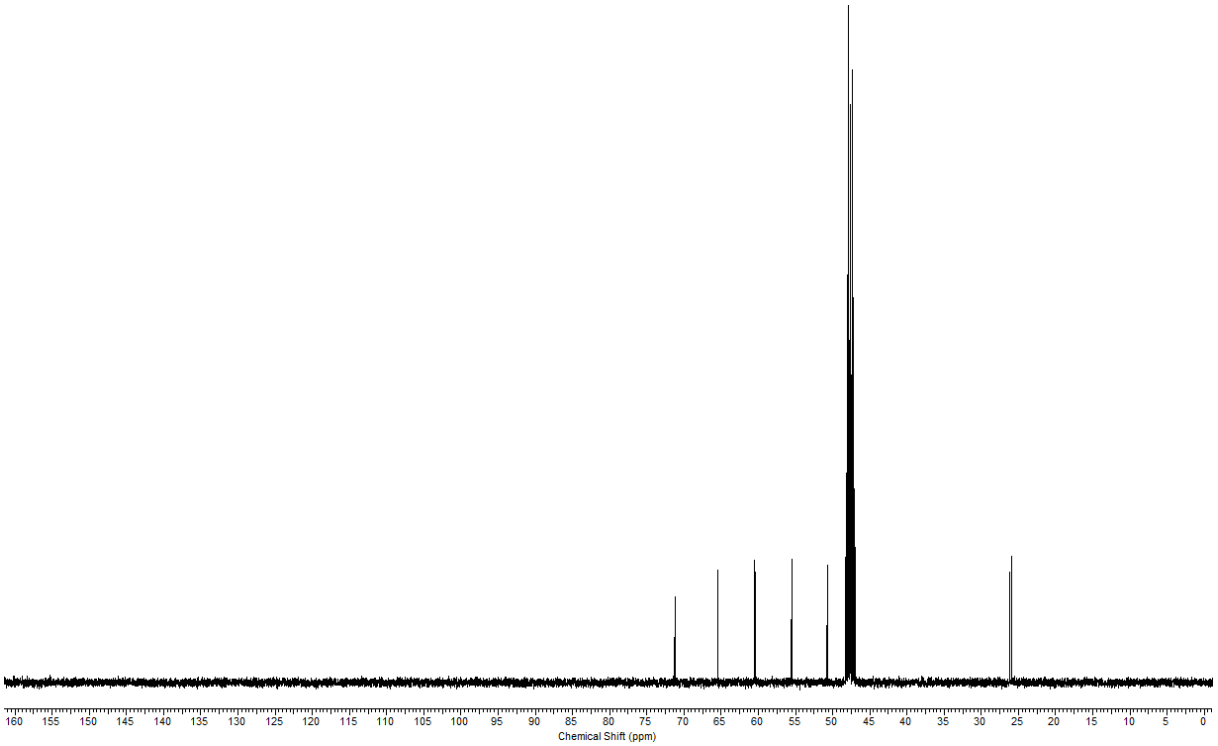


Figure 57. ^{13}C NMR spectrum (100 MHz) of (–)-1-*epi*-macronecine **300** in MeOH-d_4

