Asymmetric Synthesis of the Loline Alkaloids

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by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2016 until December 2019, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted for any other degree at this or any other university.

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Abstract

Sean Linsdall D. Phil. Thesis

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This thesis centres on the asymmetric synthesis of the loline alkaloids. Initially, a scalable synthesis of 3-hydroxyproline was developed. This synthetic route was used to prepare an advanced intermediate for the synthesis of the tricyclic loline alkaloid scaffold, from which four loline alkaloids were derived.

Chapter 1 presents a summary of 1-aminopyrrolizidines. Initially, the isolation and previous syntheses of the 1-aminopyrrolizidines absouline and laburnamine are described and discussed. Followed by a review of the isolation, biological activity and syntheses of the loline alkaloids.

Chapter 2 describes the development of two complementary syntheses of both epimers of 3-hydroxyproline utilizing either an inter- or an intra- molecular, regioselective aziridinium ring-opening reaction by oxygen nucleophiles as the key step in both syntheses.

Chapter 3 summarises the first-generation approach to the loline alkaloids. A lithium amide conjugate addition with enolate oxidation inserted the C(1) and C(3) amino and oxygen atoms of the loline alkaloids. However, this first-generation synthesises was not pursued further due to prohibitively low yields being obtained.

Chapter 4 describes the synthesis of the loline alkaloid scaffold. An enolate addition to a sulfinyl imine inserted the exocyclic amine and oxygen of the ether bridge, and was followed by pyrrolizidinone formation. Finally, a base-mediated cyclisation and deprotection gave (+)-norloline dihydrochloride.

Chapter 5 describes the synthesis of four loline alkaloids (loline, norloline, *N*-acetyl loline and *N*-methyl loline) from (+)-norloline dihydrochloride, which was followed by comparison of their spectroscopic data with those previously reported in the literature.

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

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Abbreviations

≈	Approximately equals to
(+)	Dextrorotatory
(−)	Levorotatory
±	Racemic
°	Degrees
$[\alpha]_D$	Specific Rotation
Å	Angstom
app	Apparent
anti	On the opposite face
APCI	Atmospheric Pressure Chemical Ionisation
aq	Aqueous
atm	Atmospheres
ATR	Attenuated total reflectance
Boc	*tert*-Butoxycarbonyl
br	Broad
Bus	*tert*-Butylsulfonyl
c	concentration
C	Celsius

Cat	Catalyst
Cbz	Carboxybenzyl
Chloramine T	*N*-Chloro-*para*-toluenesulfonamide sodium salt hydrate
cis	This side of
CSO	Camphorsulfoxaziridine
Δ	Difference
δ	NMR Chemical shift
D	Dextrorotatory relative to (+)-glyceraldehyde
d	Doublet
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
dec	Decomposed
deg	Degrees
DET	Diethyltartrate
DHQD	Dihydroquinidine
DIBAL-H	Diisobutylaluminium hydride

DMAP	4-Dimethylaminopyridine
DMBA	1,3-Dimethylbarbituric acid
DME	Dimethoxyethane
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
DTBMP	2,6-Di-tert-butylpyridine
ε	Molar absorption coefficient
E	Entgegen
E_1	Unimolecular elimination
ee	Enantiomeric excess
ent	Enantiomer
epi	Epimer
equiv	Equivalent
er	Enantiomeric ratio
ESI	Electrospray ionisation
FT	Fourier transform
g	Gaseous
HMBC	Heteronuclear Multiple Bond Correlation spectroscopy

HMDS	Bis(trimethylsilyl)amine
HPLC	High Performance Liquid Chromatography
hν	ultra-violet light
Hz	Hertz
i	iso
IR	Infrared
J	Coupling Constant
L	Levorotatory relative to (+)-glyceraldehyde
LDA	Lithium diisopropylamide
lit.	Literature
m	multiplet
m	*meta*
M	Molar
M^+	Molecular ion
m/z	Mass to charge ratio
m-CPBA	*meta*-Chloroperoxybenzoic acid
MHz	Megahertz
mmol	Millimoles

mol	Moles
mp	Melting point
Ms	Methanesulfonyl
MS	Mass Spectrometry
μW	Microwave
n	normal
Nap	Napthyl
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
ν_{max}	Infrared absorption maximum
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser Effect SpectroscopY
o	*ortho*
p	*para*
Pf	9-Phenylfluorene
PHAL	1,4-Phthalazinediyl diether
π*	Pi antibonding orbital
PMB	*para*-Methoxybenzyl

PMP	*para*-Methoxyphenyl
ppm	parts per million
PPTS	Pyridinium *p*-toluenesulfonate
q	quintet
quant	Quantitative
R	Rectus
R	Unspecified organic group
Ref	Reference
rt	Room temperature
s	Singlet
satd	Saturated
σ*	Sigma antibonding orbital
S_N1	Substitution, nucleophilic, unimolecular
S_N2	Substitution, nucleophilic, bimolecular
Suc	Succinimide
syn	On the same face
t	tertiary
t	triplet

TBAF	*tetra*-*N*-Butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butylhydroperoxide
TBS	*tert*-Butyldimethylsilyl
temp/T	Temperature
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
ToF	Time of Flight
TPAP	Tetrapropylammonium perruthenate
trans	The other side of
Ts	4-Toluenesulfonyl
TSP	Trimethylsilylpropanoic acid
UV	Ultraviolet

V	Volume
vide infra	See below
vide supra	See above
w	Weight
Z	Zusammen

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Chapter 1

1 Introduction

1.1 Pyrrolizidine Alkaloids

Alkaloids that contain two fused five membered rings with a bridgehead nitrogen are commonly found in biologically active compounds. 1-Amino substituted pyrrolizidines constitute a small but important sub-set of this alkaloid family and are illustrated by their presence in a range of natural products; for example, the loline alkaloids **1**–**5**,[1–6] (+)-absouline (+)-**6**,[7] isoabsouline **7**[7] and (+)-laburnamine (+)-**8**[8] all have demonstrated interesting biological activities. Synthetic species such as SC-53116 **9**,[9] a potent and selective antagonist for 5-HT_4 serotonin receptors, also contain the 1-aminopyrrolizidine motif. Consequently, there has been significant interest in the synthesis of compounds containing the 1-amino pyrrolizidine structural motif (Figure 1).

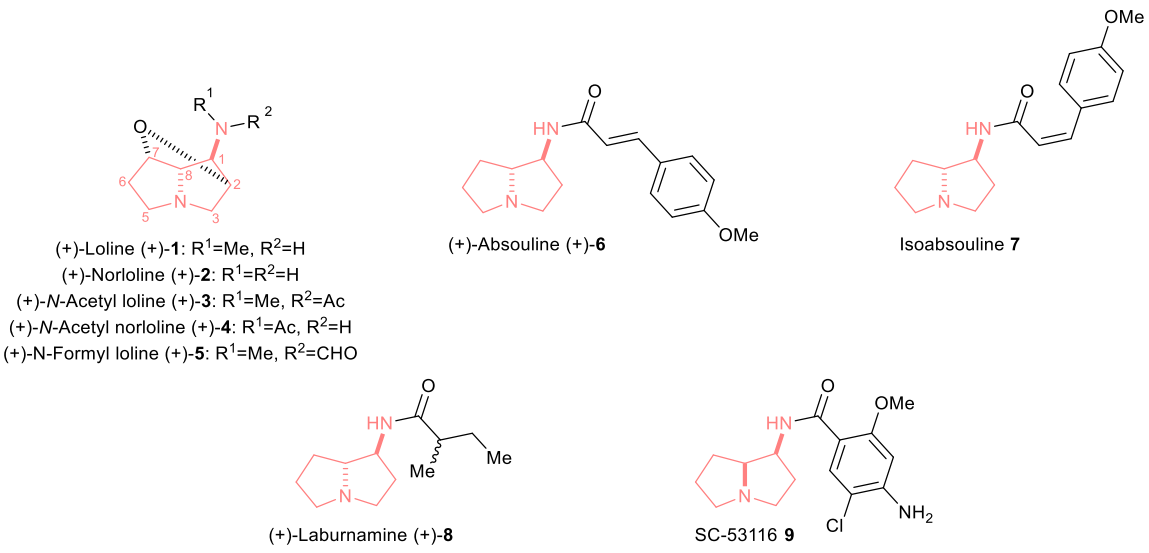


Figure 1 Pyrrolizidine alkaloids: (+)-Lolines (+)-**1**–**5**, (+)-Absouline (+)-**6**, Isoabsouline **7**, (+)-Laburnamine (+)-**8** and SC-53116 **9**.

1.2 Absouline and Laburnamine

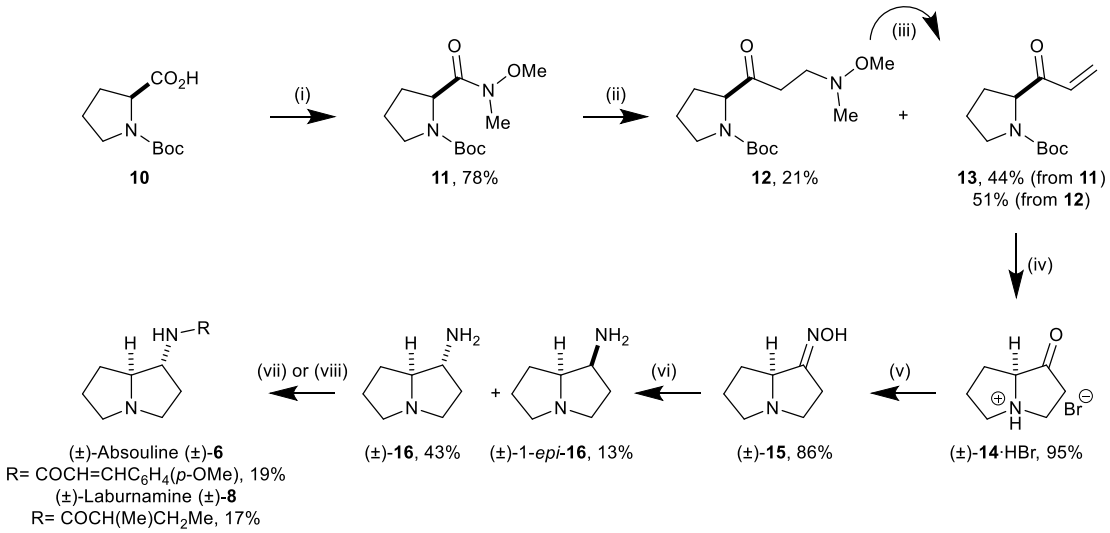
(+)-Absouline (+)-**6** {$[\alpha]_D^{20}$ +56 (c 1.0 in EtOH)} and its (*Z*)-stereoisomer isoabsouline **7**[10] were isolated from the Caledonian plants *Hugonia oregano* and *Hugonia penicllantheum* in 1987.[7]

(+)-Laburnamine (+)-**8** was first isolated in 1953 from the seeds of *Cytisus laburnum* {mp 128−129 °C; $[\alpha]_D^{20}$ +18.6 (c 3.01 in EtOH)} however no comment was made concerning its absolute configuration.[8,11] In 2015, Tasso *et al.* re-isolated (+)-laburnamine (+)-**8** {mp 124–126 °C {$[\alpha]_D^{20}$ +13.5 (c 0.54 in EtOH)} as a colourless crystalline solid as a single enantiomer and, did not comment of the absolute configuration.[12] Both (+)-absouline (+)-**6** and (+)-laburnamine (+)-**8** have been the subject of several total and formal syntheses. Some of these syntheses have used chiral pool starting materials (e.g., amino acids).[13–15] There have also been several *de novo* asymmetric syntheses.[16–21] Due to the structural similarities between (+)-absouline (+)-**6** and (+)-laburnamine (+)-**8**, a selection of their syntheses will be described and discussed together.

1.2.1 Racemic Syntheses

Poupat *et al.* reported the first racemic syntheses of (±)-absouline (±)-**6** and (±)-laburnamine (±)-**8**, despite starting with chiral proline derivative **10**. Protected proline **10** was converted to the corresponding Weinreb amide **11** in 78% yield. Addition of vinyl magnesium bromide to Weinreb amide **11** gave vinyl ketone **13** in 44% yield. However, a significant quantity of amine **12** was recovered, stirring amine **12** in the presence of CH_3I regenerated vinyl ketone **13** in 51% yield. Treatment of vinyl ketone **13** with HBr gas gave the HBr salt of pyrrolizidine (±)-**14**·HBr in 95% yield. However, during this cyclisation complete racemisation occurred and the enantiomers could not be separated. Pyrrolizidine (±)-**14**·HBr was converted to oxime (±)-**15** by addition of hydroxylamine, which gave (±)-**15** in 86% yield. Reduction of oxime (±)-**15** with Raney-Nickel gave a 3:1 mixture of (±)-**16** and (±)-1-*epi*-**16** that was separated by flash column chromatography to give (±)-**16** and (±)-1-*epi*-**16** in 43% and 13% yield, respectively. The final step was to functionalise the amino group, by coupling with the *trans*-4-methoxycinnamoyl chloride and 2-methylbutanoyl chloride, which gave racemic (±)-absouline (±)-**6** and (±)-

laburnamine (±)-**8** in 19% and 17% respectively. This concluded the synthesis of (±)-absouline (±)-**6** and (±)-laburnamine (±)-**8** in 7 steps and 2.9% and 2.6% yield, respectively, from *N*-Boc protected proline **10** (Scheme 1).[13]



Scheme 1 *Reagents and Conditions*: (i) *N*,*O*-dimethylhydroxylamine, Et_3N, CH_2Cl_2, rt, 5 min, then DCC, rt, 3 h; (ii) vinylMgBr, THF, −78 °C, then 50 °C, 2 h; (iii) CH_3I, THF, rt, 2 h; (iv) $HBr_{(g)}$, CH_3Cl; (v) $NH_2OH{\cdot}HCl$, pyridine, MeOH, reflux, 2 h; (vi) Raney Ni, $^{i}PrOH$, 8 h; (vii) *trans*-4-methoxy cinnamoyl chloride, pyridine, 0 °C, then rt, 3 h; (viii) (±)-2-methylbutanoyl chloride, pyridine, 0 °C, then rt, 2 h.

Poupat *et al.*'s sample of (±)-absouline (±)-**6** was resolved by chiral HPLC to give (1*S*,8*R*)-(+)-absouline (+)-**6** $\{[\alpha]_D^{20}$ +26 (c 1.05 in $CHCl_3)\}$ and (1*R*,8*S*)-(−)-absouline (−)-**6** $\{[\alpha]_D^{20}$ −34 (c 0.91 in $CHCl_3)\}$ (Figure 2). The sample of (±)-laburnamine (±)-**8** was not successfully resolved by chiral HPLC.[13] Despite Poupat *et al*. starting their synthesis with chiral proline derivative **10**, both (±)-absouline (±)-**6** and (±)-laburnamine (±)-**8** were synthesised as racemic samples due to the unexpected racemisation which occurred upon treatment of vinyl ketone **13** with HBr. Despite (±)-absouline (±)-**6** being successfully resolved by chiral HPLC this unexpected racemisation severely limits the practicality of this synthetic route.

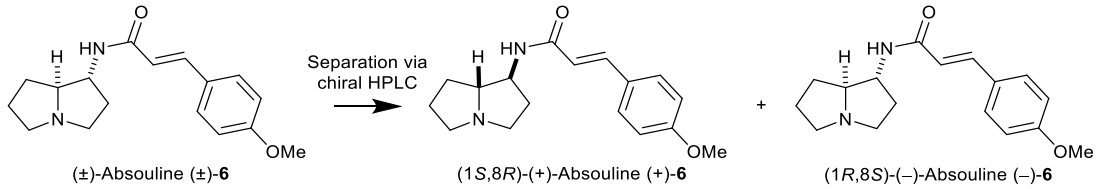
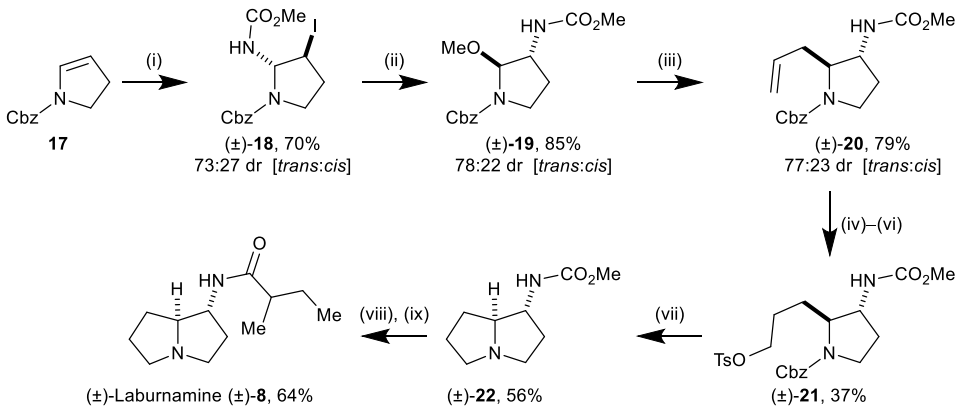


Figure 2 Poupat's chiral resolution of racemic absouline (±)-**6**.

Afonso *et al.* reported a racemic synthesis of (±)-laburnamine (±)-**8**. Treatment of enamide **17** with I_2 formed the corresponding iodonium ion followed by intramolecular ring-opening to form the corresponding iminium ion which subsequently reacted with methyl carbamate to give carbamate (±)-**18** in 70% yield and 73:27 dr [*trans*:*cis*]. Treatment of carbamate (±)-**18** with NaHMDS resulted in aziridine formation; which again underwent intramolecular ring-opening to form the corresponding iminium ion, which upon the addition of MeOH gave methyl ether (±)-**19** in 85% yield as an inseparable mixture of diastereomers. Reaction of methyl ether (±)-**19** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ gave allyl amine (±)-**20** in 79% yield and 73:27 dr [*trans*:*cis*], from which it was possible to isolate the major *trans*-isomer via flash column chromatography. The main *trans*-isomer was subjected to hydroboration, followed by tosylation of the free alcohol to give tosylate (±)-**21** in 37% yield. Hydrogenation of tosylate (±)-**21** gave pyrrolizidine (±)-**22** in 56% yield. Carbamate deprotection of pyrrolizidine (±)-**22** followed by amide bond formation upon treatment with methylbutanoyl chloride gave (±)-laburnamine (±)-**8** in 64% yield from pyrrolizidine (±)-**22**, which concluded the synthesis in 9 steps in 6% overall yield from enamide **17** (Scheme 2).[19] It has been noted that the ^{1}H NMR data for this sample of (±)-laburnamine (±)-**8** differ from those for isolated (+)-laburnamine (+)-**8**.[12] The major disadvantage of this synthesis by Afonso *et al.* is the moderate diastereoselectivity seen when the corresponding iminium ions (steps i, ii and iii) were exposed to various nucleophiles to give; (±)-**18**, (±)-**19**, and (±)-**20**.

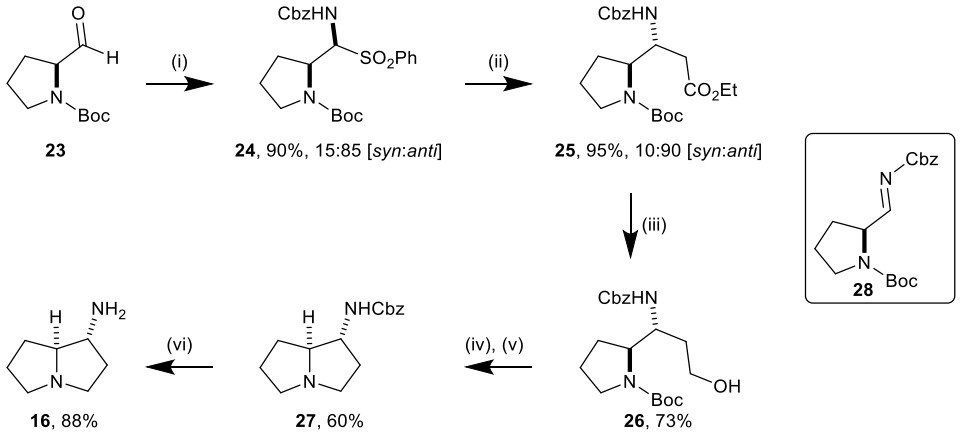


Scheme 2 *Reagents and Conditions*: (i) $NHCO_2Me$, I_2, THF, −78 °C, 10 min; (ii) NaHMDS, MeOH, THF, −78 °C, 5 min, then rt; (iii) Allyltrimethylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, then rt, 1 h; (iv) $BH_3{\cdot}Me_2S$, THF, 0 °C then, rt 1 h; (v) NaOH, H_2O_2, THF, 40 °C, 2 h; (vi) TsCl, pyridine, $CHCl_3$, rt, 3 h; (vii) H_2, Pd/C, EtOH, rt, 16 h; (viii) TMSI, $CHCl_3$, 60 °C, 4 h then, NaOMe, MeOH, 60 °C, 10 min; (ix) (±)-2-methylbutanoyl chloride, Et_3N, THF, 0 °C then rt, 4 h.

1.2.2 Chiral Pool – Proline Derivatives

Perhaps unsurprisingly, the majority of syntheses of absouline and laburnamine utilise proline or proline derivatives as their chiral pool starting material. Petrini *et al.* reported the first asymmetric synthesis of 1-aminopyrrolizidine **16** and thus the first non-racemic formal syntheses of (–)-absouline (–)-**6** and (–)-laburnamine (–)-**8**. Petrini *et al.* utilised *N*-Boc protected prolinal **23** as their chiral pool starting material, from which they synthesised the corresponding imine **28** which was trapped as the phenylsulfinic acid adduct **24** in 90% yield and 15:85 dr [*syn:anti*]. Addition of the enolate generated from the treatment of EtOAc with LDA to imine **28** produced *anti*-amino ester **25** in 95% yield and 10:90 dr [*syn:anti*]. Amino ester **25** was reduced in the presence of $NaBH_4$ and $CaCl_2$ to give amino alcohol **26** in 73% yield. Cleavage of the *N*-Boc protecting group from amino alcohol **26** followed by mesylation of the resultant primary alcohol and then *in situ* cyclisation gave pyrrolizidine **27** in 60% yield. Hydrogenolysis of pyrrolizidine **27** gave 1-aminopyrrolizidine **16** in 88% yield, completing the formal syntheses of (–)-absouline (–)-**6** and (–)-laburnamine (–)-**8** (Scheme 3).[14] The enolate addition to imine **28** proceeded with good diastereoselectivity and excellent yield, from which it was possible to isolate amino alcohol **26** as a single diastereomer. However,

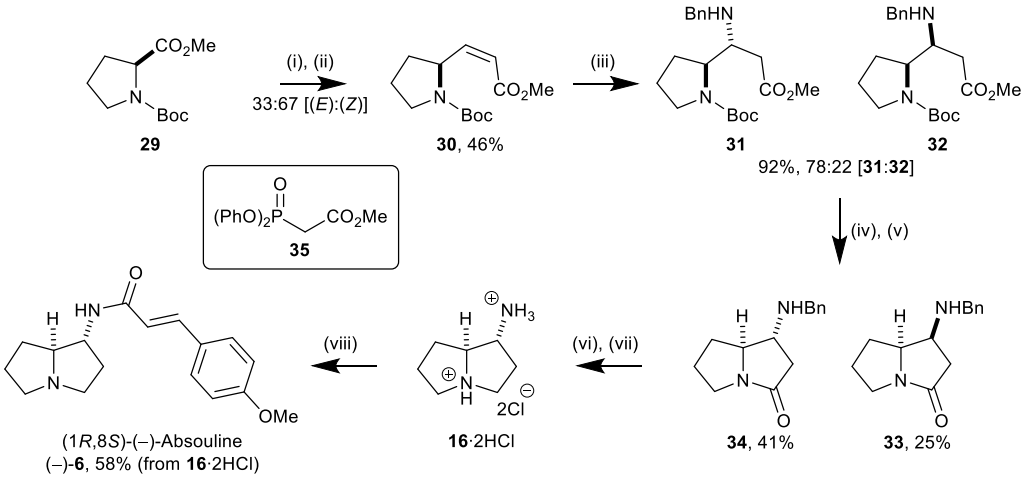
1-aminopyrrolizidine **16** was not carried forwards to synthesise (–)-absouline (–)-**6** and (–)-laburnamine (–)-**8**.



Scheme 3 *Reagents and Conditions*: (i) $CbzNH_2$, $PhSO_2H$, $MgSO_4$, CH_2Cl_2, rt; (ii) $^{i}Pr_2NH$, $^{n}BuLi$, THF, 0 °C, 30 min, then EtOAc, −78 °C, 30 min, then **24**, THF, −78 °C, 1 h; (iii) $CaCl_2$, $NaBH_4$, EtOH/THF (2:1), 0 °C, 16 h; (iv) HCl, THF, rt, 30 min, then NaOH, 0 °C, 15 min; (v) MsCl, Et_3N, CH_2Cl_2, −10 °C, 1 h, then rt, 2 h; (vi) H_2 (2 atm), Pd/C, MeOH, rt, 5 h.

Scheerer *et al*. reported the synthesis of (−)-absouline (−)-**6** using a stereoselective aza-conjugate addition reaction with methyl *N*-Boc prolinate **29** as their chiral pool starting material. *N*-Boc prolinate **29** was reduced to the corresponding aldehyde which was subjected to an Ando modified Horner-Wadsworth-Emmons reaction to give a 33:67 [(*E*):(*Z*)] mixture of α,β-unsaturated esters from which (*Z*)-α,β-unsaturated ester **30** was isolated in 46% yield. Refluxing (*Z*)-α,β-unsaturated ester **30** in the presence of benzylamine for 2 days gave a 78:22 mixture of amino esters **31** and **32**, respectively, in 92% combined yield.[22] Cleavage of the *N*-Boc protecting group and refluxing the corresponding amino esters in the presence of Et_3N for 72 h gave a separable mixture of amino pyrrolizidinones **34** and **33** in 41% and 25% yield, respectively. Reduction of amino pyrrolizidinone **34** with borane, followed by hydrogenolysis, in the presence of HCl, gave the 1-aminopyrrolizidine hydrochloride salt **16**·2HCl. Coupling of *trans*-4-methoxycinnamic acid and aminopyrrolizidine **16**·2HCl in the presence of DCC gave (−)-absouline (−)-**6** in 58% yield (from pyrrolizidinone **16**·2HCl), which concluded the synthesis in 8 steps and 10% overall yield from proline derivative **29** (Scheme 4).[15] This

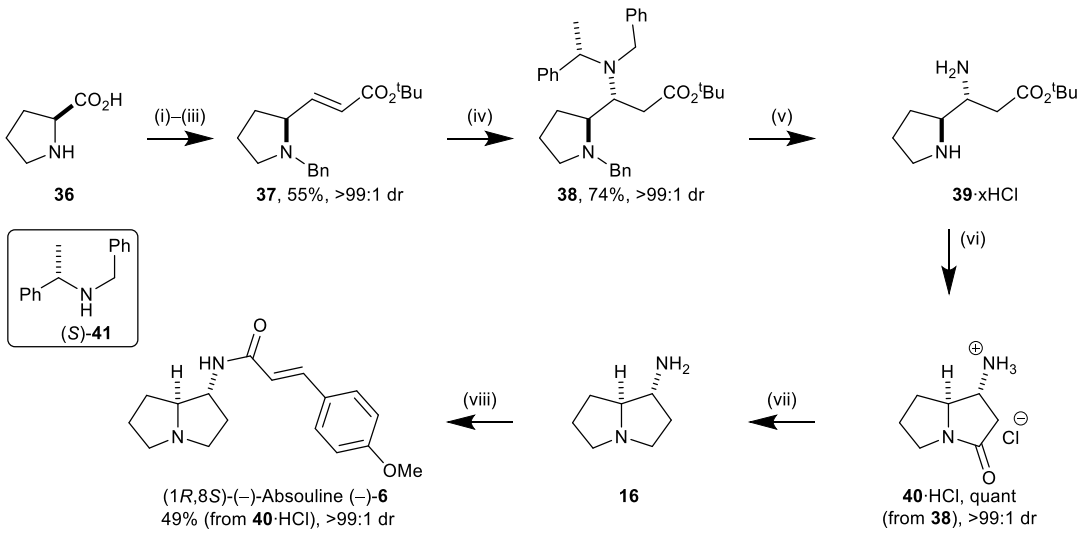
synthesis by Scheerer *et al*. has several significant selectivity issues: firstly, the 33:67 [(*E*):(*Z*)] mixture of α,β-unsaturated esters resulted in (*Z*)-α,β-unsaturated ester **30** being isolated in a poor 46% yield; secondly, the stereoselective aza-conjugate addition reaction gave a 78:22 mixture of amino esters **31** and **32**, from which amino pyrrolizidinone **34** was isolated from the next step in a low 41% yield. The combination of these selectivity issues resulted in a relatively low overall yield of (−)-absouline (−)-**6**.



Scheme 4 *Reagents and Conditions*: (i) DIBAL-H, PhMe, −60 °C; (ii) **35**, NaI, DBU, THF; (iii) H_2NBn, EtOH, 80 °C, 2 days; (iv) TFA, Me_2S, CH_2Cl_2, rt, 14 h; (v) Et_3N, EtOH, 80 °C, 72 h; (vi) $BH_3{\cdot}Me_2S$, THF, 66 °C, 18 h; (vii) H_2, Pd/C, HCl, MeOH; (viii) *trans*-4-methoxycinnamic acid, DCC, Et_3N, DMAP, CH_2Cl_2, 0 °C, 15 min, then rt, 24 h.

Davies *et al*. also reported the synthesis of (−)-absouline (−)-**6** using a diastereoselective conjugate addition reaction as the key step in a synthesis starting with L-proline **36**. L-Proline **36** was converted to (*E*)-α,β-unsaturated ester **37** via protection, reduction and oxidation followed by *in situ* Wittig olefination to give **37** in 55% yield over three steps as a single compound (>99:1 dr). Lithium amide conjugate addition to *trans*-α,β-unsaturated ester **37** with (*S*)-**41** gave amino ester **38** in 74% yield and >99:1 dr. Hydrogenolysis of amino ester **38**, followed by cyclisation of the resultant secondary amine **39** under strongly acidic conditions gave pyrrolizidinone hydrochloride **40**·HCl in quantitative yield from amino ester **38**. Reduction of pyrrolizidinone **40** with excess DIBAL-H, gave pyrrolizidine **16**, which was

coupled with *trans*-4-methoxycinnamic acid in the presence of DCC to give (−)-absouline (−)-**6** in 49% (from pyrrolizidinone **40**·HCl). This concluded the synthesis of (−)-absouline (−)-**6** in 8 steps and 20% overall yield from commercially available L-proline **36** (Scheme 5).[16] Unlike in the previous synthesis by Scheerer *et al*. this synthesis by Davies *et al*. proceeds with excellent diastereoselectivity; for the formation of (*E*)-α,β-unsaturated ester **37**, and the lithium amide conjugate addition. This contributes to the overall yield by Davies *et al*. being double of that obtained by Scheerer *et al*. despite the step count being the same.

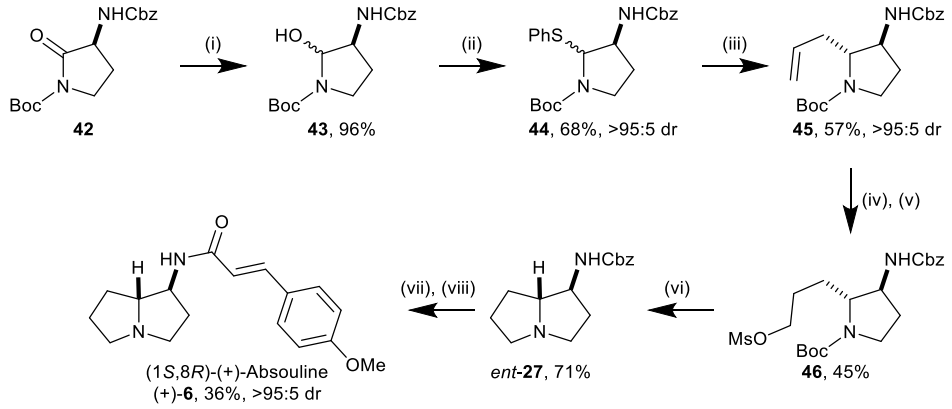


Scheme 5 *Reagents and Conditions*: (i) PhCOCl, NaOH, H_2O, 0 °C, 2 h; (ii) $LiAlH_4$, THF, reflux, 18 h; (iii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C , 1 h, then $Ph_3P{=}CHCO_2{}^tBu$, CH_2Cl_2, rt,18 h; (iv) (*S*)-**41**, ^nBuLi, THF, −78 °C, 2 h; (v) H_2 (5 atm), $Pd(OH)_2/C$, HCl, MeOH, rt, 48 h; (vi) $HCl_{(aq)}$, 90 °C, 18 h; (vii) DIBAL-H, THF, 0 °C, then rt 18 h; (viii) *trans*-4-methoxycinnamic acid, DCC, DMAP, CH_2Cl_2, 0 °C, then rt, 3 h.

1.2.3 Chiral Pool – Other Chiral Sources

Huang *et al*. have published two synthesis of (+)-absouline (+)-**6**, their first-generation synthesis starts from known pyrrolidinone **42**, which can be synthesised from commercially available aspartic acid anhydride in 5 steps and 29% overall yield.[23] Reduction of pyrrolidinone **42** with sodium borohydride gave alcohol **43** as a mixture of diastereomers in 96% yield. Treatment of alcohol **43** with thiophenol gave phenyl sulphide **44** as a single diastereomer, however due to the rotameric nature of phenyl sulfide **44** it was not possible to determine the

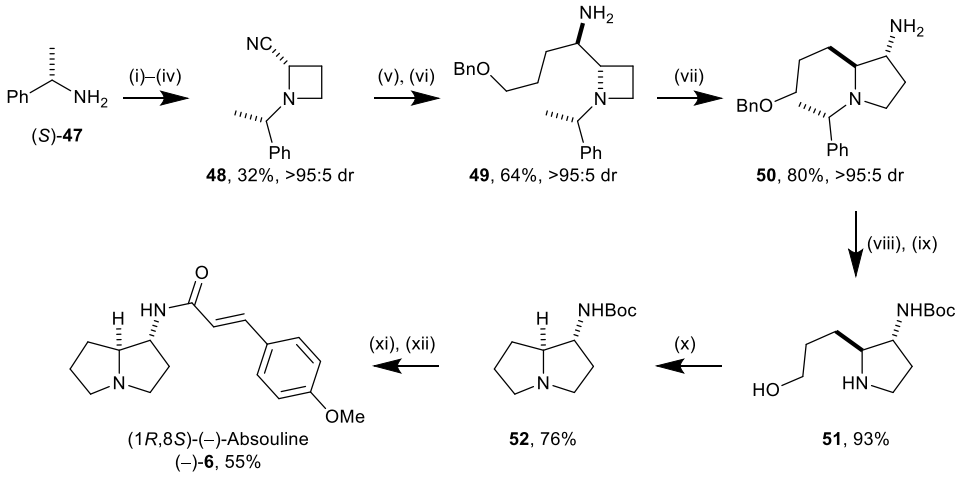
relative configuration of the sulfur-bearing stereocenter. Phenyl sulfide **44** was treated with ^{n}BuLi and lithium napthalenide to generate an *N*-α-dianionic intermediate, which could be trapped with allyl iodide to give *anti*-allyl amine **45** in 57% as a single diastereomer. Hydroboration of allyl amine **45**, followed by mesylation of the resultant alcohol gave mesylate **46** in 45% yield. Acidic deprotection followed by an *in situ* cyclisation upon treatment with NaOH gave pyrrolizidine *ent*-**27** in 71% yield. Hydrogenolysis of pyrrolizidine *ent*-**27** followed by amide coupling with *trans*-4-methoxycinnamic acid in the presence of DCC gave (+)-absouline (+)-**6** in 36% yield, which concluded the synthesis in 13 steps and 1.2% yield from commercially available aspartic acid anhydride (Scheme 6).[17] Despite Huang *et al.*'s synthesis of (+)-absouline (+)-**6** proceeding in 8 steps from pyrrolidinone **42**, an extra 5 steps were needed to prepare pyrrolidinone **42**; from commercially available aspartic acid anhydride. This results in a synthesis which is significantly longer and lower yielding that the previous chiral pool synthesis of absouline (+)-**6**.



Scheme 6 *Reagents and Conditions*: (i) $NaBH_4$, MeOH; (ii) PhSH, TsOH, PPTS, CH_2Cl_2; (iii) ^{n}BuLi, lithium naphthalenide, THF, −78 °C, 30 min, then allyl iodide, −78 °C, 1 h, then 0 °C; (iv) $BH_3{\cdot}Me_2S$, hexane, rt 12 h, then NaOH, H_2O_2, EtOH; (v) MsCl, Et_3N, CH_2Cl_2, −40 °C to 0 °C, 5 h ; (vi) 3 M HCl, dioxane, rt, 12 h, then NaOH; (vii) H_2 (1 atm), Pd/C, 6 M $HCl_{(aq)}$, rt; (viii) *trans*-4-methoxycinnamic acid, DCC, DMAP, CH_2Cl_2, 0 °C to rt.

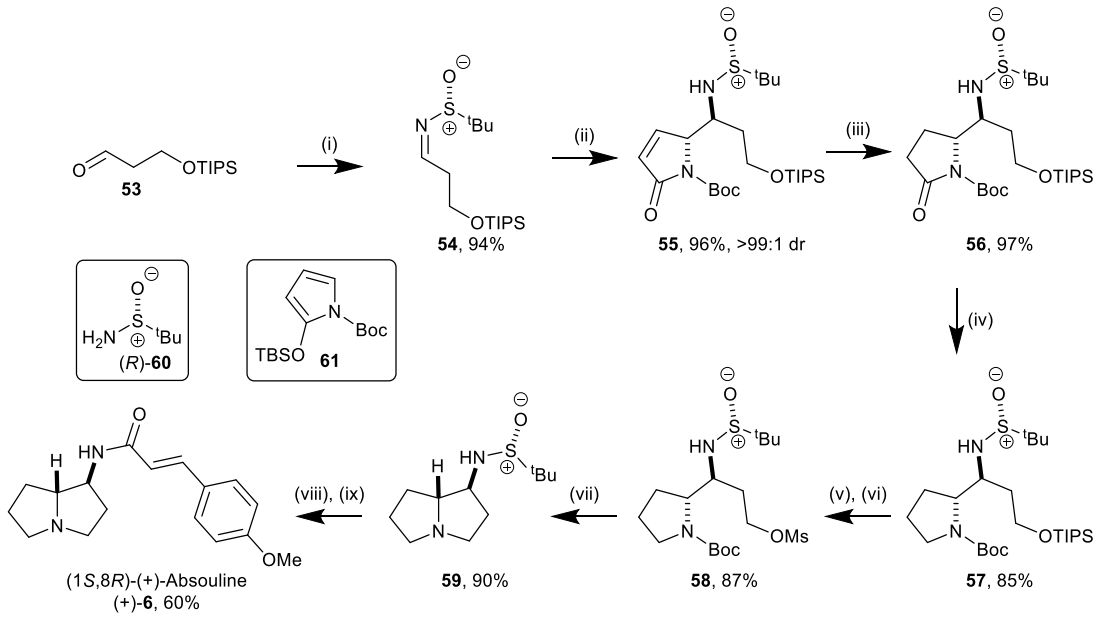
1.2.4 *De novo* Asymmetric Synthesis

Couty *et al.* reported an asymmetric synthesis of (−)-absouline (−)-**6** utilising a ring-expansion of cyanoazetidine **48**. Cyanoazetidine **48** was synthesised from (*S*)-α-methylbenzylamine (*S*)-**47** in 4 steps and 32% yield.[24] Addition of 3-benzyloxypropyllithium to cyanoazetidine **48** followed by reduction of the resultant imine gave diamine **49** in 64% yield as a single diastereomer. Treatment of diamine **49** with $BF_3{\cdot}OEt_2$ in refluxing MeCN gave the ring-expanded pyrrolidine **50** in 80% yield and >95:5 dr.[25,26] Protection of the exocyclic amine within pyrrolidine **50** followed by hydrogenolysis gave amino alcohol **51** in 93% yield. Subjecting amino alcohol **51** to Appel reaction conditions and displacement of the corresponding chloride by the nitrogen of the pyrrolidine unit gave pyrrolizidine **52** in 76% yield. Acidic deprotection and amide formation with *trans*-4-methoxycinnamic acid in the presence of DCC gave (−)-absouline (−)-**6** in 55% yield (from pyrrolizidine **52**), which concluded the synthesis in 12 steps and 6.7% yield overall from (*S*)-α-methylbenzylamine (*S*)-**47** (Scheme 7).[21] The asymmetric synthesis of (−)-absouline (−)-**6** by Couty *et al.* proceeded with excellent diastereoselectivity and moderate yields from cyanoazetidine **48**. However, the 4-step synthesis of cyanoazetidine **48** from (*S*)-α-methylbenzylamine (*S*)-**47** significantly increased the yield and step count of the overall synthesis.



Scheme 7 *Reagents and Conditions*: (i) $BrCH_2CH_2OH$, DMSO, 50 °C, 72 h; (ii) $BrCH_2CN$, K_2CO_3, MeCN, reflux, 5 h; (iii) $SOCl_2$, CH_2Cl_2, 0 °C, then reflux 2 h; (iv) ^{t}BuOK, THF, rt, 10 min; (v) 1-benzyloxy-3-bromopropane, ^{t}BuLi, Et_2O, −78 °C to rt, then **48**, PhMe, 0 °C, 2 h, then rt 30 min; (vi) $NaBH_4$, rt, 16 h; (vii) $BF_3{\cdot}Et_2O$, MeCN, rt, 12 h; (viii) Boc_2O, EtOAc, rt, 30 min; (ix) H_2, Pd/C, MeOH, rt, 12 h; (x) PPh_3, CCl_4, Et_3N, DMF, rt, 72 h; (xi) TFA, CH_2Cl_2, 0 °C, 20 min, then rt, 20 min; (xii) *trans*-4-methoxycinnamic acid, DCC, DMAP, CH_2Cl_2, 0 °C, 15 min, then rt, 30 min.

The second-generation synthesis by Huang *et al.* is an asymmetric synthesis, which utilised the addition of pyrrole **61** to an Ellman sulfinylimine. Condensation of aldehyde **53** and (*R*)-(+)-2-*tert*-butylsulfinamide **60** gave sulfinylimine **54** in 94% yield. Addition of pyrrole **61** to sulfinylimine **54** in the presence of TMSOTf gave pyrrolidone **55** in 96% yield and >99:1 dr. Hydrogenation of pyrrolidone **55** proceeded in 97% yield, which was followed by reduction to give pyrrolidine **57** in 85% yield. Desilylation followed by mesylation gave mesylate **58** in 87% yield. Acidic deprotection of *N*-Boc pyrrolidone **58** followed by *in situ* cyclisation upon treatment with K_2CO_3 gave pyrrolizidine **59** in 90% yield. Cleavage of the *N*-^{t}Bu-sulfinyl group followed by amide coupling with *trans*-4-methoxy cinnamic acid in the presence of DCC gave (+)-absouline (+)-**6** in 60% yield, concluding the synthesis in 9 steps in 35% yield from commercially available ^{t}Bu-sulfinamide **60** (Scheme 8).[20] The second-generation synthesis by Huang *et al*. was a significant improvement in yield and step count over the first-generation synthesis. This is largely due to each step being optimised to excellent yields, with the key stereo defining step optimised to an excellent 96% yield and >99:1 dr.



Scheme 8 *Regents and Conditions*: (i) (*R*)-**60**, $CuSO_4$, CH_2Cl_2, then **53** rt, 24 h;[27] (ii) **61**, TMSOTf, CH_2Cl_2, −78 °C, 7 h; (iii) H_2, Pd/C, NaOAc, EtOAc, rt, 5 h; (iv) $BH_3{\cdot}Me_2S$, THF,0 °C, then 30 °C, 20 h; (v) TBAF, THF, 0 °C to rt, 1 h; (vi) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt 1 h; (vii) TFA, CH_2Cl_2, 0 °C to rt, 1 h, then K_2CO_3, MeCN, rt, 10 h; (viii) HCl, dioxane, 0 °C, 1 h; (ix) *trans*-4-methoxycinnamic acid, DCC, DMAP, CH_2Cl_2, 0 °C, 15 min, then rt, 30 min.

1.3 Loline Alkaloids

1.3.1 Isolation

Reports of toxicity in crop grasses from as early as ancient Roman times led to chemists in the 19th century investigating these crop grasses. In 1892, Hoffmeister isolated a group of novel metabolites from *Lolium temulentum*, one of which was a compound with the elemental formula $C_7H_{12}N_2O$ and named it temulene; this is the earliest report of an alkaloid from the loline alkaloid family.[28] In 1955, Akramov *et al.* isolated two related alkaloids from Darnel seeds and named them loline (+)-**1** {HCl salt mp 256−257 °C (dec); $[\alpha]_D^{19}$ +6.2 (c 9.7 in H_2O), free base: $[\alpha]_D^{20}$ +18.9 (c 5.5 in acetone)} and lolinine (+)-**3** {HCl salt mp 197−198 °C; $[\alpha]_D^{20}$ +36.9 (c 4.1 in H_2O), free base: $[\alpha]_D^{20}$ +51.1 (c 8.8 in acetone)}.[29,30] Akramov *et al.* proposed the first structure of the loline alkaloids which contained a C(2)−C(7) ether bridge, however they suggested an *endo*-*N*-methyl-1-aminopyrrolozidine.[4] This was a similar structure to that proposed by Yates *et al.* in 1965 for the natural product festucine {HCl salt: mp 237−242 °C

(dec); $[\alpha]_D^{25}$ +4.6 (c 4.4 in H_2O)}, which was isolated from *Lolium arundinaceum;* however in the structural assignment of festucine by Yates *et al.* the *N*-methyl was on the *exo* face of the pyrrolozidine.[31,32] In 1969 Aasen *et al.* reisolated loline {HCl salt; mp 240−244 °C (dec)} and confirmed the Yates' assignment by IR and ^{1}H NMR studies as well as using mixed melting points to confirm that (+)-loline (+)-**1** and festucine have the same structure, therefore festucine is in fact a phantom natural product.[33] The absolute configuration of (+)-loline (+)-**1** was unambiguously assigned by Bates *et al.* in 1972 by X-ray diffraction analysis.[3] (+)-*N*-Acetyl norloline (+)-**4** {HCl salt: mp 232−235 °C (dec); $[\alpha]_D^{20}$ +49.8 (c 2.23 in $CHCl_3$)}[6], (+)-*N*-formyl loline (+)-**5** {mp 93−94 °C; $[\alpha]_D^{20}$ +47.9 (c 0.73 in $CHCl_3$)[6]; $[\alpha]_D^{20}$ +31.3 (c 0.96 in acetone)[2]} and several other acetylated variants were subsequently isolated (Figure 3).[5]

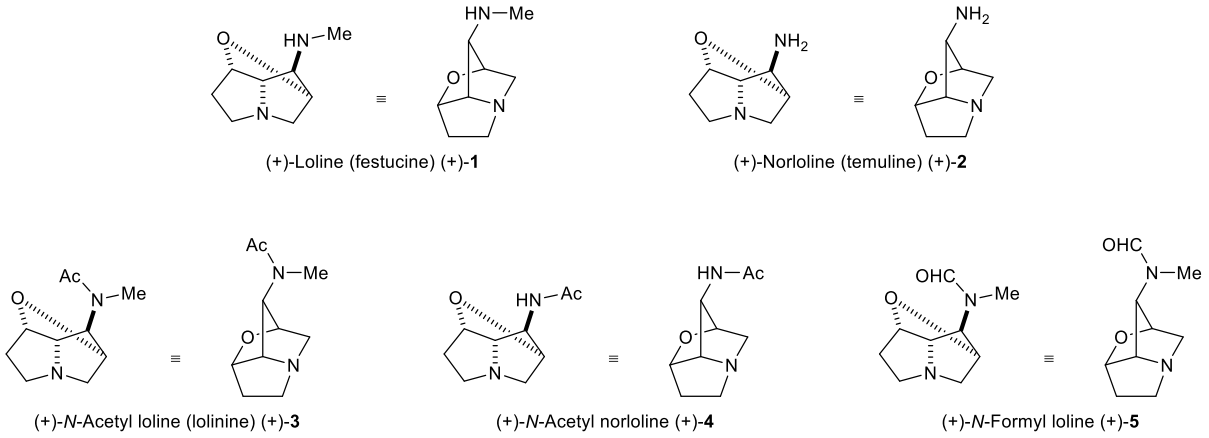


Figure 3 The loline alkaloids (+)-**1**–**5**.