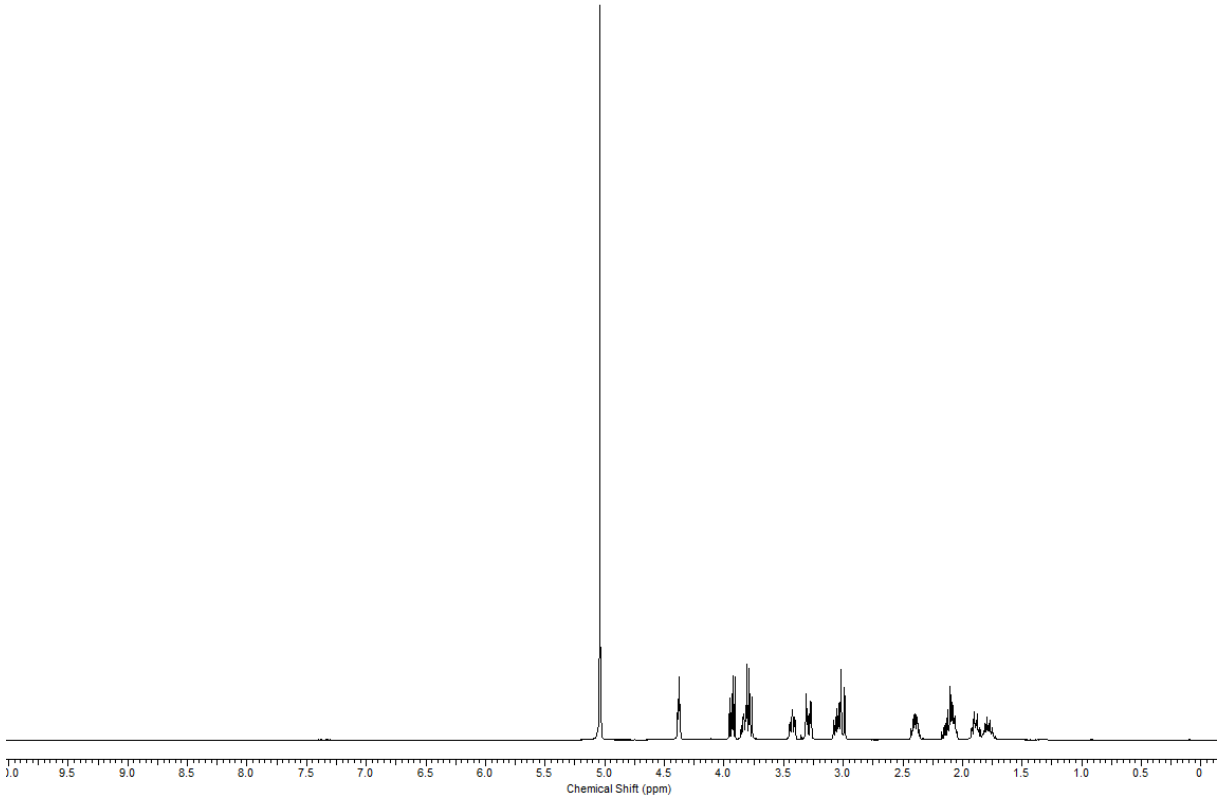


Figure 59. ^{1}H NMR spectrum (400 MHz) of (–)-petasinecine **106** in MeOH-d_4

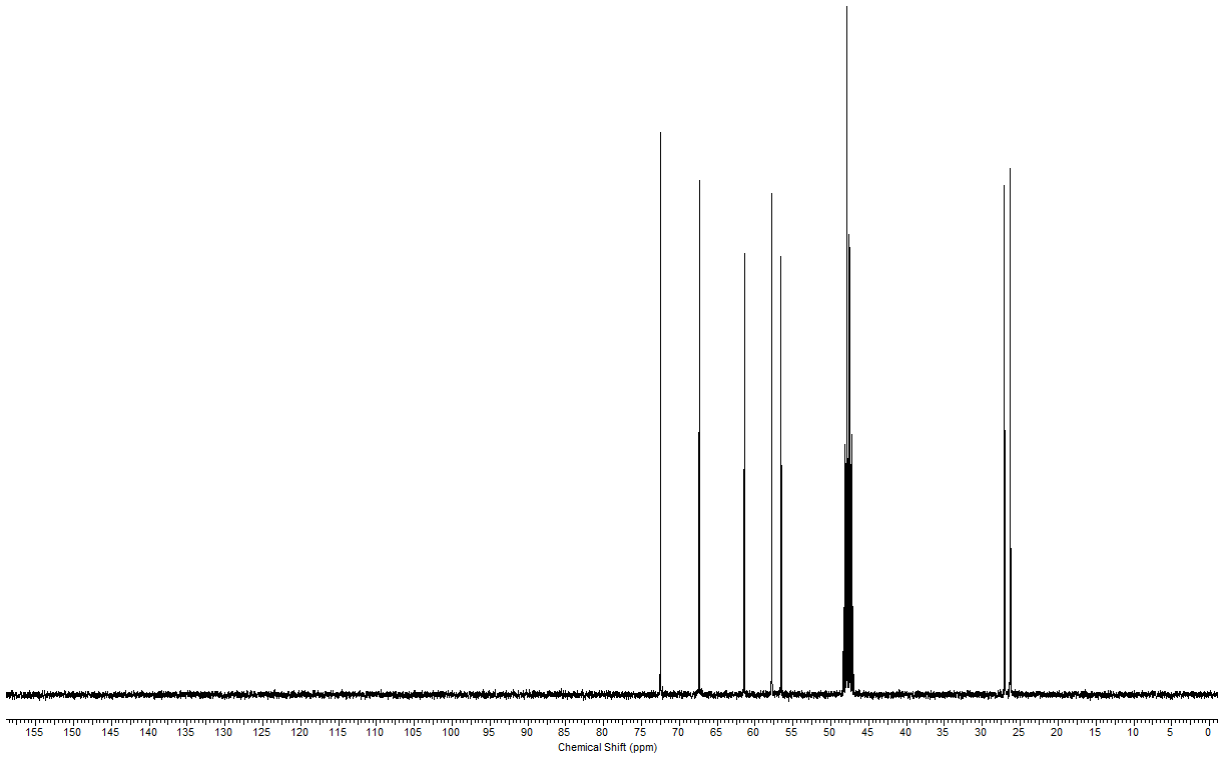


Figure 60. ^{13}C NMR spectrum (100 MHz) of (–)-petasinecine **106** in MeOH-d_4

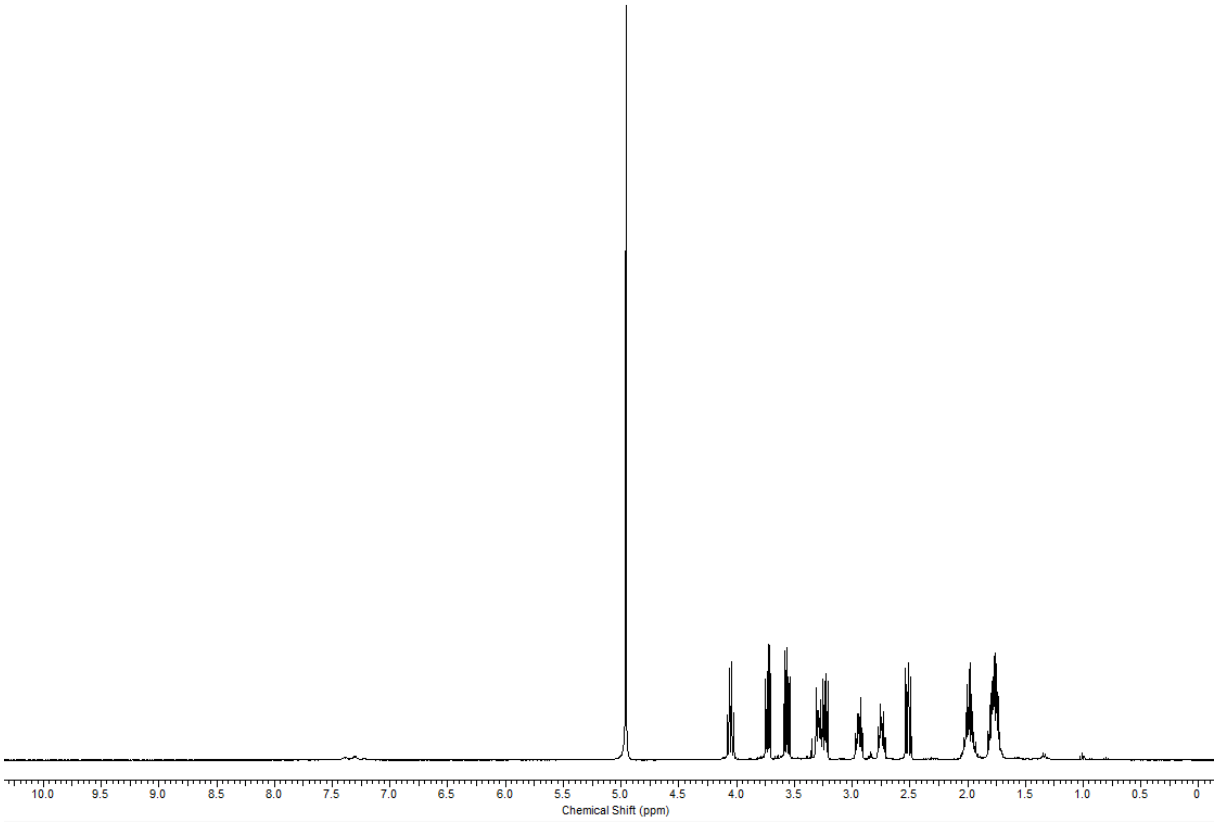


Figure 61. ^{1}H NMR spectrum (400 MHz) of (+)-1-*epi*-petasinecine **305** in MeOH-d_4

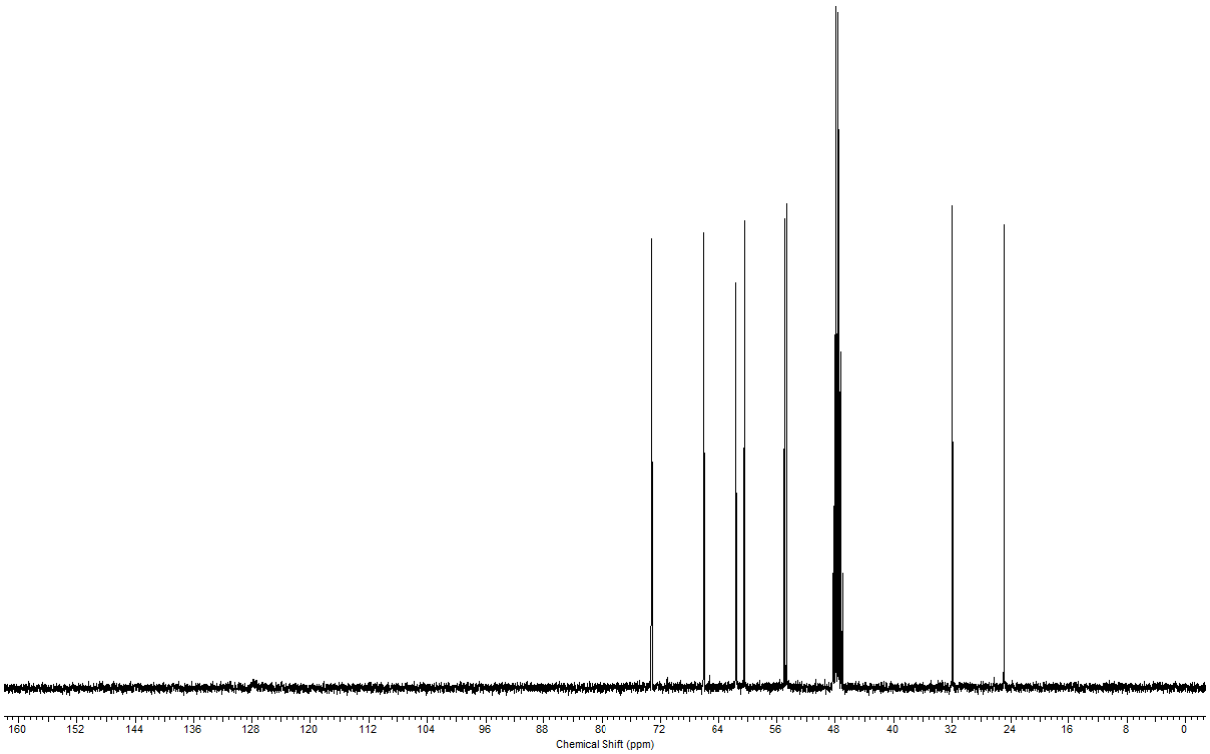


Figure 62. ^{13}C NMR spectrum (100 MHz) of (+)-1-*epi*-petasinecine **305** in MeOH-d_4

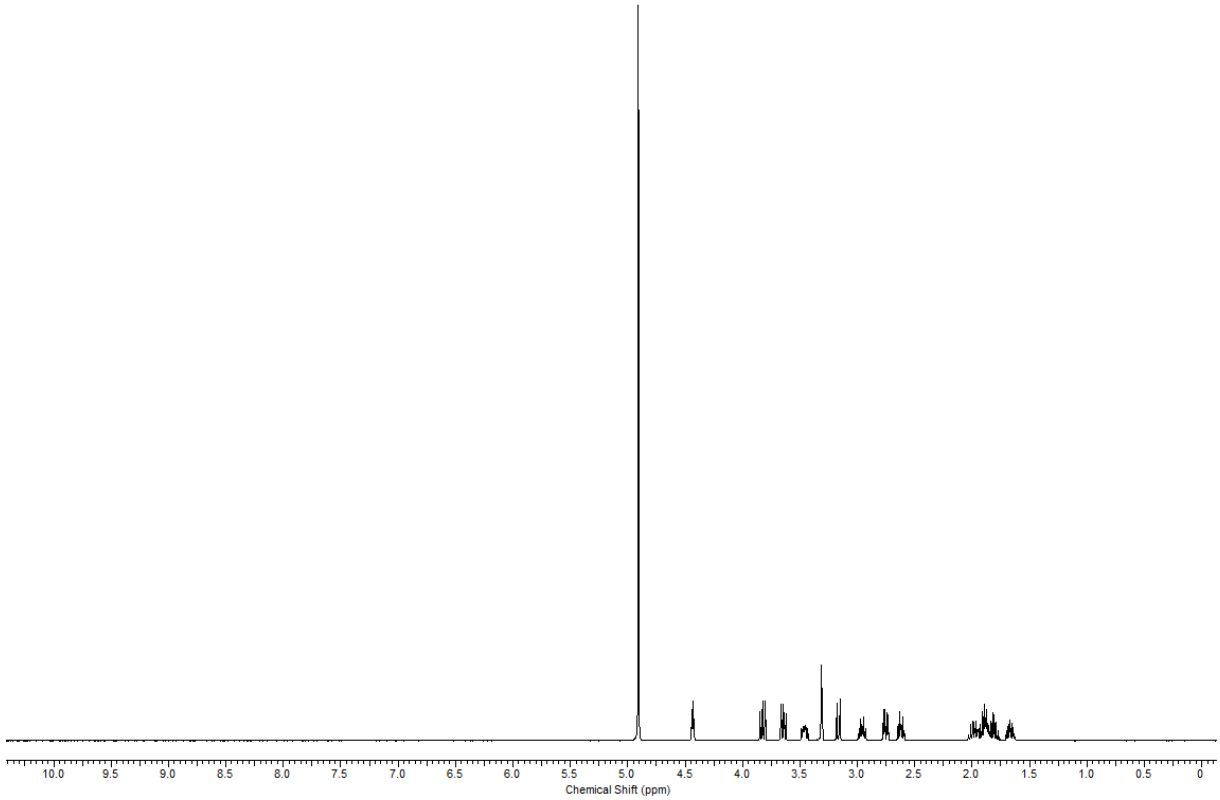


Figure 63. ^{1}H NMR spectrum (400 MHz) of (–)-macronecine **105** in MeOH-d_4

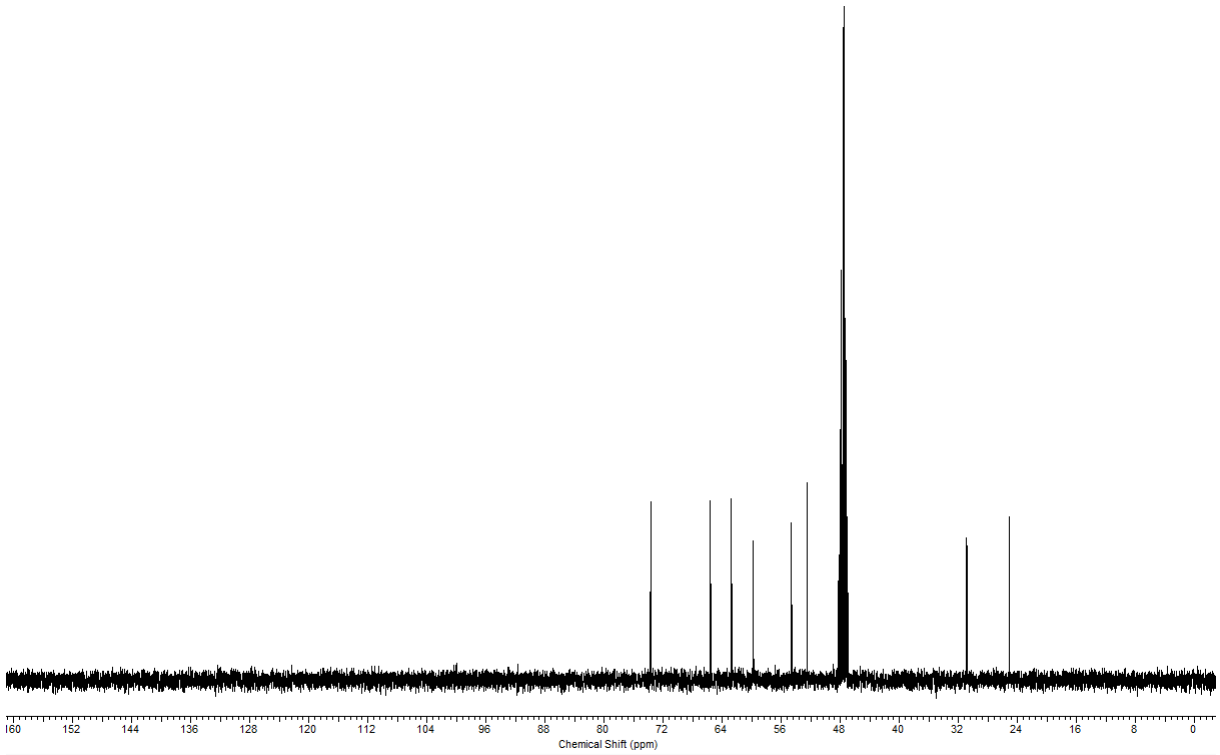


Figure 64. ^{13}C NMR spectrum (100 MHz) of (–)-macronecine **105** in MeOH-d_4

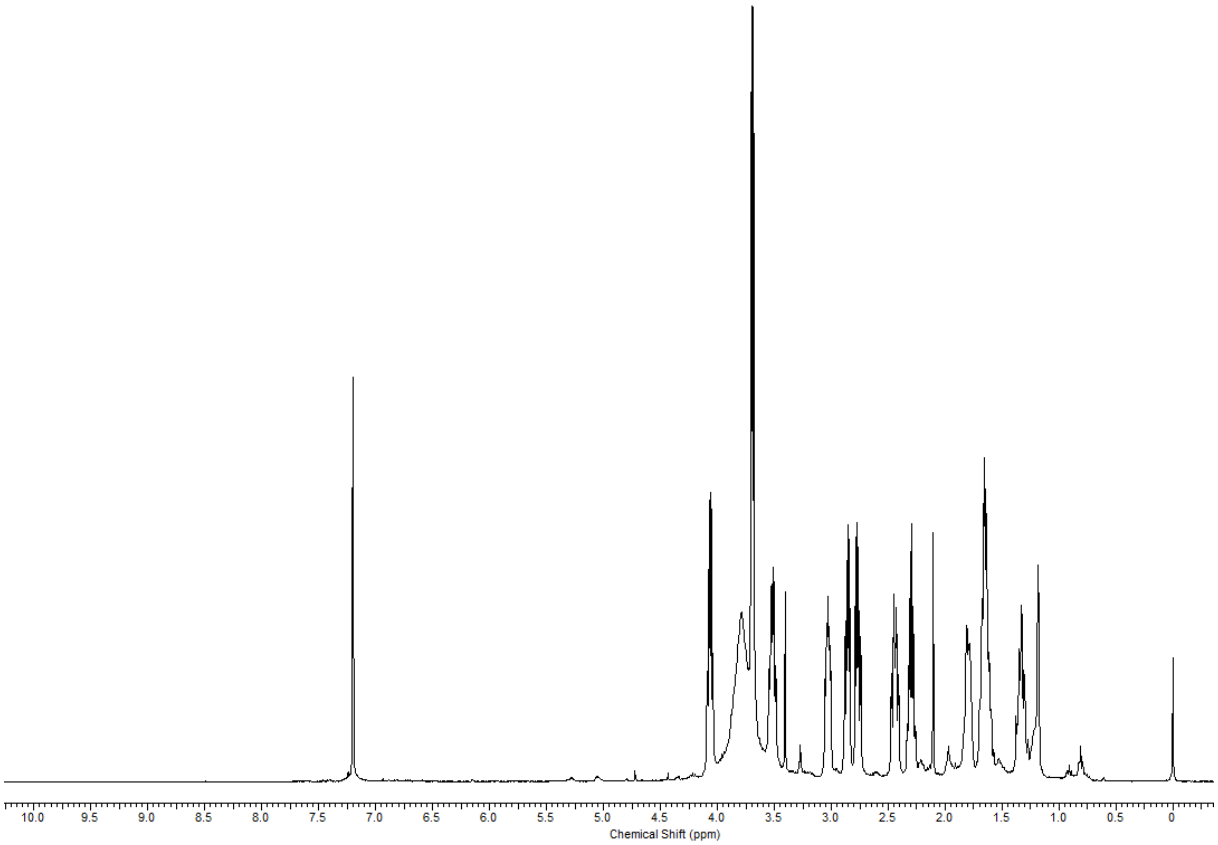