1.3.2 Biosynthesis and Biological Activity

Guérin was the first to report, in 1898, that the loline alkaloids were produced in the presence of a symbiotic fungus, however for over one hundred years it was not known if they originated from plant or fungus.[34] Then, in 2001, Schardl *et al.* grew the *Neotyphodium unicinatum* endophyte in a controlled medium with inorganic and organic nitrogen sources and sugars as carbon sources, which resulted in the production of loline, *N*-acetyl norloline and *N*-formyl

loline. This confirmed that it was the grass endophyte *Neotyphodium unicinatum*, which was responsible for the production of the loline alkaloids and not the host plants.[35]

The biological activities of the loline alkaloids have been studied extensively *in vivo*, consistently exhibiting insecticidal activity against a range of insects.[5] Early studies showed the loline alkaloids exhibited cytotoxic activity against mammalian systems.[36] However, these studies often used crude or partially purified plant extracts and probably contained significant amounts of other cytotoxic alkaloids.[37] Purified loline alkaloids have exhibited vascular effects and anti-tumour activities against a range of mammalian cell lines, but generally only at extremely high concentrations.[5,38,39]

1.3.3 Syntheses

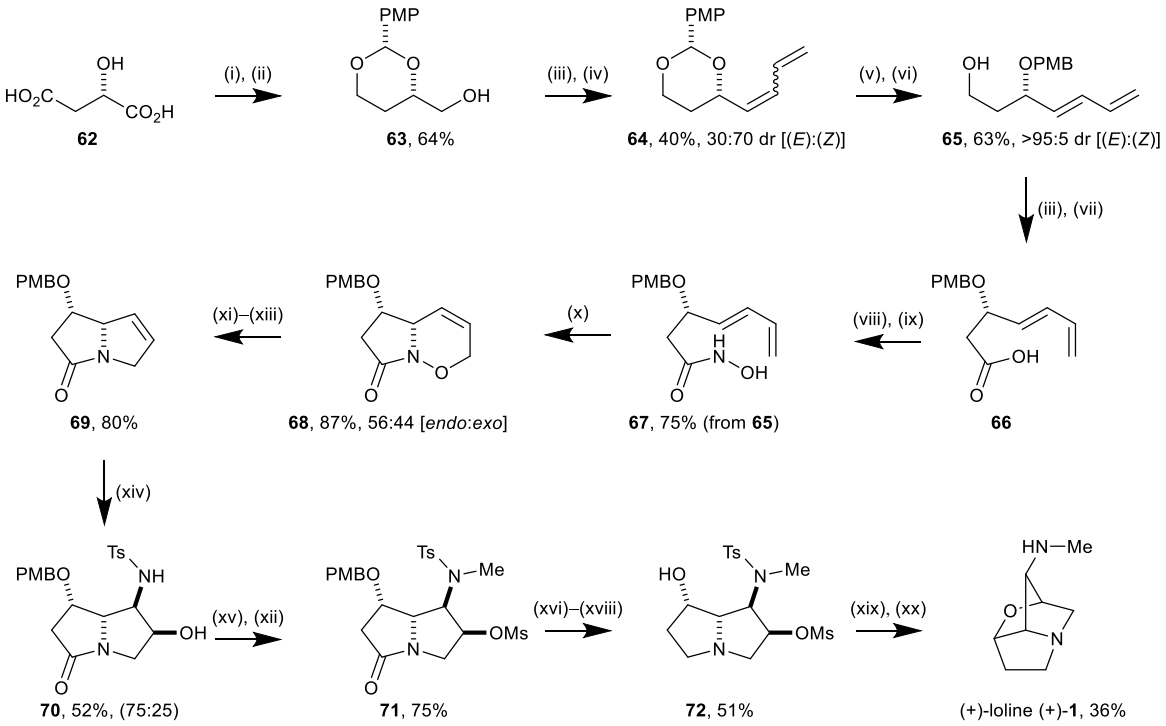
The loline alkaloids have been the subject of synthetic investigation by four research groups, with two of those subsequently publishing second syntheses to give six syntheses of the loline alkaloids and protected derivatives. These syntheses are a mixture of racemic,[40] chiral pool[41–45] and *de novo* asymmetric[46] syntheses.

1.3.4 Synthesis of (+)-Loline (+)-1 via an Intramolecular [4 + 2] Cycloaddition

White *et al.* published their synthesis of (+)-loline (+)-**1** in 2000[42] and published a more detailed account of this synthesis in 2001.[41] (−)-(*S*)-Malic acid **62** was the chiral pool starting material used; this was reduced with borane and the resultant triol was converted to acetal **63** in 64% yield as a single diastereomer. Alcohol **63** was oxidised under Swern conditions and subjected to a Wittig olefination with the ylid generated from allyltriphenylphosphonium bromide to give diene **64** in 40% yield (from alcohol **63**) as a 30:70 mixture of [(*E*):(*Z*)] isomers. Reduction of diene **64** with DIBAL-H followed by isomerisation of the mixture with catalytic iodine under a mercury lamp gave diene **65** in 63% yield with a much improved >95:5 mixture of (*E*):(*Z*)

isomers. Oxidation of alcohol **65**, first to the aldehyde under Swern conditions, then with buffered sodium chlorite gave acid **66**. This was directly converted to the corresponding succinimidyl ester and, after treatment with hydroxylamine the hydroxamic acid **67** was isolated in 75% yield over 4 steps from alcohol **65**. Oxidation of hydroxamic acid **67** by Bu_4NIO_4 gave the corresponding acylnitrosodiene, which underwent a non-selective spontaneous intramolecular cycloaddition to give dihydrooxazine **68** in 87% yield and 56:44 dr [*endo*:*exo*]. Reduction of dihydrooxazine **68** with sodium amalgam resulted in *N*−*O* bond cleavage; the hydroxyl group was mesylated and treatment of the corresponding mesylate with lithium diisopropylamine gave pyrrolizidine **69** in 80% yield over three steps from dihydrooxazine **68**. Aminohydroxylation of pyrrolizidine **69** in the presence of chloramine T and a hydroquinidine additive gave amino alcohol **70** in 52% yield as the major regioisomer in a 75:25 ratio, with the other regioisomer being the minor component. The secondary amine in amino alcohol **70** was methylated to install the *N*-Me found in loline (+)-**1**; this was followed by mesylation of the free alcohol to give mesylate **71** in 75% yield over the two steps. Pyrrolizidinone **71** was reduced with borane, followed by stirring in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] to liberate the free pyrrolizidine, from which the PMB protecting group was removed with DDQ to furnish alcohol **72** in 51% yield over three steps from pyrrolizidinone **71**. All attempts at base induced cyclisation were unsuccessful, with elimination of the mesylate being the main reaction pathway. However, thermal cyclisation resulted in formation of the ether bridge, and removal of the tosyl group then gave (+)-loline (+)-**1** in 36% yield from alcohol **72** This concluded the synthesis of (+)-loline (+)-**1** in 20 steps and 0.6% yield from (−)-(*S*)-malic acid **62** (Scheme 9).[41,42] This synthesis of (+)-loline (+)-**1** by White *et al.* had a significantly higher step count and lower yield compared to subsequent syntheses of the loline alkaloids. This is partly due to the low levels of diastereo- and regioselectivity obtained in the intramolecular cycloaddition and aminohydroxylation steps. Furthermore, the *N*-Me functionality of loline (+)-**1** was

installed in step 15 and therefore does not allow for late stage functionalisation and synthesis of other members of the loline alkaloid family.



Scheme 9 *Reagents and Conditions*: (i) $BH_3{\cdot}Me_2S$, $B(OMe)_3$, THF, 0 °C to rt, 16 h;[47] (ii) $PMPCH(OMe)_2$, PPTS, CH_2Cl_2, reflux, 20 h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, 85 min, then Et_3N, CH_2Cl_2, −60 °C to rt, 1 h; (iv) allyltriphenylphosphonium bromide, ^{n}BuLi, THF, −30 °C to rt, 2 h; (v) DIBAL-H, CH_2Cl_2, 0 °C to rt, 1.5 h; (vi) I_2, *hv*, C_6H_6, rt, 1 h; (vii) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, 2-methylbut-2-ene, ^{t}BuOH/H_2O, 0 °C, to rt, 40 min; (viii) CF_3CO_2Suc, pyridine, THF, rt, 20 h; (ix) $NH_2OH{\cdot}HCl$, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; (x) Bu_4NIO_4, $CHCl_3$, rt, 2.5 h; (xi) 6%, Na(Hg), NaH_2PO_4, EtOH, 0 °C, 14 h; (xii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, then rt, 20 min; (xiii) LDA, THF, −78 °C, 1.5 h, then rt 30 min; (xiv) $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, chloramine T, ^{t}BuOH/H_2O, rt, 4 days; (xv) MeI, ^{t}BuOK, ^{t}BuOH, 50 °C, 16 h; (xvi) $BH_3{\cdot}Me_2S$, THF, rt, 5 h; (xvii) $Pd(OH)_2$/C, MeOH, rt, 24 h; (xviii) DDQ, CH_2Cl_2/H_2O, rt, 48 h; (xix) *o*-$Cl_2C_6H_4$, 180 °C, 22 h; (xx) sodium naphthalenide, DME, −60 °C, 20 min.

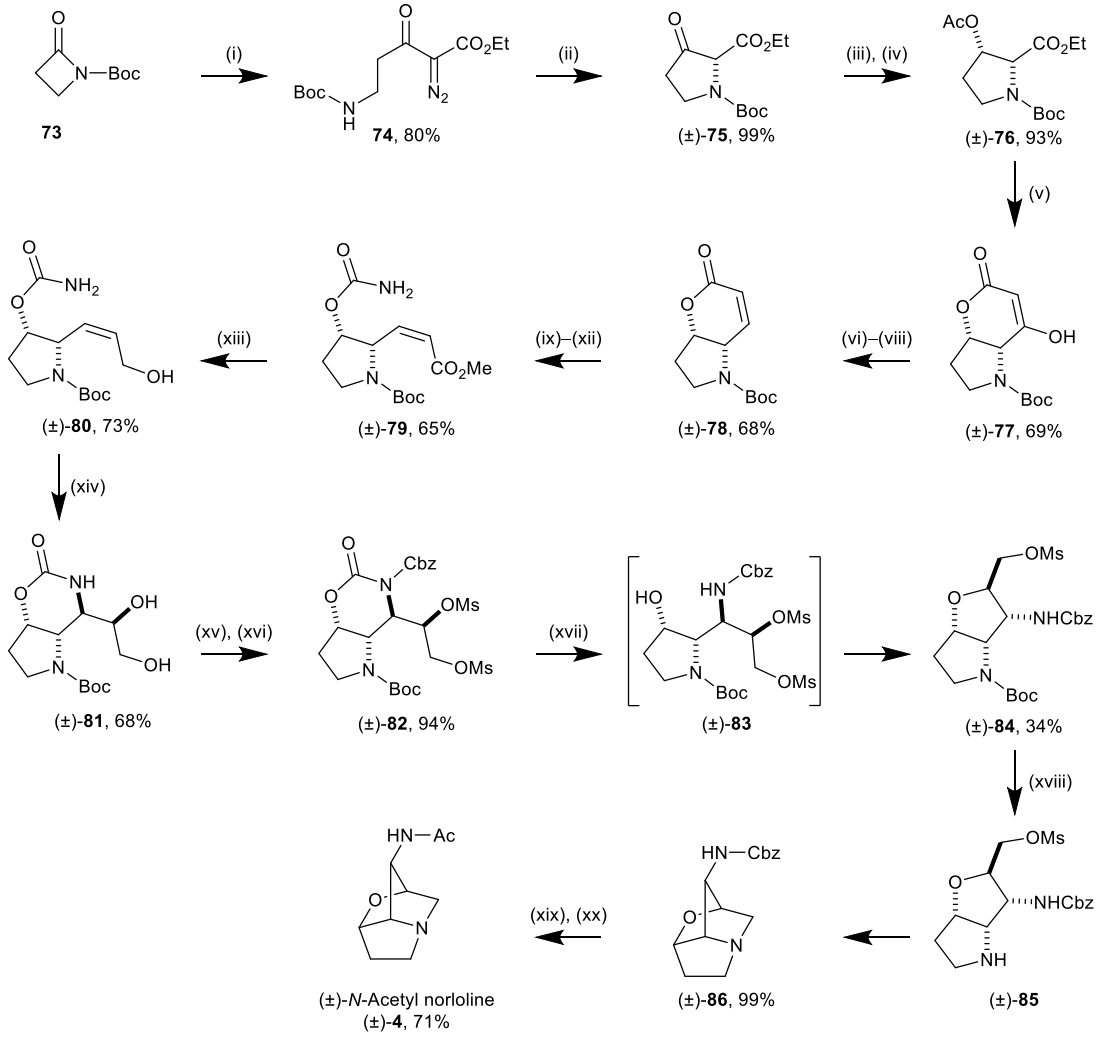
1.3.5 Synthesis of (±)-*N*-Acetyl Norloline (±)-4 and *N*-Boc Loline (+)-98 via an Amino Hydroxylation Protocol

Scheerer *et al.* have published two syntheses of the loline alkaloid scaffold. The first-generation was a racemic synthesis of (±)-*N*-acetyl norloline (±)-**4** in 2011.[40] The second-generation route was a formal synthesis starting from commercially available (*S*)-4-amino-2-hydroxybutanoic acid **87** as a chiral pool reagent to give the *N*-Boc protected loline alkaloid scaffold (+)-**98**.[43]

1.3.5.1 First-generation

The first-generation synthesis by Scheerer *et al.* used β-ketoester **75** as their first key intermediate. This was synthesised in two steps from commercially available azetidinone **73**: a Claisen condensation of **73** with ethyldiazoacetate gave α-diazo-β-keto ester **74** in 80% yield. Decomposition of the diazo functionality in the presence of $Rh_2(OAc)_4$ followed by *N–H* insertion gave β-ketoester **75** in 99% yield.[48] Reduction of β-ketoester **75** with $NaBH_4$ to give *cis*-3-hydroxyproline was followed by acetylation to give racemic acetoxyproline (±)-**76** in 93% yield. Enolization of (±)-**76** with LiHMDS proceeded at –78 °C, which upon slowly warming to –20 °C, underwent a Dieckmann condensation to give enol-lactone (±)-**77** in 69% yield. Reduction of (±)-**77** with borane gave the corresponding saturated β-hydroxy-lactone, which after acetylation and exposure to DBU, gave α,β-unsaturated lactone (±)-**78** in 68% yield. Hydrolysis of α,β-unsaturated lactone (±)-**78**, followed by etherification with MeI gave the *cis*-α,β-unsaturated ester that was trapped as the primary carbamate (±)-**79** with trichloroacetyl isocyanate in 65% yield over the three steps. α,β-Unsaturated ester (±)-**79** was reduced to allylic alcohol (±)-**80** with DIBAL-H in 73% yield. Aminohydroxylation of allylic alcohol (±)-**80** with *tert*-butyl hypochlorite gave carbamate (±)-**81** in 68% yield. Mesylation of the diol followed by protection of the free *N–H* with CbzCl gave imide (±)-**82** in 94% yield. Methanolysis of imide (±)-**82** resulted in a mixture of endocyclic cleavage to give the desired secondary alcohol (±)-**83** and exocyclic cleavage to give the carbamate that occurs due to loss of the Cbz group. Secondary alcohol (±)-**83** was not isolated and cyclised to give bicycle (±)-**84** in 34% yield, through attack on the secondary mesylate in bismesylate (±)-**83**. Cleavage of the *N*-Boc group in bicycle (±)-**84** followed by treatment with Et_3N resulted in *in situ* cyclisation to give *N*-Cbz protected loline scaffold (±)-**86** in 99% yield. (±)-*N*-Acetyl norloline (±)-**4** was prepared by hydrogenolysis and acetylation in 71% yield (from pyrrolizidine **86**), which concluded the synthesis in 20 steps in 2.5% yield from azetidinone **73** (Scheme 10).[40] The major downside to

this first-generation synthesis of (±)-*N*-Acetyl norloline (±)-**4** is it was initially envisaged as an asymmetric synthesis; however, due to scalability issues Scheerer *et al*. settled for a racemic synthesis instead.[48] Furthermore, Scheerer *et al*. does not provide any comment on the diastereoselectivity of the aminohydroxylation protocol to give carbamate (±)-**81** and therefore it is unknown if the moderate yield is due to poor diastereoselectivity or other issues.

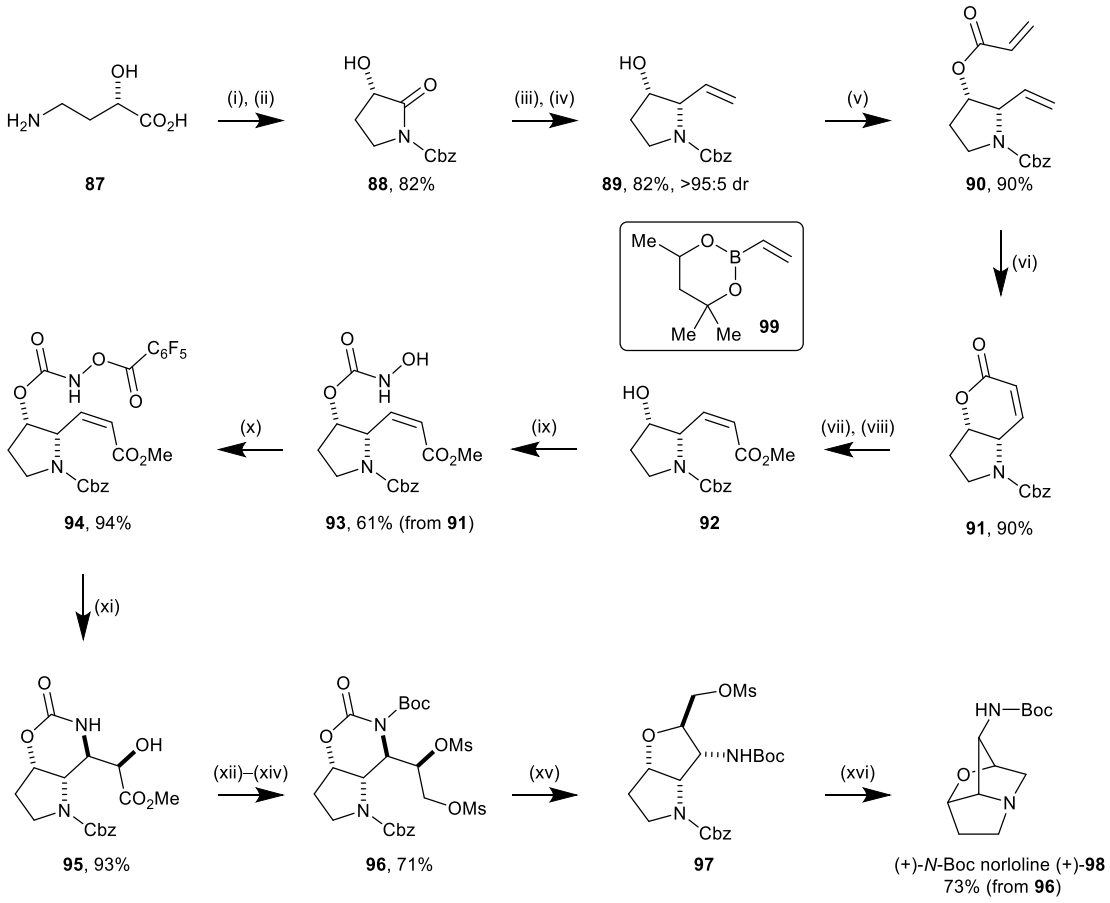


Scheme 10 *Reagents and Conditions*: (i) Ethyl diazoacetate, LiHMDS, −78 °C; (ii) $Rh_2(OAc)_4$, PhMe, 90 °C; (iii) $NaBH_4$, MeOH; (iv) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 16 h; (v) LiHMDS, THF, −78 °C, 1 h, then −20 °C, 2 h; (vi) $BH_3{\cdot}^tBuNH_2$, MeOH, citric acid, 0 °C, 1.5 h; (vii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 16 h; (viii) DBU, CH_2Cl_2, rt, 2 h; (ix) $LiOH{\cdot}H_2O$, THF, H_2O, rt, 5 h; (x) MeI, K_2CO_3, DMF, rt, 2 h; (xi) trichloroacetyl isocyanate, CH_2Cl_2, 0 °C, 10 min; (xii) $NaHCO_3$, MeOH, 0 °C to rt 16 h; (xiii) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (xiv) ^{t}BuOCl, NaOH, $K_2OsO_4{\cdot}2H_2O$, ^{i}Pr$_2$NEt, ^{n}PrOH, H_2O, rt, 20 h; (xv) MsCl, pyridine, rt, 16 h; (xvi) CbzCl, Et_3N, DMAP, THF, rt, 6 h; (xvii) $CsCO_3$, MeOH, rt, 3 h; (xviii) TFA, CH_2Cl_2, 0 °C to rt, 1 h, then Et_3N, MeOH, rt, 2 h; (xix) H_2, Pd/C, MeOH/EtOAc, rt, 40 min; (xx) Ac_2O, $CHCl_3$, rt, 1 h.

1.3.5.2 Second-Generation

The second-generation synthesis by Scheerer *et al.* is similar to the first-generation synthesis using an optimised amino hydroxylation protocol, performed on enantiopure starting material to give enantiopure product. (*S*)-4-Amino-2-hydroxybutanoic acid **87** was the chiral pool starting material used in the second-generation synthesis which was readily converted to pyrrolidone **88** in 82% over two steps. Reduction of pyrrolidone **88** with $NaBH_4$ was

immediately followed by a Petasis borono-Manich addition which utilises the C(3) hydroxy to deliver the vinyl group from boronate **99** from the top face to give vinyl proline **89** in 82% yield as a single diastereomer. Acylation of alcohol **89** with acryloyl chloride gave α,β-unsaturated ester **90** in 90% yield which was subjected to a ring-closing metathesis with Hoveyda−Grubbs II catalyst forming lactone **91** in 90% yield, a similar intermediate to lactone (±)-**78** used in the first-generation synthesis. Hydrolysis of lactone **91**, methylation and formation of *N*-hydroxy carbamate **93** proceeded in 61% yield, which was subsequently converted to the *N*-pentafluorobenzyloxy carbamate **94** in 94% yield. *N*-Pentafluorobenzyloxy carbamate **94** was ideally suited to the tethered aminohydroxylation protocol in the presence of catalytic OsO_4 to give cyclic carbamate **95** in 93% yield as a single diastereomer. Reduction of ester **95** gave the corresponding diol, which was bis-mesylated, and the carbamate activated as bis-imide **96** in 71% yield over three steps. Cleavage of imide **96** with $CsCO_3$ proceeded exclusively with endocyclic cleavage to give bicycle **97**, hydrogenolysis of this removed the *N*-Cbz group and the resultant amine underwent spontaneous cyclisation to give (+)-*N*-Boc norloline (+)-**98** in 73% yield (from imide **96**), which concluded the synthesis in 16 steps and 15% yield from (*S*)-4-amino-2-hydroxybutanoic acid **87** (Scheme 11).[43] (+)-*N*-Boc norloline (+)-**98** is an intermediate reported in the synthesis of the loline alkaloids by Trauner *et al.* (*vide infra*).[46] This second-generation synthesis by Scheerer *et al.* is a significant improvement over their first-generation synthesis. The Petasis borono-Manich proceeds with excellent diastereoselectivity to give vinyl proline **89** as a single diastereoisomer enabling the subsequent synthesis of enantiopure (+)-*N*-Boc norloline (+)-**98**. The second-generation aminohydroxylation proceeds in a significantly improved 93% yield as a single diastereomer compared to the first-generation aminohydroxylation.

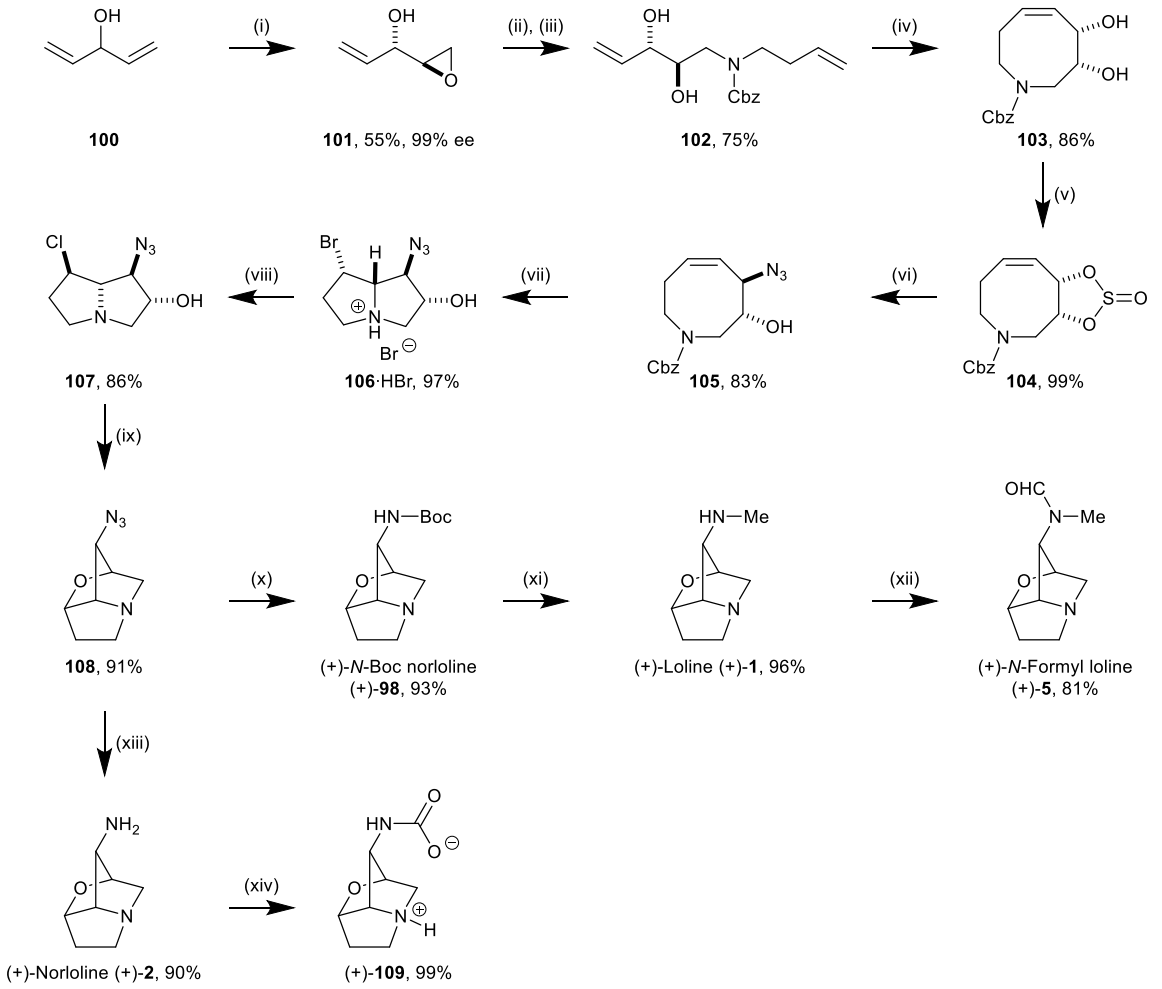


Scheme 11 *Reagents and Conditions*: (i) TMSCl, HMDS, xylene, reflux, 12 h, then EtOH; (ii) CbzCl, LiHMDS, THF, −78 °C to rt, 1 h, then HCl; (iii) $NaBH_4$, MeOH, 0 °C, 30 min; (iv) **99**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C to 0 °C, 2 h, then rt 3 h; (v) acryloyl chloride, $^iPr_3NEt$, DMAP, CH_2Cl_2, −78 °C to rt, 30 min; (vi) Hoveyda−Grubbs II, $C_2H_4Cl_2$, 77 °C, 15 h; (vii) $LiOH{\cdot}H_2O$, THF, H_2O, rt, 1 h; (viii) MeI, K_2CO_3, DMF, rt, 2h; (ix) CDI, pyridine, rt, 12 h, then $NH_2OH{\cdot}HCl$, 0 °C to rt, 5 h; (x) pentalfluorobenzoyl chloride, Et_3N, CH_2Cl_2, 0 °C, 15 min; (xi) $K_2OsO_4{\cdot}2H_2O$, ^tBuOH, H_2O, rt, 1.5 h; (xii) $LiBH_4$, THF, 0 °C, 20 min; (xiii) MsCl, pyridine, rt, 75 min; (xiv) Boc_2O, DMAP, THF, rt, 1 h; (xv) $CsCO_3$, MeOH, rt, 2.5 h; (xvi) H_2, $Pd(OH)_2/C$, MeOH, rt, 1.5 h.

1.3.6 Synthesis of Three Loline Alkaloids via a Transannular Aminobromination Cyclisation

In 2011, Trauner *at el.* published the first *de novo* asymmetric synthesis of (+)-loline (+)-**1**, (+)-norloline (+)-**2** and (+)-*N*-formyl loline (+)-**5**. Divinyl alcohol **100** was subjected to a highly regio- and diastereoselective Sharpless asymmetric epoxidation, which proceeded in 55% yield and 99% ee to give epoxide **101**.[49] Nucleophilic ring-opening of epoxide **101** with 3-butenylamine followed by *in situ* protection gave diene **102** in 75% yield. Ring-closing metathesis on diene **102** with Grubbs II catalyst gave diol **103** in 86% yield, which upon

treatment with $SOCl_2$ gave cyclic sulfite **104** in 99% yield. Treatment of sulfite **104** with lithium azide proceeded with complete regioselectivity to give azido alcohol **105** in 83% yield. Subjecting azido alcohol **105** to a solution of Br_2 in MeOH gave bromopyrrolizidine **106**·HBr in 97% yield; this proceeds by formation of the corresponding bromonium ion, which undergoes a transannular nucleophilic substitution followed by methanolysis of the benzyl carbonate. A Finkelstein reaction converts bromopyrrolizidine **106**·HBr to the corresponding chloropyrrolizidine **107** in 86% yield. Chloropyrrolizidine **107** was poised to form the ether bridge via a Williamson etherification upon treatment with potassium carbonate and microwave irradiation, to give azide **108** in 91% yield. Conversion of azide **108** to (+)-*N*-Boc norloline (+)-**98** by hydrogenation in the presence of Boc_2O proceeded in 93% yield. (+)-*N*-Boc norloline (+)-**98** was treated with $LiAlH_4$ to give (+)-loline (+)-**1** in 96% yield (11 steps and 20% yield from divinyl alcohol **100**). (+)-Loline (+)-**1** was readily converted to (+)-*N*-formyl loline (+)-**5** by treatment with Ac_2O and HCO_2H in 81% yield (12 steps and 16% yield from divinyl alcohol **100)**. Finally, hydrogenolysis of azide **108** gave (+)-norloline (+)-**2** in 90% yield (10 steps and 20% yield from divinyl alcohol **100**). Upon exposure of (+)-norloline (+)-**2** to air it reacted with CO_2; consequently (+)-norloline (+)-**2** was exposed to CO_2 in MeOH and carbamate (+)-**109** was isolated in 99% yield (Scheme 12).[46] This synthesis of the loline alkaloids by Trauner *et al*. has excellent yields and diastereoselectivities throughout, which is represented in the overall yield and step count. Trauner *et al*. also synthesised the advanced late-stage intermediate azide **108**, from which it was possible to synthesise a selection of loline alkaloids via simple chemical manipulations.



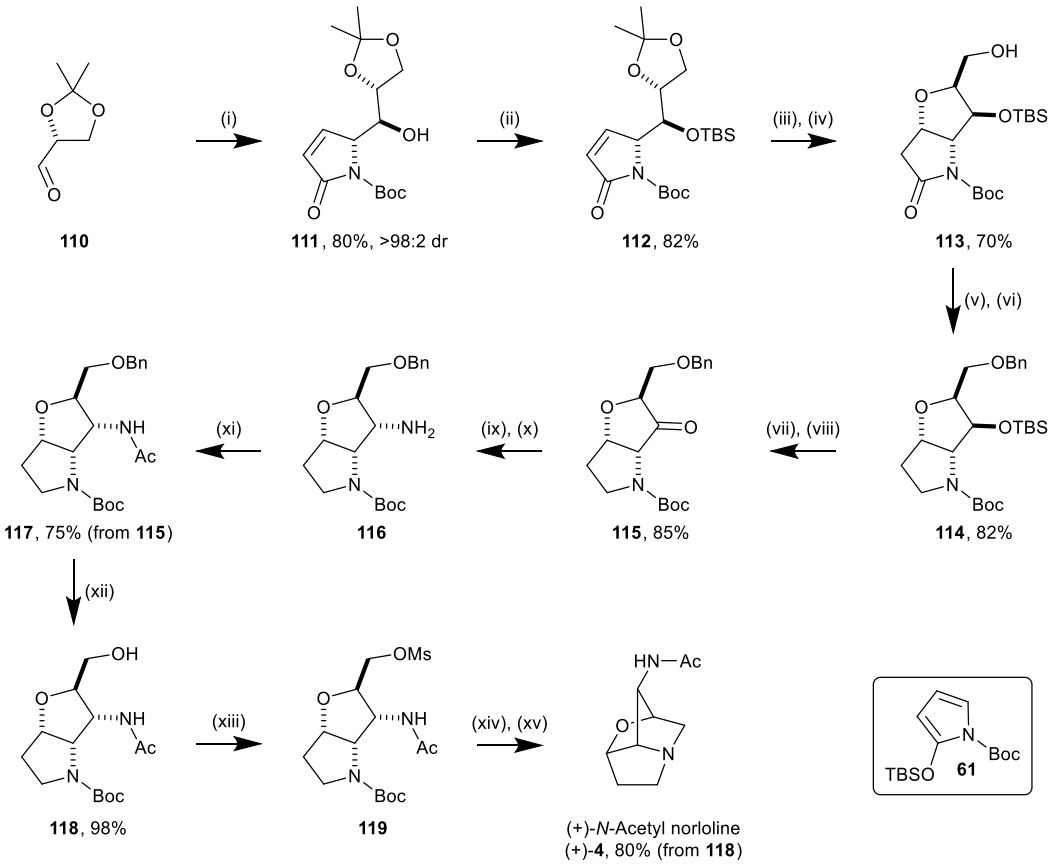
Scheme 12 *Reagents and Conditions*: (i) $Ti(O^iPr)_4$, L-(+)-diisoproply tartrate, 4 Å molecular sieves, CH_2Cl_2, −23 °C, 10 min, then **100**, ^{t}BuOOH, −15 °C, 118 h;[49] (ii) 4-butenylamine hydrochloride, $^i Pr_2NEt$, MeOH, 45 °C, 12 h; (iii) CbzCl, Na_2CO_3, 0 °C, then rt, 3 h; (iv) Grubbs II, CH_2Cl_2, reflux, 1 h; (v) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (vi) LiN_3, DMF, 130 °C, 2.5 h; (vii) Br_2, MeOH, 0 °C, 12 h; (viii) LiCl, DMF, 105 °C, 6 h; (ix) K_2CO_3, MeOH, 150 °C, μw, 10 min; (x) H_2, Pd/C, Boc_2O, THF, rt, 48 h; (xi) $LiAlH_4$, THF, reflux, 8 h; (xii) Ac_2O, HCO_2H, 55 °C, 2 h; (xiii) H_2, Pd/C, MeOH, rt, 4 h; (xiv) CO_2, MeOH, rt, 2 min.

1.3.7 Synthesis of (+)-*N*-Acetyl Norloline (+)-4 and (+)-*N*-Bus Norloline (+)-130 via Vinylogous Aldol/Mannich Reactions

Huang *et at.* have published two syntheses of the loline alkaloid scaffold, both using a similar synthetic strategy to the one used in their second-generation synthesis of (+)-absouline (+)-**6** (Scheme 8).[20] The first synthesis[44] is a total synthesis of (+)-*N*-acetyl norloline (+)-**4** and the second synthesis[45] is of (+)-*N*-Bus norloline (+)-**130**.

1.3.7.1 First Synthesis

The first syntheses by Huang *et al.* used the commercially available acetonide **110**, derived from (*R*)-glyceraldehyde. A Rassu/Casiraghi Mukayama-type aldol with pyrrole **61** and acetonide **110** gave alcohol **111** in 80% yield and >98:2 dr. Silylation of alcohol **111** to give silylether **112** proceeded in 82% yield. Treatment of acetonide **112** with HCl gave the corresponding diol, which was used without further purification, and when exposed to base underwent an intramolecular oxa-conjugate addition/cyclisation to give *cis*-fused bicycle **113** in 70% yield. Reduction of pyrrolidinone **113** with borane then protection of the free alcohol gave benzyl ether **114** in 82% yield. This was followed by desilylation of **114** followed by Swern oxidation to give ketone **115** in 85% yield. Condensation of **115** with ammonia gave the corresponding imine, which was reduced to give amine **116** and acetylated without further purification to give amino acetate **117** in 75% yield from ketone **115**. Hydrogenolysis of benzyl ether **117** gave alcohol **118** in 98% yield. Alcohol **118** was converted to (+)-*N*-acetyl norloline (+)-**4** via a one-pot reaction procedure whereby alcohol **118** was activated as mesylate **119** and immediate treated with TFA to remove the *N*-Boc group. The resultant product was immediately basified to form (+)-*N*-acetyl norloline (+)-**4** in 80% yield (from alcohol **118**), which concluded the synthesis in 15 steps and 19% yield from acetonide **110** (Scheme 13).[44] The first synthesis of (+)-*N*-acetyl norloline (+)-**4** by Huang *et al*. had a good overall yield and step count with the key stereodefining Rassu/Casiraghi Mukayama aldol proceeding in 80% yield and an excellent >98:2 dr. However, the acetate functionality was inserted early on in the synthesis which limits any opportunity for late stage functionalisation.

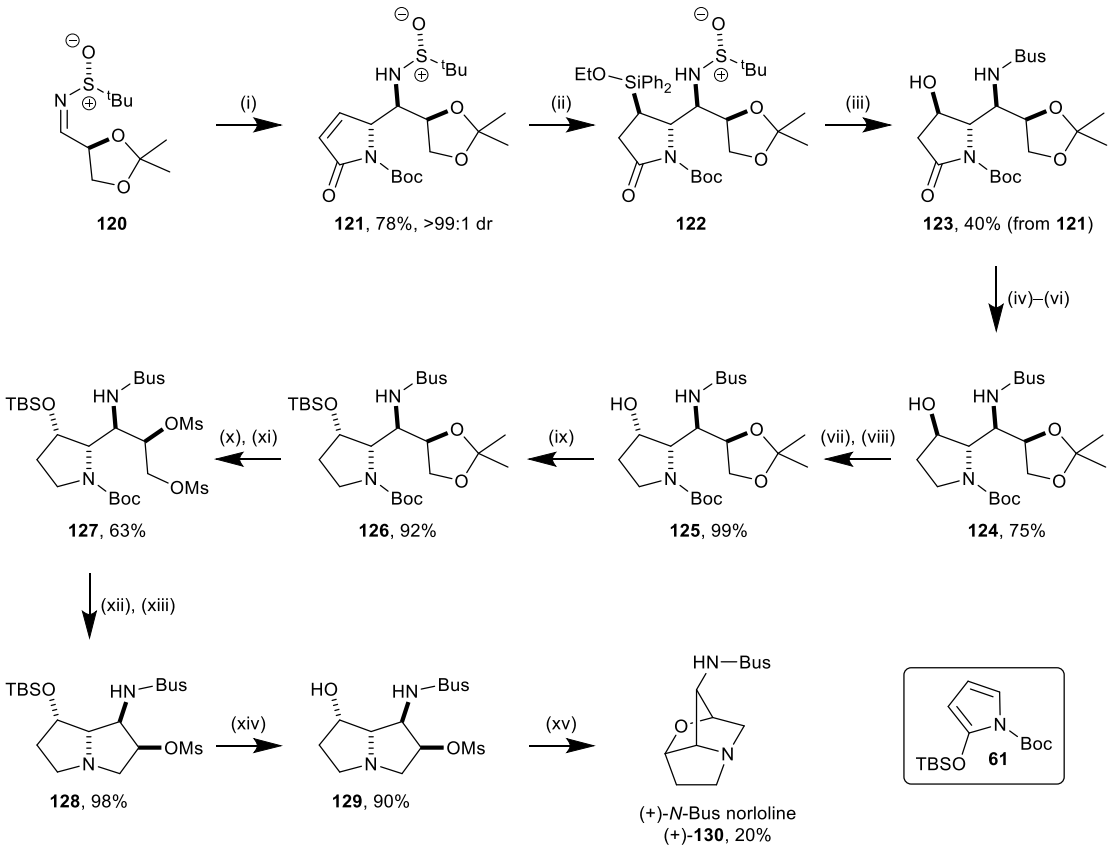


Scheme 13 *Reagents and Conditions*: (i) $SnCl_4$, Et_2O, −85 °C, 3 h;[50] (ii) TBSCl, imidazole, DMF, 5 °C, 20 h; (iii) HCl, MeOH, 0 °C, 10 min; (iv) DBU, THF, 0 °C 20 min, then rt, 6 h; (v) $BH_3{\cdot}Me_2S$, THF, 0 °C, reflux, 2 h; (vi) BnBr, NaH, TBAI, THF, 0 °C, then 40 °C, 3 h; (vii) TBAF, THF, 0 °C, 30 min, then rt, 4 h; (viii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, then 0 °C, 1 h; (ix) NH_3, $Ti(O^iPr)_4$, MeOH, rt, 10 h; (x) $NaBH_4$, MeOH, −20 °C, 30 min, then 0 °C, 2 h; (xi) Ac_2O, Et_3N, CH_2Cl_2, 0 °C, 10 min, then 38 °C, 10 h; (xii) H_2, $Pd(OH)_2/C$, MeOH, rt, 8 h; (xiii) MsCl, Et_3N, CH_2Cl_2, −20 °C; (xiv) TFA, −20 °C, 10 min, then rt, 2 h; (xv) K_2CO_3, MeCN, rt, 10 h.

1.3.7.2 Second Synthesis

The second synthesis by Huang *et al.* is very similar to the first synthesis. Acetonide **120**[51] is subjected to a $Cu(OTf)_2$ mediated Mukayama-type aldol with pyrrole **61** to give sulfinamine **121** in 78% yield and >99:1 dr. Unsaturated pyrrolidone **121** was subjected to a Et_2Zn mediated 1,4-addition to give silane **122** and then immediately subjected to a Fleming-Tamao oxidation, which also oxidised the sulfinyl group to the corresponding *N*-Bus-protected amine **123** in 40% yield.[52] Reduction of pyrrolidone **123** proceeded in a three three-step silylation, borane reduction and desilylation sequence to give pyrrolidine **124** in 75% yield over the three steps. The alcohol installed by the Fleming-Tamao oxidation was not the stereochemistry desired and

was epimerised by a Ley oxidation and stereoselective reduction with $NaBH_4$ to give epimer **125** in 99% yield, which was subsequently silylated to give silyl ether **126**. Acetonide cleavage with $FeCl_3 \cdot 6H_2O$ was followed by mesylation and gave bis-mesylate **127** in 63% yield. Treatment of bismesylate **127** with TFA, followed by basification gave pyrrolizidine **128** in 98% yield. Desilylation of pyrrolizidine **128** gave alcohol **129** in 90%, which upon refluxing in dichlorobenzene, gave (+)-*N*-Bus norloline (+)-**130** in 20% yield (from alcohol **129**), which concluded the synthesis in 16 steps and 1.5% yield from acetonide **110** (Scheme 14).[45] The step count and overall yield of the second synthesis by Huang *et al.* is significantly worse than the first synthesis. Their final product is (+)-*N*-Bus norloline (+)-**130**, a non-natural loline alkaloid, from which it was not possible to remove the *N*-Bus protecting group. The increased step count is due to the protecting group manipulation and redox chemistry needed to rectify the incorrect stereochemistry obtained from the Fleming-Tamao oxidation.



Scheme 14 *Reagents and Conditions*: (i) $Cu(OTf)_2$, CH_2Cl_2, −78 °C, 45 min, then **61**, CH_2Cl_2, −78 °C, 8 h; (ii) Et_2Zn, $(Et_2N)Ph_2SiLi$, THF, −78 °C, 10 min, then **121**, THF, −78 °C, 3 h; (iii) KHF_2, *m*-CPBA, DMF, 0 °C, 2 h; (iv) TBSOTf, imidazole, CH_2Cl_2, 0 °C to rt, 10 h; (v) $BH_3{\cdot}Me_2S$, THF, 0 °C, then reflux, 6 h; (vi) TBAF, THF, 0 °C, 30 min, then rt, 3 h; (vii) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 0 °C, 10 min, then rt, 3 h; (viii) $NaBH_4$, MeOH, 0 °C, 2 h; (ix) TBSOTf, 2,6-lutidine, −35 °C, 10 h; (x) $FeCl_3{\cdot}6H_2O$, CH_2Cl_2, rt, 20 min; (xi) MsCl, pyridine, CH_2Cl_2, 0 °C to rt, 16 h; (xii) TFA, CH_2Cl_2, 0 °C to rt, 3 h; (xiii) K_2CO_3, MeCN, rt, 10 h; (xiv) HF·pyridine, THF, 0 °C, 5 min, then 60 °C, 48 h; (xv) *o*-$Cl_2C_6H_4$, 180 °C, 22 h.

1.4 Thesis Aim

The overall aim of this thesis is to synthesise the tricyclic scaffold **135**, as an advanced intermediate, which could then be transformed into the loline alkaloids: (+)-norloline (+)-**2**, (+)-loline (+)-**1**, (+)-*N*-acetyl loline (+)-**3** and (+)-*N*-acetyl norloline (+)-**3**. (2*R*,3*S*)-*cis*-3-Hydroxyproline **131** (or a suitably protected derivative) would be the starting point for the synthesis of the loline alkaloid scaffold, which would be elaborated to α,β-unsaturated ester **132**, which would then be subjected to a lithium amide conjugate addition and enolate oxidation to give α-hydroxy-β-amino ester **133**. Intramolecular cyclisation of the pyrrolidine nitrogen onto the ester would give pyrrolizidine **134**. Williamson etherification would then give tricyclic

scaffold **135**, and elaboration to the loline alkaloids **1**–**4** could be achieved (Figure 4). The first section of work in this thesis will be to develop an efficient and scalable syntheses of (2*R*,3*S*)-*cis*-3-hydroxyproline **131**, which will enable the synthesis of the loline alkaloids to be investigated.

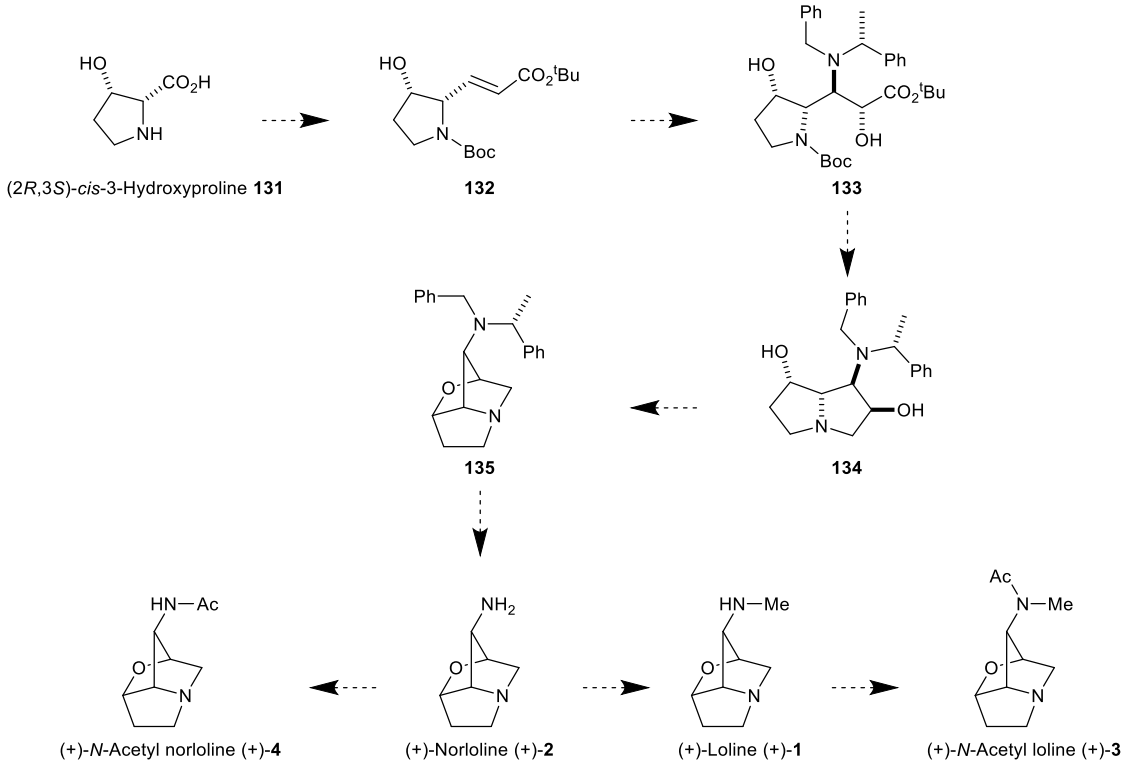


Figure 4 Thesis aim.