Figure 65. ^{1}H NMR spectrum (400 MHz) of (–)-1-*epi*-macronecine **300** in $CDCl_3$.

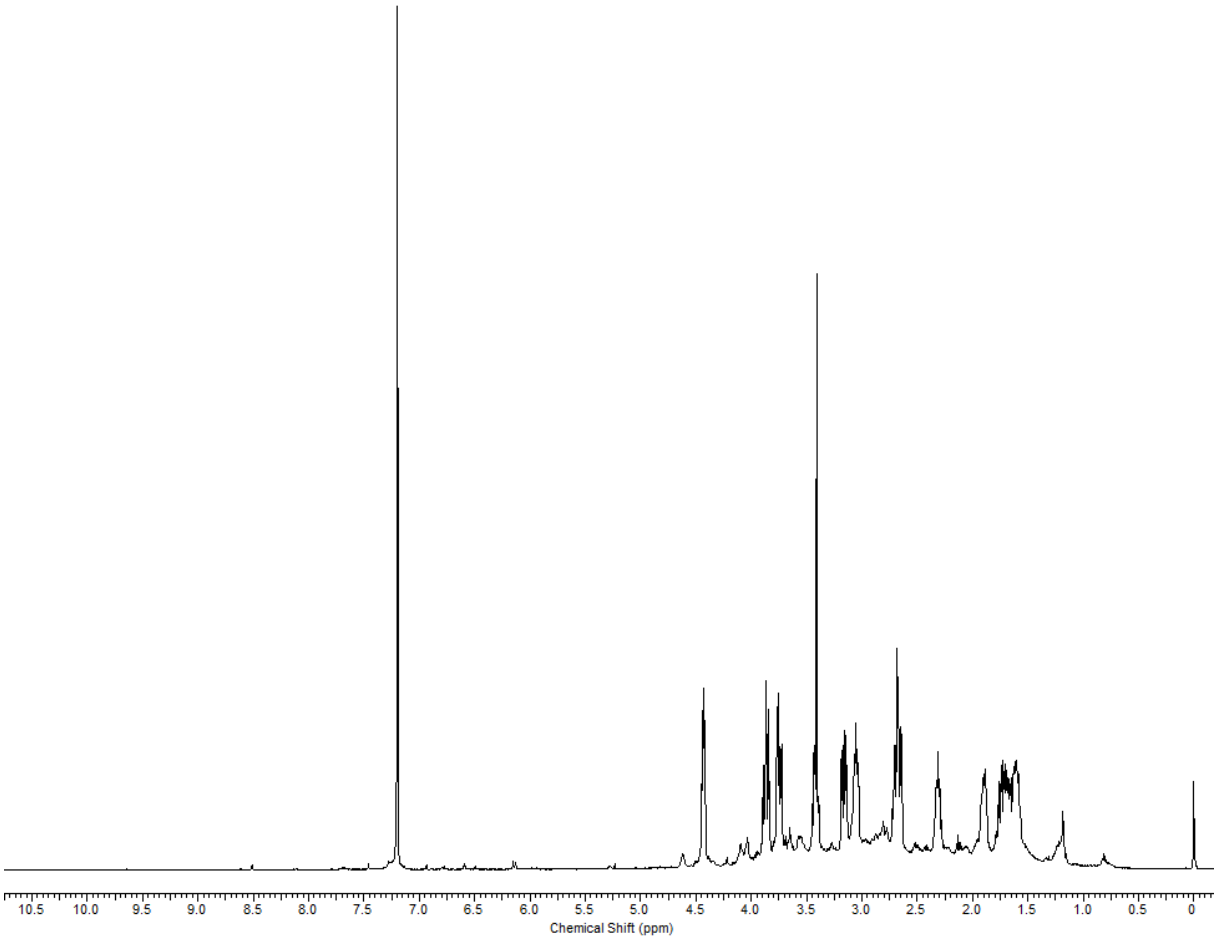


Figure 66. ^{1}H NMR spectrum (400 MHz) of (–)-petasinecine **106** in $CDCl_3$.

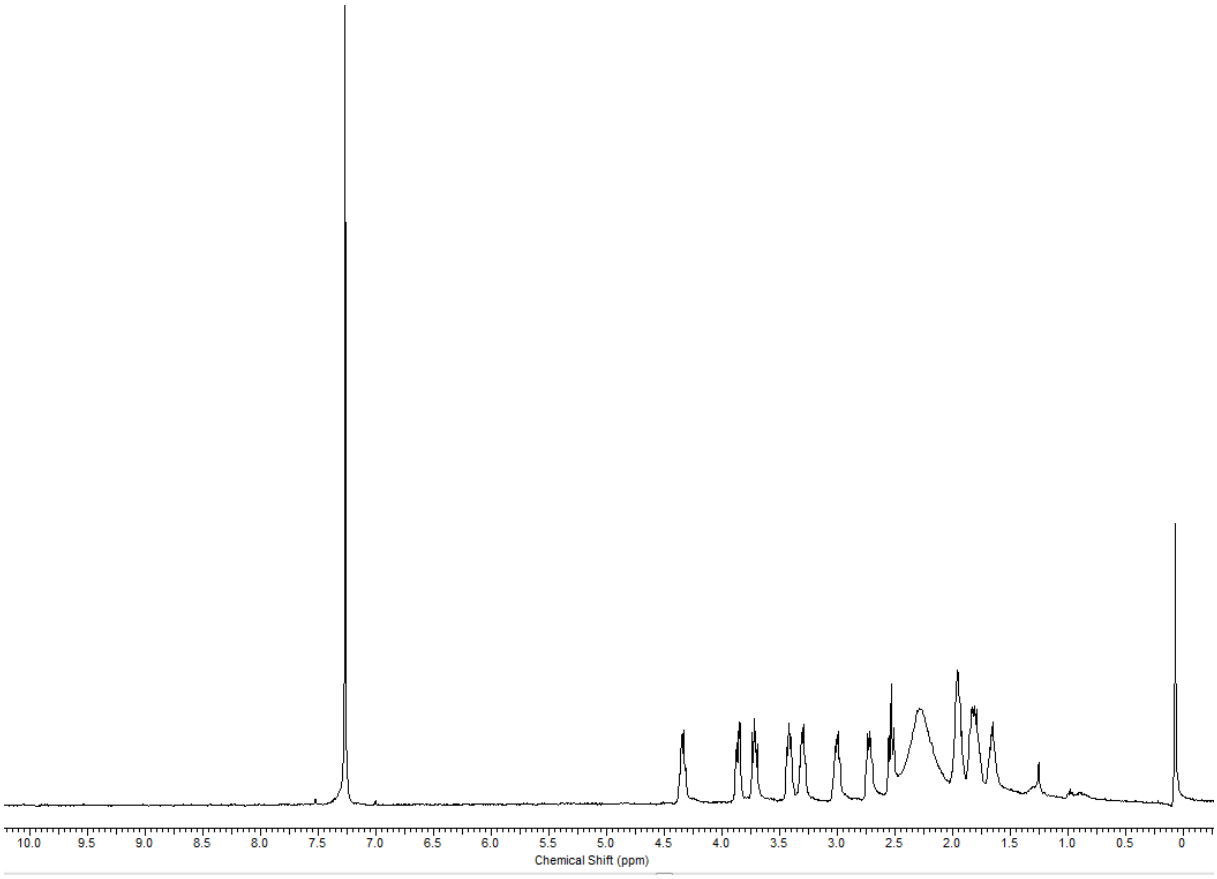


Figure 67. ^{1}H NMR spectrum (400 MHz) of (+)-1-*epi*-petasinecine **305** in $CDCl_3$.

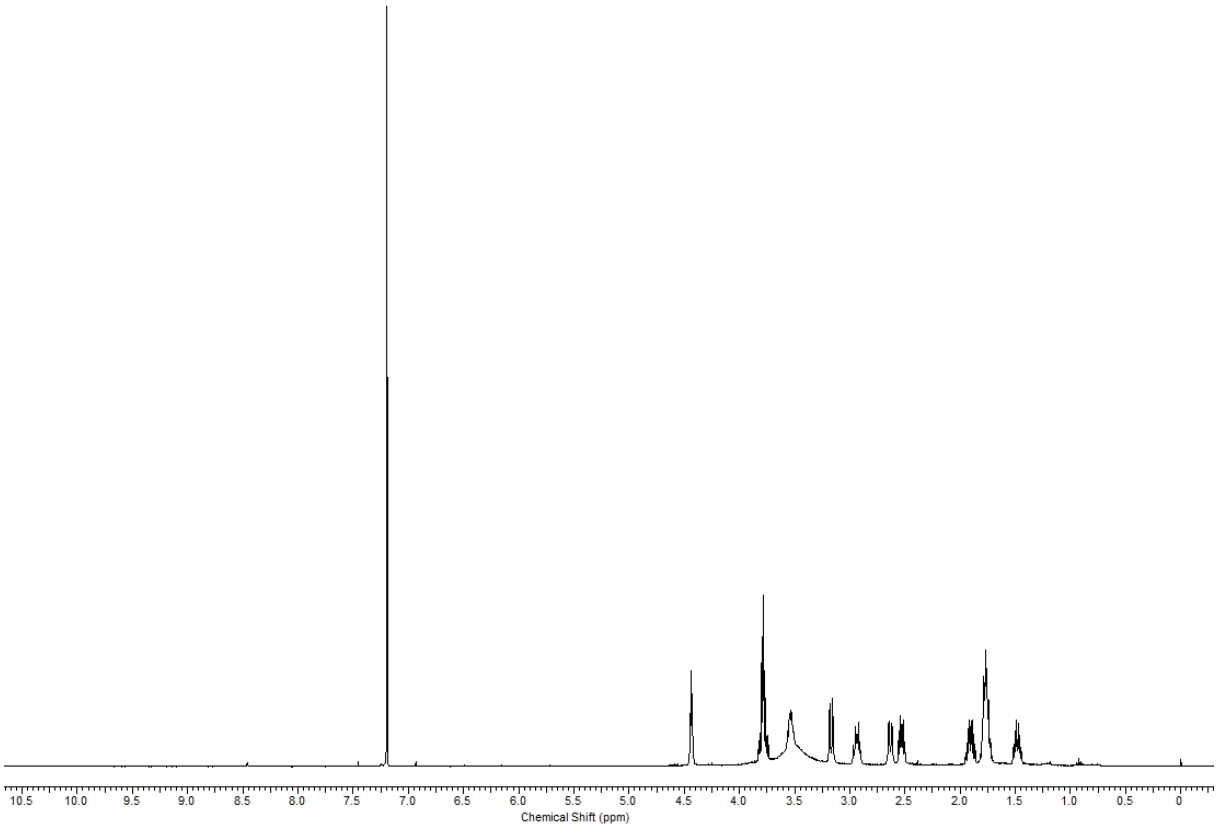


Figure 68. ^{1}H NMR spectrum (400 MHz) of (–)-macronecine **105** in $CDCl_3$

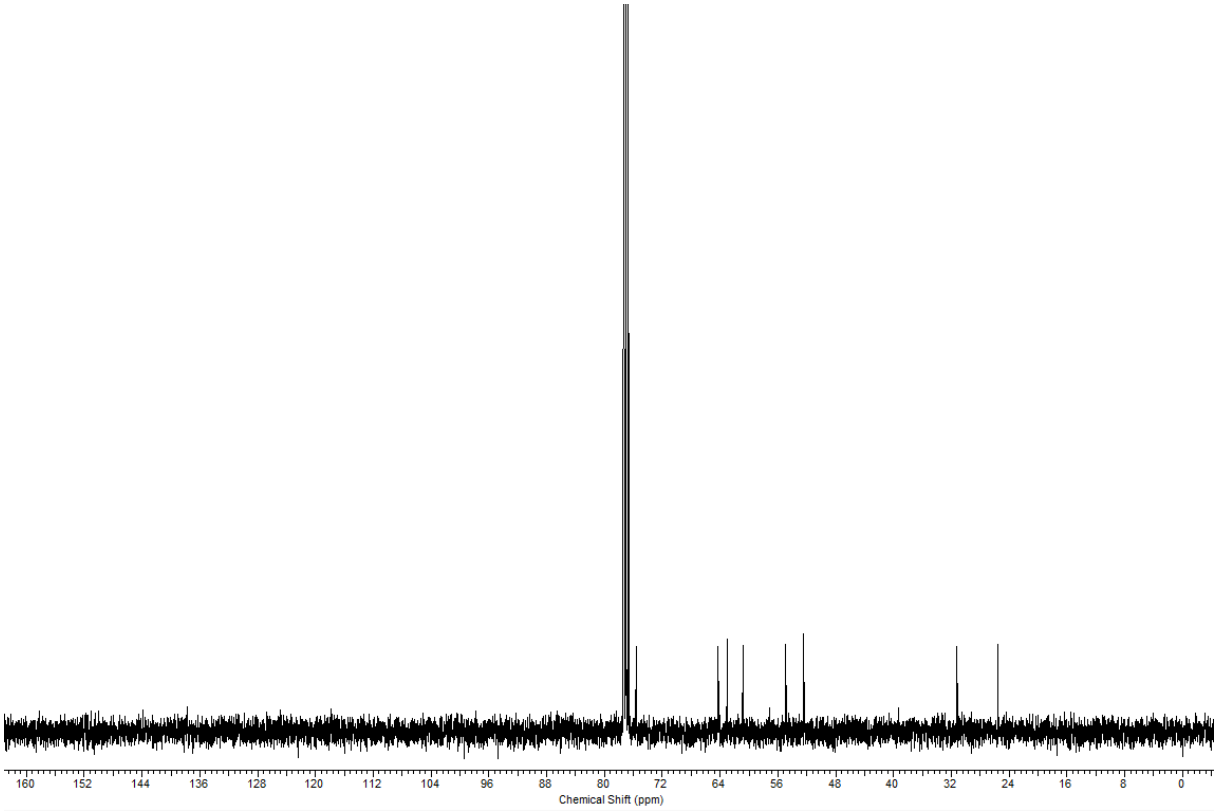
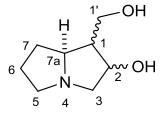


Figure 69. ^{13}C NMR spectrum (100 MHz) of (–)-macronecine **105** in $CDCl_3$

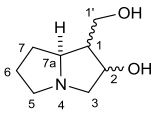
^{1}H NMR data for 1-hydroxymethyl-2-hydroxypyrrolizidines