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Chapter 2

2 Synthesis of (2*R*,3*S*)-*cis*-3-Hydroxyproline and (2*S*,3*S*)-*trans*-3-Hydroxyproline

2.1 Chapter Outline

This chapter describes the development of two complementary syntheses towards (2*R*,3*S*)-*cis*-3-hydroxyproline **131** and (2*S*,3*S*)-*trans*-3-hydroxyproline **136** utilizing either an inter- or an intra- molecular aziridinium ring-opening reaction, with oxygen nucleophiles, as the key step in both syntheses (Figure 5). This route will be employed in the synthesis of the loline alkaloids.



(2*R*,3*S*)-*cis*-3-Hydroxyproline **131** (2*S*,3*S*)-*trans*-3-Hydroxyproline **136**

Figure 5 Structures of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** and (2*S*,3*S*)-*trans*-3-hydroxyproline **136**.

2.2 3-Hydroxyproline

2.2.1 Isolation

In the early 1960's 3-hydroxyproline was isolated from a variety of natural sources. In early 1961, Ogle *et al.* reported the hydrolysis of bovine collagen by exoenzyme *Clostridium histolticum*. From this, they isolated a peptide, which after further acid hydrolysis and concentration to dryness, gave a number of amino acids, one of which novel.[1] In 1962 after further investigations Ogle *et al.* reported this unknown amino acid to be tentatively assigned as 3-hydroxyproline. A non-selective synthesis of racemic 3-hydroxyproline gave a mixture of all four possible stereoisomers which provided a synthetic sample which was determined to be identical to the natural compound upon analysis by analytical ion exchange chromatography.[2]

Later in 1962, Irreverre *et al*. also isolated 3-hydroxyproline from the hydrolysates of collagen,[3] as well as from the acid hydrolysate of dried Mediterranean sponge.[3] The key step in the separation of cyclic amino acids from primary amino acids was either nitrosation and hydrolysis or treatment of the hydrolysates with 2,4,6-trinitrobenzenesulfonic acid followed by ion exchange chromatography; this yielded both *cis*- and *trans*-3-hydroxyproline.[3,4] Irreverre *et al*. confirmed these structures by synthesising a sample of racemic *cis*-3-hydroxyproline and upon comparison with the natural sample this proved to be inseparable from the synthetic sample by paper chromatography.[4]

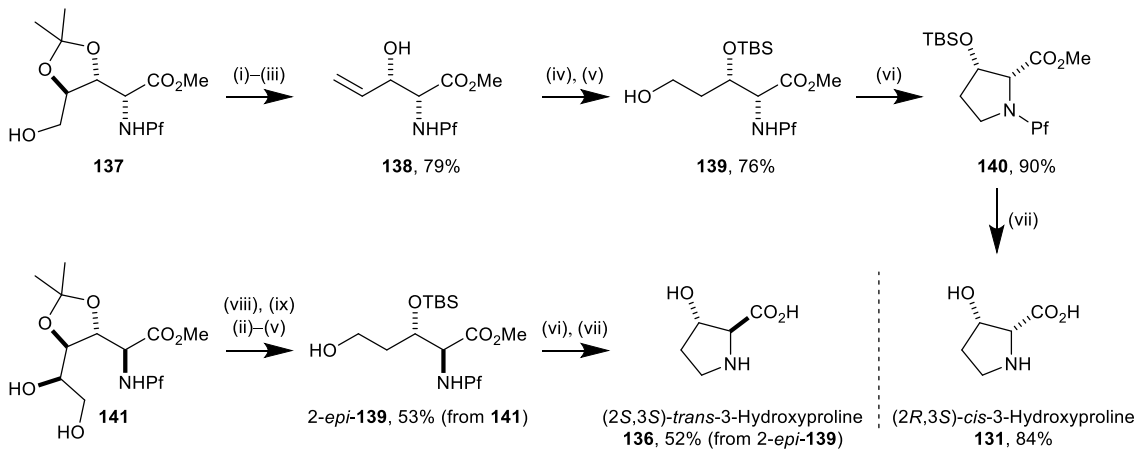
From the acid hydrolysate of the antibiotic telomycin, Irreverre *et al.* later reported 1 g of telomycin yielded 31 mg of (2*S*,*3S*)-*trans*-3-hydroxyproline **136**[5,6] and 33 mg of *cis*-3-hydroxyproline {$[\alpha]_D^{20}$ −91.5 (*c* 1.0 in H_2O)}.[7] The specific rotation of this isolated sample of **136** proved to be identical to a sample Irreverre *et al.* synthesised in the same study as their isolation of (2*S*,*3S*)-*trans*-3-hydroxyproline **136**[6] from a Mediterranean sponge.[3,4] Apparently unaware of the recent work by Irreverre *et al.*, a second isolation of (2*S*,3*R*)-*cis*- and (2*S*,*3S*)-*trans*-3-hydroxyproline *ent*-**131** and *ent*-**136**[8–10] from the hydrolysis of telomycin was reported by Sheehan *et al.* in late 1962. Sheehan *et al.* synthesised racemic samples of *cis*- and *trans*-3-hydroxyproline from which (2*S*,3*R*)-*cis*-hydroxyproline *ent*-**131**[9] {$[\alpha]_D^{20}$ −90.3 (*c* 1.0 in H_2O} and (2*S*,*3S*)-*trans*-3-hydroxyproline **136**[8] {$[\alpha]_D^{20}$ −22.8 (*c* 1.0 in H_2O} were obtained by successive recrystallizations.[10,11]

2.2.2 Synthesis

There has been significant interest in the synthesis of 3-hydroxyprolines. The vast majority of syntheses of 3-hydroxyproline have exploited chiral pool starting materials (sugars, amino acids etc.).[12–24] There has also been a smaller number of *de novo* asymmetric syntheses[25,26] as well as enzymatic syntheses.[10,27–30] Several of these syntheses will be described and discussed below.

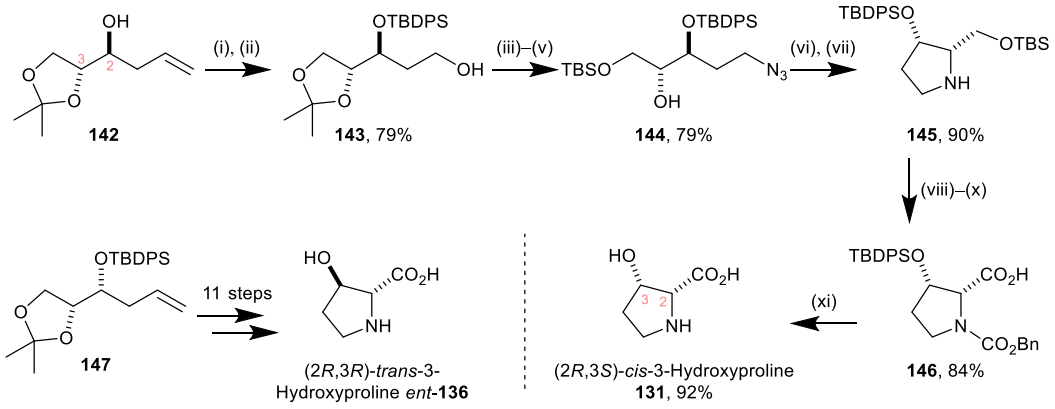
2.2.2.1 Chiral Pool Syntheses

Park *et al.* reported the synthesis of both (2*R*,3*S*)-*cis*- and (2*S*,3*S*)-*trans*-3-hydroxyproline **131** and **136** from two different sugar derivatives with the stereocenters needed in (2*R*,3*S*)-*cis*- and (2*S*,3*S*)-*trans*-3-hydroxyproline **131** and **136** being already present.[23] The synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** started with ester **137**, which can be synthesised from L-gluconic acid γ-lactone in 6 steps and 64% yield.[31] Alcohol **137** was converted to the corresponding alkene **138** via mesylation, displacement with LiI and treatment with ^{n}BuLi in 79% yield over three steps. Protection of alcohol **138** followed by hydroboration gave alcohol **139**, which upon mesylation, spontaneously cyclised to give pyrrolidine **140** in 90% yield. Deprotection of pyrrolidine **140** gave (2*R*,3*S*)-*cis*-3-hydroxyproline **131** in 84% yield, concluding the synthesis in a total yield of 29% over 13 steps from L-gluconic acid γ-lactone.[23] (2*S*,3*S*)-*trans*-3-Hydroxyproline **136** was synthesised from diol **141**, which was synthesised from D-glucono-δ-lactone in 5 steps and 53% yield.[32–34] Diol **141** was converted to alcohol 2-*epi*-**139**, via a similar sequence of reactions to the (2*R*,3*S*)-*cis*-3-hydroxyproline **131** synthesis to give alcohol 2-*epi*-**139** in 52% yield over 6 steps. Activation, cyclisation and deprotection gave (2*R*,3*R*)-*trans*-3-hydroxyproline **136** in 52% yield from 2-*epi*-**139**, which concluded the synthesis in 12 steps and 15% overall yield from D-glucono-δ-lactone (Scheme 15).[23]



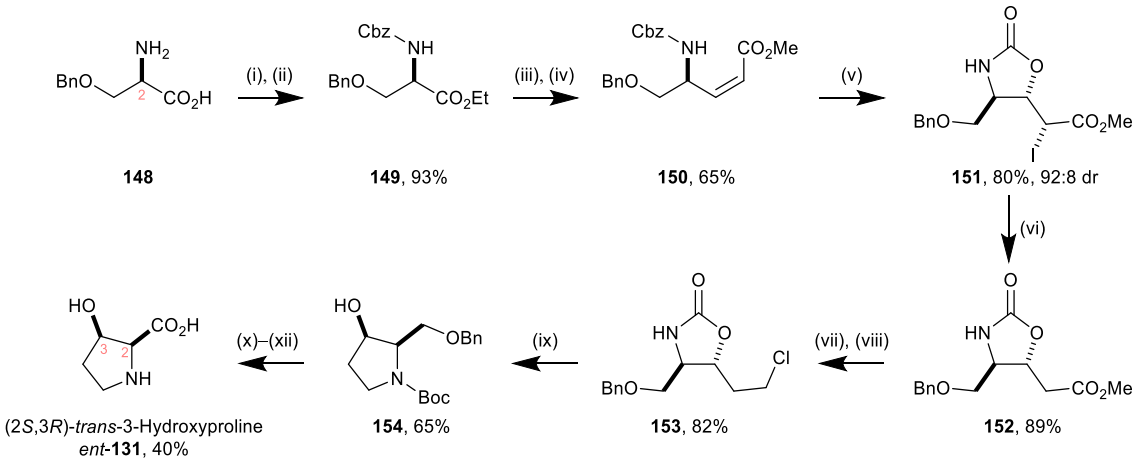
Scheme 15 *Reagents and conditions*: (i) MsCl, Et_3N, THF, 0 °C to rt, 15 min; (ii) LiI, DMF, 80 °C, 16 h; (iii) ^{n}BuLi, THF, –40 °C, 50 min; (iv) TBSCl, imidazole, DMF, rt, 12 h; (v) BH_3·DMS, THF, 0 °C, 10 h, then NaOH, H_2O_2; (vi) MsCl, Et_3N, 0 °C, 3 h; (vii) H_2 (1 atm), Pd/C, MeOH, 60 °C, 3 h, then Dowex® 50WX8, THF/H_2O (2:1), reflux, 16 h; (viii) $NaIO_4$, EtOH/H_2O (2:1), rt, 3 h, then $NaBH_4$, 0 °C, 10 min; (ix) MsCl, Et_3N, THF, 0 °C to rt, 20 min.

Luger *et al*. reported the synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** from alcohol **142**, which was obtained in three steps and 29% yield from D-mannitol.[35,36] The C(3) stereocentre in (2*R*,3*S*)-*cis*-3-hydroxyproline **131** was present in alcohol **142** and the C(2) stereochemistry in (2*R*,3*S*)-*cis*-3-hydroxyproline **131** was present but needed chemical manipulation. Protection of alcohol **142** followed by ozonolysis of the olefin and reduction with $NaBH_4$ gave alcohol **143** in 79% yield. Activation of alcohol within **143** and displacement of the corresponding mesylate with sodium azide followed by acetonide cleavage and re-protection of the primary alcohol gave azide **144** in 79% over three steps from **143**. Activation of the secondary alcohol within **143** then reduction of the azide resulted in cyclisation to give pyrrolidine **145** in 90% yield over two steps. Protecting group manipulation followed by oxidation of the resulting alcohol gave acid **146** in 84% yield, which after deprotection gave (2*R*,3*S*)-*cis*-3-hydroxyproline **131** in 92% from acid **146**, which concluded the synthesis in 14 steps and 12% overall yield from D-mannitol. They also reported (2*R*,3*R*)-*trans*-3-hydroxyproline *ent*-**136** could be synthesised from alkene **147** in 11 steps, however did not provide a yield or experimental procedures for this (Scheme 16).[21]



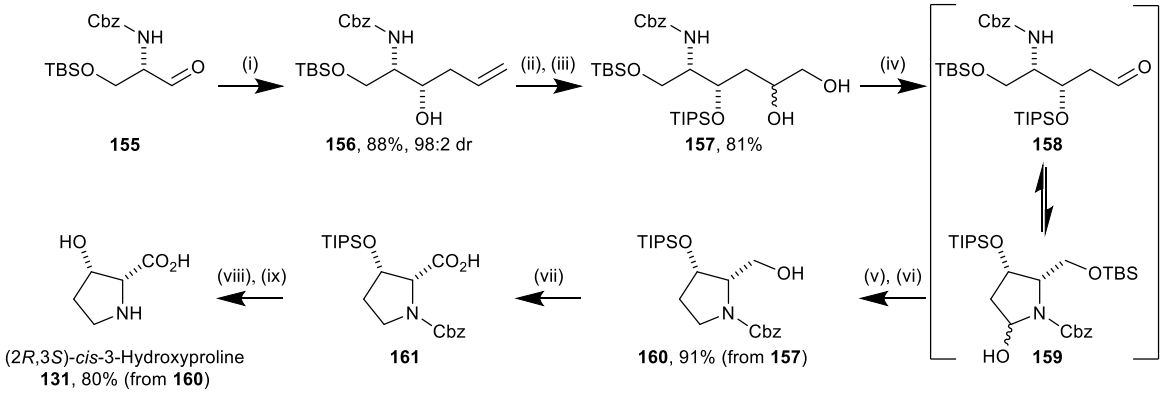
Scheme 16 *Reagents and conditions*: (i) TBDPSCl, imidazole, DMAP, DMF, rt, 24 h; (ii) O_3, MeOH, –78 °C, then $NaBH_4$, rt; (iii) MsCl, pyridine, 0 °C, 9 h, then NaN_3, DMF, 65 °C, 12 h; (iv) HOAc/H_2O (6:1), rt, 24 h; (v) TBDMSCl, DMAP, THF, 0 °C to rt, 23 h; (vi) MsCl, pyridine, 0 °C, 9 h; (vii) PPh_3, THF, rt, 7 h, then 1 M NaOH, reflux 36 h; (viii) $BnCO_2Cl$, K_2CO_3, THF/H_2O (3:1), 0 °C, 2 h; (ix) AcOH/H_2O (15:1), rt, 36 h; (x) CrO_3/H_2SO_4, acetone, 0 °C; (xi) TFA, CH_2Cl_2, reflux, 48 h.

Monache *et al*. reported the synthesis of (2*S*,3*R*)-*cis*-3-hydroxyproline *ent*-**131** starting from commercially available *O*-benzyl-D-serine **148**.[16,19] The C(2) stereocenter in (2*S*,3*R*)-*cis*-3-hydroxyproline *ent*-**131** was present in *O*-benzyl-D-serine **148**, this stereocenter was used to induce the correct configuration upon formation of the the remaining stereocenter later in the synthesis of (2*S*,3*R*)-*cis*-3-hydroxyproline *ent*-**131**. Protecting group manipulation of *O*-benzyl-D-serine **148** gave ester **149**, which after reduction to the corresponding aldehyde was immediately converted to *cis*-α,β-unsaturated ester **150** in a 65% yield via a modified Still-Gennari procedure.[37] Iodolactonisation of *cis*-α,β-unsaturated ester **150** gave oxazolidinone **151** in a 92:8 dr and an 80% yield which was dehalogenated to give ester **152** in 89% yield as a single diastereomer. Reduction of oxazolidinone **152** followed by an Appel reaction gave chloride **153** in 82% yield, which upon stirring in NaOH gave pyrrolidine **154** in 65% yield. Hydrogenolysis, oxidation and deprotection gave (2*S*,3*R*)-*cis*-3-hydroxyproline *ent*-**131** in 40% yield over three steps, concluding the synthesis in 9.2% yield and 12 steps from *O*-benzyl-D-serine **148** (Scheme 17). This synthesis was also modified to synthesise the *C*(3) epimer (2*S*,3*S*)-*trans*-3-hydroxyproline **136** by a modified Mitsunobu reaction on pyrrolidine **154**; yields were not reported, except, for its conversion to (2*S*,3*S*)-*trans*-3-hydroxyproline **136**.[16,19]



Scheme 17 *Reagents and conditions*: (i) Cbz_2O, NaOH, dioxane, rt, 1 h; (ii) *N*-methylmorpholine, $ClCO_2Et$, DMAP, CH_2Cl_2, 0 °C, 30 min; (iii) DIBAL-H, PhMe, –78 °C, 2 h; (iv) KHMDS, 18-crown-6, $(2,2,2\text{-trifluoroethyl})_2$(methoxycarbonylmethyl)phosphonate, THF, –65 °C, 15 min, then –78 °C, 1 h; (v) $NaHCO_3$, AgOTf, MeCN, I_2, rt, 2 h; (vi) AIBN, Bu_3SnH, C_6H_6, reflux, 4 h; (vii) $NaBH_4$, THF, –10 °C, 30 min; (viii) K_2CO_3, PPh_3, CCl_4, CH_2Cl_2, 50 °C, 16 h; (ix) NaOH, $MeOH/H_2O$, 80 °C, 16 h, then Boc_2O, Et_3N, THF, rt, 16 h; (x) TBDMSCl, imidazole, DMF, rt, 24 h; (xi) Pd/C, H_2 (1 atm), EtOAc, rt, 16 h; (xii) TEMPO, NaBr, PhMe, EtOAc, H_2O, 0 °C, then NaOCl, $NaHCO_3$, 40 min, 0 °C, then 5% NaH_2PO_4, $KMnO_4$, ^{t}BuOH, 0 °C, 30 min, then HCl, MeOH, rt, 2 h.

Jurczak *et al.* reported another synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** from serine derived aldehyde **155**, which can be synthesised from methyl-L-serine hydrochloride in 4 steps and 85% yield.[38,39] Alkene **156** was synthesised by the addition of allyltrimethylsilane in the presence of $SnCl_4$ in 88% yield and 98:2 dr. Silylation of alcohol **156** followed by hydroxylation with OsO_4 gave diol **157** in 81% yield. Oxidative cleavage of diol **157** afforded aldehyde **158** that exists as the cyclic aminal form **159**, reduction with sodium cyanoborohydride gave pyrrolidine **160** in 91% yield over three steps from diol **157**. Oxidation of alcohol **160** with $NaIO_4$ in the presence of $RuCl_3$ gave acid **161**, which was used without purification to give (2*R*,3*S*)-*cis*-3-hydroxyproline **131** after deprotection in 80% yield from **160**, which concluded the synthesis in 15 steps and 44% overall yield from methyl-L-serine hydrochloride (Scheme 18).[24]

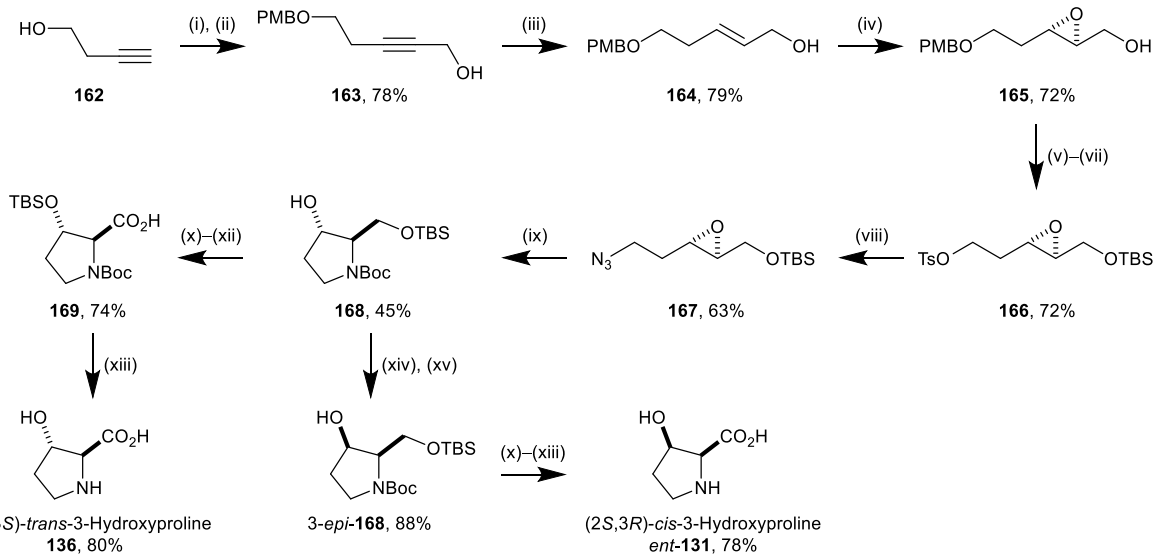


Scheme 18 *Reagents and conditions*: (i) $SnCl_4$, allyltrimethylsilane, CH_2Cl_2, –78 °C, 1.5 h; (ii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 18 h; (iii) OsO_4, NMO, acetone/water (50:7), rt, 16 h; (iv) Silica, $NaIO_4$, CH_2Cl_2, rt, 16 h; (v) $NaBH_3CN$, AcOH/MeOH (1:1), 30 °C; (vi) AcOH/MeOH (1:3), reflux, 1 h; (vii) $NaIO_4$, $RuCl_3$, CCl_4/MeCN/H_2O (2:2:3), rt, 16 h; (viii) HF, silica, MeCN, 60 °C, 50 min; (ix) H_2 (1 atm), Pd/C, MeOH, rt, 18 h.

2.2.2.2 De Novo Asymmetric Syntheses

Chandrasekhar *et al*. reported an asymmetric synthesis utilizing a Sharpless asymmetric epoxidation comprising of a late stage divergent strategy allowing for the synthesis of all four stereoisomers of 3-hydroxyproline. Following protection of commercially available 3-butyn-1-ol **162**, homologation to alcohol **163** was achieved in 78% yield. Reduction of alkyne **163** gave allylic alcohol **164**, which was subjected to a Sharpless asymmetric epoxidation to give epoxide **165** in 72% yield.[40] Protecting group manipulation followed by displacement of the intermediate tosylate with NaN_3 gave azide **167**. Reduction of azide **167** to the corresponding amine followed by *in situ* cyclisation to give pyrrolidine **168** in 45% yield. Oxidation to acid **169**, followed by removal of the protecting groups under acidic conditions gave (2*S*,3*S*)-*trans*-3-hydroxyproline **136** in 80% yield from acid **169**, which concluded the synthesis in 5.4% overall yield and 13 steps from 3-butyn-1-ol **162**. When alcohol **168** was subjected to Mitsunobu conditions with *para*-nitrobenzoic acid substitution occurred to give the epimeric alcohol 3-*epi*-**168** in 88% yield after methanolysis of the *para*-nitrobenzoic ester. The epimeric alcohol 3-*epi*-**168** was then subjected to the same conditions as the (2*S*,3*S*)-*cis*-3-hydroxyproline **136** synthesis to give (2*S*,3*R*)-*trans*-3-hydroxyproline *ent*-**131** in 78% yield

from alcohol 3-*epi*-**168**, which concluded the synthess in 6.2% overall yield over 14 steps from 3-butyn-1-ol **162** (Scheme 19). Chandrasekhar *et al.* also report that by using D-(−)-DET in the Sharpless asymmetric oxidation it is possible to synthesise the remaining two stereoisomers (2*R*,3*R*)-*trans*- and (2*R*,3*S*)-*cis*-3-hydroxyproline, however they only reported yields for the final deprotection steps.[25]



Scheme 19 *Reagents and conditions*: (i) NaH, PMBBr, THF, 0 °C, then rt, 12 h; (ii) EtMgBr, $(CH_2O)n$, THF, rt; (iii) $LiAlH_4$, THF, 0°C, 2 h; (iv) L-(+)-DET, $Ti(O^iPr_4)$, CH_2Cl_2, TBHP, –20 °C, 16 h; (v) TBSCl, imidazole, CH_2Cl_2, rt, 3 h; (vi) DDQ, CH_2Cl_2/H_2O (8:2), 3 h, 0 °C; (vii) TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 4 h; (viii) NaN_3, DMF, 80 °C; (ix) Pd/C, H_2, MeOH, rt, 24 h, then Boc_2O, NaOH, CH_2Cl_2, rt, 3 h; (x) TBSCl, imidazole, CH_2Cl_2, rt, 4 h; (xi) HF·py, THF, rt, 4 h; (xii) TEMPO, $PhI(OAc)_2$, $MeCN/H_2O$ (1:1), rt, 6 h; (xiii) 6 M HCl, EtOH, reflux, 3 h; (xiv) PPh_3, 4-nitrobenzoic acid, DEAD, THF, rt, 6 h; (xv) K_2CO_3, MeOH, 0 °C, 1 h.

2.3 Chapter Aim

The aim of this chapter is to develop an efficient and scalable asymmetric synthesis of 3-hydroxyproline for the elaboration to loline. This synthesis would ideally also enable all four stereoisomers of 3-hydroxyproline to be synthesised from a common intermediate.

2.4 (2*R*,3*S*)-*cis*-3-Hydroxyproline 131: First-Generation Synthesis

Retrosynthetic analysis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** identified α,β-unsaturated ester **170** as the starting point of the synthesis. Lithium amide conjugate addition to α,β-unsaturated

ester **170**, followed by stereoselective epimerisation of **171** at the C(2) position, would give *syn*-α-hydroxy-β-amino ester **172**.[41] *syn*-α-Hydroxy-β-amino ester **172**, would be subjected to conditions recently developed by Davies *et al.* to give the corresponding *syn*-β-hydroxy-α-amino ester **173** (i.e. formal transposition of the hydroxy and amino functionalities).[41–44] Deprotection of ester **173**, then activation and cyclisation would give protected (2*R*,3*S*)-*cis*-3-hydroxyproline **175**, which after the final deprotection would give (2*R*,3*S*)-*cis*-3-hydroxyproline **131** (Figure 6).

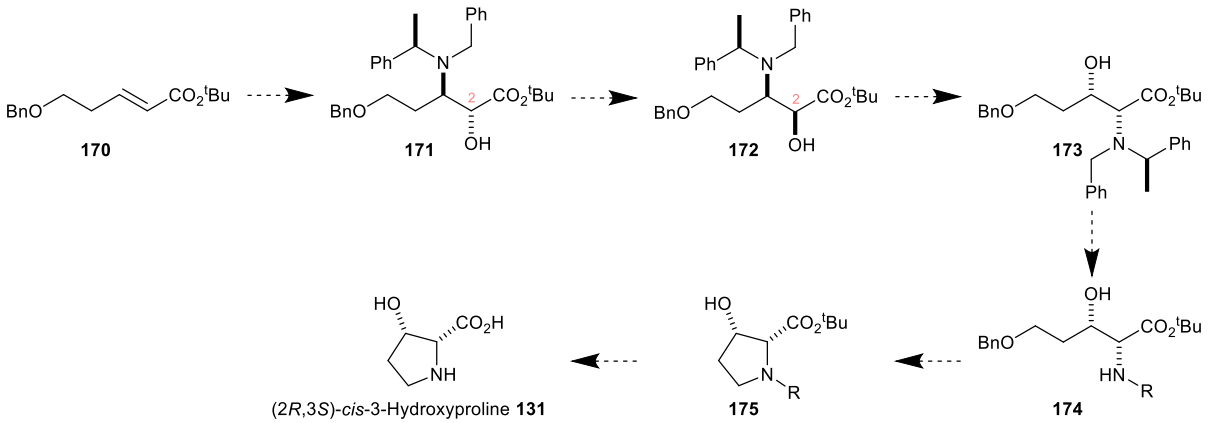
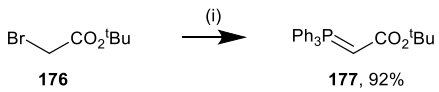


Figure 6 Proposed synthesis towards (2*R*,3*S*)-*cis*-3-hydroxyproline **131**.

2.4.1 Substrate Preparation

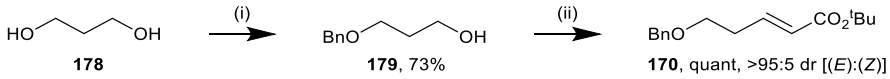
Consequently a multi-gram synthesis of α,β-unsaturated ester **170** was developed. Ylid **177** was prepared by stirring triphenylphosphine and *tert*-butyl bromoacetate **176**, followed by basifying the corresponding salt to give ylid **177** in 92% yield (Scheme 20).[45]



Scheme 20 *Reagents and conditions*: (i) PPh_3, EtOAc, rt, 16 h.

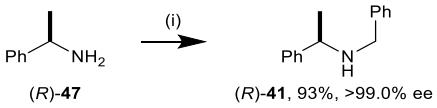
α,β-Unsaturated ester **170** was prepared by mono-protection of 1,3-propane diol **178**, to form the corresponding benzyl ether **179**, followed by oxidation of **179** to the corresponding aldehyde and an *in situ* Wittig olefination to give α,β-unsaturated ester **170** in 73% yield (from

1,3-propane diol **178**) and >95:5 dr of (*E*) and (*Z*) double bond isomers. Assignment of the double bond geometry was based on diagnostic values of the ^{1}H NMR ^{3}J coupling constants between the C(2)*H* and C(3)*H* protons:$^{3}J_{trans}$ = 15.6 Hz and $^{3}J_{cis}$ = 11.6 Hz (Scheme 21).



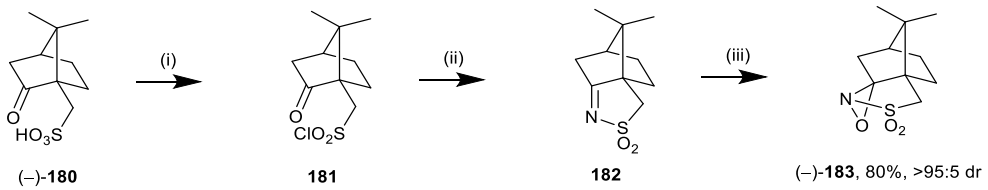
Scheme 21 *Reagents and conditions*: (i) NaH, THF, 0 °C, 45 min, then TBAI, BnBr, rt, 16 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then **179**, CH_2Cl_2, –78 °C, 30 min, then Et_3N, –78 °C to rt, 1 h, then **177**, rt, 16 h.

Secondary amine (*R*)-**41** was prepared by formation of the corresponding imine with enantiopure amine (*R*)-**47** (>99.0% ee) and benzaldehyde followed by reduction with $NaBH_4$ which gave secondary amine (*R*)-**41** in 93% yield and >99.0% ee.[46] (*R*)-**41** was determined to be of >99% ee by a ^{1}H NMR chiral shift experiment with (*S*)-*O*-acetylmandelic acid and comparison with a racemic sample (Scheme 22).



Scheme 22 *Reagents and conditions*: (i) Benzaldehyde, EtOH, reflux then $NaBH_4$, 0 °C to rt, 48 h.

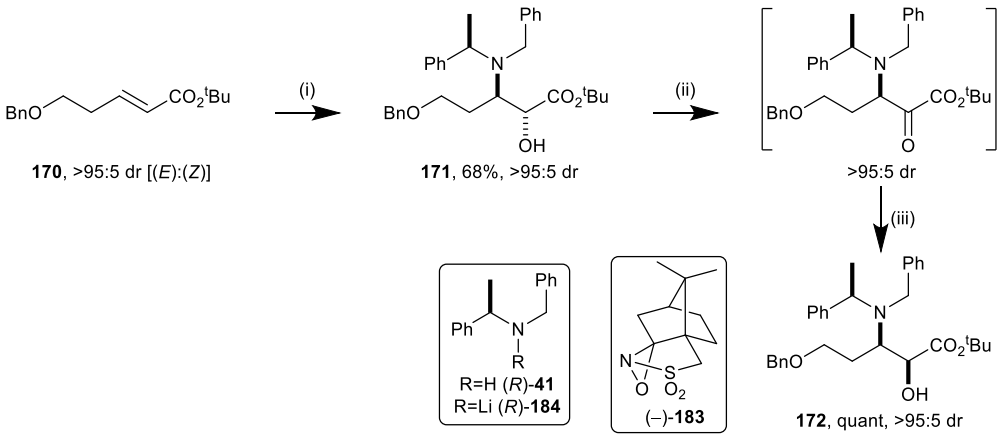
(–)-CSO (−)-**183** was prepared from (–)-camphorsulfonic acid (−)-**180** by sequential conversion to the corresponding sulfonyl chloride **181**, imine formation, dehydration and oxidation of the resulting imine **182** with peracetic acid to give oxaziridine (−)-**183** in 80% yield from (−)-**180** and >95:5 dr (Scheme 23).[47]



Scheme 23 *Reagents and conditions*: (i) $SOCl_2$, $CHCl_3$, reflux, 12 h; (ii) $NH_{3(aq)}$, $CHCl_3$, 4 h, 0 °C then Amberlyst®15, PhMe, reflux 12 h; (iii) Aliquat 336, K_2CO_3, peracetic acid, CH_2Cl_2, 5 °C to rt, 8 h.

Lithium amide reagent (*R*)-**184** was prepared upon treatment of amine (*R*)-**41** with ^{n}BuLi at –78 °C. Conjugate addition of lithium amide **184** to α,β-unsaturated ester **170**, followed by *in*

situ oxidation of the resultant enolate with (–)-CSO (−)-**183** gave α-hydroxy-β-amino ester **171** in 68% yield and >95:5 dr. The (2*R*,3*R*,α*R*)-configuration of **171** was assigned by analogy to the well-established stereochemical outcome of this aminohydroxylation protocol.[48–50] Oxidation of *anti*-α-hydroxy-β-amino ester **171** under Swern conditions resulted in complete conversion to the corresponding ketone and diastereoselective reduction of the ketone yielded *syn*-α-hydroxy-β-amino ester **172** in quantitative yield as a single diastereomer (>95:5 dr). The configuration of *syn*-α-hydroxy-β-amino ester **172** was known to be different to that of the starting material *anti*-α-hydroxy-β-amino ester **171** as the two samples produced different ^{1}H and ^{13}C NMR spectra and so the 2,3-*syn*-relative configuration within **172** was confidently assigned. This stereochemical assignment is in agreement with previous observations concerning application of this sequential oxidation/reduction protocol as well as being consistent with the Felkin-Ahn model (Scheme 24).[41]

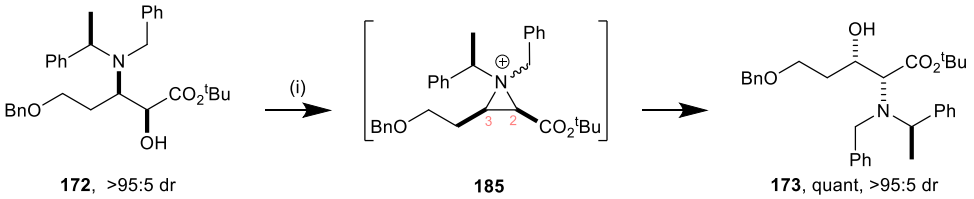


Scheme 24 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **170**, THF, –78 °C 2 h, then (−)-**183**, –78 °C to rt, 12 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then **171**, CH_2Cl_2, –78 °C, 30 min, then Et_3N, –78 °C to rt, 1 h; (iii) $NaBH_4$, MeOH, –20 °C, 2 h.

2.4.2 Hydroxy and Amino Transposition

Treatment of *syn*-α-hydroxy-β-amino ester **172** with Tf_2O and DTBMP followed by addition of water gave β-hydroxy-α-amino ester **173** in quantitative yield as a single diastereomer (>95:5 dr). The stereochemistry of β-hydroxy-α-amino ester **173** was unambiguously assigned

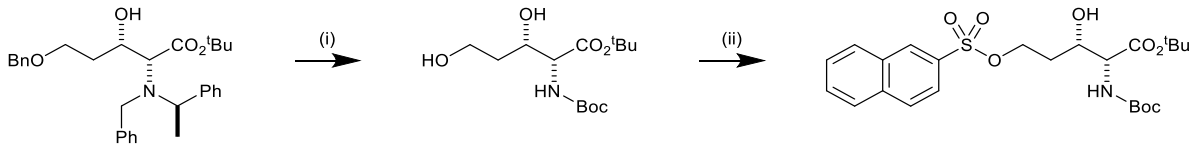
by conversion to (2*R*,3*S*)-*cis*-3-hydroxyproline **131** (*vide infra*). This stereochemical outcome is consistent with a mechanism whereby the alcohol in *syn*-α-hydroxy-β-amino ester **172** is activated as the corresponding triflate and then displacement of the triflate by the β-amino group forms aziridinium ion **185** with inversion of stereochemistry. Upon the addition of water, hydrolysis occurs via a S_N2 reaction with complete regioselectivity for attack at the C(3) position to give *syn*-β-hydroxy-α-amino ester **173** (Scheme 25). This regioselectivity is consistent with previously reported *syn*-β-hydroxy-α-amino ester examples.[41,43]



172, >95:5 dr **185** **173**, quant, >95:5 dr

Scheme 25 *Reagents and conditions*: (i) Tf_2O, DTBMP, CH_2Cl_2, 0 °C to rt, 6 h, then H_2O, rt, 24 h.

Subjecting β-hydroxy-α-amino ester **173** to hydrogenolysis at 5 atm in the presence of Boc_2O yielded diol **186** in 89% yield and >95:5 dr. Activation of diol **186** as the corresponding 2-naphthyl sulfonate proceeded selectively for the primary alcohol to give 2-naphthyl sulfonate **187** in 89% yield and >95:5 dr. The 2-naphthylsulfonyl derivative was chosen over the corresponding tosyl derivative as the additional steric bulk has been previously shown to aid in the regioselectivity of sulfonylation (Scheme 26).[51]

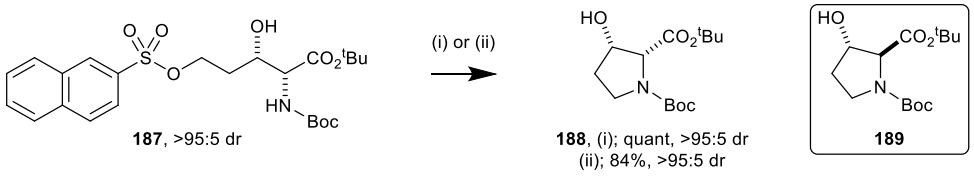


173, >95:5 dr **186**, 89%, >95:5 dr **187**, 89%, >95:5 dr

Scheme 26 *Reagents and conditions*: (i) $Pd(OH)_2/C$, Boc_2O, MeOH, H_2 (5 atm), rt, 65 h; (ii) 2-Nap-SO_2Cl, pyridine, 0 °C, 1 h.

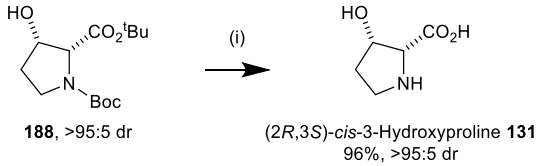
2.4.3 Elaboration to (2*R*,3*S*)-*cis*-3-Hydroxyproline 131

Displacement of 2-naphthyl sulfonate **187** to form the corresponding pyrrolidine **188** was initially achieved by addition of **187** to a stirred suspension of NaH in THF, which yielded pyrrolidine **188** in quantitative yield $\{[\alpha]_D^{25}$ +28.8 (c 1.0 in $CHCl_3)\}$. When this was increased in scale (>500 mg of **187**), the quantitative yield was not reproducible and extended reaction times became necessary in some cases. The C(2) epimer **189** $\{[\alpha]_D^{25}$ −16.7 (c 1.0 in $CHCl_3)\}$ was also isolated in significant yields when the reaction was left for 18 hours (*vide infra*).[52] It is suspected the inherent solubility issues associated with NaH, were a cause of this irreproducibility when repeated on larger scales. A potential mechanism for formation of the C(2) epimer **189** is that deprotonation occurs at the C(2) position followed by re-protonation, which is consistent with the C(2) epimer **189** being non-racemic. Therefore, ^{n}BuLi was used as an alternative base to NaH, this proceeded to give proline **188** in 84% yield and >95:5 dr with no evidence of the C(2)-epimer **189** being formed; even when conducted on a large scale (>10 g of **187**) (Scheme 27).



Scheme 27 *Reagents and conditions*: (i) NaH, THF, 15 min, then **187**, rt, 15 min; (ii) ^{n}BuLi, THF, –78 °C to rt, 2.5 h.

Hydrolysis of *N*-Boc protected amino ester **188** in 6.0 M HCl, followed by purification on Dowex® 50WX8 ion exchange resin yielded (2*R*,3*S*)-*cis*-3-hydroxyproline **131** in 96% yield and >95:5 dr (Scheme 28).

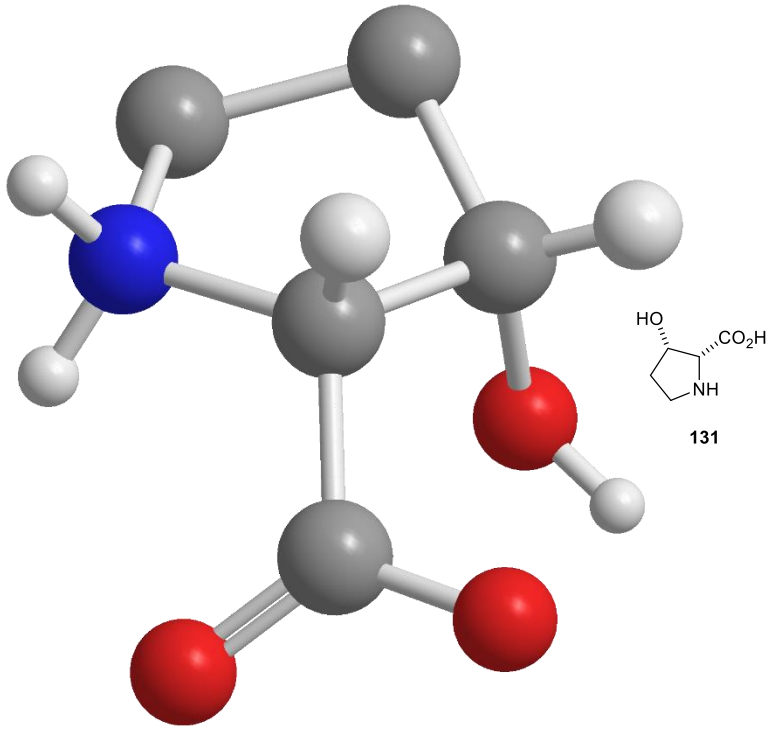


188, >95:5 dr

(2*R*,3*S*)-*cis*-3-Hydroxyproline **131**
96%, >95:5 dr

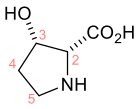
Scheme 28 *Reagents and conditions*: (i) 6.0 M $_{(aq)}$ HCl, rt, 16 h, then Dowex® 50WX8.

The relative configuration within (2*R*,3*S*)-*cis*-3-hydroxyproline **131** was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 7).[53] The melting point, specific rotation and spectroscopic data[54] (Table 1 and Table 2) for (2*R*,3*S*)-*cis*-3-hydroxyproline **131** were all in agreement with the literature values {mp 217–223 °C (dec); lit.[23] mp 210–217 °C (dec); $[\alpha]_D^{25}$+80.9 (*c* 1.0 in H_2O); lit. [23] $[\alpha]_D^{20}$+96.3 (*c* 0.92 in H_2O)}, thereby confirming the assigned configurations of all synthetic precursors **171**−**173, 186**−**188**. This first-generation synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** proceeded in 38% overall yield and 9 steps from 1,3-propanediol **178**.



131

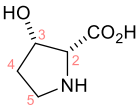
Figure 7 X-ray crystal structure of **131** (selected H atoms are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.



(2*R*,3*S*)-*cis*-3-Hydroxyproline **131**

	Chandrasekhar *et al.*[25]	Jurczak *et al.*[24]	Park *et al.*[23]	*This work*[55]
	300 MHz, D_2O	500 MHz, D_2O	500 MHz, D_2O	400 MHz, D_2O[a]
C(2)*H*	4.06	3.99	4.13	4.15
C(3)*H*	4.62	4.63	4.72	4.73
C(4)H_2	2.04−2.28	2.00−2.10 2.14−2.2	2.12 2.21	2.10−2.30
C(5)H_2	3.37−3.46	3.33 3.49	3.47 3.57	3.45−3.64

Table 1 ^{1}H NMR data for (2*R*,3*S*)-*cis*-3-hydroxyproline **131**. [a] ^{1}H NMR chemical shifts are referenced relative to D_2O (δ_H 4.79 ppm) in D_2O.



(2*R*,3*S*)-*cis*-3-Hydroxyproline **131**

	Chandrasekhar *et al.*[25]	Jurczak *et al.*[24]	Park *et al.*[23]	*This work*[55]
	75 MHz, D_2O	125 MHz, D_2O	125 MHz, D_2O	101 MHz, D_2O[a]
C(2)	70.9 (−0.6)	70.5 (−0.2)	66.7 (+3.6)	70.3
C(3)	74.2 (−0.5)	74.4 (−0.7)	70.0 (+3.7)	73.7
C(4)	35.9 (+0.1)	36.4 (−0.4)	32.3 (+3.7)	36.0
C(5)	46.6 (0.0)	46.6 (0.0)	42.9 (+3.7)	46.6
CO_2H	172.1 (+1.3)	-	169.7 (+3.7)	173.4

Table 2 ^{13}C NMR data for (2*R*,3*S*)-*cis*-3-hydroxyproline **131**. Values of $\Delta\delta_C$ are given in parentheses relative to the sample prepared in this work;[56] ^{13}C NMR chemical shifts are referenced relative to TSP (δ_C 0.0 ppm) in D_2O.

2.5 (2*S*,3*S*)-*trans*-3-Hydroxyproline 136: First-Generation Synthesis

The strategy used to successfully synthesise (2*R*,3*S*)-*cis*-3-hydroxyproline **131** was applied to the synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136**. The difference being *anti*-α-hydroxy-β-amino ester **171** will be subjected to the Tf_2O and DTBMP reaction conditions to form β-hydroxy-α-amino ester **190**, which will then be elaborated to (2*S*,3*S*)-*trans*-3-hydroxyproline **136** (Figure 8).