	MeOH-d_4 (400 MHz)				$CDCl_3$ (400 MHz)			
H	**300**	**106**	**305**	**105**	**300**	**106**	**305**	**105**
C(1)*H*	2.19 dq (*J* 7.6, 5.8)	2.25−2.35 m	1.60−1.75 m	1.78−2.07 m	2.37 q (*J* 7.0)	2.34−2.43 m	1.89−2.03 m	1.92-2.05 m
C(2)*H*	3.94 q (*J* 7.6)	4.27 t (*J* 3.7)	3.96 dt (*J* 8.1, 6.1)	4.46 t (*J* 3.6)	4.13 q (*J* 7.0)	4.47−4.54 m	4.30−4.38 m	4.51 t (*J* 3.7)
C(3)H_A	2.70−2.85 m	2.90 d (*J* 12.7)	2.42 dd (*J* 9.8, 8.1)	2.77 dd (*J* 11.1, 3.6)	2.46−2.65 m	2.69−2.82 m	2.54 t (*J* 9.1)	2.71 dd (11.0, 3.7)
C(3)H_B	2.70−2.85 m	3.19 dd (*J* 12.7, 3.7)	3.14 dd (*J* 9.8, 6.1)	3.19 d (*J* 11.1)	3.10 ddd (10.8, 7.1, 3.9)	3.09−3.17 m	2.97−3.05 m	3.23 d (*J* 11.0)
C(5)H_A	2.45 td (*J* 10.0, 6.3)	2.90−3.00 m	2.61−2.70 m	2.63 dt (*J* 10.8, 6.2)	2.84 dd (*J* 11.4, 6.8)	2.69−2.82 m	2.69−2.77 m	2.56-2.65 m
C(5)H_B	3.02 ddd (*J* 10.0, 7.0, 3.6)	3.32 t (*J* 7.9)	2.81−2.89 m	2.98 dt (*J* 10.8, 6.2)	2.93 dd (*J* 11.4, 6.3)	3.24 dd (*J* 11.7, 5.0)	3.26−3.34 m	3.01 dt (*J* 11.0, 6.6)
C(6)H_A	1.55−1.69 m	1.61−1.73 m	1.60−1.75 m	1.78−2.07 m	1.33−1.48 m	1.62−1.89 m	1.58−1.71 m	1.78-1.90
C(6)H_B	1.70−1.86 m	1.93−2.08 m	1.85−1.97 m	1.78−2.07 m	1.64−1.79 m	1.62−1.89 m	1.72−1.89 m	1.78-1.90
C(7)H_A	1.42−1.55 m	1.75−1.83 m	1.60−1.75 m	1.64−1.73 m	1.64−1.79 m	1.62−1.89 m	1.72−1.89 m	1.55 dq (*J* 11.9, 6.1)
C(7)H_B	1.70−1.86 m	1.93−2.08 m	1.85−1.97 m	1.78−2.07 m	1.81−1.94 m	1.93−2.02 m	1.89−2.03 m	1.78-1.90
C(7a)*H*	3.50−3.61 m	3.75−3.90 m	3.16−3.20 m	3.47 ddd (*J* 9.3, 7.6, 5.0)	3.55−3.63 m	3.45−3.53 m	3.42 dd (*J* 9.8, 5.6)	3.56-3.65 m
C(1')H_A	3.50−3.61 m	3.68 dd (*J* 11.0, 7.5)	3.47 dd (*J* 11.1, 7.1)	3.67 dd (*J* 10.8, 6.2)	3.76 d (*J* 7.3)	3.82 dd (*J* 10.8, 5.0)	3.72 dd (*J* 10.7, 6.9)	3.80−3.92 m
C(1')H_B	3.69 dd (*J* 10.9, 5.8)	3.83 dd (*J* 11.0, 7.3)	3.64 dd (*J* 11.1, 4.7)	3.85 dd (*J* 10.8, 7.4)	3.76 d (*J* 7.3)	3.94 dd (*J* 10.8, 9.3)	3.87 dd (*J* 10.7, 4.5)	3.80−3.92 m

Table 25. Comparison of ^{1}H NMR spectroscopic data in MeOH-d_4 and $CDCl_3$ for **300**, **106**, **305** and **105** **[**chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].

^{13}C NMR data for 1-hydroxymethyl-2-hydroxypyrrolizidines in MeOH-d_4 (100 MHz)



C	**300**	**106**	**305**	**105**
C(1)	50.7	49.1	55.0	52.5
C(2)	71.2	72.5	73.2	73.7
C(3)	60.4	61.4	60.5	62.8
C(5)	55.5	56.6	54.7	54.6
C(6)	26.2	26.3	31.9	30.9
C(7)	25.9	27.1	24.9	25.1
C(7a)	65.5	67.4	66.1	65.6
C(1')	60.5	57.8	61.6	59.8

Table 26. Comparison of ^{13}C NMR spectroscopic data in MeOH-d_4 for **300**, **106**, **305** and **105** [chemical shifts (δ_C) are reported in ppm].

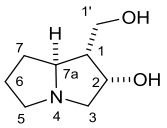
^{1}H NMR data for macronecine 105 				
H	**This study** [a](400 MHz)	**Denmark[19]** [b](500 MHz)	**Sarkar[20]** [c](400 MHz)	**Yoda[21]** [c](300 MHz)
C(1)*H*	1.92-2.05 m	1.95 dq (*J* 12.2, 7.2)	1.63−2.04 m	1.97 m
C(2)*H*	4.51 t (*J* 3.7)	4.49 t (*J* 3.7)	4.36−4.54 m	4.50 t (*J* 3.9)
C(3)H_A	2.71 dd (11.0, 3.7)	2.67 dd (*J* 11.0, 3.4)	2.40−2.73 m	2.71 dd (*J* 11.4, 3.9)
C(3)H_B	3.23 d (*J* 11.0)	3.17 d (*J* 11.0)	3.18 d (*J* 11.0)	3.22 d (*J* 11.4)
C(5)H_A	2.56-2.65 m	2.57 m	2.40−2.73 m	2.60 dt (J 10.8, 6.3)
C(5)H_B	3.01 dt (*J* 11.0, 6.6)	2.95 td (*J* 10.6, 6.5)	2.80−3.04 m	3.00 dt (*J* 10.8, 6.6)
C(6)H_A	1.78-1.90	1.76−1.86 m	1.63−2.04 m	1.77−1.90 m
C(6)H_B	1.78-1.90	1.76−1.86 m	1.63−2.04 m	1.77−1.90 m
C(7)H_A	1.55 dq (*J* 11.9, 6.1)	1.52 dq (*J* 12.2, 6.0)	1.39−1.63 m	1.54 m
C(7)H_B	1.78-1.90	1.76−1.86 m	1.63−2.04 m	1.77−1.90 m
C(7a)*H*	3.56-3.65 m	3.51−3.57 m	3.39−3.60 m	3.59 m
C(1')H_A	3.80−3.92 m	3.82−3.88 m	3.71−3.85 m	3.84 dd (*J* 11.4, 6.9)
C(1')H_B	3.80−3.92 m	3.82−3.88 m	3.71−3.85 m	3.91 dd (*J* 11.4, 4.8)

Table 9. Comparison of ^{1}H NMR spectroscopic data in $CDCl_3$ for macronecine **105** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz]. [[a]data for (–)-macronecine **105**; [b]data for (+)-macronecine **105**; [c]data for (±)-macronecine **105**]

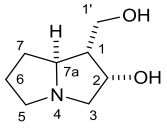
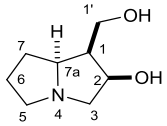
^{13}C NMR data for macronecine 105 				
C	**This study** [a](100 MHz)	**Denmark[19]** [b](125 MHz)	**Sarkar[20]** [c](50 MHz)	**Yoda[21]** [c](75 MHz)
C(1)	52.4	52.5	52.5	52.2
C(2)	75.6	75.3	75.1	75.6
C(3)	62.9	62.9	63.0	62.8
C(5)	54.9	55.0	54.9	54.7
C(6)	25.5	25.4	25.4	25.5
C(7)	31.2	31.2	31.2	31.0
C(7a)	64.2	64.0	63.9	64.5
C(1')	60.9	60.6	60.4	60.8

Table 10. Comparison of ^{13}C NMR spectroscopic data in $CDCl_3$ for (–)-macronecine **105** [chemical shifts (δ_C) are reported in ppm]. [[a]data for (–)-macronecine **105**; [b]data for (+)-macronecine **105**; [c]data for (±)-macronecine **105**].

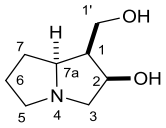
^{1}H NMR data for petasinecine 106



	MeOH-d_4			$CDCl_3$		
H	**This study** [a](400 MHz)	**Mulzer**[2] [a](250 MHz)	**Denmark**[19] [b](500 MHz)	**This study** [a](400 MHz)	**Ma**[22] [a](500 MHz)	[a]**Yamada**[23]
C(1)*H*	2.25−2.35 m	2.22−2.37 m	2.31 m	2.34−2.43 m	2.40 m	1.50−3.70 m
C(2)*H*	4.27 t (*J* 3.7)	4.29 m	4.30 dt (*J* 4.4, 1.25)	4.47−4.54 m	4.53 m	4.54 dt (*J* 5.5, 5.0)
C(3)H_A	2.90 d (*J* 12.7)	2.79 ddd (*J* 12.7, 1.25, 0.5)	2.83 dd (*J* 12.7, 1.2)	2.69−2.82 m	2.75 m	1.50−3.70 m
C(3)H_B	3.19 dd (*J* 12.7, 3.7)	3.10 ddd (*J* 12.7, 5.0, 4.5)	3.13 dd (*J* 12.7, 3.9)	3.09−3.17 m	3.11 m	1.50−3.70 m
C(5)H_A	2.90−3.00 m	2.86−2.95 m	2.91 dt (*J* 9.9, 5.7)	2.69−2.82 m	2.75 m	1.50−3.70 m
C(5)H_B	3.32 t (*J* 7.9)	3.19 ddd (*J* 12.7, 5.0, 4.5)	3.21 ddd (*J* 9.5, 7.0, 2.5)	3.24 dd (*J* 11.7, 5.0)	3.23 dd (*J* 11.6, 7.1)	1.50−3.70 m
C(6)H_A	1.61−1.73 m	1. 57−1.81 m	1. 67−1.79 m	1.62−1.89 m	1.66−1.99 m	1.50−3.70 m
C(6)H_B	1.93−2.08 m	1.87−2.08 m	1.96−2.04 m	1.62−1.89 m	1.66−1.99 m	1.50−3.70 m
C(7)H_A	1.75−1.83 m	1. 57−1.81 m	1. 67−1.79 m	1.62−1.89 m	1.66−1.99 m	1.50−3.70 m
C(7)H_B	1.93−2.08 m	1.87−2.08 m	1.96−2.04 m	1.93−2.02 m	1.66−1.99 m	1.50−3.70 m
C(7a)*H*	3.75−3.90 m	3.46−3.62 m	3.59 m	3.45−3.53 m	3.48 m	1.50−3.70 m
C(1')H_A	3.68 dd (*J* 11.0, 7.5)	3.76 dd (*J* 7.5, 7.0)	3.76 dd (*J* 10.8, 7.3)	3.82 dd (*J* 10.8, 5.0)	3.86 dd (*J* 10.8, 5.2)	3.89 dd (*J* 11.0, 6.0)
C(1')H_B	3.83 dd (*J* 11.0, 7.3)	3.92 dd (*J* 8.0, 7.5)	3.92 dd (*J* 10.8, 7.3)	3.94 dd (*J* 10.8, 9.3)	3.96 dd (*J* 10.8, 8.8)	3.94 dd (*J* 11.0, 8.0)

Table 11. Comparison of ^{1}H NMR spectroscopic data in MeOH-d_4 and $CDCl_3$ for petasinecine **106** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz].[[a]data for **(−)**-petasinecine **106**; [b]data for (+)-petasinecine **106**].

^{13}C NMR data for petasinecine 106



C	**This study** [a](100 MHz)	**Denmark**[19] [b](125 MHz)	**Mulzer**[2] [a](63 MHz)
C(1)	49.4	49.7	49.6
C(2)	74.0	74.5	74.3
C(3)	62.9	63.5	63.3
C(5)	58.1	57.8	57.7
C(6)	27.8	27.9	27.8
C(7)	28.5	28.6	28.5
C(7a)	68.8	67.8	67.7
C(1')	59.3	59.8	59.6

Table 12. Comparison of ^{13}C NMR spectroscopic data in MeOH-d_4 for **(−)**-petasinecine **106** [chemical shifts (δ_C) are reported in ppm]. [[a]data for **(−)**-petasinecine **106**; [b]data for (+)-petasinecine **106**].

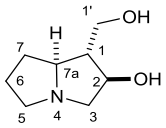
^{1}H NMR data for 1-*epi*-petasinecine 305 			
H	**This study** [a](400 MHz)	**Ha[24]** [b](300 MHz)	**Yoda[21]** [c](300 MHz)
C(1)*H*	1.89−2.03 m	1. 63−1.92 m	2.31 m
C(2)*H*	4.30−4.38 m	4.30 m	4.33 m
C(3)H_A	2.54 t (*J* 9.1)	2.67 m	2.83 dd (*J* 12.7, 1.2)
C(3)H_B	2.97−3.05 m	3.29 m	3.13 dd (*J* 12.7, 3.9)
C(5)H_A	2.69−2.77 m	2.90 m	2.91 dt (*J* 9.9, 5.7)
C(5)H_B	3.26−3.34 m	3.29 m	3.21 ddd (*J* 9.5, 7.0, 2.5)
C(6)H_A	1.58−1.71 m	1.63−1.92 m	1. 67−1.79 m
C(6)H_B	1.72−1.89 m	1.63−1.92 m	1.96−2.04 m
C(7)H_A	1.72−1.89 m	1.63−1.92 m	1. 67−1.79 m
C(7)H_B	1.89−2.03 m	1.63−1.92 m	1.96−2.04 m
C(7a)*H*	3.42 dd (*J* 9.8, 5.6)	-	3.59 m
C(1')H_A	3.72 dd (*J* 10.7, 6.9)	3.67 dd (*J* 11.0, 5.0)	3.59 m
C(1')H_B	3.87 dd (*J* 10.7, 4.5)	3.84 dd (*J* 11.0, 4.0)	3.76 dd (*J* 10.8, 7.3)

Table 13. Comparison of ^{1}H NMR spectroscopic data in $CDCl_3$ for 1-*epi*-petasinecine **305** [chemical shifts (δ_H) are reported in ppm and coupling constants (*J*) in Hz]. [[a]data for (+)-1-*epi*-petasinecine **305**; [b]data for (–)-1-*epi*-petasinecine **305**; [c]data for (±)-1-*epi*-petasinecine **305**].

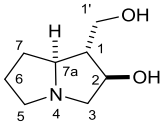
^{13}C NMR data for 1-*epi*-petasinecine 305 			
C	**This study** (100 MHz)	**Ha[24]** [a](75 MHz)	**Yoda[21]** [b](75 MHz)
C(1)	56.2	56.1	56.2
C(2)	74.7	74.5	74.7
C(3)	62.0	62.9	63.0
C(5)	56.5	56.3	56.4
C(6)	26.4	26.3	26.3
C(7)	33.4	33.3	33.3
C(7a)	67.6	67.5	67.7
C(1')	63.1	61.8	61.9

Table 14. Comparison of ^{13}C NMR spectroscopic data in MeOH-d_4 for 1-*epi*-petasinecine **305** [chemical shifts (δ_C) are reported in ppm]. [[a]data for (+)-1-*epi*-petasinecine **305**; [b]data for **(–)**-1-*epi*-petasinecine **305**; [c]data for (±)-1-*epi*-petasinecine **305**].