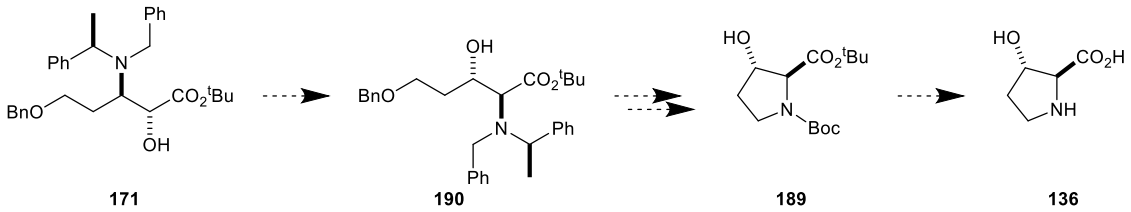
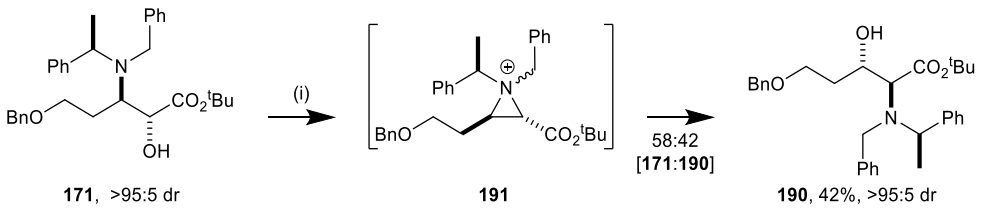


Figure 8 Proposed synthesis towards (2*S*,3*S*)-*trans*-3-hydroxyproline **136**.

2.5.1 Hydroxy and Amino Transposition

Subjecting *anti*-α-hydroxy-β-amino ester **171** to Tf_2O and DTBMP followed by hydrolysis of the resultant intermediate gave a 58:42 mixture of *anti*-α-hydroxy-β-amino ester **171** and *anti*-β-hydroxy-α-amino ester **190**. This resulted in β-hydroxy-α-amino ester **190** being isolated in 42% yield and >95:5 dr. The stereochemistry of β-hydroxy-α-amino ester **190** was unambiguously assigned by conversion to (2*S*,3*S*)-*trans*-3-hydroxyproline **136** (*vide infra*). Returned α-hydroxy-β-amino ester **171** was obtained in 55% yield and >95:5 dr and could be resubjected to the reaction conditions[57] (Scheme 29).

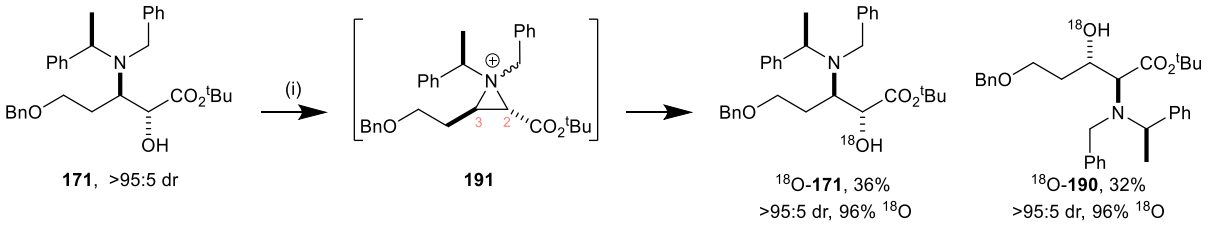


Scheme 29 *Reagents and conditions*: (i) Tf_2O, DTBMP, CH_2Cl_2, 0 °C to rt, 6 h, then H_2O, rt 24 h. **171** was isolated in 55% yield and >95:5 dr.

2.5.2 Regioselectivity Investigation

There are two possible reasons for the low yield of **190** obtained in Scheme 29. Firstly, incomplete aziridinium ion formation would result in the isolated α-hydroxy-β-amino ester **171** arising from unreacted starting material. Secondly, hydrolysis of aziridinium ion **191** proceeding with poor regioselectivity would lead to α-hydroxy-β-amino ester **170** via ring-opening of aziridinium ion **191** at the C(2) position. To determine the origin of this result, α-hydroxy-β-amino ester **171** was subjected to standard Tf_2O and DTBMP activation conditions, followed by the addition of isotopically labelled water, $H_2{}^{18}O$. ^{18}O α-Hydroxy-β-amino ester ^{18}O-**171** and ^{18}O β-hydroxy-α-amino-ester ^{18}O-**190** were obtained both with 96% ^{18}O incorporation (determined by mass spectrometry).

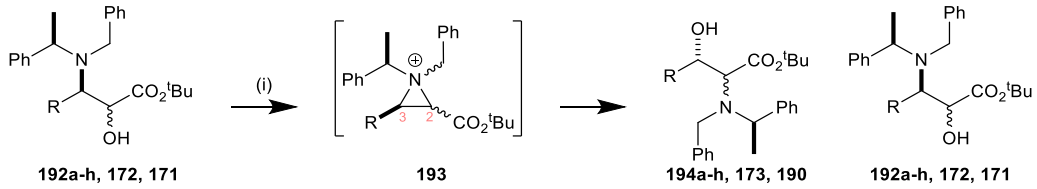
In order to unambiguously confirm the position of the isotopically labelled oxygen in ^{18}O labelled α-hydroxy-β-amino ester ^{18}O-**171** and ^{18}O labelled β-hydroxy-α-amino ester ^{18}O-**190** they were subjected to electrospray ionisation mass spectrometry (ESI-MS/MS) and atmospheric pressure chemical ionisation mass spectrometry (APCI-MS); however, both of these methods proved to be inconclusive. Therefore, analysis of the $^{16}O/^{18}O$ isotope-induced chemical shifts in the ^{13}C NMR spectrum was employed to unambiguously assign the position of the ^{18}O atom. Incorporation of the ^{18}O labelled oxygen at the C(2) position in ^{18}O labelled α-hydroxy-β-amino ester ^{18}O-**171** and the C(3) position in ^{18}O labelled β-hydroxy-α-amino ester ^{18}O-**190** was >95% in both examples (Appendix 2).[58,59] Therefore the low yield of **190** reported in Scheme 29 is due to poor regioselectivity during hydrolysis of aziridinium ion **191** as opposed to returned starting material being isolated (Scheme 30).



Scheme 30 *Reagents and conditions*: (i) Tf_2O, DTBMP, CH_2Cl_2, 0 °C to rt, 6 h, then $H_2{}^{18}O$ (>99.4% ^{18}O), rt 24 h.

This result is inconsistent with the previous observations reported by Davies *et al*. where β-hydroxy-α-amino esters are the major component in all reported examples bearing aliphatic substituents at the β-position (Table 3 entries *a*, *b*, *d* and *e*).[41] For both *syn*-configured substrates **192a** (R = Me) and **192b** (R = ^{i}Pr) (Table 3 entries *a* and *b*) the ring-opening of the corresponding *syn*-aziridinium ion is completely regioselective for the formation of the β-hydroxy-α-amino ester, and is consistent with the outcome for the *syn*-δ-benzyloxy analogue **172** (Table 3 entry *c*) (*vide supra*). However, the *anti*-configured epimers **192d** (R = Me) and **192e** (R = ^{i}Pr) (Table 3 entries *d* and *e*) display slightly poorer regioselectivity upon hydrolysis of the corresponding aziridinium ions. The inherent selectivity for C(3) aziridinium ring-opening for all of these substrates is due to the inductively electron donating character of the C(3) alkyl group stabilising the positively charged transition state (the leaving group carries a positive charge and the nucleophile is neutral) for ring-opening. The C(3) regioselectivity is eroded in *anti*-configured epimers **192d** (R = Me) and **192e** (R = ^{i}Pr) (Table 3 entries *d* and *e*) due to the carbonyl $\pi^*_{C=O}$ orbital being able to overlap with the σ^*_{C-N} orbital, therefore lowering the energy of the transition state for aziridinium ion hydrolysis at the C(2) position. This orbital overlap is not possible in *syn*-α-hydroxy-β-amino esters due to the steric compression of the C(3) substituent and the carbonyl resulting in the $\pi^*_{C=O}$ orbital being orthogonal with the σ^*_{C-N} orbital.[60] Despite this orbital overlap in *anti*-configured epimers **192d** (R = Me) and **192e** (R = ^{i}Pr) (Table 3 entries *d* and *e*) the inductively electron donating ability of the C(3)

substituent still dominates and the favourable orbital overlap is only responsible for a small erosion in regioselectivity.



192a-h, 172, 171 **193** **194a-h, 173, 190** **192a-h, 172, 171**

	R		*syn*/*anti*	α-Amino ester: β-Amino ester[a]	α-Amino ester	β-Amino ester
a[41]	Me	**192a**	*syn*	>99:1	**194a**, 67%	-
b[41]	^{i}Pr	**192b**	*syn*	>99:1	**194b**, 57%	-
c	CH_2CH_2OBn	**172**	*syn*	>95:5	**173**, quant	-
d[41]	Me	**192d**	*anti*	83:17	**194d**, 68%	**192d**, 12%
e[41]	^{i}Pr	**192e**	*anti*	90:10	**194e**, 68%	**192e**, 10%
f[61,b]	$CH_2CH_2CH_2OBn$	**192f**	*anti*	>99:1	**194f**, 51%	-
g	CH_2CH_2OBn	**171**	*anti*	42:58	**190**, 42%	**171**, 55%
h[61,62,b]	CH_2OBn	**192h**	*anti*	1:>99	-	-

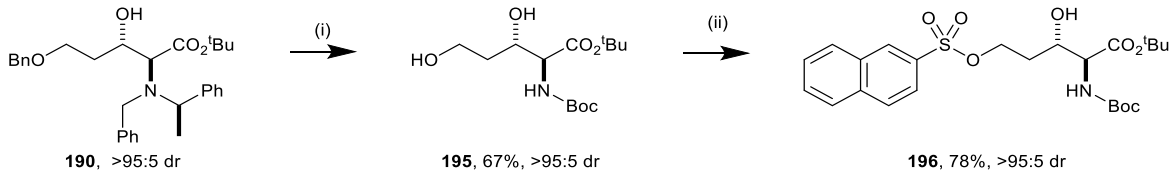
Table 3 *Reagents and conditions*: (i) Tf_2O, DTBMP, CH_2Cl_2, 0 °C to rt, 6 h, then H_2O, rt 24 h. [a] Determined by NMR spectroscopic analysis of crude mixtures. [b] These results are from the enantiomeric series.

In this study, *anti*-α-hydroxy-β-amino ester **171** is anomalous because α-hydroxy-β-amino ester **171** is the major component isolated from a 58:42 mixture of *anti*-α-hydroxy-β-amino ester **171** and *anti*-β-hydroxy-α-amino ester **190** (Table 3 entry *g*). In a parallel investigation,[61] for *anti*-ε-benzyloxy ester **192f** (Table 3, entry *f*) the ring-opening of the corresponding *anti*-aziridinium ions is completely regioselective for the formation of the β-hydroxy-α-amino ester **194f** [i.e., exclusive ring-opening at C(3)]; whereas, for *anti*-γ-benzyloxy ester **192h** (Table 3, entry *h*), the ring-opening of the corresponding *anti*-aziridinium ions is completely regioselective for the formation of the α-hydroxy-β-amino ester **192h** [i.e., exclusive ring-opening at C(2)]. A longer alkyl chain resulted in complete C(3) regioselectivity due to the inductively electron

withdrawing oxygen atom being sufficiently distal from the C(3) position to not affect the inherent C(3) regioselectivity (Table 3 entry *f*). A shorter alkyl chain resulted in complete C(2) regioselectivity due to the inductively electron withdrawing ability of the benzyl ether two carbons closer to the C(3) position of the aziridinium ion intermediate. In this study, the electron donating ability of the β-substituent in *anti*-α-hydroxy-β-amino ester **171** is substantially reduced, relative to the corresponding β-alkyl substituted analogues. This is to such an extent the competitive ring-opening at C(2) proceeds at a comparable rate and this reaction is essentially unselective and is consisitent with this result being intermediate in terms of regioselectivity between ε-benzyloxy ester **192f** and γ-benzyloxy ester **192h**.

2.5.3 Elaboration to (2*S*,3*S*)-*trans*-3-Hydroxyproline 136

Hydrogenolysis of β-hydroxy-α-amino ester **190** in the presence of Boc_2O gave diol **195** in 67% yield and >95:5 dr. Activation of diol **195** with 2-napthylsulfonyl chloride gave the corresponding sulfonate ester **196**, with no evidence of reaction at the secondary hydroxyl group, in 78% yield and >95:5 dr (Scheme 31).

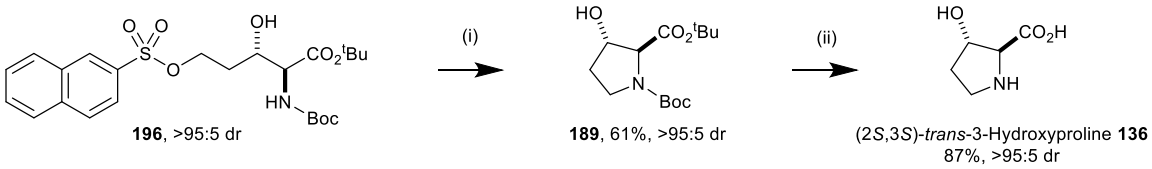


190, >95:5 dr **195**, 67%, >95:5 dr **196**, 78%, >95:5 dr

Scheme 31 *Reagents and conditions*: (i) $Pd(OH)_2/C$, Boc_2O, MeOH, H_2 (5 atm), rt, 65 h; (ii) 2-Nap-SO_2Cl, pyridine, 0 °C, 5 h.

Addition of sulfonate ester **196** to a stirred solution of NaH in THF formed pyrrolidine **189** in 61% yield and >95:5 dr. The relative configuration within pyrrolidine **189** was unambiguously confirmed by single crystal X-ray diffraction analysis of solvate **189**·$CHCl_3$ (Figure 9).[53] A Flack *x* parameter[63] of –0.015(10) for the crystal structure of **189**·$CHCl_3$ was also consistent with the assigned absolute (*S*,*S*)-configuration within **189**. Deprotection of *N*-Boc ester **189**

with 6.0 M HCl yielded (2*S*,3*S*)-*trans*-3-hydroxyproline **136** in 87% yield and >95:5 dr (Scheme 32).



Scheme 32 *Reagents and conditions*: (i) NaH, THF, **196**, rt, 2 h; (ii) 6.0 M $_{(aq)}$ HCl, rt, 16 h, then Dowex® 50WX8.

The relative configuration within (2*S*,3*S*)-*trans*-3-hydroxyproline **136** was unambiguously confirmed by single crystal X-ray diffraction analysis of the hydrate **136**·H_2O (Figure 10).[53] The melting point, specific rotation and spectroscopic data[54] for (2*S*,3*S*)-*trans*-3-hydroxyproline **136** were all in agreement with the literature values {mp 231 °C (dec); lit.[23] mp 231–234 °C (dec); $[\alpha]_D^{25}$ –15.8 (*c* 1.0 in H_2O); lit.[23] $[\alpha]_D^{20}$ –18.8 (*c* 0.92 in H_2O)}, thereby confirming the assigned configurations of all synthetic precursors. This first-generation synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136** proceeded in 5.8% yield and 8 steps from 1,3-propanediol.

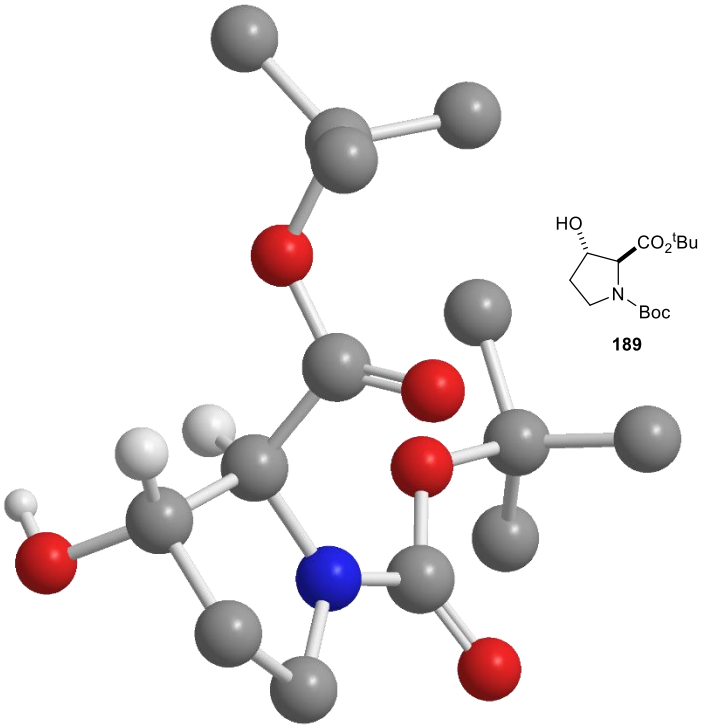


Figure 9 X-ray crystal structure of **189**·$CHCl_3$ (selected H atoms and $CHCl_3$ are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

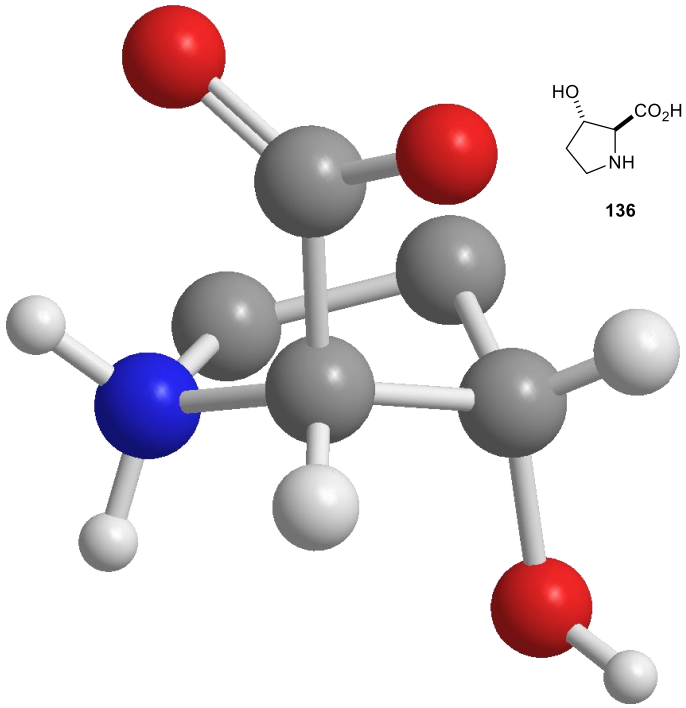
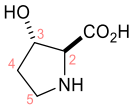


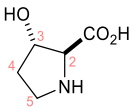
Figure 10 X-ray crystal structure of **136**.H_2O (selected H atoms and H_2O are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.



(2*S*,3*S*)-*trans*-3-Hydroxyproline **136**

	Chandrasekhar *et al.*[25]	Park *et al.*[23]	*This work*[55]
	300 MHz, D_2O	500 MHz, D_2O	400 MHz, D_2O[a]
C(2)*H*	4.06	4.06	4.08
C(3)*H*	4.67	4.67	4.69
C(4)H_2	2.01	2.04	2.01−2.11
C(5)H_2	3.48 3.42	3.48 3.58	3.46−3.56 3.56−3.65

Table 4 ^{1}H NMR data for (2*S*,3*S*)-*trans*-3-hydroxyproline **136**. [a] ^{1}H NMR chemical shifts are referenced relative to D_2O (δ_H 4.79 ppm) in D_2O.



(2*S*,3*S*)-*trans*-3-Hydroxyproline **136**

	Chandrasekhar et al.[25]	Park *et al.*[23]	*This work*[55]
	75 MHz, D_2O	125 MHz, D_2O	101 MHz, D_2O[a]
C(2)	72.1 (−0.4)	67.6 (+4.1)	71.7
C(3)	75.8 (+0.9)	72.5 (+4.2)	76.7
C(4)	34.3 (0.0)	30.1 (+4.2)	34.3
C(5)	46.8 (+0.2)	42.8 (+4.2)	47.0
CO_2H	174.4 (0.0)	170.2 (+4.2)	174.4

Table 5 ^{13}C NMR data (2*S*,3*S*)-*trans*-3-hydroxyproline **136**. Values of $\Delta\delta_C$ given in parenthesis relative to the samples prepared in this work.[56] ^{13}C NMR chemical shifts are referenced relative to TSP (δ_C 0.0 ppm) in D_2O.

2.6 First-Generation Synthesis Conclusion

The first-generation synthesis enabled the efficient and scalable synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** in 38% yield and 9 steps from commercially available 1,3-propanediol **178**. However the synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136**, only proceeded in a 5.8% yield despite being only 8 steps. The main reason for this low yield is due to the lack of regioselectivity during the ring-opening of the intermediate aziridinium ion **191**. Therefore, a second-generation synthesis which overcomes this regioselectivity issue was needed to achieve a scalable and efficient synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136**.

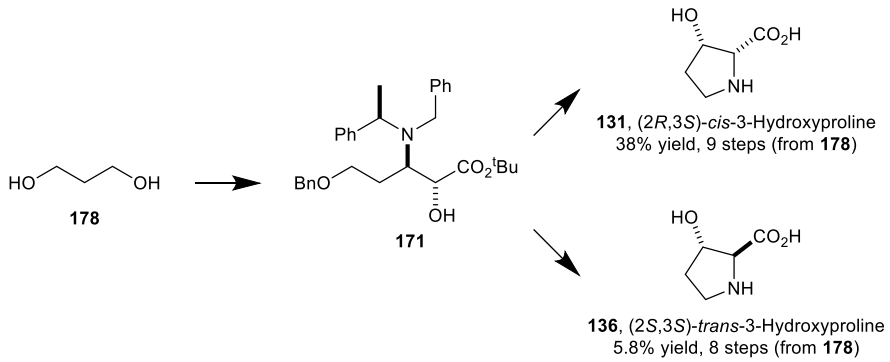


Figure 11 Summary of the first-generation synthesis of (2*R*,3*S*)-*cis*-hydroxyproline **131** and (2*S*,3*S*)-*trans*-3-hydroxyproline **136**.

2.7 (2*S*,3*S*)-*trans*-3-Hydroxyproline 136: Second-Generation Synthesis

To overcome the regioselectivity issues experienced in the first-generation synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136** an alternative synthetic strategy was envisaged which utilises a tethered nucleophile. It was thought that a C(5) acetate functionality would be a tethered nucleophile to open aziridinium ion **198** in a regioselective fashion at the C(3) position to form the corresponding acetoxonium ion **199**, which would undergo hydrolysis to form either β-hydroxy-α-amino ester **200** or γ-hydroxy-α-amino ester **201**.

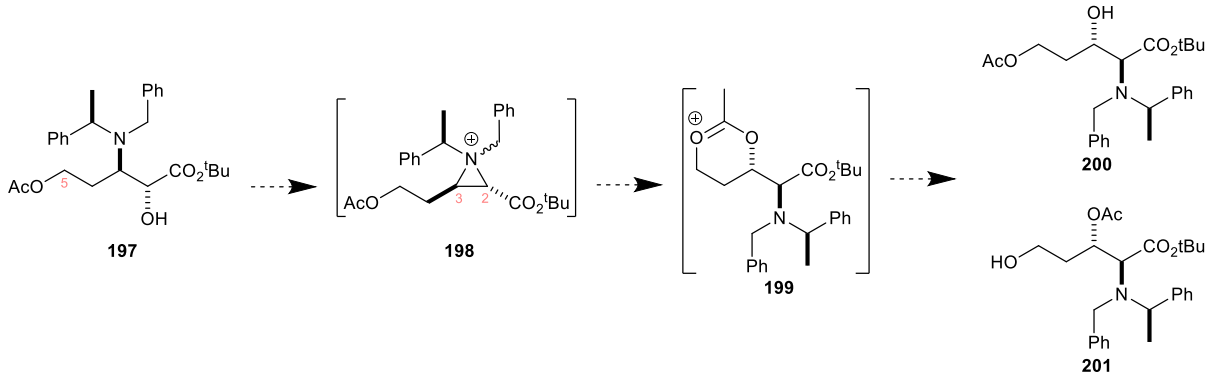
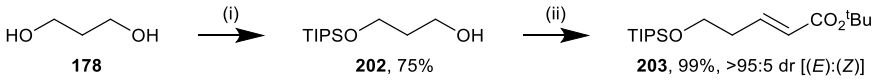


Figure 12 Proposed second-generation synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136**.

2.7.1 Substrate Preparation

It was envisaged that a C(5)-acetoxy protected α,β-unsaturated ester would be incompatible with the lithium amide reaction conditions so an indirect route for the synthesis of α-hydroxy-β-amino ester **197** was investigated. α,β-Unsaturated ester **203** was prepared in two steps from 1,3-propanediol **178**. 1,3-Propanediol **178** was mono-silylated to give alcohol **202** in 75% yield. Oxidation of alcohol **202** to the corresponding aldehyde was subjected to an *in situ* Wittig olefination to give α,β-unsaturated ester **203** in 99% yield and >95:5 dr ($^3J_{trans}$ = 15.7 Hz) (Scheme 33).

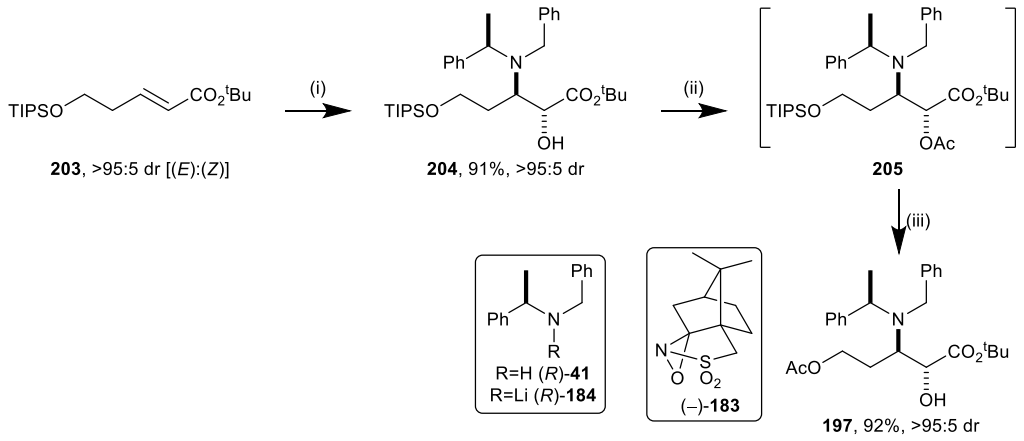


Scheme 33 *Reagents and conditions*: (i) NaH, THF, 0 °C, 45 min, then TIPSCl, rt, 6 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then **202**, CH_2Cl_2, –78 °C, 30 min, then Et_3N, –78 °C to rt, 1 h, then **177**, rt, 16 h.

Conjugate addition of lithium amide (*R*)-**184** to α,β-unsaturated ester **203**, followed by *in situ* oxidation of the corresponding enolate with (–)-CSO (−)-**183** gave α-hydroxy-β-amino ester **204** in 91% yield and >95:5 dr (Scheme 34). The relative configuration within α-hydroxy-β-amino ester **204** was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 13).[53] A Flack *x* parameter[63] of –0.01(2) for the crystal structure of α-hydroxy-β-amino ester **204** was supportive of its assigned absolute (*R*,*R*,*R*)-configuration as well as being

consistent with the well-established stereochemical outcome of this aminohydroxylation protocol.[48–50]

Acetylation of α-hydroxy-β-amino ester **204** gave α-acetoxy ester **205**, which when treated with TBAF resulted in desilylation and concomitant acetate migration from the secondary alcohol to the primary alcohol to give α-hydroxy-γ-acetoxy ester **197**, in accordance with the observed acetate migration seen by Zbiral *et al.*[64–66] (Scheme 34). The relative configuration within α-hydroxy-γ-acetoxy ester **197** was also unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 14).[53] A Flack *x* parameter[63] of –0.00(11) for the crystal structure of α-hydroxy-γ-acetoxy ester **197** was consistent with its assigned absolute (*R*,*R*,*R*)-configuration.



Scheme 34 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **203**, THF, –78 °C 2 h, then (−)-**183** –78 °C to rt, 12 h; (ii) Ac_2O, DMAP, pyridine, THF, rt 18 h; (iii) TBAF, THF, rt, 24 h.

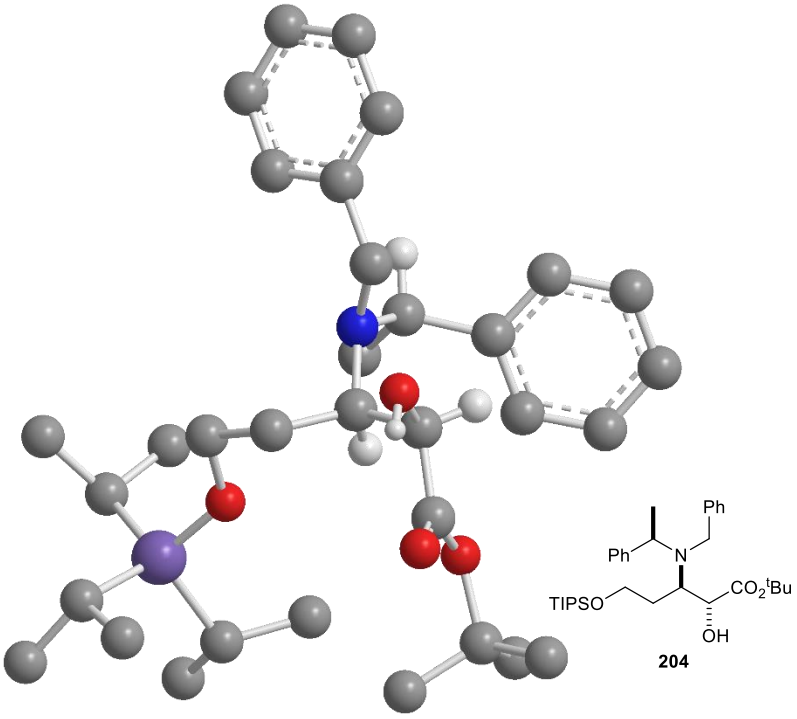


Figure 13 X-ray crystal structure of **204** (selected H atoms are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

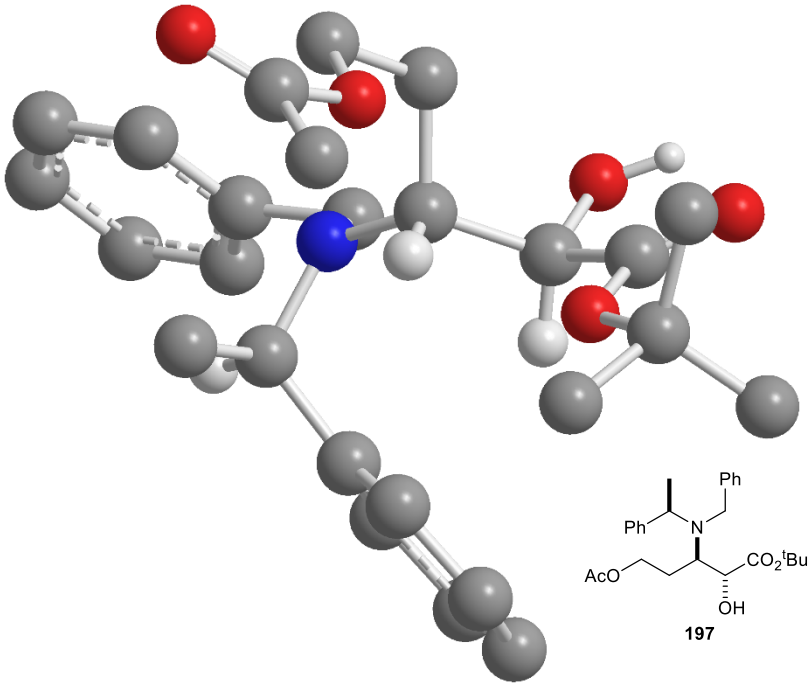
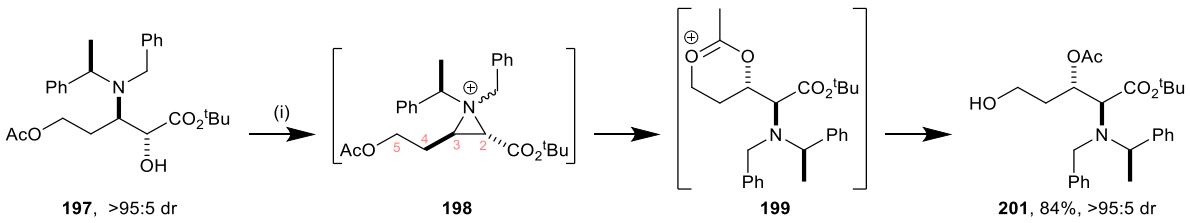


Figure 14 X-ray crystal structure of **197** (selected H atoms are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

2.7.2 Hydroxy and Amino Transposition

Treatment of α-hydroxy-β-amino ester **197** with Tf_2O and DTBMP, followed by H_2O, gave β-acetoxy-α-amino ester **201** as a single regioisomer in 84% yield and >95:5 dr. The regiochemistry within **201** was confirmed by HMBC spectroscopic analysis whereby a strong correlation could be seen between C(O)*Me* and *C*(3). This is consistent with a mechanism whereby α-hydroxy-β-amino ester **197** forms the corresponding aziridinium ion **198** which is followed by ring-opening upon participation of the C(5)-acetate group to give acetoxonium ion **199**, which after hydrolysis, gives β-acetoxy-α-amino ester **201** exclusively (Scheme 35).



197, >95:5 dr **198** **199** **201**, 84%, >95:5 dr

Scheme 35 *Reagents and conditions*: (i) Tf_2O, DTBMP, CH_2Cl_2, 0 °C to rt, 2 h, then H_2O.

2.7.3 Mechanistic Investigation

There are several mechanisms by which hydrolysis of acetoxonium ion **199** could occur. Attack of acetoxonium **199** by H_2O in an S_N2 manner may occur at either C(3) [Route 1] to give **206** or C(5) [Route 2] to give **201**. Alternatively, hydrolysis of acetoxonium ion **199** by addition of H_2O at the acetoxonium carbonyl position [Route 3] followed by collapse of the adduct **207** would give either primary acetate **200** [Route 3a] or secondary acetate **201** [Route 3b]. S_N2 hydrolysis at the C(3) position [Route 1], which proceeds with inversion of configuration at C(3), and hydrolysis of acetoxonium ion **199** to give primary acetate **200** [Route 3a] are inconsistent with the experimental observations. But S_N2 hydrolysis at the C(5) position [Route 2] and hydrolysis of acetoxonium ion **199** to give secondary acetate **201** [Route 3b] give rise to the same product (Figure 15).

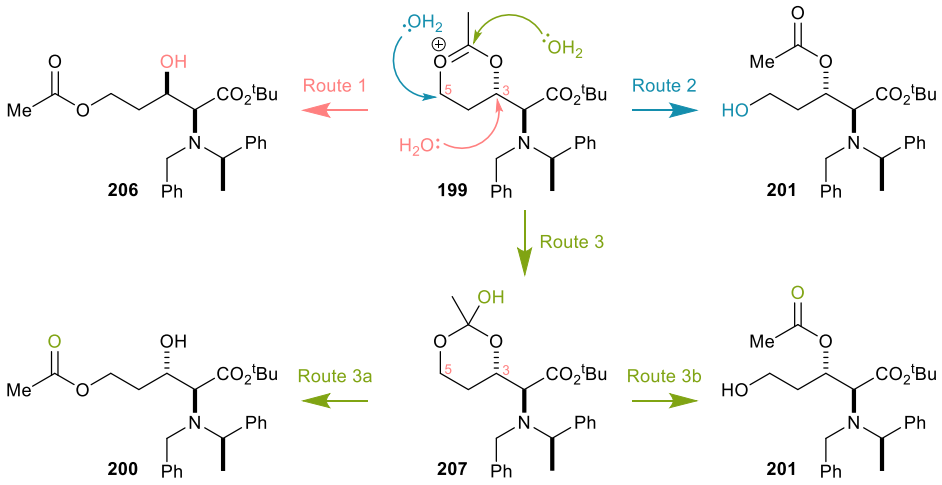
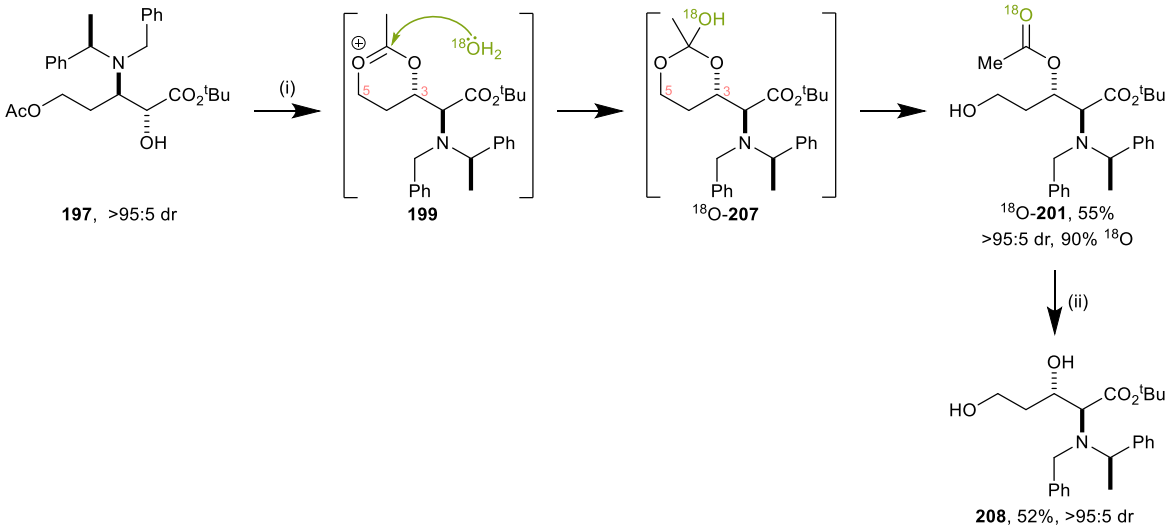


Figure 15 Potential mechanisms of acetoxonium hydrolysis.

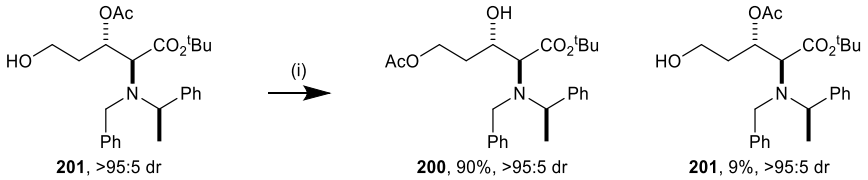
The remaining mechanisms of hydrolysis can be distinguished by addition of isotopically labelled water ($H_2{}^{18}O$) to acetoxonium **199**, after treatment of α-hydroxy-β-amino ester **197** with Tf_2O and DTBMP, which gave isotopically labelled β-acetoxy-α-amino ester ^{18}O-**201**, whereby one ^{18}O was incorporated as determined by mass spectrometric analysis (90% ^{18}O). A diagnostic red shift of 48 cm^{-1} was observed for the C=^{18}O peak in the infrared spectrum of ^{18}O-**201**, which is consistent with the ^{18}O being incorporated in the carbonyl of the acetate group [Route 3b].[67] Methanolysis of β-acetoxy-α-amino ester ^{18}O-**201** gave diol **208** and mass spectrometric analysis of diol **208** confirmed that the ^{18}O isotopic label was not present within diol **208**. This outcome is consistent with a mechanism whereby the acetoxonium ion **199** undergoes hydrolysis at the carbonyl position and the resultant adduct **207** fragments to give β-acetoxy-α-amino ester ^{18}O-**201**, and so also ruling out S_N2 hydrolysis at the C(5) position. The regioselectivity for the decomposition of adduct **207** is consistent with protonation occurring selectively at the C(5) oxygen followed by decomposition to give β-acetoxy-α-amino ester ^{18}O-**201**. Selective protonation may occur due to the inductively electron withdrawing effect of the substituents adjacent to the C(3) oxygen. These would significantly disfavour protonation at the C(3) oxygen relative to the C(5) oxygen; therefore making protonation at the C(5) oxygen kinetically favoured. This is consistent with the hydrolysis of a similar system,[68]

where it has been proposed that this may be due the secondary acetate being the kinetic fragmentation product due to the greater solvation (and therefore protonation) of the oxygen connected to the primary C(5) position in the transition state of fragmentation (Scheme 36).



Scheme 36 *Reagents and conditions*: (i) Tf_2O, DTBMP, CH_2Cl_2, 0 °C to rt, 2 h, then $H_2{}^{18}O$ (>99.4% ^{18}O); (ii) K_2CO_3, MeOH, rt, 2 h.

Treatment of secondary acetate **201** with TBAF for 24 h predominantly resulted in acetate migration to the C(5) alcohol to give primary acetate **200** in 90% yield with 9% of secondary acetate **201** recovered (Scheme 37). The regiochemistry within **200** was confirmed by HMBC spectroscopic analysis whereby a strong correlation could be seen between *C*(O)Me and C(5)*H*$_2$. These reaction conditions have previously given the primary, and presumably thermodynamically more stable, acetate on similar substrates (Scheme 34). This supports the theory that secondary acetate **201** is the kinetic decomposition product arising from acetoxonium hydrolysis.[69]

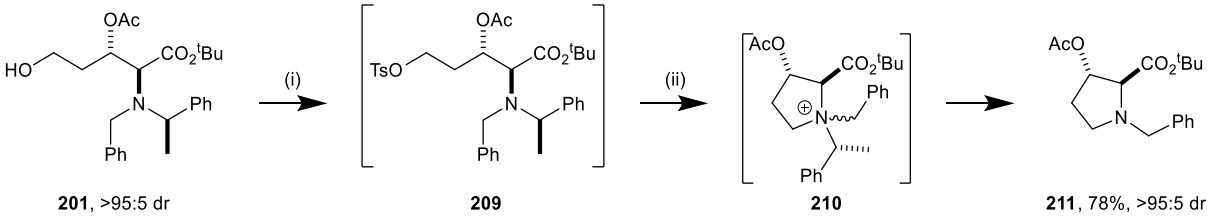


201, >95:5 dr **200**, 90%, >95:5 dr **201**, 9%, >95:5 dr

Scheme 37 *Reagents and conditions*: (i) TBAF, THF, rt, 24 h.

2.7.4 Elaboration to (2*S*,3*S*)-*trans*-3-Hydroxyproline 136

As the γ-oxygen is now free, an alternative approach for cyclisation will be considered – direct activation and *in situ* cyclisation. Tosylation of γ-hydroxy ester **201** gave tosylate **209** that upon heating in MeCN gave pyrrolidine **211** in 78% yield and >95:5 dr (Scheme 38). This outcome is consistent with the formation of pyrrolidinium **210** followed by S_N1/E1 type loss of the *N*-α-methylbenzyl group.[70] The relative configuration within pyrrolidine **211** was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 16).[53] A Flack *x* parameter[63] of –0.03(15) for the crystal structure of pyrrolidine **211** was consistent with its assigned absolute (*S*,*S*)-configuration.



201, >95:5 dr **209** **210** **211**, 78%, >95:5 dr

Scheme 38 *Reagents and conditions*: (i) TsCl, pyridine, rt, 2 h; (ii) MeCN, 70 °C, 1 h.

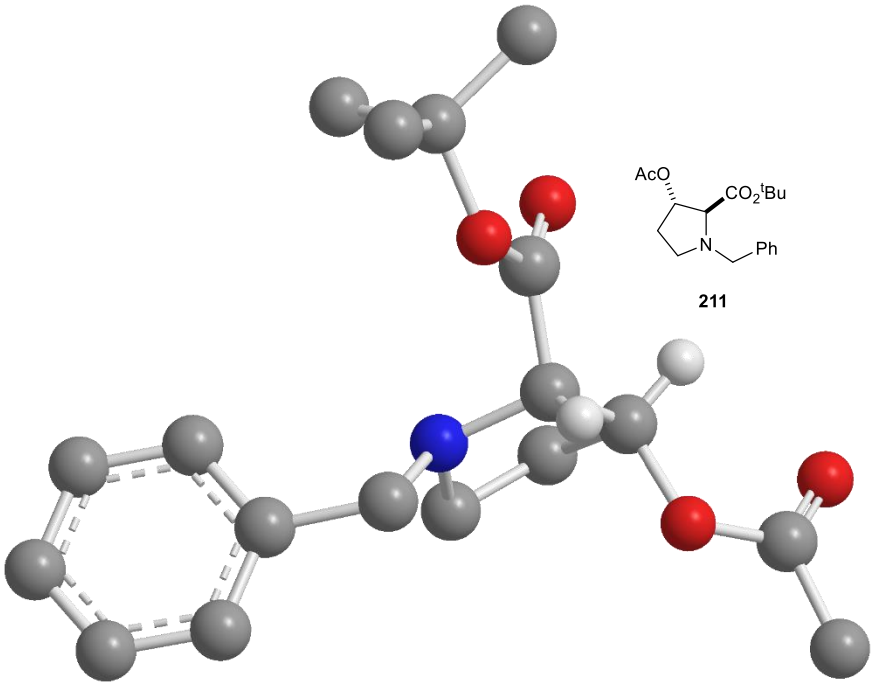
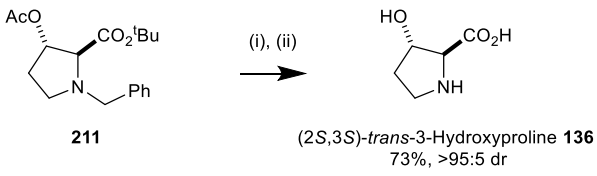


Figure 16 X-ray crystal structure of **211** (selected H atoms are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

Sequential deprotection of pyrrolidine **211** via hydrogenolysis and hydrolysis gave (2*S*,3*S*)-*trans*-3-hydroxyproline **136** in 73% yield from pyrrolidine **211** and >95:5 dr {mp 230−234 °C (dec); lit.[23] mp 231–234 °C (dec); $[\alpha]_D^{25}$ –12.4 (*c* 1.0 in H_2O); lit. [23] $[\alpha]_D^{20}$ –18.8 (*c* 0.92 in H_2O)}. This second-generation synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136** proceeded in 30% yield and 9 steps from 1,3-propanediol which, despite being one extra synthetic step, was a significant improvement on the 5.8% yield from the first-generation synthesis (Scheme 39).

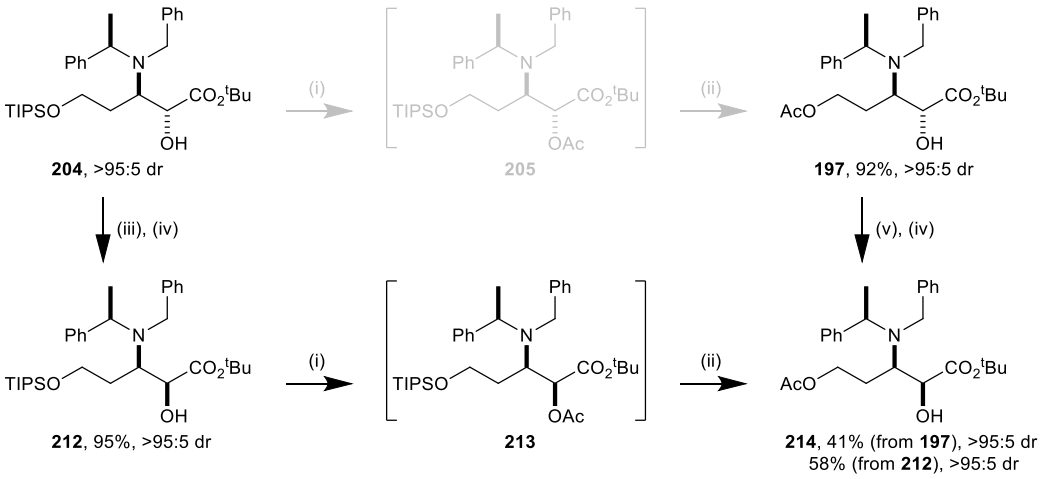


Scheme 39 *Reagents and conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH/H_2O/AcOH, rt, 72 h; (ii) 6.0 M (aq) HCl, rt, 16 h, then Dowex® 50WX8.

2.8 (2*R*,3*S*)-*cis*-3-Hydroxyproline 131: Second-Generation Synthesis

Although the first-generation synthesis of (2*S*,3*S*)-*cis*-3-hydroxyproline **131** was already high yielding (38% yield and 9 steps from 1,3-propanediol **178**) the second-generation synthesis was applied to (2*S*,3*S*)-*cis*-3-hydroxyproline **131** to determine whether intramolecular aziridinium ring-opening via a tethered nucleophile is also a viable strategy in this epimeric system.