NMR data for (+)-2-*epi*-rosmarinecine 149

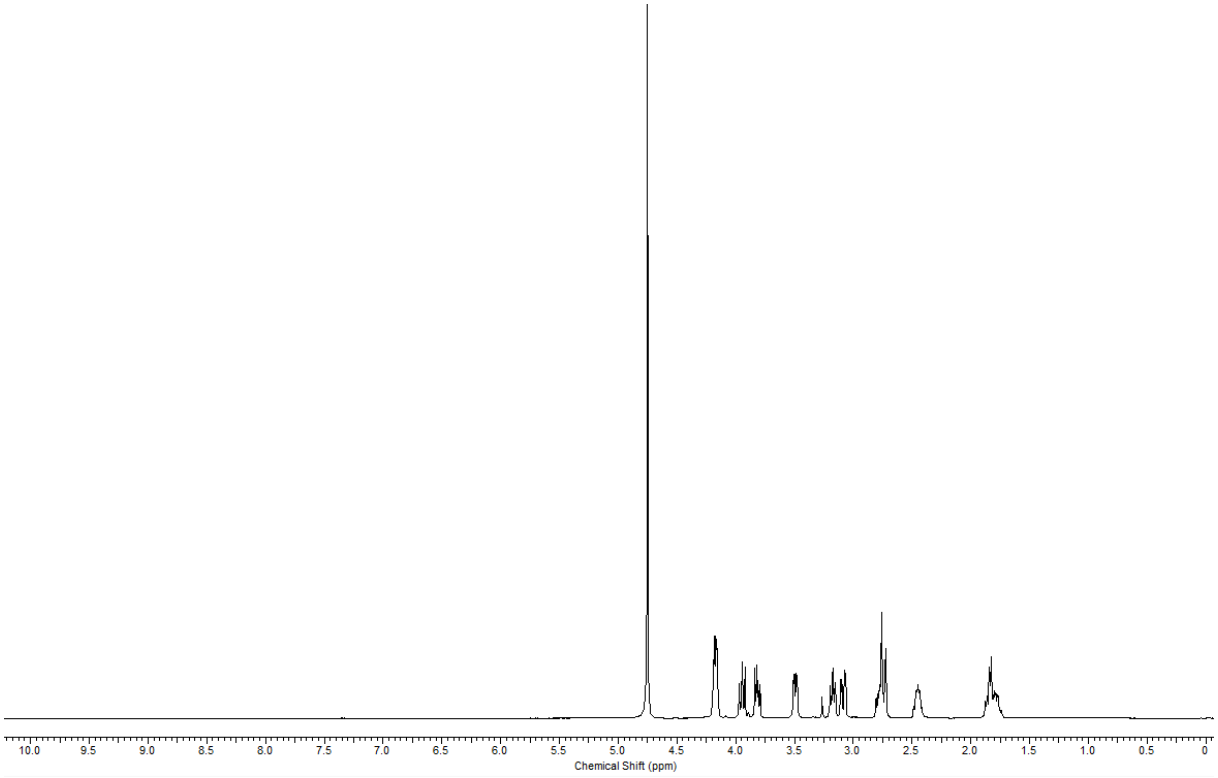


Figure 70. ^{1}H NMR spectrum (400 MHz) of (+)-2-*epi*-rosmarinecine **149** in D_2O.

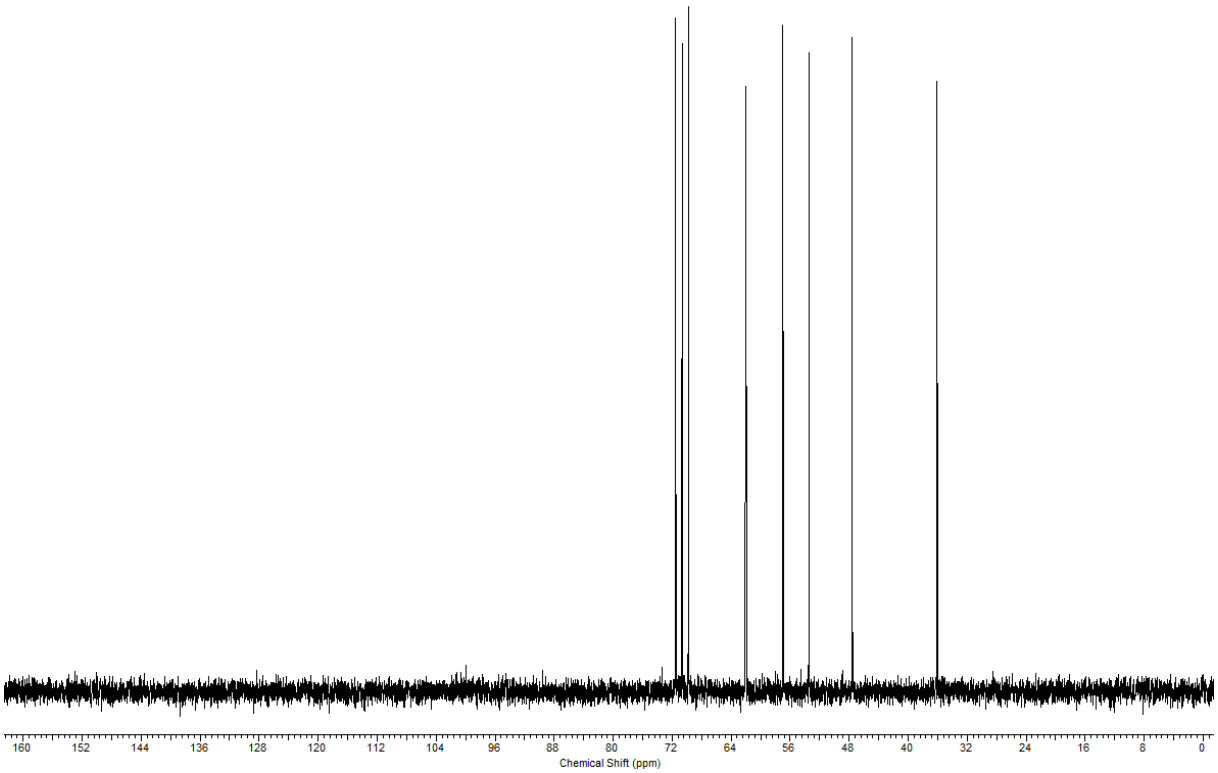
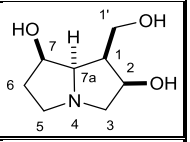


Figure 71. ^{13}C NMR spectrum (100 MHz) of (+)-2-*epi*-rosmarinecine **149** in D_2O.

^{1}H NMR data for 2-*epi*-rosmarinecine 149 		
H	**This study (+)-149** (400 MHz)	**Chakraborty[25] (±)-149** (500 MHz)
C(1)*H*	2.40−2.50 m	2.68 m
C(2)*H*	4.13−4.21 m	4.45 m
C(3)H_A	2.70−2.83 m	3.86 dd (*J* 11.5, 6.0)
C(3)H_B	3.08 dd (*J* 13.4, 4.0)	3.08 dd (*J* 11.5, 7.9)
C(5)H_A	2.70−2.83 m	3.35 dd (*J* 11.4, 6.4)
C(5)H_B	3.14−3.23 m	3.81-3.74 m
C(6)H_A	1.71−1.92 m	2.22-2.34 m
C(6)H_B	1.71−1.92 m	2.22-2.34 m
C(7)*H*	4.13−4.21 m	4.60 m
C(7a)*H*	3.49 dd (*J* 9.1, 3.6)	4.03 dd (*J* 7.4, 5)
C(1')H_A	3.81 dd (*J* 11.0, 6.3)	3.81-3.74 m
C(1')H_B	3.95 dd, (*J* 11.1, 8.5)	3.81-3.74 m

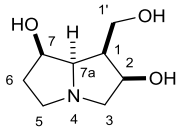
^{13}C NMR data for 2-*epi*-rosmarinecine 149 		
H	**This study (+)-149** (100 MHz)	**Chakraborty[25] (±)-149** (125 MHz)
C(1)	47.1	48.4
C(2)	70.6	74.7
C(3)	62.0	62.7
C(5)	53.4	55.8
C(6)	36.1	37.4
C(7)	71.5	75.4
C(7a)	69.8	72.3
C(1')	57.0	62.1

Table 15 and 16. Comparison of ^{1}H and ^{13}C NMR spectroscopic data in D_2O for (+)-2-*epi*-rosmarinecine **149** [chemical shifts (δ_H and δ_C) are reported in ppm and coupling constants (*J*) in Hz].

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