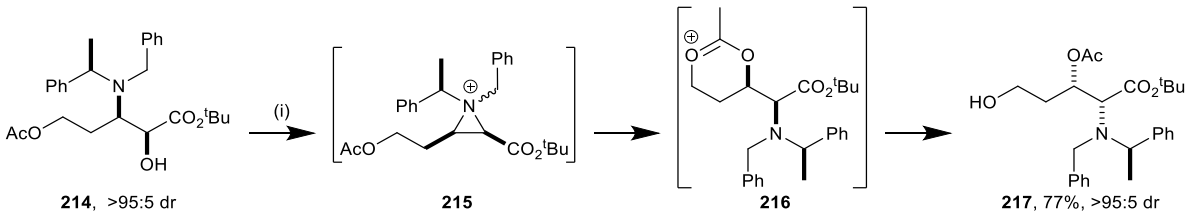
syn-α-Hydroxy-γ-acetoxy ester **214** was synthesised via two parallel routes. The first of which involved the oxidation of *anti*-α-hydroxy-γ-acetoxy ester **197** and diastereoselective reduction of the corresponding ketone to give *syn*-α-hydroxy-γ-acetoxy ester **214** which proceeded in a 41% yield and >95:5 dr. The second route utilised the same oxidation and diastereoselctive reduction conditions but this time on *anti*-α-hydroxy-γ-silylated ester **204**, which proceeded in 95% yield and >95:5 dr. *syn*-α-Hydroxy-γ-silylated ester **212** was acetylated and the resultant acetate **213** was treated with TBAF and desilylation followed by acetate migration gave *syn*-α-hydroxy-γ-acetoxy ester **214** in 58% yield and >95:5 dr; with the route via *syn*-α-hydroxy-γ-silyloxy ester **212** proceeding in a better 55% yield (from **204**) compared to the route via *anti*-α-hydroxy-γ-acetoxy ester **197** in 41% yield (from **204**) (Scheme 40).



Scheme 40 *Reagents and conditions*: (i) Ac_2O, DMAP, pyridine, THF, rt 18 h; (ii) TBAF, THF, rt, 24 h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then **204**, CH_2Cl_2, –78 °C, 30 min, then Et_3N, –78 °C to rt, 1 h;

(iv) $NaBH_4$, MeOH, –20 °C, 2 h; (v) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then **197**, CH_2Cl_2, –78 °C, 30 min, then Et_3N, –78 °C to rt, 1 h

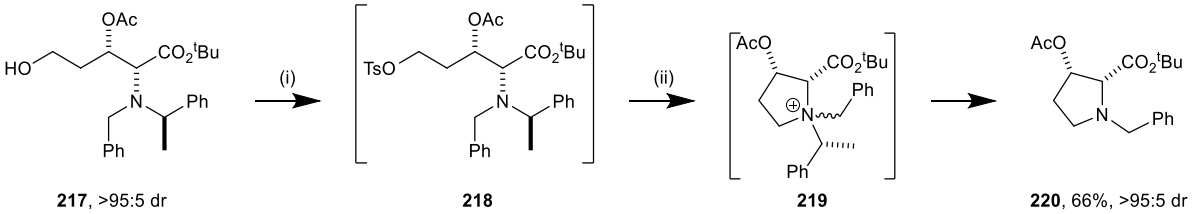
α-Hydroxy ester **214** was treated with Tf_2O and DTBMP, which upon the addition of H_2O gave β-acetoxy-α-amino ester **217** in 77% yield and >95:5 dr, which is consistent with the hydrolysis mechanism discussed previously (Scheme 41).



214, >95:5 dr **215** **216** **217**, 77%, >95:5 dr

Scheme 41 *Reagents and conditions*: (i) Tf_2O, DTBMP, CH_2Cl_2, 0 °C to rt, 2 h, then H_2O.

Tosylation of γ-hydroxy ester **217** gave tosylate **218**, and heating **218** in MeCN gave pyrrolidine **220** in 66% yield and >95:5 dr. The relative configuration within pyrrolidine **220** was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 17).[53] A Flack *x* parameter[63] of –0.09(15) for the crystal structure of pyrrolidine **220** was consistent with its assigned absolute (2*R*,3*S*)-configuration (Scheme 42).



217, >95:5 dr **218** **219** **220**, 66%, >95:5 dr

Scheme 42 *Reagents and conditions*: (i) TsCl, pyridine, rt, 2 h; (ii) MeCN, 70 °C, 1 h.

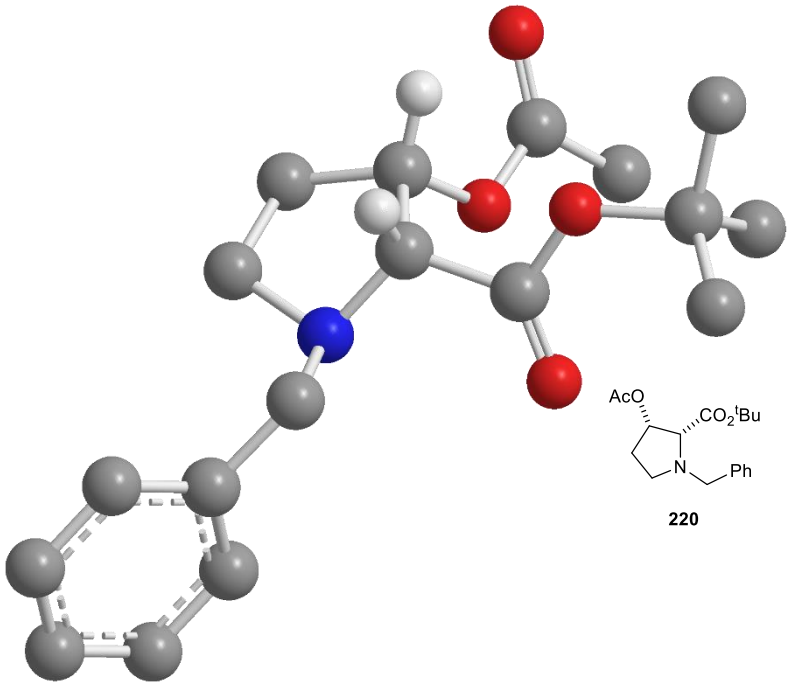
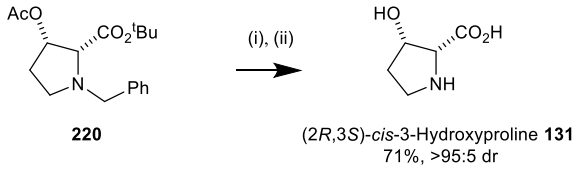


Figure 17 X-ray crystal structure of **220** (selected H atoms are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

Hydrogenolysis and hydrolysis of pyrrolidine **220** gave (2*R*,3*S*)-*cis*-3-hydroxyproline **131** in 71% yield and >95:5 dr {mp 210–217 °C (dec); lit.[23] mp 210–217 °C (dec); $[\alpha]_D^{25}$ +80.4 (*c* 1.0 in H_2O); lit.[23] $[\alpha]_D^{20}$ +96.3 (*c* 0.92 in H_2O)} (Scheme 43).



Scheme 43 *Reagents and conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$, MeOH/H_2O/AcOH, rt, 72 h; (ii) 6.0 M $_{(aq)}$ HCl, rt, 16 h. then Dowex® 50WX8.

This second-generation synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** proceeded in 14% yield and 10 steps from 1,3-propanediol. This is lower than the excellent yield of the the first-generation synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** (38% yield and 9 steps from 1,3-propanediol **178**). However, this second-generation synthesis demonstrates that intramolecular aziridinium ring-opening is a viable protocol on both *syn*- and *anti*-α-hydroxy-β-amino esters.

2.9 Chapter Conclusion

In conclusion, two complementary routes have been developed to synthesise (2*R*,3*S*)-*cis*-3-hydroxyproline **131** and (2*S*,3*S*)-*trans*-3-hydroxyproline **136** (Table 6). The optimal route to (2*R*,3*S*)-*cis*-3-hydroxyproline **131** utilised intermolecular aziridinium ring-opening to give (2*R*,3*S*)-*cis*-3-hydroxyproline **131**, resulting in the second highest yielding synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** reported and the lowest step count (Table 7). The application of this first-generation methodology to the synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136** resulted in a low overall yield, mainly due to the poor regioselectivity upon intermolecular aziridinium ring-opening. To overcome this, a second-generation synthesis which utilised intramolecular aziridinium ring-opening, with a tethered acetate group as the nucleophile, was developed, resulting in the highest yielding and lowest step count synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136** developed to date (Table 7).[55]

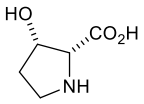
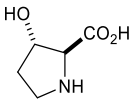
	 (2*R*,3*S*)-*cis*-3-Hydroxyproline **131**		 (2*S*,3*S*)-*trans*-3-Hydroxyproline **136**	
First-generation	38%	9 steps	5.8%	8 steps
Second-generation	14%	10 steps	30%	9 steps

Table 6 Comparison of the first and second-generation synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** and (2*R*,3*S*)-*trans*-3-hydroxyproline **136**.

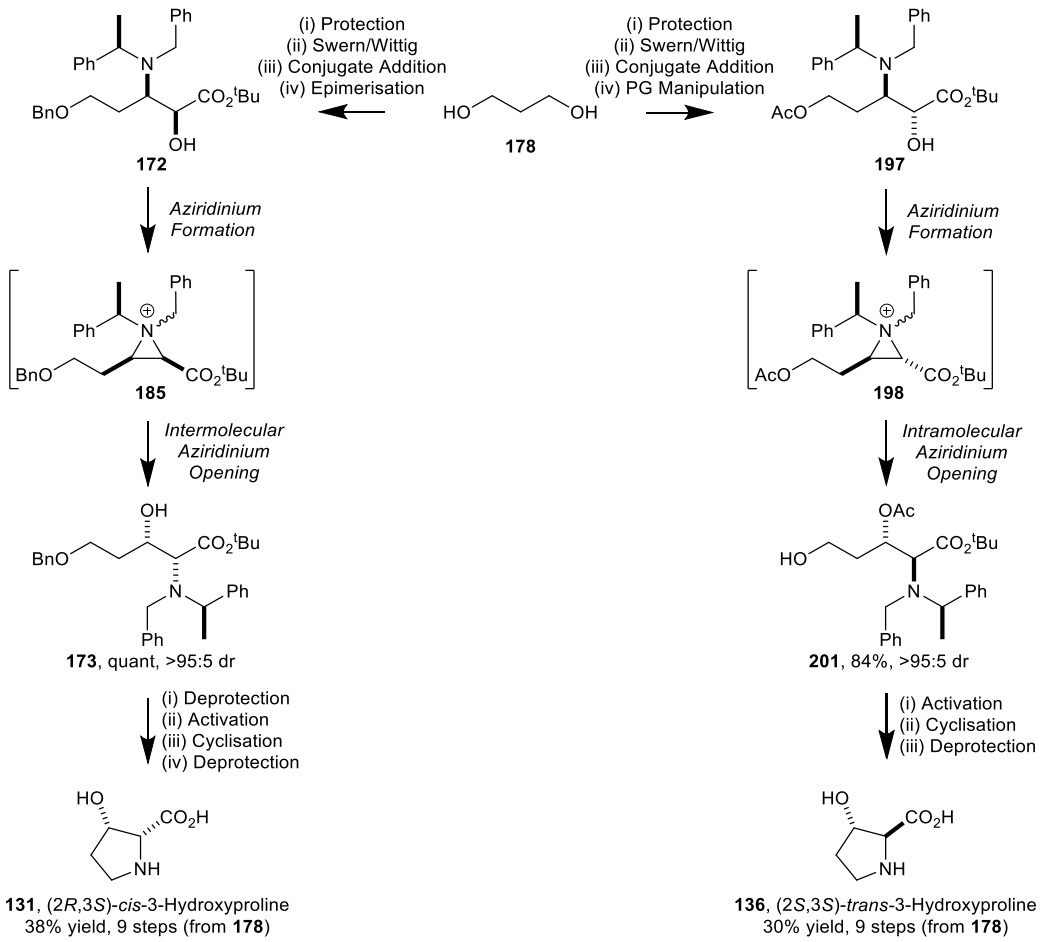
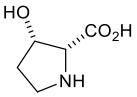
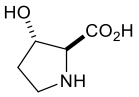


Figure 18 Summary of the first-generation synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** and the second-generation synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136**.



(2*R*,3*S*)-3-Hydroxyproline **131**



(2*S*,3*S*)-3-Hydroxyproline **136**

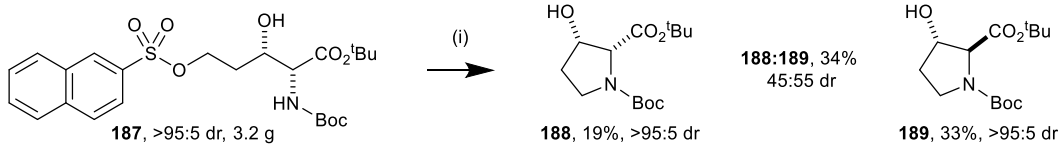
Luger et al. [21]	12%	14 steps	-	-
Park et al.[23]	29%	13 steps	-	-
Jurczak et al. [24]	44%	15 steps	-	-
Chandrasekaran et al.[26]	-	-	20%[a]	11 steps
Chandrasekhar et al. [25]	n/a	14 steps	5.4%	13 steps
This work [55]	38%	9 steps	30%	9 steps

Table 7 Summary of previous 3-hydroxyproline syntheses compared to this work; [a] based on recovered starting material and not from commercially available starting materials.

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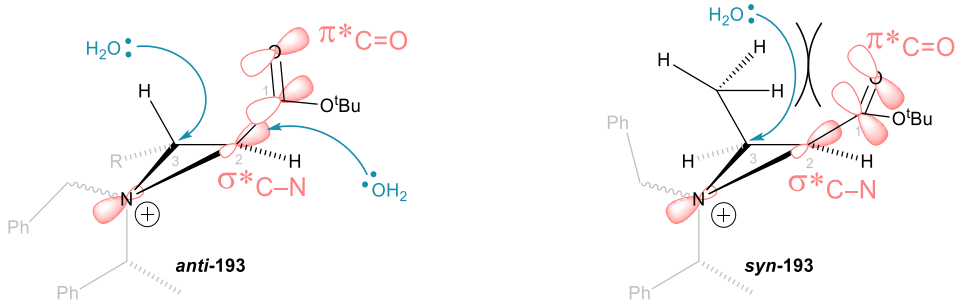
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(52)



187, >95:5 dr, 3.2 g **188**, 19%, >95:5 dr **189**, 33%, >95:5 dr

Reagents and conditions: (i) NaH, THF, 15 min, then **187**, rt, 18 h.

(53) X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.
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Chapter 3

3 First-Generation Approach Towards the Loline Alkaloid Scaffold

3.1 Chapter Outline

This chapter describes the work towards a first-generation synthesis of the loline alkaloids **1**–**4** (Figure 19). This strategy uses *N*-Boc *cis*-pyrrolidine **188**, an advanced intermediate from the synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** as a precursor to the target compounds. A lithium amide conjugate addition will be used to insert the C(3) exocyclic amino group of the loline alkaloids **1**–**4** (Figure 19).

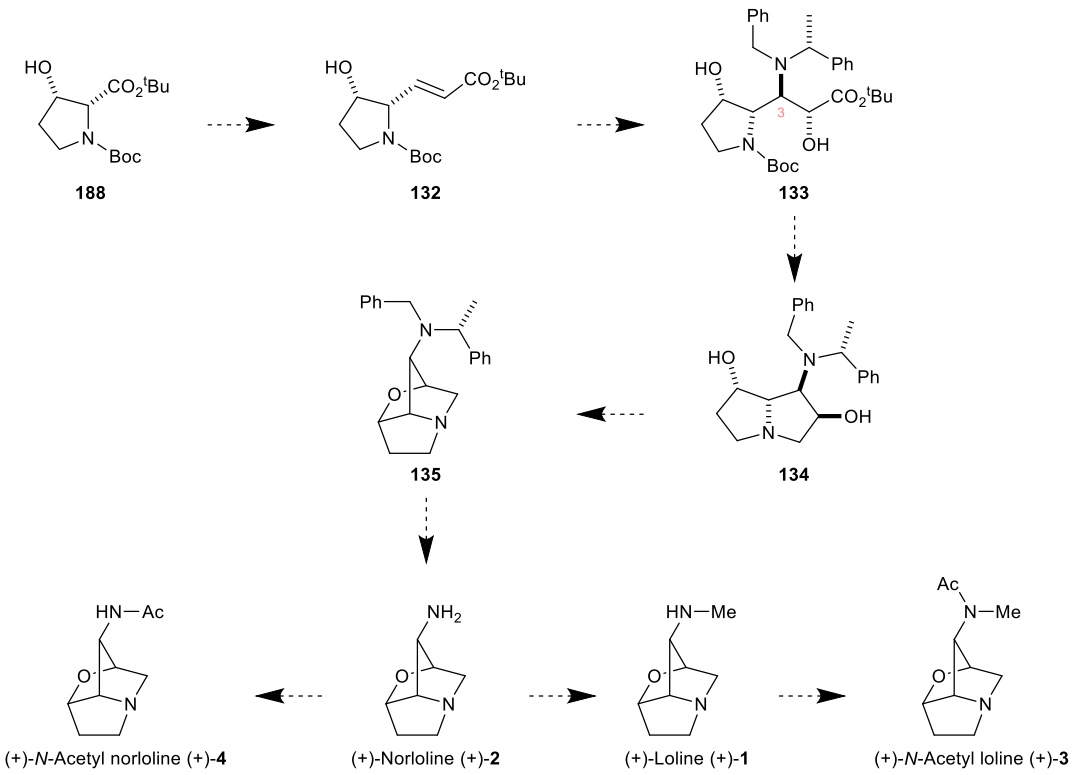
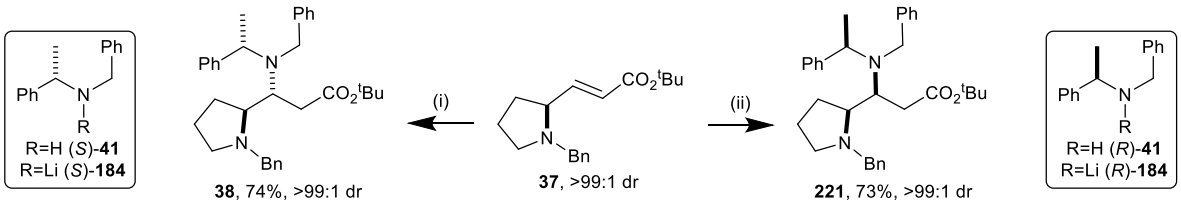


Figure 19 The proposed synthesis of the loline alkaloids (+)-**1**–**4** from *N*-Boc *cis*-pyrrolidine **188**.

3.2 Previous Work

In the synthesis of absouline (+)-**6** by Davies *et al.*'s, they report the lithium amide conjugate addition to α,β-unsaturated ester **37** with both (*S*)- and (*R*)-configured lithium amides (*S*)-**184**

and (*R*)-**184** in 74% and 73% yield, respectively.[1] This confirms that the addition of both (*S*)-**184** and (*R*)-**184** is reagent controlled, as opposed to being dominated by any inherent substrate control from α,β-unsaturated ester **37** (Scheme 44). Therefore, (*R*)-lithium amide (*R*)-**184** will be used for the addition to α,β-unsaturated ester **132**, needed for the synthesis of the loline alkaloids.



Scheme 44 *Reagents and conditions:* (i) ^{n}BuLi, (*S*)-**41**, THF, –78 °C, 30 min, then **37**, THF, –78 °C, 2 h; (ii) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **37**, THF, –78 °C, 2 h.

3.3 Proposed Synthesis

The proposed synthesis of the loline alkaloids **1**–**4** utilised *N*-Boc *cis*-pyrrolidine **188** – an intermediate in the first-generation synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** as the starting point. Preliminary investigations in this work will use the *N*-Boc protecting group to evaluate its efficiency in contrast to the *N*-benzyl protected α,β-unsaturated ester **37** used by Davies *et al*.[1] Protection of the free hydroxy in *N*-Boc pyrrolidine **188** as silyl ether **222** would be followed by reduction of the ester to the corresponding aldehyde followed by *in situ* Wittig olefination to give α,β-unsaturated ester **223**. A conjugate addition, with (*R*)-lithium amide (*R*)-**184**, followed by oxidation of the resulting enolate with (–)-CSO (−)-**183** will give α-hydroxy-β-amino ester **224** in the key stereo-defining step in this synthesis. Cyclisation of the deprotected cyclic amine onto the ester and reduction of the corresponding pyrrolidinone would give pyrrolizidine **225**. Activation of the C(2) alcohol in pyrrolizidine **225** upon tosylation followed by deprotection of the corresponding C(7) silyl ether would give alcohol **226**, which

upon heating[2] was expected to cyclise to give the loline scaffold **135**. Final *N*-deprotection and functionalisation would give the loline alkaloids **1**–**4** (Figure 20).

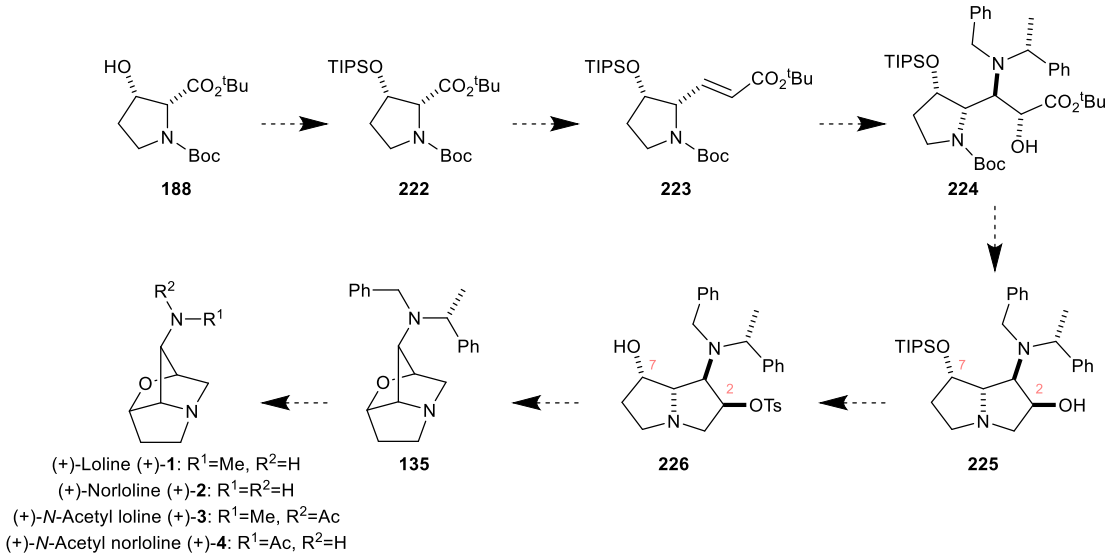
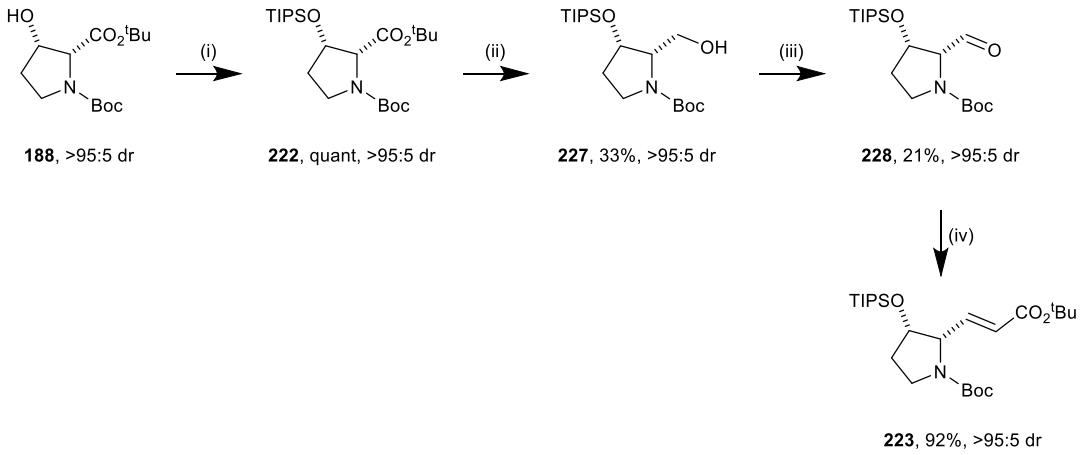


Figure 20 Proposed synthesis of the loline alkaloids (+)-**1**–**4** from *N*-Boc *cis*-pyrrolidine **188.**

3.3.1 Substrate Preparation

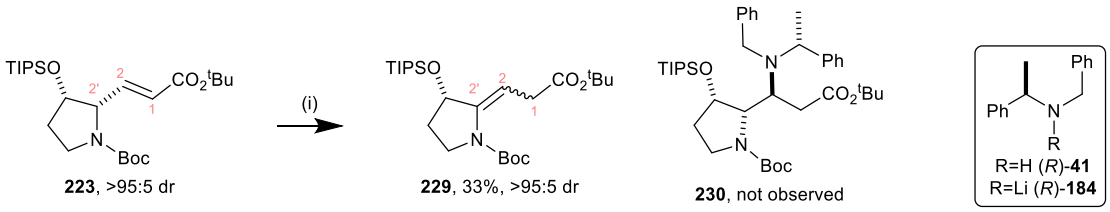
Protection of *N*-Boc *cis*-pyrrolidine **188** as the corresponding silyl ether **222** proceeded in a quantitative yield and >95:5 dr; with no evidence of C(2) epimerisation (*vide supra*) when exposed to NaH. All attempts at reduction of ester **222** to aldehyde **228** in one step yielded an inseparable mixture of ester **222**, aldehyde **228** and the alcohol **227**. Therefore, it was carried out via a two-step process; reduction to alcohol **227** using an excess of DIBAL-H, followed by Swern oxidation to give aldehyde **228** in a 7% overall yield for the two steps. Wittig olefination with aldehyde **228** and ylid **177** gave (*E*)-α,β-unsaturated ester **223** in 92% yield and >95:5 dr ($^3J_{trans}$ = 15.7 Hz) (Scheme 45).



Scheme 45 *Reagents and conditions*: (i) NaH, THF, rt, 15 min, then TIPSCl, rt, 16 h; (ii) DIBAL-H, CH_2Cl_2, –78 °C, 10 min, then rt 4 h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then **227**, CH_2Cl_2, –78 °C, 30 min, then Et_3N, –78 °C, 30 min; (iv) **177**, CH_2Cl_2, rt, 16 h.

3.3.2 Lithium Amide Conjugate Addition

Conjugate addition of lithium amide (*R*)-**184**, generated from treatment of the corresponding amine (*R*)-**41** with ^{n}BuLi, did not result in formation of β-amino ester **230**. Instead, β,γ-unsaturated ester **229** was obtained as the only identifiable product and isolated in 33% yield and >95:5 dr. This is presumably due to the presence of the *N*-Boc group increasing the acidity of the C(2′) proton resulting in γ-deprotonation instead of conjugate addition (Scheme 46). This observation is consistent with previous observations by Greenaway *et al*.[3]



Scheme 46 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **223**, THF, –78 °C, 2 h.

3.4 Revised Protecting Group Strategy

In light of the C(2′) deprotonation seen when an *N*-Boc protecting group was used, it was envisaged that incorporation of an *N*-benzyl group (analogous to the protecting group strategy used by Davies *et al*. in their synthesis of absouline (+)-**6**)[1] would prove more efficient.

Therefore, the revised synthesis would use benzyl protected α,β-unsaturated ester **231** and again utilise a lithium amide conjugate addition followed by oxidation of the resultant enolate with (–)-CSO (−)-**183** to give α-hydroxy-β-amino ester **232**. Hydrogenolysis of α-hydroxy-β-amino ester **232** would give diamine **233**, which upon treatment with base and reduction, would give pyrrolizidine **234**. Protection of the exocyclic amine, tosylation of the C(2) hydroxy group followed by desilylation would give pyrrolizidine **235**, which upon heating, was anticipated to give *N*-Boc norloline (+)-**98**. *N*-Boc norloline (+)-**98**, is an advance intermediate synthesised by Trauner *et al.*[4] and Scheerer *et al.*[5] and can be readily converted to (+)-loline (+)-**1** by reduction with $LiAlH_4$ (Figure 21).[4]

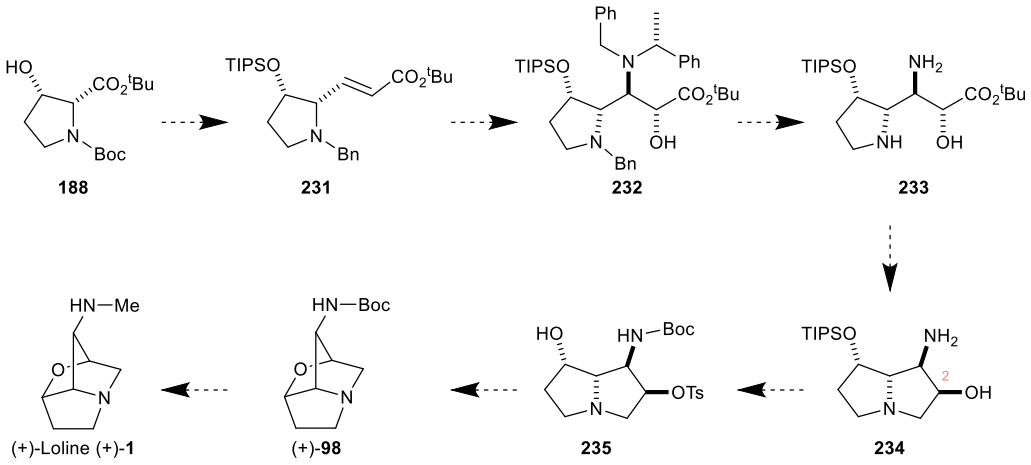
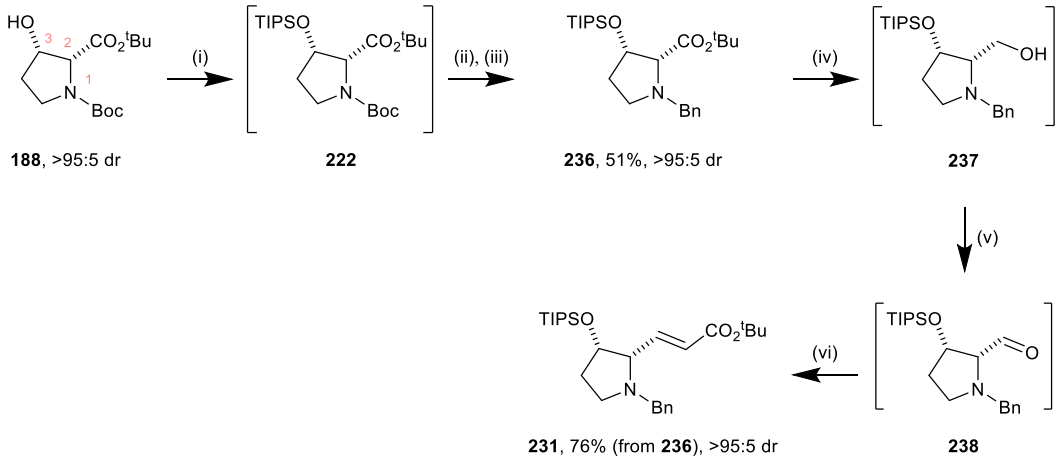


Figure 21 Revised synthesis of (+)-loline (+)-**1** from *N*-Boc *cis*-pyrrolidine **188**.

3.4.1 Substrate Preparation

N-Benzyl protected α,β-unsaturated ester **231** was prepared via silylation of the C(3) hydroxy group within **188** to give the corresponding silyl ether **222**, which was then treated with TFA and the resultant amine was exposed to BnBr in the presence of Et_3N to give *N*-benzyl pyrrolidine **236** in 51% yield over the three steps from pyrrolidine **188**. All attempts at selective reduction of ester **236** to aldehyde **238** proved to be unsuccessful. Therefore, ester **236** was reduced to alcohol **237** and oxidised back to aldehyde **238** via Swern oxidation. Interestingly,

the Swern oxidation needed to be stirred for 16 hours after the addition of Et_3N in order to obtain an acceptable yield. Aldehyde **238** was used without further purification in the subsequent Wittig olefination to give (*E*)-α,β-unsaturated ester **231** in 76% and >95:5 dr ($^3J_{trans}$ = 15.7 Hz) (Scheme 47).

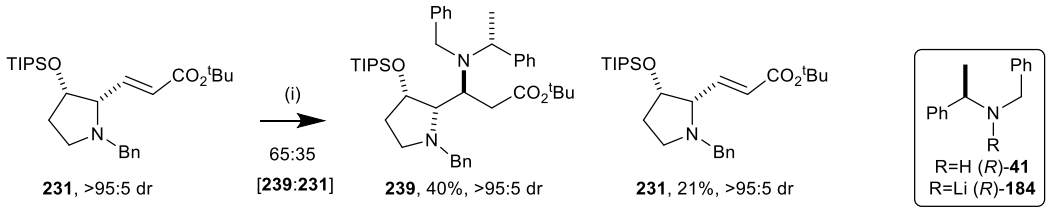


Scheme 47 *Reagents and conditions*: (i) NaH, THF, rt, 15 min, then TIPSCl, rt, 16 h; (ii) TFA, CH_2Cl_2, rt, 2 h; (iii) Et_3N, CH_2Cl_2, rt, 15 min, then BnBr, rt, 16 h; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 10 min, then rt 2 h; (v) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then **237**, CH_2Cl_2, –78 °C, 30 min, then Et_3N, –78 °C, 30 min, then rt, 16 h; (vi) **177**, CH_2Cl_2, 45 °C, 16 h.

3.5 Lithium Amide Conjugate Addition

α,β-Unsaturated ester **231** was subjected to standard lithium amide conjugate addition conditions;[6–8] lithium amide (*R*)-**184** was generated by treatment of (*R*)-amine (1.6 equiv) (*R*)-**41** with ^{n}BuLi (1.55 equiv) at –78 °C this was followed by addition of α,β-unsaturated ester **231** at –78 °C, and stirring for 2 h before quenching with saturated NH_4Cl solution. This gave a 65:35 mixture of β-amino ester **239** and α,β-unsaturated ester **231**, respectively. Purification via flash column chromatography gave β-amino ester **239** in 40% yield and >95:5 dr, and α,β-unsaturated ester **231** in 21% yield and >95:5 dr. The (3*S*,α*R*)-configuration of **239** was tentatively assigned by analogy to the well-established stereochemical outcome of this amination protocol, assuming the stereochemical outcome of the conjugate addition was dominated by reagent control.[6–8] Work was commenced to optimise this addition so that

complete consumption of α,β-unsaturated ester **231** occurs, in order to obtain β-amino ester **239** in a synthetically useful yield (Scheme 48).

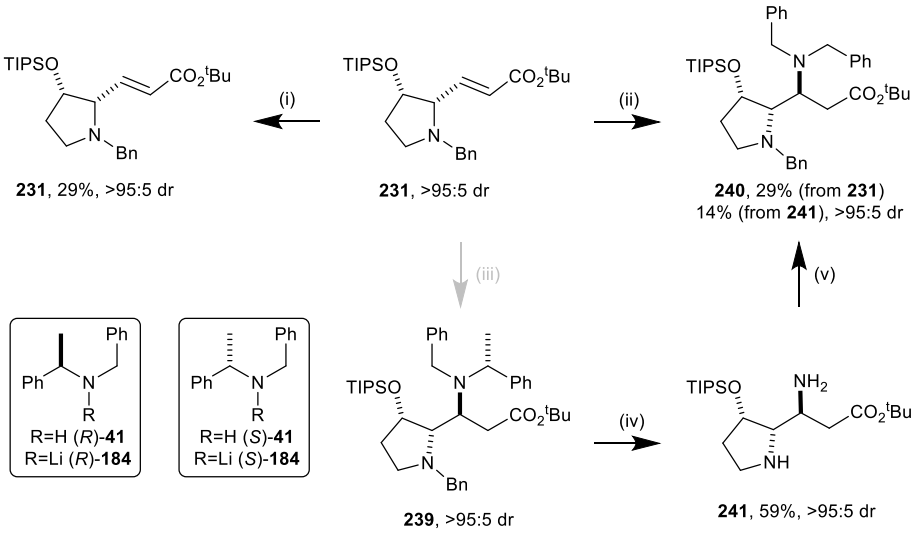


Scheme 48 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **231**, THF, –78 °C, 2 h.

3.5.1 'Matched'/'Mismatched'

Work by Davies *et al*. on the synthesis of absouline (+)-**6** showed there was essentially no inherent substrate control on the diastereoselectivity of lithium amide conjugate addition to α,β-unsaturated ester **37** (Scheme 44).[1] Contrary to this it was envisaged the presence of the C(3′) silyl ether could result in the conjugate addition being doubly diastereoselective and the combination of α,β-unsaturated ester **231** and lithium amide (*R*)-**184** being the 'mismatched' pairing. A lithium amide conjugate addition with (*S*)-amide (*S*)-**184** was carried out, however this resulted in no addition and only unreacted α,β-unsaturated ester **231** being recovered in 29% yield. The lithium amide conjugate addition was also carried out with achiral lithium dibenzylamide which gave β-amino ester **240** as a single compound in 29% yield and >95:5 dr {$[\alpha]_D^{25}$ +1.4 (*c* 1.0 in $CHCl_3$)}. In order to correlate the stereochemical outcome of this conjugate addition with the corresponding reaction with amide (*R*)-**184**, β-amino ester **239** was subjected to hydrogenolysis to give diamine **241** in 59% yield and >95:5 dr. This was tri-benzylated to give β-amino ester **240** in 14% yield and >95:5 dr {$[\alpha]_D^{25}$ +5.8 (*c* 1.0 in $CHCl_3$)} therefore confirming the stereochemical outcome of the addition of dibenzylamine to α,β-unsaturated ester **231** (Scheme 49). These data are consistent with the combination of

α,β-unsaturated ester **231** and (*R*)-amine (*R*)-**41** being the 'matched' pairing in this doubly diastereoselective conjugate addition (Scheme 49).



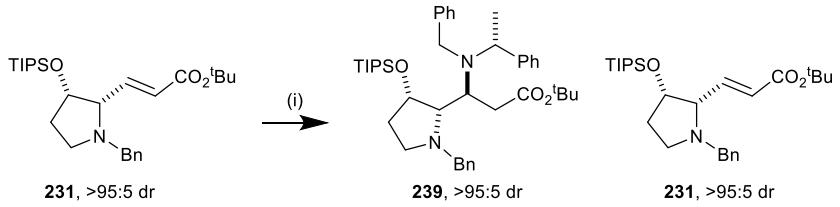
Scheme 49 *Reagents and conditions*: (i) ^{n}BuLi, (*S*)-**41**, THF, –78 °C, 30 min, then **231**, THF, –78 °C 2 h; (ii) ^{n}BuLi, $NHBn_2$, THF, –78 °C, 30 min, then **231**, THF, –78 °C 2 h; (iii) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **231**, THF, –78 °C 2 h; (iv) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 48 h; (v) BnBr, Et_3N, TBAI, CH_2Cl_2, rt, 16 h.

Presumably the origin of this 'mismatched' pairing is due to (*S*)-amine (*S*)-**41** undergoing conjugate addition from the *Re* face of α,β-unsaturated ester **231**, which is hindered by the close proximity of the silyl ether group on the bottom face of the pyrrolidine ring. Whereas, the pairing with (*R*)-amine (*R*)-**41** and α,β-unsaturated ester **231** is 'matched' due to the conjugate addition occurring on the *Si* face of α,β-unsaturated ester **231** and therefore experiencing no adverse interactions with the silyl ether.

Having established that the conjugate addition of (*R*)-amide (*R*)-**184** to α,β-unsaturated ester **231** was the likely 'matched' doubly diastereoselective combination, work was now carried out to optimise this reaction.

3.5.2 Conjugate Addition Optimisation

There are several examples in the literature where lithium amide conjugate additions have needed increased temperatures to increase both rate of addition and, hence, yield of β-amino ester products.[9–11] Therefore, a temperature screen was first undertaken. A range of temperatures was investigated: –78 °C, –60 °C, –50 °C and –40 °C (Table 8). The ratio of β-amino ester **239** to α,β-unsaturated ester **231** in the crude reaction mixture shifted in favour of α,β-unsaturated ester **231** as the temperature was increased from –78 °C to –50 °C (Table 8, entries *a*–*c*). Although, when the reaction was carried out at –40 °C, a complex mixture was obtained, from which it was not possible to determine a ratio (Table 8, entry *d*). Despite the increased amount of β-amino ester **239** detected in the crude reaction mixture, the isolated yields of β-amino ester **239** remained relatively similar as the temperature was increased from –78 °C to –40 °C (Table 8, entries *a*–*d*). However, the isolated yields of α,β-unsaturated ester **231** did increase from –78 °C to –50 °C (Table 8, entry *a*–*c*), but with the isolated yield of α,β-unsaturated ester **231** at –40 °C being anomalously low (Table 8, entry *d*). These observations are inconsistent with what was expected; as the temperature increases the rate of β-amino ester **239** formation also decreases, however the low mass recovery makes it difficult to draw definitive conclusions regarding the ratio of products. The ratio of products observed implies, as the temperature is increased, that α,β-unsaturated ester **231** increasingly undergoes competitive deprotonations, however these are not detectable due to either; regeneration of α,β-unsaturated ester **231** upon quenching of the reaction, or decomposition to non-isolated derivatives. In an attempt to identify any of these competitive deprotonation pathways Table 8, entries *a* was repeated and quenched with D_2O, however, no evidence of deuterium incorporation was seen.[12,13]

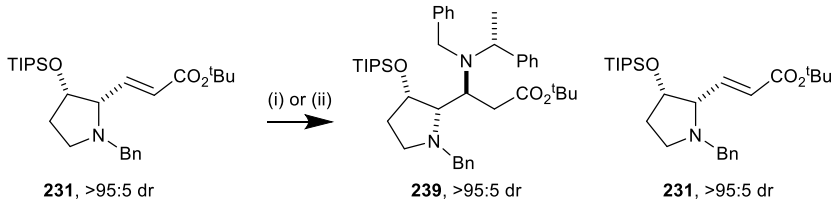


231, >95:5 dr **239**, >95:5 dr **231**, >95:5 dr

	Temperature	Crude Ratio **239**:**231**	**239**	**231**
a	–78 °C	65:35	40%	21%
b	–60 °C	42:58	32%	37%
c	–50 °C	35:65	30%	55%
d	–40 °C	-	35%	4%

Table 8 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, THF, T °C, 30 min, then **231**, THF, T °C, 2 h.

Changing the solvent in which lithium amide conjugate additions are performed has been reported to increase both the yield and diastereoselectivity of particularly troublesome conjugate additions; PhMe[14,15] and Et_2O[16,17] have both been investigated as alternative solvents for the reaction. When α,β-unsaturated ester **231** was exposed to lithium amide (*R*)-**184** in both PhMe and Et_2O at –78 °C (Table 9, entries *b* and *c*) the ratio of β-amino ester **239** to α,β-unsaturated ester **231** significantly favoured α,β-unsaturated ester **231** and the yields of β-amino ester **239** were significantly worse than in THF (Table 9, entry *a*). Davies *et al*. reported that conjugate additions carried out in Et_2O at –20 °C instead of –78 °C resulted in a significant increase in yield of the conjugate addition product.[16] This was investigated on α,β-unsaturated ester **231**, however it resulted in a complex mixture, from which no β-amino ester **239** was obtained and α,β-unsaturated ester **231** was only recovered in 18% yield (Table 9, entry *d*).

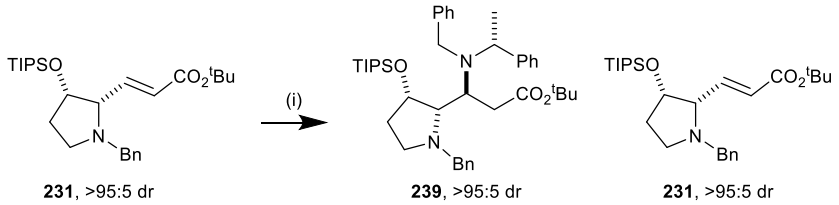


231, >95:5 dr **239**, >95:5 dr **231**, >95:5 dr

	(i) *or* (ii)	Solvent	Crude Ratio **239**:**231**	**239**	**231**
a	(i)	THF	65:35	40%	21%
b	(i)	PhMe	8:92	3%	73%
c	(i)	Et_2O	25:75	7%	54%
d	(ii)	Et_2O	-	-	18%

Table 9 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, solvent, –78 °C, 30 min, then **231**, solvent, –78 °C, 2 h; (ii) ^{n}BuLi, (*R*)-**41**, solvent, –20 °C, 30 min, then **231**, solvent, –20 °C, 5 h.

Increasing the equivalents of amine has been previously used to increase the yield of several lithium amide conjugate aditions.[1] When 10.0 equivalents of (*R*)-amine (*R*)-**41** were used a significant improvement was seen, and a 75:25 ratio of β-amino ester **239** to α,β-unsaturated ester **231** was observed with β-amino ester **239** isolated in a much improved 74% yield, with 15% α,β-unsaturated ester **231** also recovered (Table 10, entry *b*).



231, >95:5 dr **239**, >95:5 dr **231**, >95:5 dr

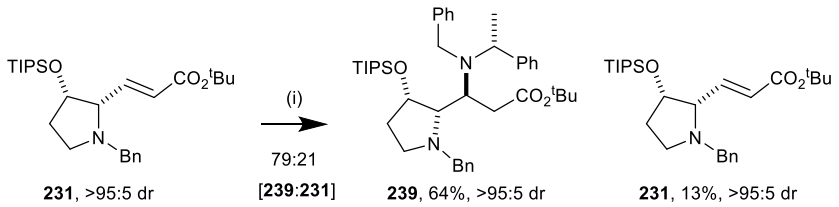
	Amide Equiv	Crude Ratio **239**:**231**	**239**	**231**
a	1.6	65:35	40%	21%
b	10.0	75:25	74%	15%

Table 10 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **231**, THF, –78 °C, 2 h.

3.5.3 Optimised conditions

The optimised reaction conditions (Table 10, entry *b*) were applied to the synthesis of β-amino ester **231** on a larger scale reaction (1 g of α,β-unsaturated ester **231**). This resulted in a slightly improved product ratio of 79:21 β-amino ester **239** to α,β-unsaturated ester **231**, which were isolated in in 64% and 13% yield, respectively (Scheme 50). It should however be noted that

when 10.0 equivalents of (*R*)-amine (*R*)-**41** were used 9.7 equivalents of ^{n}BuLi (2.5 M in hexanes) were needed to generate the corresponding amide (*R*)-**184**. This will significantly alter the polarity and concentration of the reaction medium and may affect the subsequent *in situ* enolate oxidation.

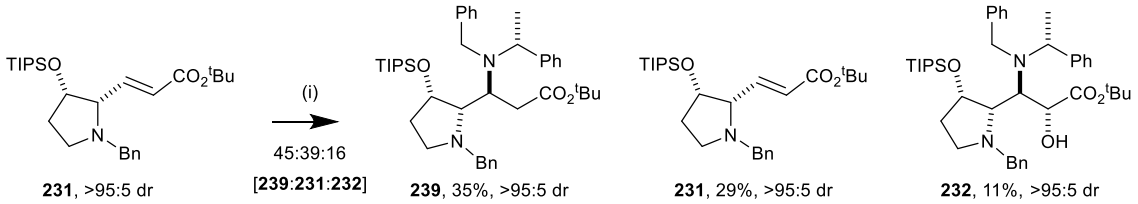


Scheme 50 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **231**, THF, –78 °C, 2 h.

3.6 α-Hydroxylation

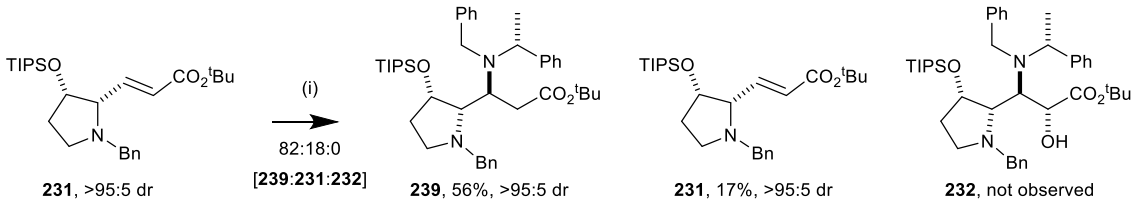
3.6.1 *In Situ* Oxidation

α-Hydroxylation was initially attempted using standard lithium amide conjugate addition conditions [1.6 equiv (*R*)-**41**, 1.55 equiv ^{n}BuLi, THF, −78 °C] followed by the addition of (−)-CSO (−)-**183** and stirring for 16 h to give a 45:39:16 mixture of β-amino ester **239**, α,β-unsaturated ester **231** and α-hydroxy-β-amino ester **232**, respectively. This resulted in isolation of α-hydroxy-β-amino ester **232** in 11% yield and >95:5 dr. The (2*R*,3*R*,α*R*)-configuration of **232** was tentatively assigned by analogy to the well-established stereochemical outcome of this aminohydroxylation protocol (Scheme 51).[6–8] α,β-Unsaturated ester **231** was isolated in 29% yield, this is similar to Scheme 48 where α,β-unsaturated ester **231** was isolated in 21% yield. The high proportion of β-amino ester **239** isolated is likely due to the resultant enolate being slow to undergo oxidation (Scheme 51).



Scheme 51 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **231**, THF, –78 °C, 2 h, then (–)-**183**, –78 °C to rt, 16 h.

As a result of the high proportion of α,β-unsaturated ester **231** being observed in Scheme 51, the 'optimised' conjugate addition protocol (10.0 equiv (*R*)-**41**, 9.7 equiv ^{n}BuLi, THF, −78 °C) was applied to the *in situ* enolate oxidation with (–)-CSO (–)-**183**. α,β-Unsaturated ester **231** was exposed to lithium amide (*R*)-**184** [10.0 equiv (*R*)-**41**, 9.7 equiv ^{n}BuLi] for two hours followed by addition of (−)-CSO (−)-**183** (12 equiv) and stirring at rt for 16 h to give an 82:18:0 mixture of β-amino ester **239**, α,β-unsaturated ester **231** and α-hydroxy-β-amino ester **232**, respectively, from which α-hydroxy-β-amino ester **232** was not isolated. The complete absence of α-hydroxy-β-amino ester **232** and high proportion of β-amino ester **239** in the reaction mixture implies the *in situ* enolate oxidation is incompatible with these conjugate addition conditions (Scheme 52).

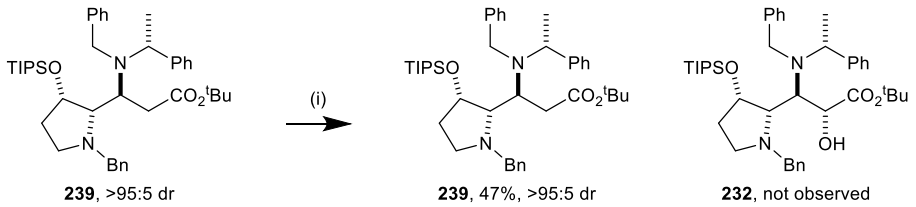


Scheme 52 *Reagents and conditions*: (i) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **231**, THF, –78 °C, 2 h, then (–)-**183**, –78 °C to rt, 16 h.

3.6.2 Step-Wise Oxidation

In an attempt to overcome the apparent incompatibility of the *in situ* enolate oxidations with the optimised conjugate additions conditions [10.0 equiv (*R*)-**41**, 9.7 equiv ^{n}BuLi, THF, −78 °C] a step wise oxidation was investigated.[18,19] β-Amino ester **239** was exposed to LDA

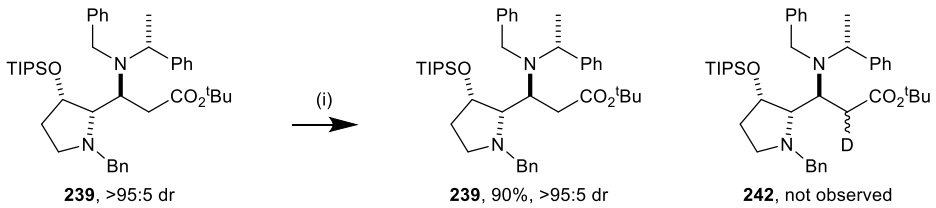
followed by addition of (–)-CSO (–)-**183** and allowing the respective mixture to warm to rt overnight. Unfortunately, this did not result in the formation of any α-hydroxy-β-amino ester **232**, only β-amino ester **239** was recovered in 47% yield and >95:5 dr (Scheme 53).



239, >95:5 dr — **239**, 47%, >95:5 dr — **232**, not observed

Scheme 53 *Reagents and conditions*: (i) $^{i}Pr_2NH$, $^{n}BuLi$, THF, –78 °C, 2 h, then (–)-**183**, –78 °C to rt, 16 h.

β-Amino ester **239** was again exposed to LDA, however this time was quenched with D_2O.[20] This resulted in the isolation of unreacted β-amino ester **239** in 90% yield and >95:5 dr. The reason for no α-deuterio-β-amino ester **242** being formed in Scheme 54 is likely to be due to α-deprotonation not occurring. Hence, the stepwise oxidation of β-amino ester **239** with LDA in Scheme 53 is likely to have been unsuccessful due to α-deprotonation not occurring; however, this does not rule out the enolate oxidation also being problematic (Scheme 54).[21]



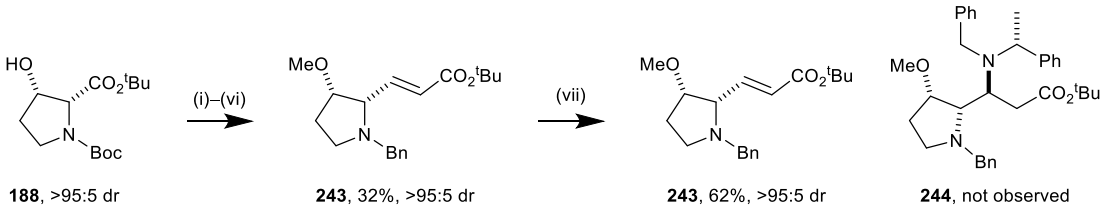
239, >95:5 dr — **239**, 90%, >95:5 dr — **242**, not observed

Scheme 54 *Reagents and conditions*: (i) $^{i}Pr_2NH$, $^{n}BuLi$, THF, –78 °C, 2 h, then D_2O.

3.7 Protecting Group Modification

In order to minimise any steric effects the silyl ether, in α,β-unsaturated ester **231**, may be adversely having on the conjugate addition of (*R*)-amide (*R*)-**184** to silyl ether α,β-unsaturated ester **231**. Methyl ether α,β-unsaturated ester **243** was synthesised from *N*-Boc *cis*-pyrrolidine **188** in six steps and 32% yield without purification of any of the intermediates. Treatment of α,β-unsaturated ester **243** with (*R*)-amide (*R*)-**184** [1.6 equiv (*R*)-**41**, 1.55 equiv $^{n}BuLi$, THF,

−78 °C] resulted in no β-amino ester **244** formation and 62% yield of recovered α,β-unsaturated ester **243** in >95:5 dr (Scheme 55). Consequently, this was not investigated any further.



188, >95:5 dr **243**, 32%, >95:5 dr **243**, 62%, >95:5 dr **244**, not observed

Scheme 55 *Reagents and conditions*: (i) NaH, THF, 0 °C, 15 min, then MeI, rt, 16 h; (ii) TFA, CH_2Cl_2, rt, 2 h; (iii) Et_3N, CH_2Cl_2, rt, 15 min, then BnBr, rt, 16 h; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 15 min, then rt 2 h; (v) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, CH_2Cl_2, –78 °C, 30 min, then Et_3N, –78 °C, 30 min, then rt, 16 h; (vi) **177**, CH_2Cl_2, 45 °C, 16 h; (vii) ^{n}BuLi, (*R*)-**41**, THF, –78 °C, 30 min, then **243**, THF, –78 °C, 2 h.

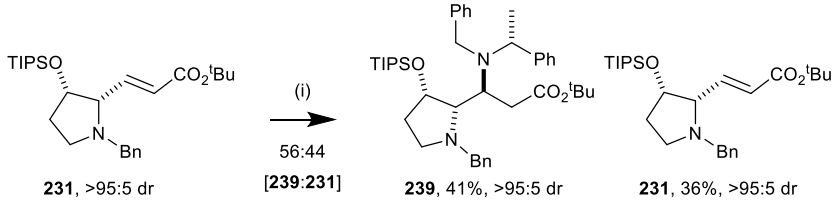
3.8 Chapter Conclusion

In conclusion, the initial protecting group strategy for the first-generation synthesis of the loline alkaloid scaffold with an *N*-Boc protecting group proved to be incompatible with the reaction conditions. An alternative *N*-benzyl protecting group was therefore investigated, and the corresponding *N*-benzyl substituted α,β-unsaturated ester **231** was successfully synthesised. Initial results for the lithium amide conjugate addition to α,β-unsaturated ester **231** were promising, however attempts to optimise this proved troublesome. Eventually the lithium amide conjugate addition yield was improved to 74%, however this required 10 equivalents of (*R*)-amine (*R*)-**41**. Attempts at α-hydroxylation of β-amino ester **239** both *in situ* and step-wise proved unsuccessful. Due to the less than ideal lithium amide conjugate addition conditions and unsuccessful α-hydroxylation this first-generation synthesis towards the loline alkaloids was abandoned and alternative approaches were investigated.

3.9 References and Notes

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(12)



Reagents and conditions: (i) ^{n}BuLi, (*R*)-**47**, THF, T °C, 30 min, then **231**, Solvent, −78 °C, 2 h, then D_2O.

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Chapter 4

4 Synthesis of the Loline Alkaloid Tricyclic Scaffold

4.1 Chapter Outline

This chapter describes the work carried out on the synthesis of the loline alkaloid tricyclic core **248** and its elaboration to (+)-norloline (+)-**2** (Figure 22). This strategy uses *N*-Boc *trans*-pyrrolidine *ent*-**189** as a precursor to the target compounds. An enolate addition to sulfinyl imine **245** is used to install the remaining two stereocenters of the loline alkaloids **1**–**4** (Figure 22).

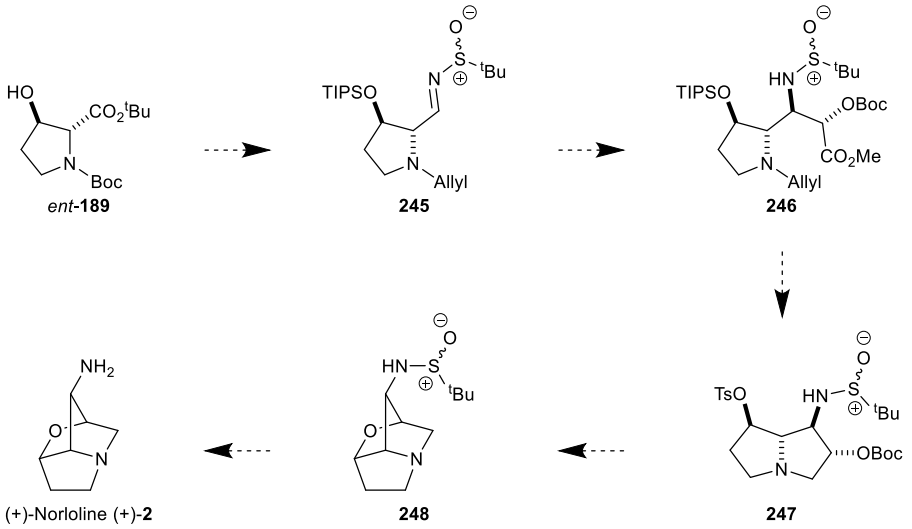
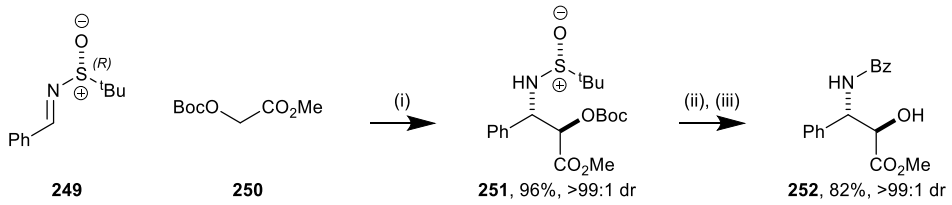


Figure 22 Proposed synthesis of (+)-norloline (+)-**2** from *N*-Boc *trans*-pyrrolidine *ent*-**189**.

4.2 α-Amino Hydroxylation

In 2006, Qin *et al*. reported the diastereoselective addition of an enolate generated from an *O*-protected methyl glycolate to *tert*-butyl sulfinylimines. Initial experiments showed that a carbonate protecting group was crucial to achieving high to excellent levels of diastereoselectivity, with the *tert*-butoxycarbonyl group (*O*-Boc) yielding the highest diastereoselectivity and yields. The absolute configuration of the adduct **251** was established by X-ray crystallographic analysis of sulfinamide **251**, with the reported structure having the

(2*R*,3*S*,*R*$_S$)-configuration. Qin *et al*. elaborated sulfinamide **251** to the known ester **252** and reported the ^{1}H NMR spectroscopic and specific rotation values matched those previously reported in the literature, further confirming the stereochemical outcome of the enolate addition (Scheme 56).[1,2]



249 **250** **251**, 96%, >99:1 dr **252**, 82%, >99:1 dr

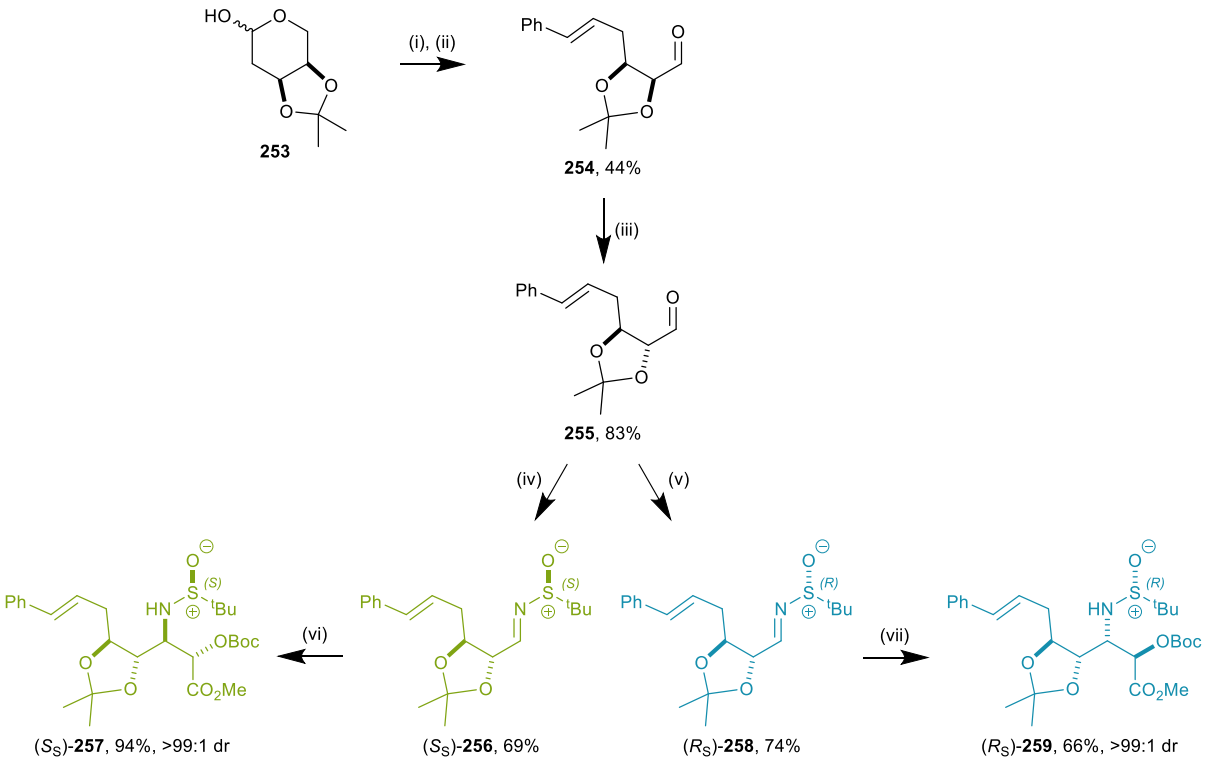
Scheme 56 *Reagents and conditions*: (i) **250**, LiHMDS, −78 °C, 1 h, then **249**, −78 °C, 3 h; (ii) HCl, MeOH, rt, 16 h; (iii) BzCl, $NaHCO_{3(aq)}$, THF, 0 °C, 2 h.

This enolate addition of *O*-protected α-hydroxyacetates to sulfinylimines has been applied to total/formal syntheses,[1,3–8] syntheses of biological agents[4,7] and for the stereoselective synthesis of chiral amino acids/esters.[9,10] In several of these cases,[3,5] the sulfinylimines are derived from chiral aldehydes, leading to the possibility of these stereocenters also influencing the stereochemical outcome of the enolate addition.

4.2.1 Enolate Addition Application

Aitkin *et al.* reported the synthesis of fragments of microsclerodermin C, D and E utilising the enolate addition of *O*-protected α-hydroxyacetates to sulfinylimines. During the synthesis of the microsclerodermin C and D fragments, Aitkin *et al.* subjected both S-epimers of sufinylimine **256** and **258** to the enolate addition reaction conditions. Acetonide **253** was subjected to a Horner-Wadsworth-Emmons olefination, followed by oxidation to give aldehyde **254** in 44% yield over two steps. Isomerisation of acetonide **254** generated aldehyde **255** in 83% yield. Aldehyde **255** was exposed to (*S*)- and (*R*)-*tert*-butanesulfinamide in the presence of $Ti(OEt)_4$ to give (*S*$_S$)-sulfinylimine (*S*$_S$)-**256** in 69% yield and (*R*$_S$)-sulfinylimine (*R*$_S$)-**258** in 74% yield, respectively. Addition of the enolate derived from ester **250** gave (*S*$_S$)-**257** and (*R*$_S$)-

259 in 94% and 66% yield, respectively and excellent diastereoselectivity (only a single diastereoisomer was detectable in both cases). The absolute configuration of the newly formed stereocenters in (S_S)-**257** and (R_S)-**259** were confirmed by single crystal X-ray diffraction. These results show that the stereochemical outcome of the enolate addition is principally directed by the stereocenter within the *N-tert*-butylsulfinyl unit (Scheme 57).[3]



Scheme 57 *Reagents and conditions*: (i) $PhCH_2P(O)(OEt)_2$, ^nBuLi, THF, 0 °C, 20 min, then **253**, THF, 45 °C, 19 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h, then Et_3N, –78 °C to –5 °C, 2.5 h; (iii) K_2CO_3, MeOH, rt, 4 h; (iv) (*S*)-*tert*-butanesulfinamide, $Ti(OEt)_4$, THF, 5.5 h; (v) (*R*)-*tert*-butanesulfinamide, $Ti(OEt)_4$, THF, 6 h; (vi) **250**, LiHMDS, THF, –78 °C, 1 h then, (S_S)-**256**, THF, –78 °C, 1 h; (vii) **250**, LiHMDS, THF, –78 °C, 30 min, then (R_S)-**258**, THF, –78 °C, 1 h.

4.3 Loline Alkaloid Second-Generation Retrosynthesis

The second-generation retrosynthesis of the loline alkaloids will utilise the enolate addition of an *O*-protected α-hydroxy acetate to sulfinylimine **260** to install the α-hydroxy-β-amino functionality.[1] However, due to the predicted stereochemical outcome of enolate addition, the configuration of the C(3)-stereogenic centre on the proline residue must be inverted compared

to the first-generation synthesis. Therefore, this second-generation synthesis starts from (2*R*,3*R*)-*N*-Boc pyrrolidine *ent*-**189**, and an *N*-allyl protecting group was chosen over the *N*-benzyl group due to the lack of literature precedent of subjecting sulfinamies to hydrogenation conditions. It was therefore proposed to convert (2*R*,3*R*)-*N*-Boc pyrrolidine *ent*-**189** into *N*-allyl sulfinylimine (*S*S)-**260**. Enolate addition to *N*-allyl sulfinylimine (*S*S)-**260**, followed by de-allylation and subsequent cyclisation would be predicted to give pyrrolizidinone **262**. Reduction of pyrrolizidinone **262** followed by desilylation of the corresponding silyl ether would give C(7)-hydroxy pyrrolizidine **263**. C(7)-Hydroxy pyrrolizidine **263** would be selectively activated as the corresponding tosylate and then the C(2)-hydroxy group would be liberated by exposure to formic acid to give hydroxy pyrrolizidine **264**. Either thermolysis or base induced cyclisation of hydroxy pyrrolizidine **264** would then give the tricyclic scaffold **265**. This would be subsequently converted to the loline alkaloids **1**–**4** (Figure 23).

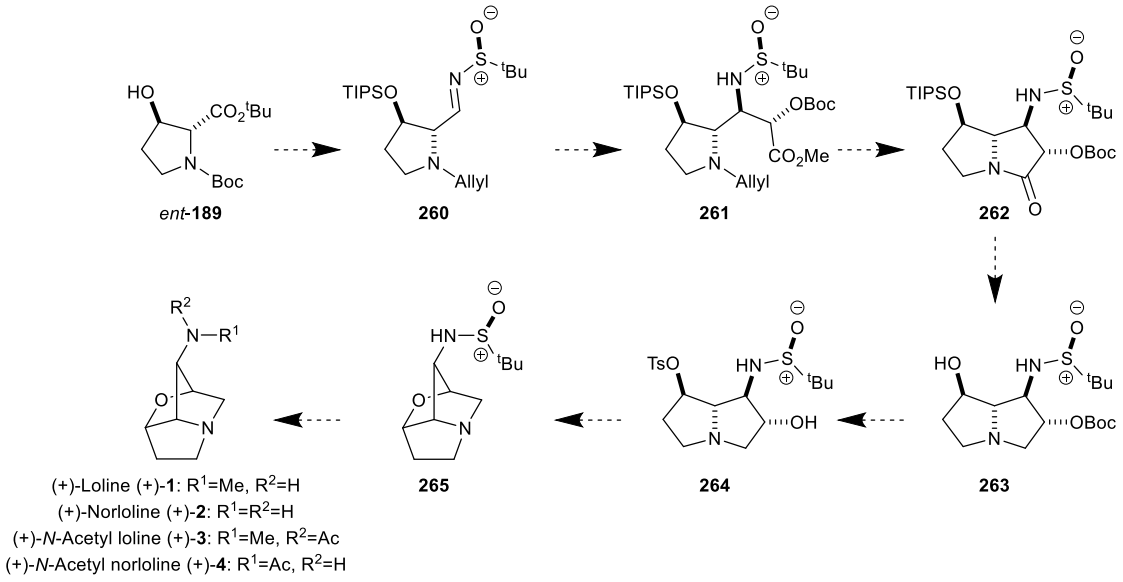
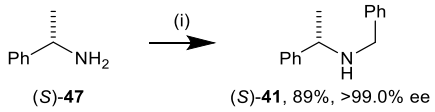


Figure 23 Second-generation synthesis towards the loline alkaloids **1**–**4.**

4.4 Substrate Preparation

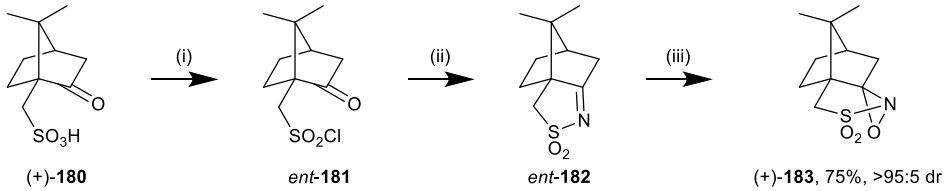
The enantiomeric series of reagents to those prepared in Chapter 2 were needed for this second-generation synthesis to enable preparation of *ent*-**189**. Due to scalability issues and protecting

group desirability the first-generation synthesis of 3-hydroxyproline was applied to the synthesis of *N*-Boc-*trans*-pyrrolidine *ent*-**189**. Secondary amine (*S*)-**41** was prepared by formation of the corresponding imine with enantiopure amine (*S*)-**47** (>99.0% ee) and benzaldehyde followed by reduction with $NaBH_4$ which gave secondary amine (*S*)-**41** in 89% yield. Amine (*S*)-**41** was determined to be of >99% ee by ^1H NMR spectroscopic analysis in the presence of the chiral solvation agent (*R*)-*O*-acetylmandelic acid and comparison with an authentic racemic sample (Scheme 58). [11]



Scheme 58 *Reagents and conditions*: (i) Benzaldehyde, EtOH, reflux, then $NaBH_4$, 0 °C to rt, 48 h.

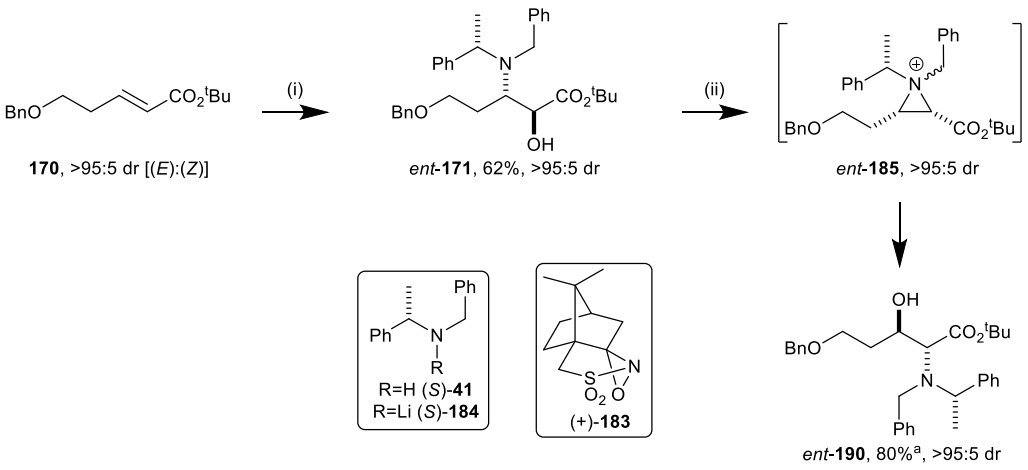
(+)-CSO **183** was prepared from (+)-camphorsulfonic acid **180** by sequential conversion to the to the corresponding sulfonyl chloride *ent*-**181**, sulfonyl imine formation and oxidation of the imine *ent*-**182** with peracetic acid to give oxaziridine (+)-**183** in 75% yield from (+)-**180** and >95:5 dr (Scheme 59).[12]



Scheme 59 *Reagents and conditions*: (i) $SOCl_2$, $CHCl_3$, reflux, 12 h; (ii) $NH_{3(aq)}$, $CHCl_3$, 4 h, 0 °C, then Amberlyst®15, PhMe, reflux, 12 h; (iii) Aliquat 336, K_2CO_3, peracetic acid, CH_2Cl_2, 5 °C to rt, 8 h.

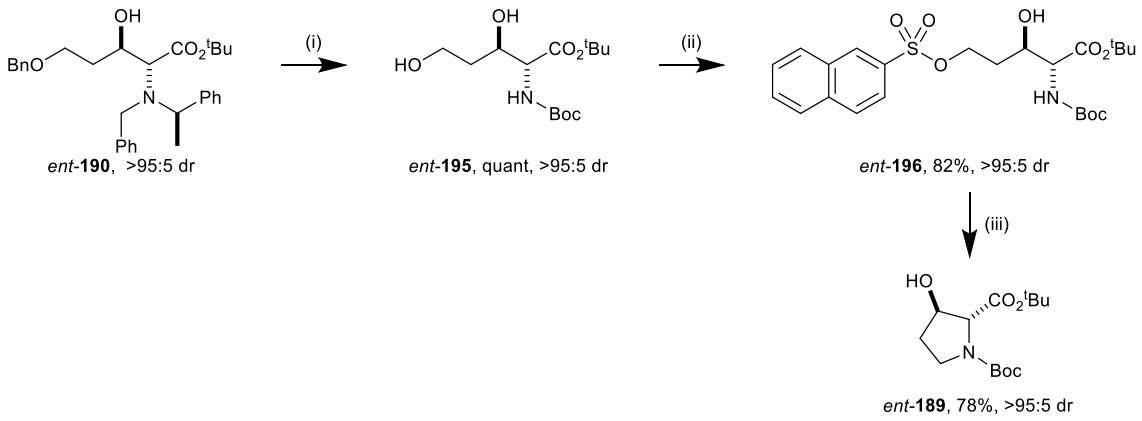
Conjugate addition of lithium amide (*S*)-**184** to α,β-unsaturated ester **170**, followed by *in situ* oxidation of the corresponding enolate with (+)-CSO **183** gave α-hydroxy-β-amino ester *ent*-**171** in 62% yield and >95:5 dr. Treatment of α-hydroxy-β-amino ester *ent*-**171** with Tf_2O and DTBMP followed by the addition of water gave β-hydroxy-α-amino ester *ent*-**190** in 80% yield as a single diastereoisomer (>95:5 dr) after three iterations of the reaction.[13] The stereochemistry of β-hydroxy-α-amino ester *ent*-**190** was unambiguously assigned by

comparison of spectroscopic data and specific rotation {**190** $[\alpha]_D^{20}$−30.2 (*c* 1.0 in $CDCl_3$)} to its enantiomer β-hydroxy-α-amino ester **190** {*ent*-**190** $[\alpha]_D^{20}$+36.0 (*c* 1.0 in $CDCl_3$)} from the first-generation synthesis of (2*S*,3*S*)-*cis*-3-hydroxyproline **136** (*vide supra*) (Scheme 60).



Scheme 60 *Reagents and conditions*: (i) ^{n}BuLi, (*S*)-**41**, THF, –78 °C, 30 min, then **170**, THF, –78 °C 2 h, then, (+)-**183**, –78 °C to rt, 12 h; (ii) Tf_2O, DTBMP, CH_2Cl_2, 0 °C to rt, 6 h, then H_2O, rt 16 h. [a] isolated yield of *ent*-**190** after three iterations.

Subjecting β-hydroxy-α-amino ester *ent*-**190** to hydrogenolysis at 5 atmospheres in the presence of Boc_2O yielded diol *ent*-**195** in quantitative yield and >95:5 dr. Diol *ent*-**195** was activated as the 2-napththyl sulfonate *ent*-**196** in 82% yield and >95:5 dr. Displacement of 2-naphthyl sulfonate *ent*-**196** was achieved by exposure to ^{n}BuLi to form the corresponding pyrrolidine *ent*-**189** in 78% yield and >95:5 dr with no evidence of C(2) epimerisation (Scheme 61). The relative configuration within pyrrolidine *ent*-**189** was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 24).[14] A Flack *x* parameter[15] of –0.009(8) for the crystal structure of *ent*-**189** was also consistent with its assigned absolute (*R*,*R*)-configuration.



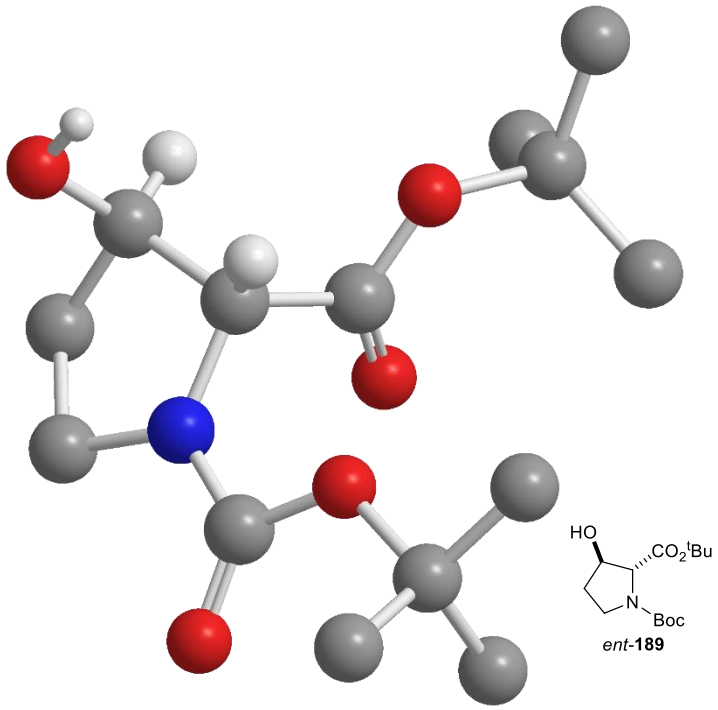
ent-**190**, >95:5 dr

ent-**195**, quant, >95:5 dr

ent-**196**, 82%, >95:5 dr

ent-**189**, 78%, >95:5 dr

Scheme 61 *Reagents and conditions*: (i) $Pd(OH)_2/C$, Boc_2O, MeOH, H_2 (5 atm), rt, 96 h; (ii) 2-Nap-SO_2Cl, pyridine, 0 °C, 1 h; (iii) ^{n}BuLi, THF, –78 °C to rt, 2.5 h.



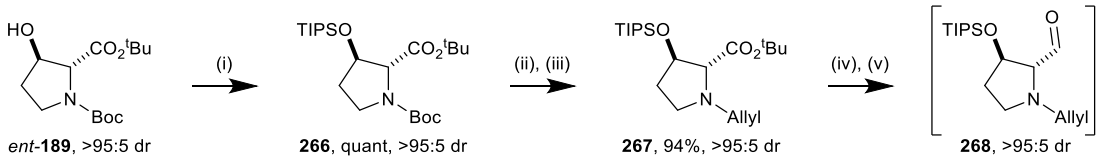
ent-**189**

Figure 24 X-ray crystal structure of *ent*-**189**·$CHCl_3$ (selected H atoms and $CHCl_3$ are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

4.5 Stereochemical Investigation of Enolate Addition to Sulfinamide

The free hydroxy group in pyrrolidine *ent*-**189** was protected as the corresponding silyl ether **266**, which was obtained in quantitative yield and >95:5 dr. Treatment of *N*-Boc pyrrolidine **266** with TFA gave the corresponding pyrrolidine which, without further purification, was subjected to allylation conditions to give *N*-allyl pyrrolidine **267** in 94% yield (from **266**) and

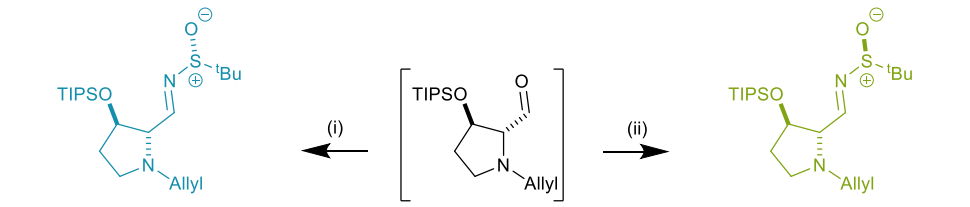
>95:5 dr. Reduction of ester **267** to the corresponding alcohol followed by Swern oxidation gave aldehyde **268** as a single diasteroisomer. Aldehyde **268** was used in the subsequent reactions without purification (Scheme 62).



ent-**189**, >95:5 dr — **266**, quant, >95:5 dr — **267**, 94%, >95:5 dr — **268**, >95:5 dr

Scheme 62 *Reagents and conditions*: (i) NaH, THF, rt, 15 min, then TIPSCl, rt, 16 h; (ii) TFA, CH_2Cl_2, rt, 2 h; (iii) Et_3N, CH_2Cl_2, rt, 15 min, then allylBr, rt, 16 h; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 15 min, then rt, 2 h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 20 min, then –78 °C, 30 min, then Et_3N, –78 °C to rt, 16 h.

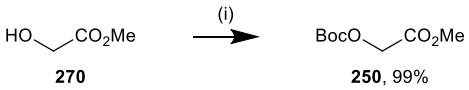
In order to investigate any effect of the C(2) and C(3) stereocenters on the diastereoselectivity of the addition to the corresponding sulfinylimine, aldehyde **268** was reacted with both (*R*)- and (*S*)-*tert*-butanesulfinamide in the presence of $Ti(OEt)_4$. (R_S)-Sulfinylimine (R_S)-**269** was isolated in 59% yield and >95:5 dr from ester **266**. (S_S)-Sulfinylimine (S_S)-**260** was isolated in 67% yield and >95:5 dr from ester **266**. Both (R_S)- and (S_S)-sulfinylimine (R_S)-**269** and (S_S)-**260** were synthesised from ester **266** without chromatography of the corresponding intermediates (Scheme 63).



(R_S)-**269**, 59% (from **266**), >95:5 dr — **268**, >95:5 dr — (S_S)-**260**, 67% (from **266**), >95:5 dr

Scheme 63 *Reagents and conditions*: (i) (*R*)-*tert*-butanesulfinamide, $Ti(OEt)_4$, THF, rt, 24 h; (ii) (*S*)-*tert*-butanesulfinamide, $Ti(OEt)_4$, THF, rt, 24 h.

Ester **250** was prepared in 99% yield according to the procedure of Mangelinckx *et al.* from methyl glycolate **270** upon the reaction with Boc_2O in the presence of DMAP (Scheme 64).[1,10]

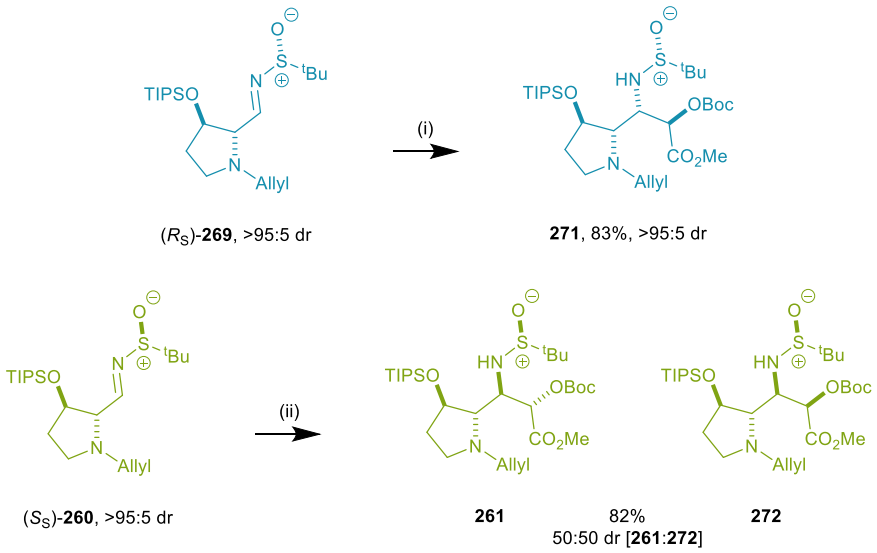


270 **250**, 99%

Scheme 64 *Reagents and conditions*: (i) Boc_2O, DMAP, MeCN, rt, 72 h.

4.5.1 Enolate Addition

Following the literature procedure, treatment of ester **250** (5 equiv) with LiHMDS (5 equiv) followed by addition of (R_S)-sulfinylimine (R_S)-**269** (1 equiv) gave α-hydroxy-β-amino ester **271** in 83% yield as a single diastereoisomer. However when (S_S)-sulfinylimine (S_S)-**260** was subjected to the same reaction conditions, an inseparable 50:50 dr mixture of C(2) epimers **261** and **272** was obtained (*vide infra*) (Scheme 65).



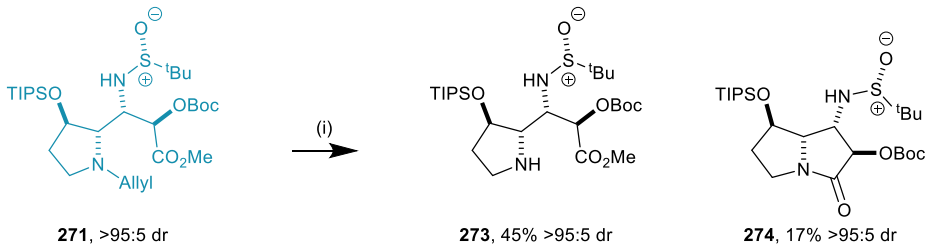
(R_S)-**269**, >95:5 dr **271**, 83%, >95:5 dr

(S_S)-**260**, >95:5 dr **261** 82% **272**
50:50 dr [**261**:**272**]

Scheme 65 *Reagents and Conditions*: (i) **250**, LiHMDS, −78 °C, 1 h, then (R_S)-**269**, −78 °C, 3 h; (ii) **250**, LiHMDS, −78 °C, 1 h, then (S_S)-**260**, −78 °C, 3 h.

In order to establish the stereochemistry of the enolate adducts **271**, **261** and **272** they were cyclised to the corresponding pyrrolizidinone derivatives in an effort to generate crystalline derivatives, enable examination of nOe correlations in the cyclic systems, and ultimately elaborate to the loline alkaloids **1**−**4**. α-Hydroxy-β-amino ester **271** derived from (R_S)-sulfinylimine (R_S)-**269** was treated with $Pd(PPh_3)_4$ and DMBA to give pyrrolidine **273** in 45%

yield and >95:5 dr and the cyclised pyrrolizidinone **274** in 17% yield and >95:5 dr. The relative configuration within pyrrolizidinone **274** was established unambiguously by single crystal X-ray diffraction analysis (Figure 25).[14] A Flack *x* parameter[15] of +0.007(16) for the crystal structure of pyrrolizidinone **274** was also consistent with its assigned absolute (1*S*,2*R*,7*R*,7a*S*,R_S)-configuration, thereby also establishing the assigned configuration of α-hydroxy-β-amino ester **271** and pyrrolidine **273**.



Scheme 66 *Reagents and Conditions*: (i) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, rt, 18 h.

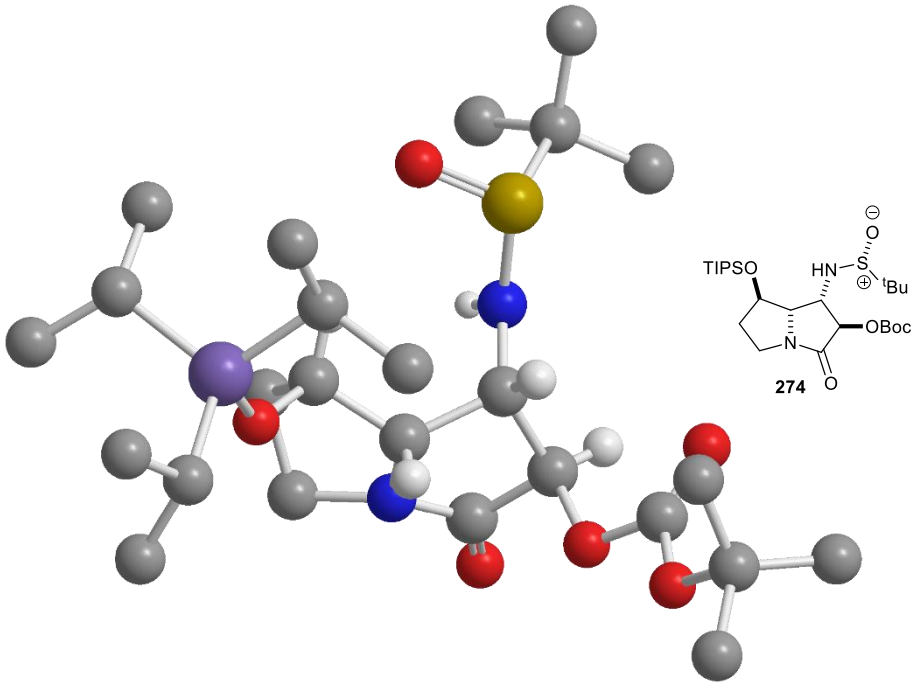
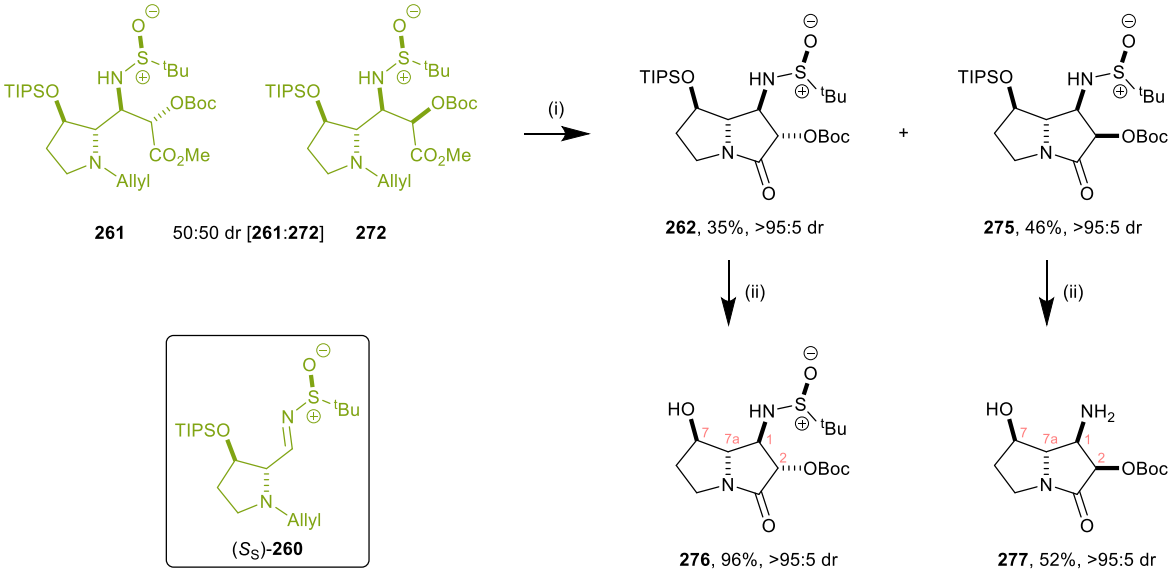


Figure 25 X-ray crystal structure of **274** (selected H atoms are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

Following the same approach, the ≈ 50:50 mixture of α-hydroxy-β-amino esters **261** and **272** derived from (S_S)-sulfinylimine (S_S)-**260** was treated with polymer supported $Pd(PPh_3)_4$ and

DMBA, which gave a separable ≈ 50:50 mixture of pyrrolizidinones **262** and **275**. Purification via chromatography gave **262** and **275** in 35% and 46% yield, respectively.[10] Upon treatment of pyrrolizidinone **262** with TBAF alcohol **276** was isolated in 96% yield and >95:5 dr (Scheme 67). The relative configuration within pyrrolizidinone **276** was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 26).[14] A Flack *x* parameter[15] of –0.011(17) for the crystal structure of pyrrolizidinone **276** was also consistent with its assigned absolute (1*R*,2*S*,7*R*,7a*S*,S_S)-configuration, thereby establishing the configurations of pyrrolizidinone **262** and α-hydroxy-β-amino ester **261**. Surprisingly, treatment of pyrrolizidinone **275** with TBAF under the same conditions gave amino alcohol **277** in 52% yield and >95:5 dr, in which deprotection of both the *N*-*tert*-butyl sulfinyl and OTIPS groups had occurred (Scheme 67). The stereochemistry of amino alcohol **277** was partly established by NOESY analysis in C_6D_6, where a strong correlation could be seen between C(1)*H* and C(7)*H* suggesting that they were *cis*- in pyrrolizidinone **277** (Figure 27). However, due to overlapping proton resonances in the ^{1}H NMR spectrum it was not possible to determine the relative configuration at C(2) or C(7a) by NOESY analysis. The absolute configuration at the C(1), C(2), C(7) and C(7a) stereocenters in pyrrolizidinone **276** is known from single crystal X-ray diffraction analysis (Figure 26) and the relative configuration of C(1) and C(7) in pyrrolizidinone **277** is known from NOESY analysis. When combined with the fact that pyrrolizidinones **276** and **277** are both derived from (S_S)-sulfinylimine (S_S)-**260**, the stereochemistry at C(7) and C(7a) in pyrrolizidinones **276** and **277** must be the same. Therefore, the configurations of C(1), C(7) and C(7a) in pyrrolizidinones **276** and **277** are common, and they must be epimeric at C(2). Thus, the configurations in **272**, **275** and **277** were assigned accordingly.



Scheme 67 *Reagents and Conditions*: (i) Polymer bound $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, rt, 18 h; (ii) TBAF, THF, rt, 2 h.

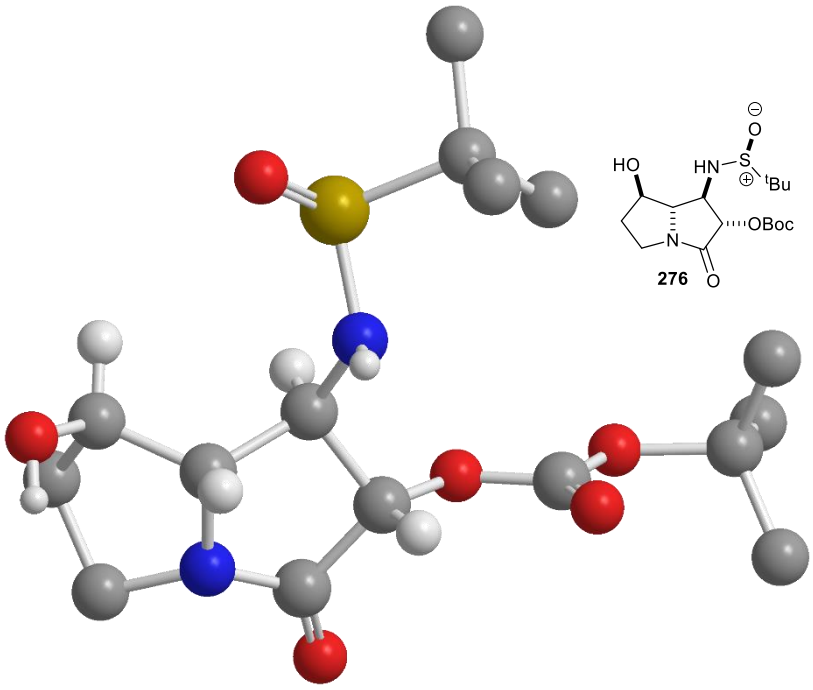
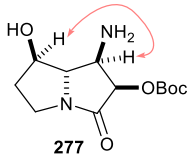


Figure 26 X-ray crystal structure of **276** (selected H atoms are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.



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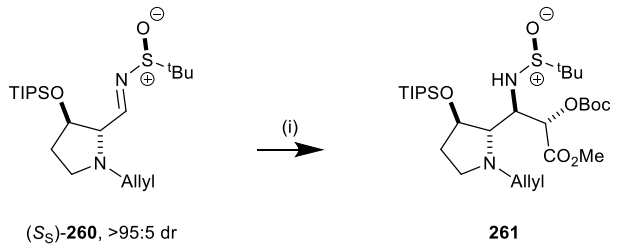
Figure 27 NOESY analysis of **277**.

4.5.2 Section Conclusion

The stereochemical outcome of the enolate addition to both (R_S)- and (S_S)-sulfinylimine (R_S)-**269** and (S_S)-**260** has been established. The enolate addition to (S_S)-sulfinylimine (S_S)-**260** gave a 50:50 mixture of C(2) epimers including the α-hydroxy-β-amino ester **261** needed for the synthesis of the loline alkaloids **1**–**4** Studies next focussed on improving the diastereoselectivity.

4.6 Enolate Addition Optimisation

The base used to generate the enolate from ester **250** was varied to see if this improved the diastereoselectivity of the enolate addition. LDA was initially investigated (Table 11 entry *b*) as an alternative lithium base; however, this gave an inseparable mixture of C(2) epimers **261** and **272** in 64% combined yield and 48:52 dr. Due to the similarities of these results with those from LiHMDS it was decided to vary the cation. Use of NaHMDS and KHMDS both resulted in formation of α-hydroxy-β-amino ester **261** as a single diastereoisomer in 76% and 61% yield, respectively (Table 11 entry *c* and *d*).



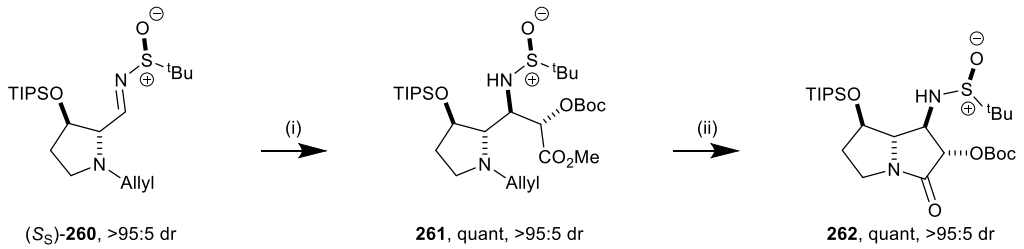
(S_S)-**260**, >95:5 dr → **261**

	Base	Crude Ratio 261:272	Yield of 261	261 dr
a	LiHMDS	-	82%	50:50
b	LDA	48:52	64%	48:52
c	NaHMDS	>95:5	76%	>95:5
d	KHMDS	>95:5	61%	>95:5

Table 11 *Reagents and conditions*: (i) **250**, base, −78 °C, 1 h, then (S_S)-**260**, −78 °C, 3 h.

4.6.1 Optimised Enolate Addition Conditions

The enolate addition to (S_S)-sulfinylimine (S_S)-**260** using NaHMDS gave α-hydroxy-β-amino ester **261** in a quantitative yield and >95:5 dr when repeated on a 1.5 g scale. α-Hydroxy-β-amino ester **261** was treated with $Pd(PPh_3)_4$ and DMBA to give pyrrolizidinone **262** in quantitative yield and >95:5 dr. The spectroscopic data for this sample of pyrrolizidinone **262** were identical to the sample of **262** prepared previously; therefore, confirming the stereochemical outcome of the addition of the enolate generated with NaHMDS to (S_S)-sulfinylimine (S_S)-**260** and unambiguously confirming the configurations of **261** and **262** (Scheme 68).



(S_S)-**260**, >95:5 dr → **261**, quant, >95:5 dr → **262**, quant, >95:5 dr

Scheme 68 *Reagents and conditions*: (i) **250**, NaHMDS, −78 °C, 1 h, then (S_S)-**260**, −78 °C, 3 h; (ii) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, rt, 18 h.

4.6.2 Section Conclusion

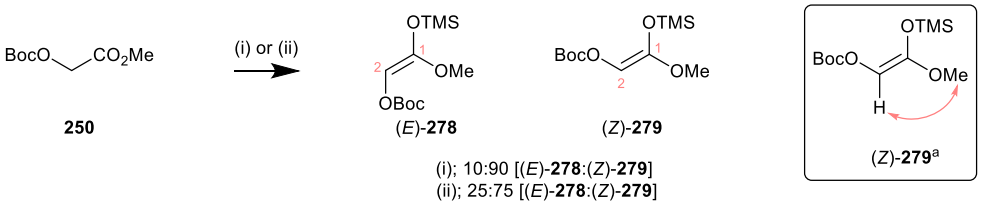
The addition of the enolate derived from ester **250** to (S_S)-sulfinylimine (S_S)-**260** was optimised by varying the base used to generate the requisite enolate.[16] When LiHMDS was used to generate the enolate the reaction proceeded in an 82% yield and resulted in formation of an inseparable 50:50 mixture α-hydroxy-β-amino ester C(2)-epimers **261** and **272**. However, when NaHMDS was used to generate the enolate this proceeded to give α-hydroxy-β-amino ester **261** in a quantitative yield and >95:5 dr.

4.7 Diastereoselectivity Investigation

Four models justify the observed stereochemical outcomes upon the addition of the enolate (generated from the treatment of *O*-Boc methylglycolate **250** with base) to *tert*-butylsulfinylimines were previously reported: both cyclic[1,3,10] and non-chelated[3,9] transition states have been proposed, all of which incorporate (*E*)-enolates.[1,3,9,10,17] However, no experimental evidence has been provided to support these models.

In light of the improved diastereoselectivity upon switching from LiHMDS to NaHMDS, it was of interest to determine the (*E*):(*Z*) diastereomeric ratio of intermediate enolate(s) generated. Therefore, the corresponding silyl enol ethers were synthesised from ester **250**. Generation of silyl enol ethers from ester **250** in the presence of LiHMDS and TMSCl resulted in a 10:90 mixture of silyl enol ethers (*E*)-**278** and (*Z*)-**279**.[18] Meanwhile the silyl enol ethers generated from ester **250** in the presence of NaHMDS and TMSCl resulted in a 25:75 mixture of silyl enol ethers (*E*)-**278** and (*Z*)-**279** (Scheme 69).[19] The geometry of the (*Z*)-silyl enol ether (*Z*)-**279** was assigned by NOESY analysis whereby a strong through-space correlation between C(2)-*H* and

O*Me* was observed for the major component when both LiHMDS and NaHMDS were used (Scheme 69).

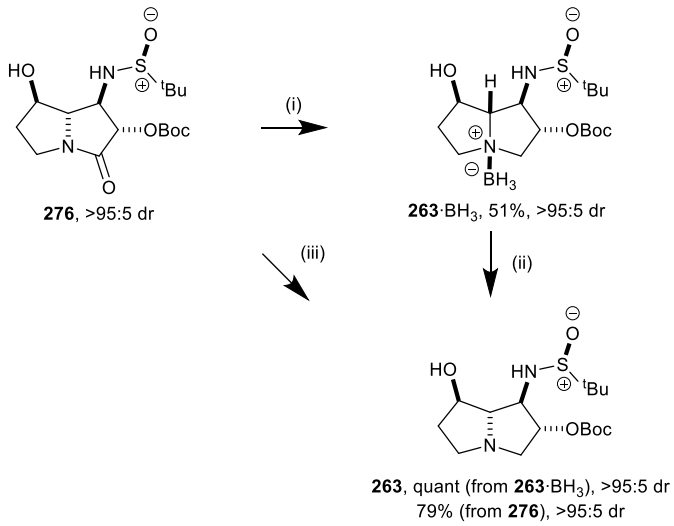


Scheme 69 *Reagents and conditions*: (i) **250**, LiHMDS, TMSCl, −78 °C, 2 h, then rt, 30 min; (ii) **250**, NaHMDS, TMSCl, −78 °C, 2 h, then rt, 30 min. [a]NOESY analysis of (*Z*)-**279**

Preparation of the enolates of α-alkyl and α-aryl enolates under these conditions is known to preferentially give the (*E*)-enolate,[20] which is consistent with deprotonation according to the Ireland model.[21] Preferential formation of the (*Z*)-enolate from ester **250** with both LiHMDS and NaHMDS is therefore in direct contrast to these observations. It is however consistent with chelation of the metal cation between the *O*-Boc group and the ester carbonyl in the transition state for deprotonation; the higher proportion of (*Z*)-enolate formed when using LiHMDS over NaHMDS is further supportive of this proposal.[22] The preferential formation of the (Z)-enolate with LiHMDS in this system thus brings into question the previously proposed transition states.[1,3,9,10] Considering the stoicheiometry (5 equiv ester **250**) and enolate geometry [10:90 (*E*):(*Z*)] there is only ≈0.5 equivalent of (*E*)-enolate present in the reaction medium which cannot therefore alone account for the previously reported yields (96% [Scheme 56];[1] 94% and 66% [Scheme 57][3]). Therefore, (i) interconversion of the (*E*)- and (*Z*)-enolates occurs under the reaction conditions and the reaction proceeds via the (*E*)-enolate; (ii) the reaction proceeds preferentially though a transition state with the (*Z*)-enolate; (iii) reaction of both enolates gives rise to the same distribution of products (and the issue of interconversion is irrelevant). With the evidence currently available, it is consequently not possible to propose a meaningful transition state and further investigation into this reaction is therefore needed.

4.8 Pyrrolizidinone Reduction

Treatment of pyrrolizidinone **276** with $BH_3 \cdot Me_2S$ in THF followed by quenching with MeOH gave borane complex **263**·BH_3 in 51% yield and >95:5 dr after chromatography. The identity and relative configuration in borane complex **263**·BH_3 was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 28).[14] A Flack *x* parameter[15] of –0.02(3) for the crystal structure of borane complex **263**·BH_3 was also consistent with its assigned absolute (1*R*,2*R*,4*S*,7*R*,7a*S*,S_S)-configuration. This identity was confirmed by the observation of a single resonance in the ^{11}B NMR spectrum (δ_B −6.2 ppm), a characteristic B–H stretch in the IR spectrum of borane complex **263**·BH_3 (ν_{max} = 2378 cm^{-1}) and by high resolution mass spectrometry {*m/z* ([**263**·BH_3+Na]$^+$) requires 398.2096; found 398.2093}.[23] Heating borane complex **263**·BH_3 in MeOH for 16 h resulted in decomplexation and gave **263** in quantitative yield and >95:5 dr. Treatment of pyrrolizidinone **276** with BH_3·THF, followed by addition of MeOH and heating to 70 °C for 16 h gave pyrrolizidine **263** in 79% yield and >95:5 dr, representing an improvement in yield over the two step reduction/decomplexation protocol. The relative configuration of pyrrolizidine **263** was unambiguously confirmed by single crystal X-ray diffraction analysis of the hemihydrate **263**·0.5H_2O (Figure 29).[14] A Flack *x* parameter[15] of –0.016(14) for the crystal structure of **263**·0.5H_2O was also consistent with the assigned absolute (1*R*,2*R*,7*R*,7a*S*,S_S)-configuration of **263**, thereby confirming the assigned configuration of pyrrolizidine **263** (Scheme 70).[24]



Scheme 70 *Reagents and Conditions*: (i) $BH_3 \cdot Me_2S$, THF, rt, 2 h; (ii) MeOH-d_4, 60 °C, 16 h; (iii) $BH_3 \cdot$THF, THF, rt, 2 h, then MeOH , 70 °C, 16 h.

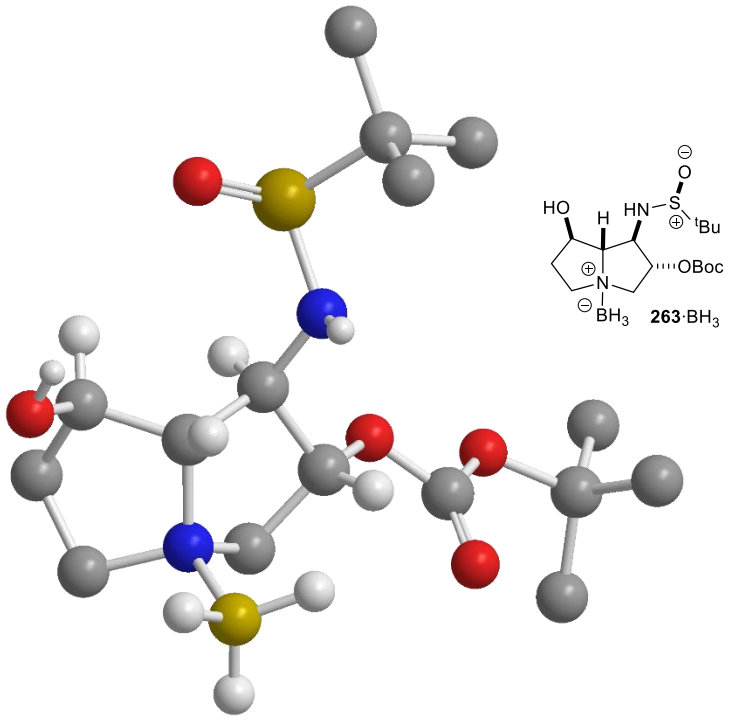


Figure 28 X-ray crystal structure of **263**·BH_3 (selected H atoms are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

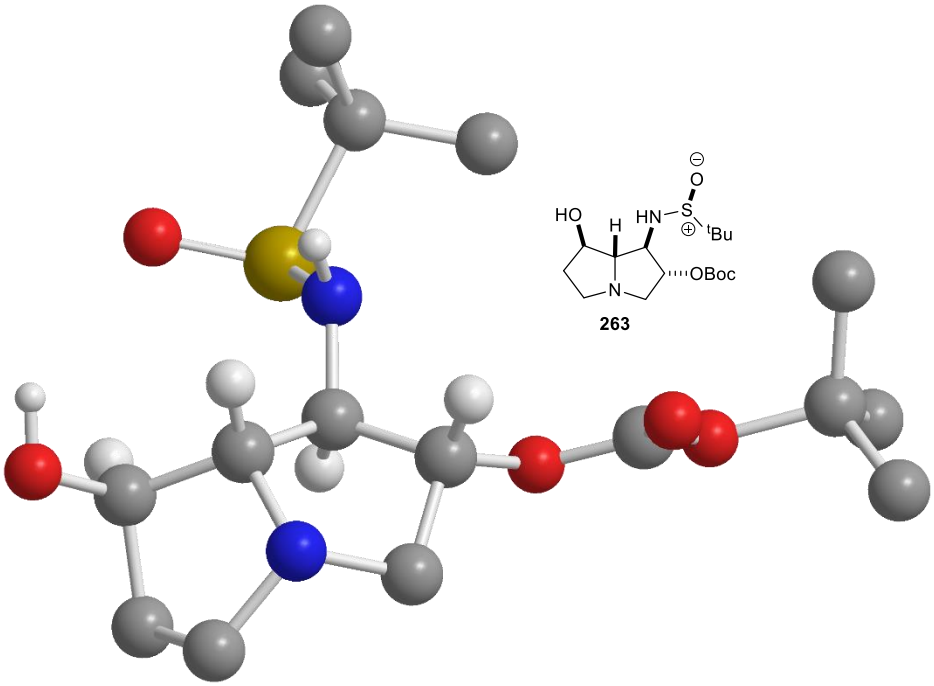


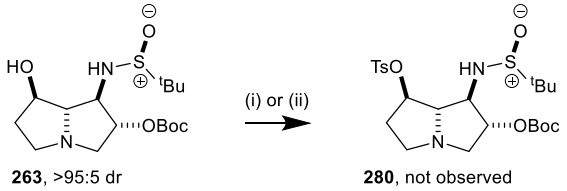
Figure 29 X-ray crystal structure of **263**·0.5H_2O (selected H atoms and H_2O are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

4.9 Ether Bridge Formation

The next key step in the synthesis of the loline alkaloids is the formation of the C(2)–C(7) ether bridge. It was initially proposed to achieve this via activation of the C(7) hydroxy group followed by removal of the *O*-Boc group followed by cyclisation.

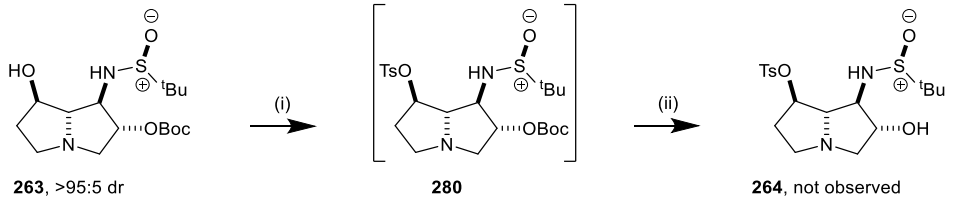
4.9.1 Acid Promoted *O*-Boc Removal

Tosylation of **263** followed by formic acid mediated chemoselective *O*-Boc removal[9] was initially investigated. Treatment of pyrrolizidine **263** with TsCl and Et_3N in CH_2Cl_2 for 18 h resulted in consumption of pyrrolizidine **263** by TLC however, tosylate **280** was not observed after the reaction had been worked up. Tosylation conditions were repeated in the presence of DMAP, although again pyrrolizidine **263** was not observed by TLC after 5 hours; however, after work up of the reaction, tosylate **280** was not observed (Scheme 71).



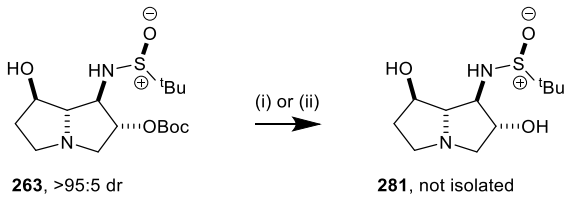
Scheme 71 *Reagents and Conditions*: (i) TsCl, Et_3N, CH_2Cl_2, rt, 18 h; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 5 h.

In order to overcome the potential stability issues of tosylate **280**, pyrrolizidine **263** was subjected to tosylation conditions with the resultant solution being concentrated *in vacuo* and immediately subjected to the formic acid conditions reported by Sorochinsky *et al.*[9] Disappointingly, this resulted in no product formation with complete decomposition of all reagents observed (Scheme 72).



Scheme 72 *Reagents and Conditions*: (i) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 2 h; (ii) Formic acid, rt, 1 h.

In order to investigate the chemoselective removal of the *O*-Boc group in the presence of sulfinylimine **263**, a solution of pyrrolizidine **263** in CH_2Cl_2 was treated with formic acid; although this resulted in no evidence of formation of diol **281**, with only the formate salt of pyrrolizidine **263** being observed. Therefore, pyrrolidine **263** was treated with neat formic acid at rt for 16 h. Trace amounts of diol **281** were observed; however, isolation of the free base of diol **281** proved to be impossible (Scheme 73). Due to the harsh acidic conditions needed to remove the *O*-Boc group and difficulties tosylating pyrrolizidine **263**, this approach was abandoned.

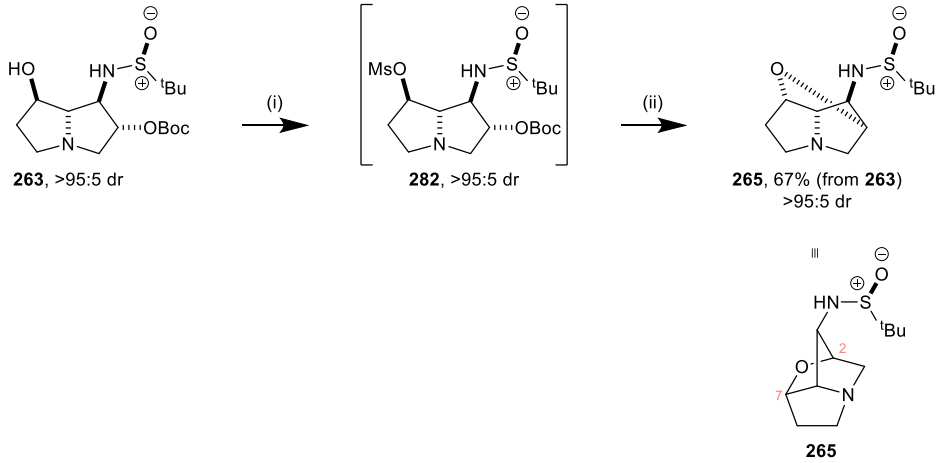


263, >95:5 dr **281**, not isolated

Scheme 73 *Reagents and Conditions*: (i) Formic acid, CH_2Cl_2, rt, 2 h; (ii) Formic acid, rt, 16 h.

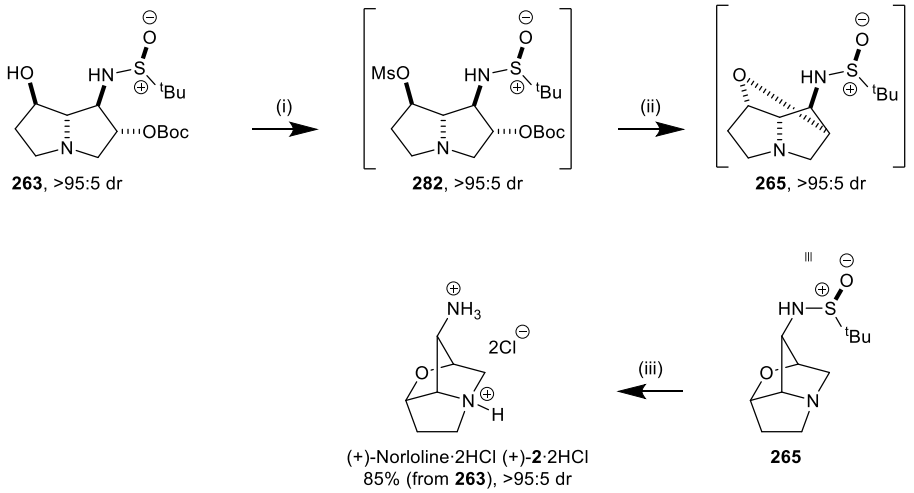
4.9.2 Base Promoted *O*-Boc Removal

In order to overcome these issues alternative conditions to both activate C(7)-OH and to remove the *O*-Boc group were investigated. Krische *et al*. reported the use of K_2CO_3/MeOH to remove *O*-Boc groups.[25] Considering the problems previously experienced during the tosylation of alcohol **263**, formation of the corresponding mesylate was next investigated. Treatment of alcohol **263** with Ms_2O and Et_3N gave mesylate **282** which was maintained at 0 °C throughout the workup of the resultant reaction mixture and used without any further purification. Treatment of mesylate **282** with K_2CO_3 in MeOH at 70 °C resulted in formation of *tert*-butylsulfinyl loline **265** in 67% yield (from **263**) and >95:5 dr. Formation of the ether bridge within **265** was confirmed by HMBC spectroscopic analysis whereby strong correlations could be seen between C(2)*H*−*C*(7)H and C(7)*H*−*C*(2)H. However, *tert*-butylsulfinyl loline **265** proved to be unstable and, upon standing overnight at room temperature overnight, decomposed (Scheme 74).



Scheme 74 *Reagents and Conditions*: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (ii) K_2CO_3, MeOH, 70 °C, 20 h.

Alcohol **263** was again mesylated to give mesylate **282** that was subjected to the ether bridge forming conditions (K_2CO_3 in MeOH) to give *tert*-butylsulfinyl loline **265**. In order to overcome the stability issues previously seen with *tert*-butylsulfinyl loline **265**, the reaction mixture was concentrated, filtered through a plug of silica and immediately used in the next reaction without further purification. Treatment of *tert*-butylsulfinyl loline **265** with HCl in MeOH at 70 °C resulted in complete removal of the *N*-*tert*-butylsulfinyl group to give (+)-norloline dihydrochloride (+)-**2**·2HCl {$[\alpha]_D^{25}$ +7.0 (*c* 1.0 in H_2O} in 85% yield and >95:5 dr. The relative configuration within (+)-norloline dihydrochloride (+)-**2**·2HCl was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 30).[14] A Flack *x* parameter[15] of −0.016(19) for the crystal structure of (+)-norloline dihydrochloride (+)-**2**·2HCl was also consistent with the assigned absolute (1*R*,2*R*,7*S*,8*S*)-configuration within **2**, thereby confirming the assigned configuration of (+)-norloline dihydrochloride (+)-**2**·2HCl.



Scheme 75 *Reagents and Conditions*: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (ii) K_2CO_3, MeOH, 70 °C, 20 h; (iii) HCl, MeOH, 70 °C, 20 h.

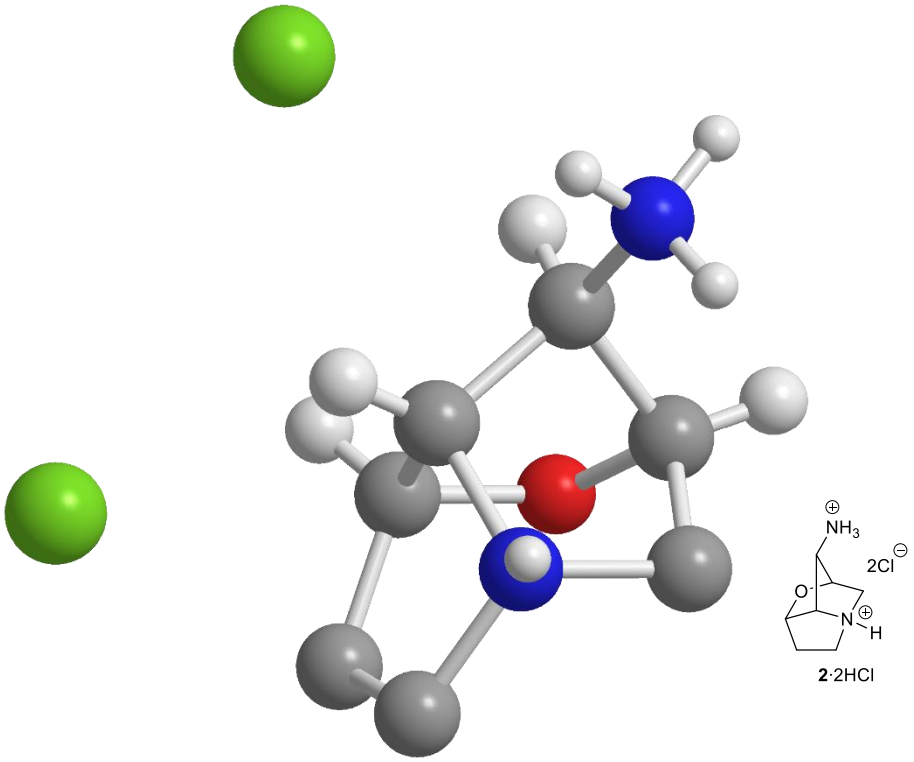


Figure 30 X-ray crystal structure of **2**·2HCl (selected H atoms are omitted for clarity). X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.

4.10 Chapter Conclusion

In conclusion, (+)-norloline dihydrochloride (+)-**2**·2HCl has been synthesised from *N*-Boc *trans*-pyrrolidine *ent*-**189** in 13 steps and 43% overall yield. Initially, the stereochemical

outcome of the addition of the enolate of *O*-Boc ester **250** was investigated and from this is was confirmed that (*S*s)-sulfinylimine (*S*)-**260** was the sulfinyl imine needed to give the desired α-hydroxy-β-amino ester **261**. Addition of the enolate of ester **250** generated with LiHMDS resulted in an inseparable 50:50 mixture of C(2) epimers, but upon switching the base to NaHMDS, addition to sulfinyl imine (S_S)-**260** proceeded in quantitative yield and >95:5 dr to give α-hydroxy-β-amino ester **261**. Pyrrolidine **261** was subjected to deallylation conditions which also resulted in *in situ* cyclisation and pyrrolidinone formation. Mesylation of alcohol **263** followed by the *in situ* removal of *O*-Boc and ether formation gave *N*-*tert*-butylsulfinyl loline **265**. *N*-*tert*-butylsulfinyl loline **265** proved to be unstable so was immediately treated with HCl to give (+)-norloline dihydrochloride (+)-**2**·2HCl, concluding the synthesis of (+)-norloline dihydrochloride (+)-**2**·2HCl in 43% yield and 13 steps from *ent*-**189** (Figure 31).

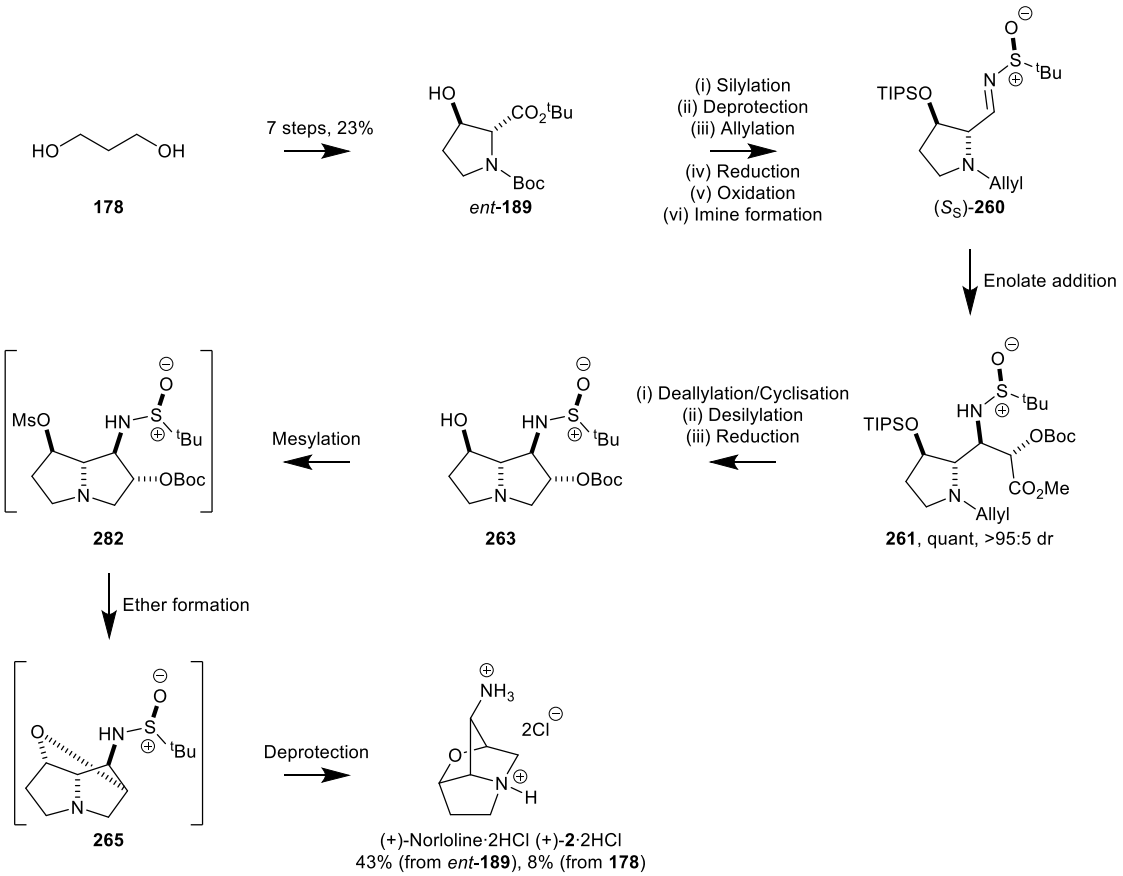


Figure 31 Summary of the synthesis of (+)-norloline dihydrochloride (+)-**2**·2HCl from 1,3-propane diol **178**.

4.11 References and Notes

(1) Yin, W.; Qin-Fei, H.; Hao-Wei, W.; Xuan, Z.; Huang, Z.-Y.; Qin, Y. *J. Org. Chem.* **2006**, *71*, 1588–1591.

(2) Qin *et al*. have drawn the (S_S) orientated sulfinylimine throughout their publication. However in the text they refer to using the (R_S) orientated sulfinylimine. X-ray crystallographic analysis of sulfinamide **251** and chemical correlation implies the error lies in the schemes being drawn incorrectly and the body of the text is correct.

(3) Hjelmgaard, T.; Faure, S.; Lemoine, P.; Viossat, B.; Aitken, D. J. *Org. Lett.* **2008**, *10*, 841–844.

(4) Ke, B.; Qin, Y.; Zhao, F.; Qu, Y. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4783–4785.

(5) Burnett, C. M.; Williams, R. M. *Tetrahedron Lett.* **2009**, *50*, 5449–5451.

(6) Okuyama, K.; Momoi, Y.; Sugimoto, K.; Okano, K.; Tokuyama, H. *Synlett* **2011**, 73–76.

(7) Jing, Y.; Zhou, W.; Li, W.; Zhao, L.; Wang, Y. *Bioorg. Med. Chem.* **2014**, *22*, 194–203.

(8) Momoi, Y.; Okuyama, K.; Toya, H.; Sugimoto, K.; Okano, K.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 13215–13219.

(9) Shevchuk, M. V.; Kukhar, V. P.; Röschenthaler, G.-V.; Bassil, B. S.; Kawada, K.; Soloshonok, V. A.; Sorochinsky, A. E. *RSC Adv.* **2013**, *3*, 6479–6484.

(10) Callebaut, G.; Colpaert, F.; Nonn, M.; Kiss, L.; Sillanpää, R.; Törnroos, K. W.; Fülöp, F.; De Kimpe, N.; Mangelinckx, S. *Org. Biomol. Chem.* **2014**, *12*, 3393–3405.

(11) Bunnage, M. E.; Davies, S. G.; Parkin, R. M.; Roberts, P. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 3337–3354.

(12) Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Kumar, A.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158–168.

(13) *Iteration 1* yielded α-hydroxy-β-amino ester *ent*-**171** in 56% yield and >95:5 dr and α-amino-β-hydroxy ester *ent*-**190** in 44% yield and >95:5 dr. *Iteration 2* yielded α-hydroxy-β-amino ester *ent*-**171** in 55% yield and >95:5 dr and α-amino-β-hydroxy ester *ent*-**190** in 44% yield (68% combined yield) and >95:5 dr. *Iteration 3* yielded α-hydroxy-β-amino ester *ent*-**171** in 54% yield and >95:5 dr and α-amino-β-hydroxy ester *ent*-**190** in 39% yield (80% combined yield) and >95:5 dr.

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

(15) Flack, H. D.; Bernardinelli, G. *Acta Crystallogr. Sect. A* **1999**, *55*, 908–915.

(16) Varying the protecting group (OCbz, OTBS, OAllyl and OMe) on the ester from which the enolate was generated did not result in any significant increase in yields or diastereoselectivity compared to ester **250**.

(17) Sorochinsky *et al*. report a (*Z*)-enolate in their non-chelated transition state, however this assignment is based on conventional [(*E*):(*Z*)] nomenclature opposed to the enolate nomenclature applied in this work.

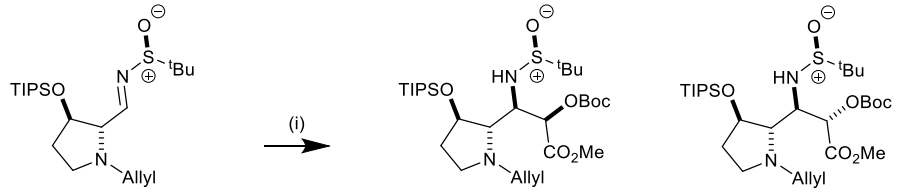
(18) The assignment of enolate geometries is contrary to conventional [(*E*):(*Z*)] nomenclature, the highest priority designation is allocated to the *O*-metal or *O*-silyl group of the enolate substituent.

(19) Höferl-Prantz, K.; Nerdinger, S.; Benito-Garagorri, D.; Felzmann, W. *Heterocycles* **2020**, *101*, 299–242.

(20) Davies, S. G.; Fletcher, A. M.; Shah, R. S.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2015**, *80*, 4017–4029.

(21) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, *16*, 3975–3978.

(22) Addition of the enolate derived from ester **250** to sulifinyl imine (S_S)-**260** in the presence of 12-crown-4 was investigated to see if the proposed enolate chelation model could be disrupted. However, this had no significant effect on the yield or diastereoselctivity of the addition.



(S_S)-**260**, >95:5 dr — **272** — **2261**

72%, 47:53 [**272**:**261**]

Reagents and conditions: (i) **250**, LiHMDS, 12-crown-4, −78 °C, 1 h, then (S_S)-**260**, −78 °C, 3 h.

(23) Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Lorkin, T. J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 9779–9803.

(24) Treatment of silyl ether pyrrolizidinone **262** with $BH_3{\cdot}Me_2S$ followed by heating at 60 °C in MeOH for 18 h yielded the corresponding silyl ether pyrrolizidine in a disappointing 41% yield and was therefore not investigated further.

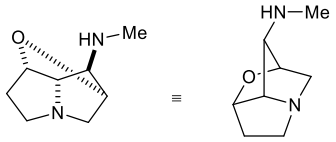
(25) Itoh, T.; Montgomery, T. P.; Recio, A.; Krische, M. J. *Org. Lett.* **2014**, *16*, 820–823.

Chapter 5

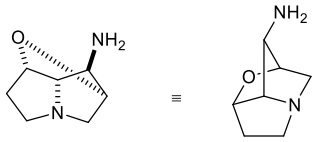
5 Synthesis and Analysis of the Loline Alkaloids

5.1 Chapter Outline

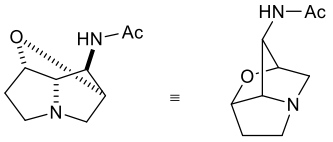
This chapter describes the synthesis of the loline alkaloids (+)-**1**, (+)-**2**, (+)-**4** and (+)-**283** from (+)-norloline·dihydrochloride (+)-**2**·2HCl. Followed by the subsequent comparison of the specific rotation and spectroscopic data for these alkaloids with the data reported for previously prepared samples (Table 12).



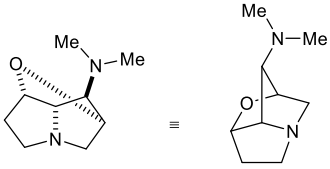
(+)-Loline (+)-**1**



(+)-Norloline (+)-**2**



(+)-*N*-Acetyl norloline (+)-**4**



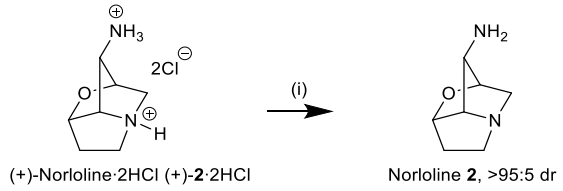
(+)-*N*-Methyl loline (+)-**283**

	(+)-**1**	(+)-**1**·2HCl	(+)-**2**	(+)-**4**	(+)-**283**
Powell *et al.*[1]	**X**	**X**	**X**	**X**	**X**
White *et al.*[2,3]	-	**X**	-	-	-
Scheerer *et al.*[4]	-	-	-	**X**	-
Trauner *et al.*[5]	-	**X**	**X**	-	-
Huang *et al.*[6]	-	-	-	**X**	-
This work	**X**	**X**	**X**	**X**	**X**

Table 12 Previous reported syntheses of the loline alkaloids (+)-**1**, (+)-**2**, (+)-**4** and (+)-**283**.

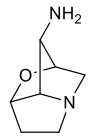
5.2 Norloline 2

Powell *et al.*[1] and Trauner *et al.*[5] have reported that (+)-norloline (+)-**2** is a volatile, water-soluble oil, which readily forms the corresponding CO_2 adduct on exposure to air. Therefore, norloline **2** free base was generated *in situ* by treatment of (+)-norloline dihydrochloride (+)-**2**·2HCl with NaOH in $CDCl_3$ which was immediately followed by spectroscopic analysis of the resultant solution, thereby minimising exposure to air (Scheme 76).



Scheme 76 *Reagents and Conditions*: (i) NaOH, $CDCl_3$, rt, 30 min.

The relative configuration within norloline **2** was assigned following comparison of spectroscopic data with previously reported data.[1,5] ^{1}H NMR spectroscopic analysis of this sample of norloline **2** showed agreement ($\Delta\delta_H \leq 0.02$ ppm)[7] with the sample prepared by Trauner *et al.*[5] The sample prepared by Powell *et al*.,[1] which was derived from natural (+)-loline (+)-**1**, was in accord with this sample, however it possessed a systematic error ($\Delta\delta_H \leq +0.11$ ppm),[7] which is most likely due to a difference in the reference frequencies used for the two samples (Table 13). The absolute configuration was assigned by chemical correlation to (+)-norloline dihydrochloride (+)-**2**·2HCl.

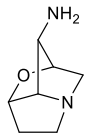


Norloline **2**

	Powell *et al.*[1] 300 MHz, $CDCl_3$[a]	Trauner *et al.*[5] 400 MHz, $CDCl_3$[b]	*This work* 400 MHz, $CDCl_3$[b]
C(1)*H*	3.48 (+0.10)	3.60 (−0.02)	3.58
C(2)*H*	3.72 (+0.11)	3.84 (−0.02)	3.83
C(3)H_A	3.38 (+0.10)	3.50 (−0.02)	3.48
C(3)H_B	2.29 (+0.12)	2.42 (−0.01)	2.41
C(5)H_A	2.80 (+0.12)	2.93 (−0.01)	2.92
C(5)H_B	2.98 (+0.11)	3.10 (−0.01)	3.09
C(6)H_A	1.84 (+0.12)	1.97 (−0.01)	1.96
C(6)H_B	1.94 (+0.11)	2.03 (−0.02)	2.05
C(7)*H*	4.29 (+0.11)	4.40 (0.00)	4.40
C(8)*H*	2.92 (+0.11)	3.05 (−0.02)	3.03

Table 13 ^{1}H NMR data for Norloline **2**. Values of $\Delta\delta_H$ are given in parentheses relative to the sample prepared in this work; [a] ^{1}H NMR chemical shifts are referenced relative to TMS in $CDCl_3$; [b] ^{1}H NMR chemical shifts are referenced relative to $CDCl_3$ (δ_H 7.26 ppm) in $CDCl_3$.

^{13}C NMR spectroscopic analysis of this sample of norloline **2** showed excellent agreement ($\Delta\delta_C \leq 0.2$ ppm)[8] with the sample prepared Trauner *et al.*[5] and the sample derived from the natural source prepared by Powell *et al.*[1] (Table 14).



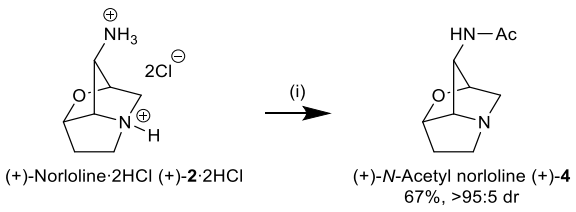
Norloline **2**

	Powell *et al.*[1] 75.5 MHz, $CDCl_3$[a]	Trauner *et al.*[5] 100 MHz, $CDCl_3$[a]	*This work* 101 MHz, $CDCl_3$[a]
C(1)	60.5 (−0.2)	60.5 (−0.2)	60.3
C(2)	76.2 (0.0)	76.2 (0.0)	76.2
C(3)	60.8 (0.0)	60.8 (0.0)	60.8
C(5)	54.5 (+0.1)	54.5 (+0.1)	54.6
C(6)	34.1 (+0.1)	34.1 (+0.1)	34.2
C(7)	81.7 (0.0)	81.7 (0.0)	81.7
C(8)	71.9 (0.0)	71.9 (0.0)	71.9

Table 14 ^{13}C NMR data for Norloline **2**. Values of $\Delta\delta_C$ are given in parentheses relative to the sample prepared in this work; [a] ^{13}C NMR chemical shifts are referenced relative to $CDCl_3$ (δ_C 77.0 ppm) in $CDCl_3$.

5.3 (+) *N*-Acetyl Norloline (+)-4

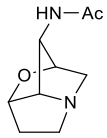
Treatment of (+)-norloline dihydrochloride (+)-**2**·2HCl with Ac_2O in the presence of Et_3N gave (+)-*N*-acetyl norloline (+)-**4** in 67% yield and >95:5 dr. This concluded the synthesis of (+)-*N*-acetyl norloline (+)-**4** in 29% yield and 14 steps from *N*-Boc *trans*-pyrrolidine *ent*-**189** (Scheme 77).



(+)-Norloline·2HCl (+)-**2**·2HCl → (+)-*N*-Acetyl norloline (+)-**4** 67%, >95:5 dr

Scheme 77 *Reagents and Conditions*: (i) Ac_2O, Et_3N, CH_2Cl_2, rt, 2 h.

The relative configuration within (+)-*N*-acetyl norloline (+)-**4** was assigned following comparison of the spectroscopic data for this sample with the data for previously prepared samples.[1,4,6] The value of the specific rotation for this sample of (+)-*N*-acetyl norloline (+)-**4** {$[\alpha]_D^{20}$+54.6 (*c* 0.5 in $CHCl_3$)} was in agreement with the previously reported synthetic[6] {$[\alpha]_D^{20}$+49.8 (*c* 0.5 in $CHCl_3$)} and natural[9] {$[\alpha]_D^{20}$+49.8 (*c* 2.23 in $CHCl_3$)} samples. ^{1}H NMR spectroscopic analysis of this sample of (+)-*N*-acetyl norloline (+)-**4** showed very close agreement ($\Delta\delta_H \leq 0.06$ ppm)[7,10] with the sample derived from the natural source by Powell *et al.*[1] and the synthetic sample prepared by Huang *et al.*[6] With the exception of the signal associated with the N*H* proton ($\Delta\delta_H \leq 0.09$ ppm), which may be expected to be somewhat sensitive to effects of concentration and/or the presence of trace amounts of H_2O (Table 15).

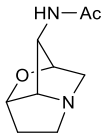


(+)-*N*-Acetyl norloline (+)-**4**

	Powell *et al.*[1] 300 MHz, $CDCl_3$[a]	Scheerer *et al.*[4] 400 MHz, $CDCl_3$[b]	Huang *et al.*[6] 600 MHz, $CDCl_3$[a]	*This work* 400 MHz, $CDCl_3$[b]
C(1)*H*	4.41 (+0.03)	4.44 (+0.00)	4.41 (+0.03)	4.44
C(2)*H*	4.17 (+0.02)	4.18 (+0.01)	4.17 (+0.02)	4.19
C(3)H_A	3.29 (+0.03)	3.30–3.33	3.31 (+0.01)	3.32
C(3)H_B	2.42 (+0.03)	2.43–2.46	2.43 (+0.02)	2.45
C(5)H_A	2.90 (+0.03)	2.89 (+0.04)	2.93 (+0.00)	2.93
C(5)H_B	3.10 (+0.03)	3.10–3.15	3.09 (+0.04)	3.13
C(6)H_A	1.98 (+0.06)	2.02–2.14	1.98 (+0.06)	2.04
C(6)H_B	2.08 (+0.02)		2.07 (+0.03)	2.10
C(7)*H*	4.44 (+0.02)	4.46–4.48	4.43 (+0.03)	4.46
C(8)*H*	3.09 (+0.01)	3.12 (−0.02)	3.15 (−0.05)	3.10
N*H*	6.21 (+0.09)	-	-	6.30
C(O)*Me*	1.97 (+0.02)	1.99 (+0.00)	1.95 (+0.04)	1.99

Table 15 ^{1}H NMR data for (+)-*N*-acetyl norloline (+)-**4**. Values of $\Delta\delta_H$ are given in parentheses relative to the sample prepared in this work; [a] ^{1}H NMR chemical shifts are referenced relative to TMS in $CDCl_3$; [b] ^{1}H NMR chemical shifts are referenced relative to $CDCl_3$ (δ_H 7.26 ppm) in $CDCl_3$.

^{13}C NMR spectroscopic analysis of this sample of (+)-*N*-acetyl norloline (+)-**4** showed good agreement ($\Delta\delta_C \leq 0.2$ ppm)[8] with the natural product derived sample prepared by Powell *et al.*[1] and the synthetic samples prepared by Scheerer *et al.*[4] and Huang *et al.*[6] (Table 16).



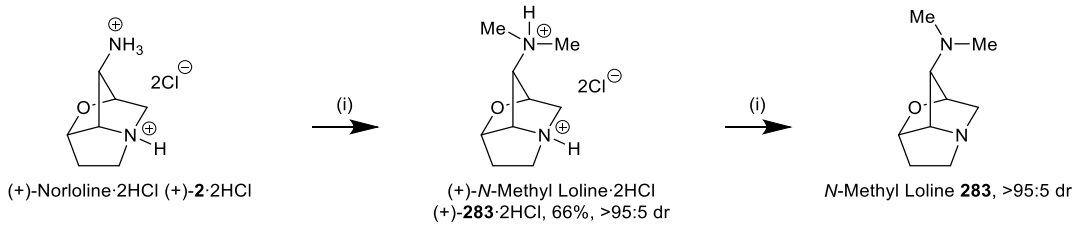
(+)-*N*-Acetyl norloline (+)-**4**

	Powell *et al.*[1] 75.5 MHz, $CDCl_3$[a]	Scheerer *et al.*[4] 100 MHz, $CDCl_3$[a]	Huang *et al.*[6] 150 MHz, $CDCl_3$[a]	*This work* 101 MHz, $CDCl_3$[a]
C(1)	57.6 (0.0)	57.6 (0.0)	57.6 (0.0)	57.6
C(2)	73.8 (0.0)	73.8 (0.0)	73.8 (0.0)	73.8
C(3)	60.9 (0.0)	60.9 (0.0)	61.0 (–0.1)	60.9
C(5)	54.6 (0.0)	54.6 (0.0)	54.6 (0.0)	54.6
C(6)	33.9 (–0.1)	33.9 (–0.1)	33.6 (+0.2)	33.8
C(7)	80.9 (0.0)	81.0 (–0.1)	80.8 (+0.1)	80.9
C(8)	69.6 (0.0)	69.7 (–0.1)	69.7 (–0.1)	69.6
C(O)*Me*	23.1 (+0.1)	23.2 (0.0)	23.1 (+0.1)	23.2
C(O)Me	170.2 (+0.2)	170.3 (+0.1)	170.5 (–0.1)	170.4

Table 16 ^{13}C NMR data for (+)-*N*-acetyl norloline (+)-**4**. Values of $\Delta\delta_C$ are given in parentheses relative to the sample prepared in this work; [a] ^{13}C NMR chemical shifts are referenced relative to $CDCl_3$ (δ_C 77.0 ppm) in $CDCl_3$.

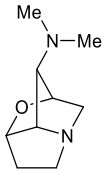
5.4 *N*-Methyl Loline 283

Treatment of (+)-norloline dihydrochloride (+)-**2**·2HCl with formaldehyde in the presence of $NaCNBH_3$ gave the (+)-*N*-methyl loline·(+)-**283**, which was isolated as the corresponding dihydrochloride salt (+)-**283**·2HCl, for ease of handling, in 66% yield and >95:5 dr. *N*-methyl loline **283** free base was generated *in situ* by treatment of (+)-*N*-methyl loline dihydrochloride (+)-**283**·2HCl with NaOH in $CDCl_3$, which was immediately followed by spectroscopic analysis of the resultant solution (Scheme 78).



Scheme 78 *Reagents and Conditions*: (i) Formaldehyde, $NaCNBH_3$, MeCN, 0 °C, 30 min, then rt, 16 h, then HCl, MeOH; (ii) NaOH, $CDCl_3$, rt, 30 min.

The relative configuration within *N*-methyl loline **283** was assigned following comparison of the spectroscopic data for this sample with the data for the previously prepared sample.[1] ^{1}H NMR spectroscopic analysis of this sample of *N*-methyl loline **283** agreed with the sample prepared by Powell *et al.*,[1] however it possessed a systematic error ($\Delta\delta_H \leq +0.17$ ppm),[7] again suggesting a referencing irregularity (Table 17).

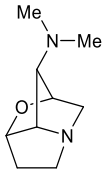


N-Methyl Loline **283**

	Powell *et al.*[1] 300 MHz, $CDCl_3$[a]	*This work* 400 MHz, $CDCl_3$[b]
C(1)*H*	2.53 (+0.17)	2.70
C(2)*H*	3.82 (+0.18)	4.00
C(3)H_A	3.36 (+0.18)	3.54
C(3)H_B	2.18 (+0.18)	2.36
C(5)H_A	2.78 (+0.17)	2.95
C(5)H_B	2.89 (+0.17)	3.06
C(6)H_A	1.75 (+0.17)	1.92
C(6)H_B	1.86 (+0.17)	2.03
C(7)*H*	4.25 (+0.17)	4.42
C(8)*H*	3.01 (+0.17)	3.18
NMe_2	2.12 (+0.17)	2.29

Table 17 ^{1}H NMR data for *N*-methyl loline **283**. Values of $\Delta\delta_H$ are given in parentheses relative to the sample prepared in this work; [a] ^{1}H NMR chemical shifts are referenced relative to TMS in $CDCl_3$; [b] ^{1}H NMR chemical shifts are referenced relative to $CDCl_3$ (δ_H 7.26 ppm) in $CDCl_3$.

^{13}C NMR spectroscopic analysis of this sample of *N*-methyl loline **283** showed agreement with the natural product derived sample prepared by Powell *et al.*[1] however it possessed a systematic error ($\Delta\delta_C \leq +0.4$ ppm)[8] most likely due to a referencing irregularity (Table 20).



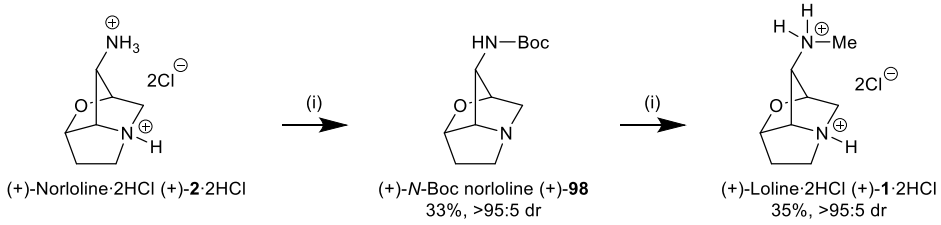
N-Methyl Loline **283**

	Powell *et al.*[1] 75.5 MHz, $CDCl_3$[a]	*This work* 101 MHz, $CDCl_3$[a]
C(1)	74.1 (+0.4)	74.5
C(2)	74.2 (+0.5)	74.7
C(3)	61.2 (+0.4)	61.6
C(5)	54.3 (+0.4)	54.7
C(6)	33.4 (+0.4)	33.8
C(7)	82.0 (+0.4)	82.4
C(8)	69.2 (+0.5)	69.7
N*Me*$_2$	44.4 (+0.5)	44.8

Table 18 ^{13}C NMR data for *N*-methyl loline **283**. Values of $\Delta\delta_C$ are given in parentheses relative to the sample prepared in this work; [a] ^{13}C NMR chemical shifts are referenced relative to $CDCl_3$ (δ_C 77.0 ppm) in $CDCl_3$.

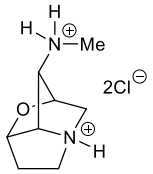
5.5 Loline 1

In order to install only one *N*-Me group, treatement of (+)-norloline dihydrochloride (+)-**2**·2HCl with Boc_2O in the presence of K_2CO_3 gave (+)-*N*-Boc norloline (+)-**98** in 33% yield and >95:5 dr. Reduction of (+)-*N*-Boc norloline (+)-**98** with $LiAlH_4$ according to the method of Trauner *et al.*[5] gave (+)-loline (+)-**1**, which was isolated as the dihydrochloride salt (+)-**1**·2HCl, for ease of handling, in 35% yield and >95:5 dr. This concluded the synthesis of (+)-loline dihydrochloride (+)-**1**·2HCl in 5% overall yield in 16 steps from *N*-Boc *trans*-pyrrolidine *ent*-**189** (Scheme 79).



Scheme 79 *Reagents and Conditions*: (i) Boc_2O, K_2CO_3, MeOH, rt, 24 h; (ii) $LiAlH_4$, THF, 70 °C, 8 h, then HCl, MeOH.

The relative configuration within (+)-loline dihydrochloride (+)-**1**·2HCl was assigned following comparison of the spectroscopic data for this sample with the data for previously prepared samples.[1–3,5] The value of the specific rotation for this sample of (+)-loline dihydrochloride (+)-**1**·2HCl {$[\alpha]_D^{25}$+3.3 (*c* 0.31 in H_2O)} was in agreement with the previously reported synthetic[5] {$[\alpha]_D^{25}$+5.4 (*c* 0.31 in H_2O)} and natural[11] {$[\alpha]_D^{19}$+6.2 (*c* 9.7 in H_2O)} samples. ^{1}H NMR spectroscopic analysis of this sample of (+)-loline dihydrochloride (+)-**1**·2HCl agreed with the natural product derived sample prepared by Powell *et al.*[1] and the synthetic samples prepared by White *et al.*[2,3] and Trauner *et al.*[5] however all three sets of data possessed systematic errors ($\Delta\delta_H \leq +0.17$ ppm, [1] $\Delta\delta_H \leq +0.18$ ppm[2,3] and $\Delta\delta_H \leq +0.14$ ppm[5]),[7] again suggesting a referencing irregularity (Table 19).

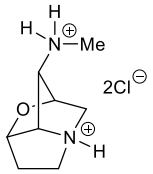


(+)-Loline·2HCl (+)-**1**·2HCl

	Powell *et al.*[1] 300 MHz, D_2O[a]	White *et al.*[2,3] 300 MHz, D_2O[b]	Trauner *et al.*[5] 400 MHz, D_2O[b]	*This work* 400 MHz, D_2O[c]
C(1)*H*	4.23 (+0.17)	4.23 (+0.17)	4.26 (+0.14)	4.40
C(2)*H*	4.79 (+0.17)	4.77–4.80	4.80 (+0.16)	4.96
C(3)H_A	4.15 (+0.15)	4.12 (+0.18)	4.15 (+0.15)	4.30
C(3)H_B	3.55 (+0.19)	3.57 (+0.17)	3.60 (+0.14)	3.74
C(5)H_A	3.73 (+0.17)	3.70 (+0.20)	3.79 (+0.11)	3.90
C(5)H_B	3.73 (+0.17)	3.75 (+0.15)	3.73 (+0.17)	3.90
C(6)H_A	2.28 (+0.17)	2.27 (+0.18)	2.31 (+0.14)	2.45
C(6)H_B	2.37 (+0.19)	2.38 (+0.18)	2.42 (+0.14)	2.56
C(7)*H*	4.72 (+0.18)	-[d]	4.75 (+0.15)	4.90
C(8)*H*	4.79 (+0.17)	4.77–4.80	4.82 (+0.14)	4.96
N*H*	4.76	-[d]	-	-
N*Me*	2.79 (+0.18)	2.79 (+0.18)	2.83 (+0.14)	2.97

Table 19 ^{1}H NMR data for (+)-loline dihydrochloride **1**·2HCl. Values of $\Delta\delta_H$ are given in parentheses relative to the sample prepared in this work; [a] ^{1}H NMR chemical shifts are referenced relative to internal Me_2CO (δ_H 2.12 ppm) in D_2O; [b] No comment is made on the value to which value ^{1}H NMR chemical shifts are referenced; [c] ^{1}H NMR chemical shifts are referenced relative to D_2O (δ_H 4.79 ppm) in D_2O; [d] obscured by HOD.

^{13}C NMR spectroscopic analysis of this sample of (+)-loline dihydrochloride (+)-**1**·2HCl showed agreement with the natural product derived sample prepared by Powell *et al.*[1] and the synthetic samples prepared by White *et al.*[2,3] and Trauner *et al.*[5] however it possessed a systematic error ($\Delta\delta_C \leq +0.4$ ppm[1] and $\Delta\delta_C \leq +0.3$ ppm[2,3,5])[8] most likely due to a referencing irregularity (Table 20).

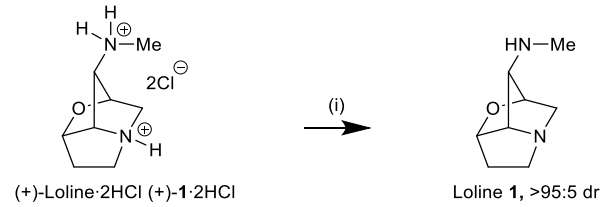


(+)-Loline·2HCl (+)-**1**·2HCl

	Powell *et al.*[1] 75.5 MHz, D_2O[a]	White *et al.*[2,3] 75 MHz, D_2O[b]	Trauner *et al.*[5] 100 MHz, D_2O[b]	*This work* 101 MHz, D_2O[c]
C(1)	65.9 (+0.4)	66.0 (+0.3)	66.0 (+0.3)	66.3
C(2)	73.9 (+0.4)	74.0 (+0.3)	74.0 (+0.3)	74.3
C(3)	64.2 (+0.3)	64.2 (+0.3)	64.2 (+0.3)	64.5
C(5)	58.1 (+0.4)	58.2 (+0.3)	58.2 (+0.3)	58.5
C(6)	31.6 (+0.3)	31.6 (+0.3)	31.6 (+0.3)	31.9
C(7)	83.2 (+0.4)	83.4 (+0.2)	83.4 (+0.2)	83.6
C(8)	72.2 (+0.3)	72.2 (+0.3)	72.2 (+0.3)	72.5
N*Me*	36.5 (+0.2)	36.4 (+0.3)	36.4 (+0.3)	36.7

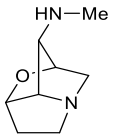
Table 20 ^{13}C NMR data for (+)-loline dihydrochloride **1**·2HCl. Values of $\Delta\delta_C$ are given in parentheses relative to the sample prepared in this work; [a] ^{1}H NMR chemical shifts are referenced relative to internal Me_2CO (δ_H 2.12 ppm) in D_2O; [b] no comment is made on the value to which value ^{13}C NMR chemical shifts are referenced; [c] ^{13}C NMR chemical shifts are referenced relative to TSP (δ_C 0.0 ppm) in D_2O.

Loline **1** free base was generated *in situ* by treatment of (+)-loline dihydrochloride (+)-**1**·2HCl with NaOH in $CDCl_3$ which was immediately followed by spectroscopic analysis of the resultant solution, thereby minimising exposure to air (Scheme 80).



Scheme 80 *Reagents and Conditions*: (i) NaOH, $CDCl_3$, rt, 30 min.

The relative configuration within loline **1** was assigned following spectroscopic data comparison with previously reported data.[1] ^{1}H NMR spectroscopic analysis of this sample of *N*-methyl loline **1** agreed with the sample prepared by Powell *et al.*,[1] however it possessed a systematic error ($\Delta\delta_H \leq +0.31$ ppm),[7] again suggesting a referencing irregularity (Table 21).

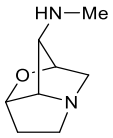


Loline **1**

	Powell *et al.*[1] 300 MHz, $CDCl_3$[a]	*This work* 500 MHz, $CDCl_3$[b]
C(1)*H*	3.03 (+0.31)	3.34
C(2)*H*	3.71 (+0.32)	4.03
C(3)H_A	3.10 (+0.31)	3.41
C(3)H_B	2.10 (+0.32)	2.42
C(5)H_A	2.62 (+0.31)	2.93
C(5)H_B	2.77 (+0.31)	3.08
C(6)H_A	1.65 (+0.32)	1.97
C(6)H_B	1.74 (+0.31)	2.05
C(7)*H*	4.10 (+0.31)	4.41
C(8)*H*	2.84 (+0.31)	3.15
N*Me*	2.19 (+0.30)	2.49

Table 21 ^{1}H NMR data for loline **1**. Values of $\Delta\delta_H$ are given in parentheses relative to the sample prepared in this work; [a] ^{1}H NMR chemical shifts are referenced relative to TMS in $CDCl_3$; [b] ^{1}H NMR chemical shifts are referenced relative to $CDCl_3$ (δ_H 7.26 ppm) in $CDCl_3$.

^{13}C NMR spectroscopic analysis of this sample of (+)-loline (+)-**1** showed agreement with the natural product derived sample prepared by Powell *et al.*[1] however it possessed a systematic error ($\Delta\delta_C \leq +0.6$ ppm)[8] most likely due to a referencing irregularity (Table 22).



Loline **1**

	Powell *et al.*[1] 75.5 MHz, $CDCl_3$[a]	*This work* 126 MHz, $CDCl_3$[a]
C(1)	67.8 (+0.5)	68.3
C(2)	73.4 (+0.7)	74.1
C(3)	60.6 (+0.6)	61.2
C(5)	54.0 (+0.7)	54.7
C(6)	33.5 (+0.6)	34.1
C(7)	81.0 (+0.8)	81.8
C(8)	69.0 (+0.6)	69.6
N*Me*	34.7 (+0.5)	35.2

Table 22 ^{13}C NMR data for loline **1**. Values of $\Delta\delta_C$ are given in parentheses relative to the sample prepared in this work; [a] ^{13}C NMR chemical shifts are referenced relative to $CDCl_3$ (δ_C 77.0 ppm) in $CDCl_3$.

5.6 Chapter Conclusion

In conclusion, (+)-norloline **2**, (+)-*N*-acetyl norloline (+)-**4**, (+)-*N*-methyl loline (+)-**283** and (+)-loline (+)-**1** have been synthesised from the common intermediate (+)-norloline·dihydrochloride **2**·2HCl. For ease of handling, (+)-norloline **2**, (+)-*N*-methyl loline (+)-**283** and (+)-loline (+)-**1** were isolated as the corresponding dihydrochloride salts and their free bases were generated *in situ*. The relative configurations of these alkaloids have been established by comparison of the spectroscopic data to the data reported for previously prepared samples. The absolute configurations were established via inference from the known (1*R*,2*R*,7*S*,8*S*)-configuration of the common precursor (+)-norloline·dihydrochloride (+)-**2**·2HCl which was established by single crystal X-ray diffraction analysis and by comparison of the specific rotations with those reported previously.

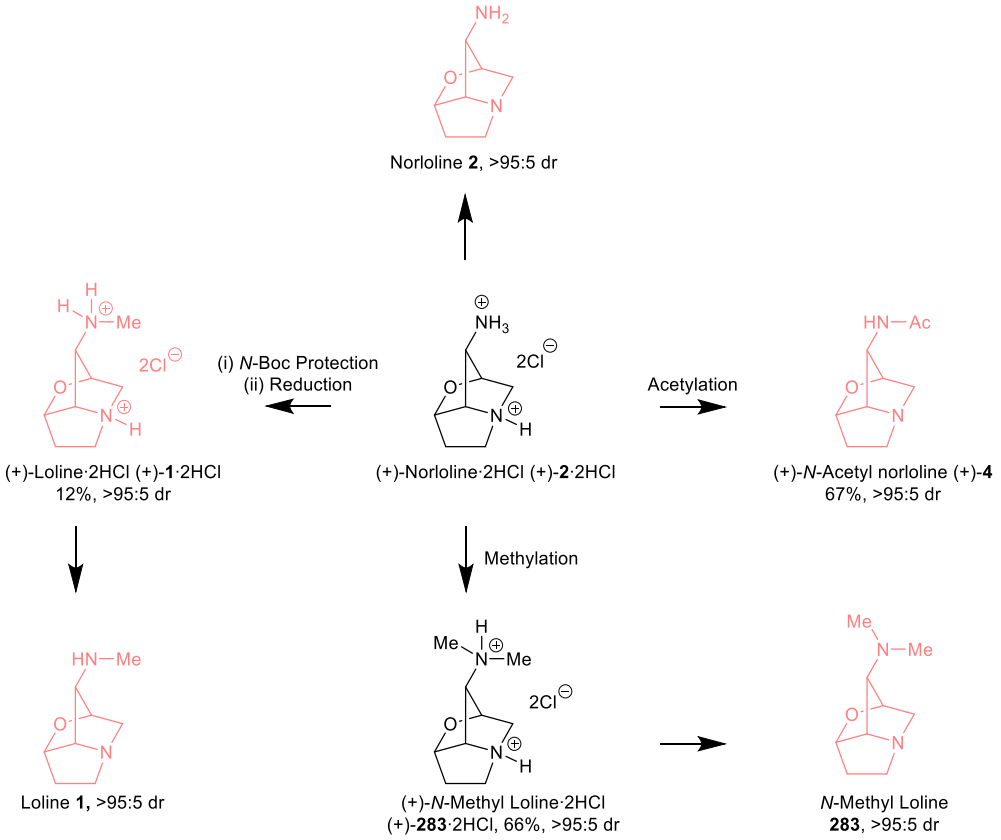


Figure 32 Summary of the synthesis of the loline alkaloids **1**, **2**, (+)-**4** and **283** from (+)-norloline dihydrochloride (+)-**2**·2HCl.

5.7 References and Notes

(1) Petroski, R. J.; Yates, S. G.; Weisleder, D.; Powell, R. G. *J. Nat. Prod.* **1989**, *52*, 810–817.
(2) Blakemore, P. R.; Schulze, V. K.; White, J. D. *Chem. Commun.* **2000**, 1263–1264.
(3) Blakemore, P. R.; Kim, S. K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831–1847.
(4) Hovey, M. T.; Eklund, E. J.; Pike, R. D.; Mainkar, A. A.; Scheerer, J. R. *Org. Lett.* **2011**, *13*, 1246–1249.
(5) Cakmak, M.; Mayer, P.; Trauner, D. *Nat. Chem.* **2011**, *3*, 543–545.
(6) Ye, J. L.; Liu, Y.; Yang, Z. P.; Huang, P. Q. *Chem. Commun.* **2016**, *52*, 561–563.
(7) $\Delta\delta_H = |\delta_H\,\text{(this work)} - \delta_H\,\text{(previously reported)}|$
(8) $\Delta\delta_C = |\delta_C\,\text{(this work)} - \delta_C\,\text{(previously reported)}|$
(9) Batirov, E. K.; Khamidkhodzhaev, S. A.; Malikov, V. M.; Yunusov, S. Y. *Chem. Nat. Compd.* **1976**, *12*, 50–52.
(10) Scheerer *et al.* reported a significant number of the ^{1}H NMR chemical shifts for (+)-**4** as multiplets with a range for δ_H so $\Delta\delta_H$ was not calculated.
(11) Yunusov, S. Y.; Akramov, S. T. *Russ. J. Gen. Chem.* **1955**, *25*, 1765–1771.

Chapter 6

6.1 Thesis Conclusion

In chapter 2 two complementary routes were developed to synthesise (2*R*,3*S*)-*cis*-3-hydroxyproline **131** and (2*S*,3*S*)-*trans*-3-hydroxyproline **136**. The first-generation synthesis utilised intermolecular aziridinium ring-opening and the second-generation synthesis utilised intramolecular aziridinium ring-opening, with a tethered acetate group as the nucleophile. The first-generation synthesis resulted in the second highest yielding synthesis of (2*R*,3*S*)-*cis*-3-hydroxyproline **131** reported and the lowest step count. The second-generation synthesis resulted in the highest yielding and lowest step count synthesis of (2*S*,3*S*)-*trans*-3-hydroxyproline **136** developed to date.

In chapter 3, the conjugate addition to *N*-benzyl substituted α,β-unsaturated ester **231** was optimised to give β-amino ester **239** in 74% yield. Attempts at α-hydroxylation of β-amino ester **239** both *in situ* and stepwise proved unsuccessful. Due to the less than ideal lithium amide conjugate addition conditions and unsuccessful α-hydroxylation this first-generation synthesis towards the loline alkaloids was abandoned.

In chapter 4, addition of the enolate of ester **250** generated with LiHMDS to sulfinyl imine (S_S)-**260** resulted in an inseparable 50:50 mixture of C(2) epimers, but upon switching the base to NaHMDS, it proceeded in quantitative yield and >95:5 dr to give α-hydroxy-β-amino ester **261**. From α-hydroxy-β-amino ester **261** (+)-norloline dihydrochloride (+)-**2**·2HCl was successfully synthesised, concluding the synthesis of (+)-norloline dihydrochloride (+)-**2**·2HCl in 43% yield and 13 steps from *ent*-**189**.

In chapter 5, norloline **2**, (+)-*N*-acetyl norloline (+)-**4**, (+)-*N*-methyl loline (+)-**283** and loline **1** have been synthesised from the common intermediate (+)-norloline·dihydrochloride **2**·2HCl. The relative configurations of these alkaloids have been established by comparison of the spectroscopic data to the data reported for previously prepared samples and by comparison of the specific rotations with those reported previously.

6.2 Future Work

Future investigations will be focussed on the work conducted in chapter 4. Initially, work could be carried out to develop a streamlined synthesis of *N*-Boc *trans*-pyrrolidine *ent*-**189**. This could include an enzymatic synthesis or partial synthesis of enantiopure precursors of *N*-Boc *trans*-pyrrolidine *ent*-**189**. Secondly, further work will be carried out to fully investigate and understand the mechanism of the addition of the enolate of ester **250** to sulfinyl imine (S_S)-**260**.

Chapter 7

7 Experimental

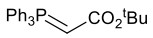
7.1 General Experimental

Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere unless otherwise stated 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. Allyl bromide was distilled from $MgSO_4$. ^{n}BuLi was purchased from Sigma-Aldrich (as a 2.50 M solution in hexanes) and was titrated against diphenylacetic acid before use. All other reagents were used as supplied. Organic layers were dried over $MgSO_4$ unless otherwise stated. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm) and 1% $KMnO_4$. Flash column chromatography was performed on Kieselgel 60 silica. For biphasic eluents, the aqueous phase was removed prior to flash column chromatography. Melting points were recorded on a Gallenkamp Hot Stage apparatus. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer on a diamond ATR module (ATR). Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated and at rt unless otherwise specified. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Multiplicities are reported as; singlet (s), doublet (d), triplet (t), quintet (q) and multiplet (m) or as a combination of the above multiplicities. The lock frequencies for the residual solvent peaks in the ^{1}H NMR spectra were defined as 7.26 ppm, 4.87 ppm, 7.09 ppm and 4.79 ppm for $CDCl_3$, MeOH-d_4, PhMe-d_8 and D_2O, respectively. ^{13}C NMR spectra were defined as 77.0 ppm, 49.0

ppm, 137.9 ppm and 0.0[2] ppm for $CDCl_3$, MeOH-d_4, PhMe-d_8 and D_2O, respectively. Owing to the rotameric nature of some compounds, several resonances in the rt ^1H and ^{13}C NMR spectra were doubled and/or broadened. 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.

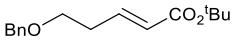
7.2 Experimental Data for Chapter 2

tert-Butyl 2-(triphenylphosphaneylidene)acetate 177[3]



176 (42.0 mL, 285 mmol) was added to a solution of PPh_3 (75.0 g, 285 mmol) in EtOAc (570 mL) and the resultant solution was stirred at rt for 16 h. The resultant suspension was filtered and washed with Et_2O (350 mL). The precipitate was dissolved in CH_2Cl_2 (500 mL) and the resultant solution was washed with 2.0 M aq NaOH (285 mL), extracted with CH_2Cl_2 (2 x 250 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo* to give **177** as a white amorphous solid (98.7 g, 92%); mp 152–155 °C; {lit.[3] mp 154–155 °C)};δ_H (400 MHz, $CDCl_3$) 1.21 (9H, s, C*Me*$_3$), 2.68 (1H, s, PC*H*), 7.38–7.71 (15H, m, *Ph*).

tert-Butyl (*E*)-5-(benzyloxy)pent-2-enoate 170[4]

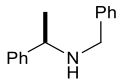


Step 1: **178** (20.0 g, 263 mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 10.5 g, 263 mmol) in THF (526 mL) at 0 °C, and the resultant mixture was stirred at rt for 45 min. TBAI (9.71 g, 26.3 mmol) and BnBr (44.5 g, 263 mmol) were added and the resultant mixture was stirred at rt for 16 h. H_2O (500 mL) was added at 0 °C and the resultant mixture was extracted with Et_2O (3 × 500 mL). The combined organic extracts were washed with brine (500 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash

column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1 to 0:1) gave **179** as a yellow oil (31.7 g, 73%); δ_H (400 MHz, $CDCl_3$) 1.76–1.83 (2H, m, C(2)H_2), 2.23 (1H, t, *J* 5.4, O*H*), 3.59 (2H, t, *J* 5.8, C(3)H_2), 3.71 (2H, dd, *J* 5.5, 5.4, C(1)H_2), 4.45 (2H, s, OCH_2Ph), 7.16–7.31 (5H, m, *Ph*).

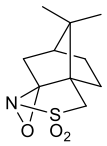
Step 2: DMSO (55.0 mL, 764 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (31.0 mL, 382 mmol) in CH_2Cl_2 (555 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min. A solution of **179** (31.7 g, 191 mmol) in CH_2Cl_2 (400 mL) was added dropwise and the resultant mixture was stirred at –78 °C for 30 min. Et_3N (160 mL, 1.14 mol) was added and stirring was continued at –78 °C for 30 min. The reaction mixture was allowed to warm to rt and was stirred at rt for 30 min. **177** (72.0 g, 191 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (1.0 L) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (500 mL) and brine (500 mL), then dried, filtered and concentrated *in vacuo* to give **170** in >95:5 dr [(*E*):(*Z*)]. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **170** as a colourless oil (50.6 g, 73% from **178**, >95:5 dr [(*E*):(*Z*)]); ν_{max} 1711 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.42 (2H, app qd, *J* 6.6, 1.6, C(4)H_2), 3.50 (2H, t, *J* 6.6, C(5)H_2), 4.45 (2H, s, OCH_2Ph), 5.74 (1H, dt, *J* 15.6, 1.6, C(2)*H*), 6.80 (1H, dt, *J* 15.6, 6.9, C(3)*H*), 7.17–7.31 (5H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 32.5 (*C*(4)), 68.4 (*C*(5)), 73.0 (O*C*H_2Ph), 80.2 (*C*Me_3), 124.7 (*C*(2)), 127.7, 127.7, 128.4 (*o,m,p-Ph*), 138.1 (*i-Ph*), 144.2 (*C*(3)), 165.8 (*C*(1)); *m/z* (ESI$^+$) 285 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{22}NaO_3^+$ ([M+Na]$^+$) requires 285.1461; found 285.1460.

(*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (*R*)-41[5]



Benzaldehyde (83.8 mL, 826 mmol) was added to a stirred solution of (*R*)-**47** (100 mL, 786 mmol, 99.9% ee) in EtOH (500 mL) at rt and the reaction mixture was heated at reflux for 3 h before being cooled to 0 °C. $NaBH_4$ (29.7 g, 786 mmol) was added portionwise and the resultant suspension was stirred at rt for 48 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (500 mL) and CH_2Cl_2 (750 mL). The organic layer was washed with brine (400 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (150 mL) and the resultant suspension was added dropwise to a flask containing 10 M aq HCl (100 mL) and Et_2O (1.0 L) at 0 °C. The white precipitate was collected by filtration, washed with Et_2O (250 mL) and dissolved in CH_2Cl_2 (1.0 L). The resultant solution was dried, filtered and concentrated *in vacuo* to give (*R*)-**41**·HCl as a white solid (184 g). The free amine was regenerated by treatment of (*R*)-**41**·HCl with 2.0 M aq NaOH, followed by extraction with CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give (*R*)-**41** as a pale yellow oil (154 g, 93%, >99.0% ee[6]); $[\alpha]_D^{25}$ +55.3 (*c* 2.0 in EtOH); {lit.[5] $[\alpha]_D^{25}$ +53.3 (*c* 2.0 in EtOH)}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.6, C(α)*Me*), 1.64 (1H, br s, N*H*), 3.64 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.71 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.86 (1H, q, *J* 6.6, C(α)*H*), 7.25−7.43 (10H, m, *Ph*).

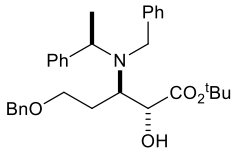
(–)-Camphorsulfonyloxaziridine [(–)-CSO] (–)-183[7]



$SOCl_2$ (252 mmol, 3.45 mmol) was added dropwise to a stirred solution on (−)-**180** (200 g, 861 mmol) in $CHCl_3$ (1.00 L) and the resultant mixture was heated at reflux for 12 h. The volatiles were then removed *in vacuo*, the residue was dissolved in $CHCl_3$ (1.00 L) and the resultant solution was added dropwise to a stirred solution of 35% aq NH_3 (2.00 L) at 0 °C. The resultant mixture was stirred for 4 h at 0 °C then the aqueous layer was extracted with CH_2Cl_2 (2 x 800 mL). The combined organics were dried, filtered and concentrated *in vacuo*. The residue was dissolved in PhMe (1.00 L) and Amberlyst® 15 (wet) ion exchange resin (12.0 g) was added to the resultant solution. A Dean-Stark apparatus was fitted and the resultant mixture heated to reflux for 12 h. After cooling to room temperature, the mixture was filtered through Celite® and the solvent removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.50 L) and Aliquat 336 (17.0 g, 42.1 mmol) was added. 2.0 M aq K_2CO_3 (750 mL, 1.43 mol) was added dropwise at 0 °C, maintaining the reaction temperature below 5 °C. Peracetic acid solution (39% in AcOH, 217 mL, 1.31 mol) was added dropwise, maintaining the reaction temperature below 5 °C and the resultant mixture was allowed to warm to rt over 8 h. The resultant mixture was quenched with Na_2SO_3 (1.0 equiv) and 1.0 M aq NaOH (800 mL) added. The aqueous layer was extracted with CH_2Cl_2 (3 x 800 mL) and the combined organic extracts were washed sequentially with H_2O (200 mL) and satd aq $NaHCO_3$ (400 mL) before being dried, filtered and concentrated *in vacuo*. Purification via recrystallisation (CH_2Cl_2/30−40 °C petroleum ether) gave (–)-**183** as a white amorphous solid (162 g, 80%); mp 169–172 °C {lit.[7] mp 165–167 °C}; $[\alpha]_D^{25}$ −44.9 (*c* 1.0 in $CHCl_3$); {lit.[7] $[\alpha]_D^{22}$ −40.8 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, s, *Me*), 1.18 (3H, s, *Me*), 1.46–1.58 (1H, m, C*H*), 1.78 (1H, d, *J* 15.5, CH_ACN), 1.89–2.15

(5H, m, CH_BCN, CH_2CH_2), 2.60–2.67 (1H, m, C*H*), 3.10 (1H, d, *J* 14.0, CH_ASO$_2$), 3.27 (1H, d, *J* 14.0, CH_BSO$_2$).

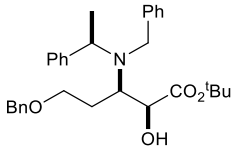
tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-benzyloxy pentanoate 171



^{n}BuLi (2.5 M in hexanes, 34.5 mL, 86.3 mmol) was added dropwise to a stirred solution of (*R*)-**41** (18.8 g, 89.1 mmol, >99.0% ee) in THF (308 mL) at –78 °C, and the resultant mixture was stirred at –78 °C for 30 min. A solution of **170** (14.6 g, 55.7 mmol) in THF (156 mL) was added via cannula and the resultant mixture was stirred at –78 °C for 2 h. (–)-**183** (21.7 g, 94.7 mmol) was added and the reaction mixture was allowed to warm to rt and was stirred at rt for 12 h. Satd aq NH_4Cl (100 mL) was added, and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1 to 7.5:1) gave **171** as a colourless oil (18.4 g, 68%, >95:5 dr); $[\alpha]_D^{25}$ –38.5 (*c* 1.0 in $CHCl_3$); ν_{max} 3500 (O−H), 2980 (C−H), 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 7.1, C(α)*Me*), 1.31 (9H, s, C*Me*$_3$), 1.33–1.42 (1H, m, C(4)H_A), 1.68–1.81 (1H, m, C(4)H_B), 2.87 (1H, d, *J* 5.8, O*H*), 3.51–3.69 (5H, m, C(2)*H*, C(3)*H*, C(5)H_2, NCH_AH$_B$Ph), 3.84 (1H, q, *J* 7.1, C(α)*H*), 4.22 (1H, d, *J* 15.5, NCH$_A$$H_B$Ph), 4.36 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 4.42 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 7.11–7.39 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 19.3 (C(α)*Me*), 27.9 (C*Me*$_3$), 28.0 (*C*(4)), 50.9 (N*C*H$_2$Ph), 55.2 (*C*(3)), 57.9 (*C*(α)), 67.5 (*C*(5)), 71.4 (*C*(2)), 72.9 (O*C*H$_2$Ph),

82.6 (*C*Me$_3$), 126.4, 127.0, 127.4, 127.7, 128.1, 128.1, 128.2, 128.2, 128.3 (*o,m,p-Ph*), 138.7, 142.3, 142.6 (*i-Ph*), 174.4 (*C*(1)); *m/z* (ESI$^+$) 490 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_4^+$ ([M+H]$^+$) requires 490.2952; found 490.2949.

tert-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-benzyloxy pentanoate 172

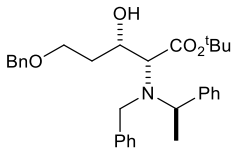


Step 1: DMSO (11.7 mL, 163 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (6.60 mL, 81.7 mmol) in CH_2Cl_2 (150 mL) and the resultant mixture was stirred at –78 °C for 20 min. A solution of **171** (20.0 g, 40.8 mmol) in CH_2Cl_2 (54.0 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 30 min. Et_3N (34.4 mL, 245 mmol) was added and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to rt and was stirred at rt for 30 min. H_2O (250 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo* to give a yellow oil.

Step 2: $NaBH_4$ (1.54 g, 40.8 mmol) was added to a stirred solution of the residue from the previous step in MeOH (2.0 L) at –20 °C and the resultant mixture was stirred at –20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated *in vacuo*. The residue was partitioned between H_2O (500 mL) and CH_2Cl_2 (500 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL) and the combined organic extracts were dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **172** as a colourless oil (20.7 g, quant (from **171**), >95:5 dr); $[\alpha]_D^{25}$ −16.7 (*c* 1.0 in $CHCl_3$); ν_{max} 2977 (C−H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 7.0,

C(α)*Me*), 1.32 (9H, s, C*Me*$_3$), 1.80–1.88 (2H, m, C(4)*H*$_2$), 3.22–3.29 (2H, m, C(3)*H*, O*H*), 3.35–3.47 (2H, m, C(5)*H*$_2$), 3.67 (1H, d, *J* 14.5, NC*H*$_A$H$_B$Ph), 3.75–3.82 (2H, m, C(2)*H*), 3.81 (1H, d, *J* 14.5, NCH$_A$*H*$_B$Ph), 3.99 (1H, q, *J* 7.0, C(α)*H*), 4.35 (1H, d, *J* 11.9, OC*H*$_A$H$_B$Ph), 4.41 (1H, d, *J* 11.9, OCH$_A$*H*$_B$Ph), 7.01–7.35 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 28.0 (C*Me*$_3$), 28.7 (*C*(4)), 50.7 (N*C*H$_2$Ph), 57.3 (*C*(3)), 59.9 (*C*(α)), 68.2 (*C*(5)), 73.0 (O*C*H$_2$Ph), 73.7 (*C*(2)), 82.0 (*C*Me$_3$), 126.8, 127.1, 127.6, 127.7, 128.2, 128.2, 128.3, 128.4, 128.7 (*o,m,p-Ph*), 138.5, 141.2, 143.4 (*i-Ph*), 173.2 (*C*(1)); *m/z* (ESI$^+$) 490 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_4^+$ ([M+H]$^+$) requires 490.2952; found 490.2951.

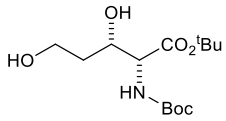
***tert*-Butyl (2*R*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)]-3-hydroxy-5-benzyloxy pentanoate 173**



Tf_2O (35.7 g, 126 mmol) was added to a stirred solution of **172** (41.3 g, 84.4 mmol) and DTBMP (52.0 g, 253 mmol) in CH_2Cl_2 (422 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h then at rt for 5 h. H_2O (83.5 mL) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1.00 L) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (750 mL), and the resultant suspension was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **173** as a colourless oil (41.4 g, quant, >95:5 dr); $[\alpha]_D^{25}$ +40.9 (*c* 1.0 in $CHCl_3$); ν_{max} 2859 (O−H), 2325 (C−H), 1721 (C=O); δ_H (500 MHz, $CDCl_3$) 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 1.61–1.67 (1H, m, C(4)*H*$_A$), 1.79–1.86 (1H, m, C(4)*H*$_B$), 3.34 (1H, d, *J* 9.4, C(2)*H*), 3.59 (2H, t, *J* 6.8, C(5)*H*$_2$), 3.77 (1H, s, O*H*), 3.81 (1H, d, *J* 15.1,

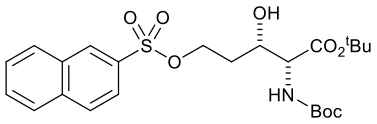
NC*H*$_A$H$_B$Ph), 3.87 (1H, td, *J* 8.9, 2.5, C(3)*H*), 4.12 (1H, q, *J* 7.0, C(α)*H*), 4.27 (1H, d, *J* 15.1, NCH$_A$*H*$_B$Ph), 4.43 (2H, s, OC*H*$_2$Ph), 7.15–7.49 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.3 (C(α)*Me*), 28.1 (C*Me*$_3$), 33.7 (*C*(4)), 52.0 (N*C*H$_2$Ph), 60.6 (*C*(α)), 66.1, 66.1 (*C*(2), *C*(3)), 67.2 (*C*(5)), 72.9 (O*C*H$_2$Ph), 81.5 (*C*Me$_3$), 127.0, 127.4, 127.6, 128.1, 128.3, 128.3, 128.5, 128.6 (*o*,*m*,*p*-*Ph*), 138.6, 140.7, 142.8 (*i*-*Ph*), 170.3 (*C*(1)); *m/z* (ESI$^+$) 490 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_4^+$ ([M+H]$^+$) requires 490.2952; found 490.2957.

***tert*-Butyl (2*R*,3*S*)-2-[(*tert*-butoxycarbonyl)amino]-3,5-dihydroxypentanoate 186**



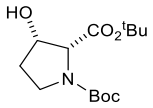
$Pd(OH)_2$/C (570 mg, 20% w/w) was added to a degassed solution of **173** (2.85 g, 5.82 mmol) and Boc_2O (2.54 g, 11.6 mmol) in MeOH (5.00 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and was stirred at rt for 65 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1 increased to 0:1) gave **186** as a white solid (1.57 g, 89%, >95:5 dr); mp 82–84 °C; $[\alpha]_D^{25}$ +5.6 (*c* 1.0 in MeOH); ν_{max} 3431 (O−H), 2979 (C−H), 1697 (C=O); δ_H (400 MHz, MeOH-d_4) 1.45 (9H, s, C*Me*$_3$), 1.48 (9H, s, C*Me*$_3$), 1.66–1.72 (2H, m, C(4)*H*$_2$), 3.30 (1H, br s, N*H*), 3.67 (2H, t, *J* 6.3, C(5)*H*$_2$), 4.05 (1H, d, *J* 2.9, C(2)*H*), 4.20–4.25 (1H, m, C(3)*H*); δ_C (101 MHz, MeOH-d_4) 26.9, 27.3 (2 × C*Me*$_3$), 36.5 (*C*(4)), 58.2 (*C*(5)), 58.9 (*C*(2)), 68.4 (*C*(3)), 79.4, 81.5 (2 × *C*Me$_3$), 156.9 (N*C*O), 170.5 (*C*(1)); *m/z* (ESI$^+$) 328 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{27}NNaO_6^+$ ([M+Na]$^+$) requires 328.1731; found 328.1728.

tert-Butyl (2*R*,3*S*)-2-(_tert_-butoxycarbonylamino)-3-hydroxy-5-(naphthalen-2′-ylsulfonyloxy)pentanoate 187



2-NapSO$_2$Cl (10.5 g, 46.1 mmol) was added to a stirred solution of **186** (9.39 g, 30.8 mmol) in pyridine (61.5 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. EtOAc (100 mL) was added and the reaction mixture was washed with satd aq $CuSO_4$ (3 × 100 mL). The combined aqueous extracts were extracted with EtOAc (2 × 200 mL), then the combined organic extracts were washed sequentially with H_2O (5 × 200 mL), satd aq $NaHCO_3$ (3 × 200 mL) and brine (2 × 200 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **187** as a white solid (13.5 g, 89%, >95:5 dr); mp 44–47 °C; $[\alpha]_D^{25}$ –3.4 (*c* 1.0 in MeOH); ν_{max} 3415 (O−H), 2979 (C−H), 1742 (C=O), 1710 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, C*Me*$_3$), 1.43 (9H, s, C*Me*$_3$), 1.74–1.94 (2H, m, C(4)*H*$_2$), 2.69 (1H, br s, O*H*), 4.10 (1H, d, *J* 7.2, C(2)*H*), 4.15–4.24 (2H, m, C(3)*H*, C(5)*H*$_A$), 4.29 (1H, td, *J* 9.7, 4.9, C(5)*H*$_B$), 5.30 (1H, d, *J* 9.0, N*H*), 7.58–7.69 (2H, m, C(6′)*H*, C(7′)*H*), 7.81–7.99 (4H, m, C(3′)*H*, C(4′)*H*), C(5′)*H*, C(8′)*H*), 8.48 (1H, d, *J* 1.8, C(1′)*H*); δ_C (101 MHz, $CDCl_3$) 28.0, 28.2 (2 × C*Me*$_3$), 33.2 (*C*(4)), 58.2 (*C*(2)), 67.8 (*C*(5)), 68.3 (*C*(3)), 80.0, 82.7 (2 × *C*Me$_3$), 122.4 (*C*(3′)), 127.9, 128.0, 129.4, 129.4, 129.8, 129.8 (*C*(1′), *C*(4′)–*C*(8′)), 131.9, 132.6 (*C*(4a′), *C*(8a′)), 135.3 (*C*(2′)), 156.1 (N*C*O), 170.0 (*C*(1)); *m/z* (ESI$^+$) 518 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}NNaO_8S^+$ ([M+Na]$^+$) requires 518.1819; found 518.1815.

di-tert-Butyl (2*R*,3*S*)-*N*-1,2-dicarboxylate-3-hydroxypyrrolidine 188

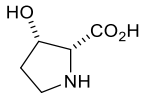


Method A: NaH (60% dispersion in mineral oil, 44.4 mg, 1.11 mmol) in THF (5.00 mL) was stirred at rt for 10 min. The suspension was allowed to settle and the THF was removed, then this process was repeated three times. The residual NaH was suspended in THF (5.00 mL) and a solution of **187** (500 mg, 1.01 mmol) in THF (5.0 mL) was added at rt, and the resultant mixture was stirred at rt for 15 min. H_2O (10 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave **188** as a colourless oil (290 mg, quant, >95:5 dr); $[\alpha]_D^{25}$ +28.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3349 (O−H), 2978 (C−H), 1702 (C=O), 1679 (C=O); δ_H (500 MHz, PhMe-d_8, 363 K) 1.42 (9H, s, C*Me*$_3$), 1.45 (9H, s, C*Me*$_3$), 1.60 (1H, ddd, *J* 12.8, 6.4, 1.8, C(4)H_A), 1.66–1.88 (2H, m, C(4)H_B, O*H*), 3.20–3.30 (1H, m, C(5)H_A), 3.45–3.55 (1H, m, C(5)H_B), 4.03–4.21 (2H, m, C(2)*H*, C(3)*H*); δ_C (125 MHz, PhMe-d_8, 363K) 28.6, 28.9 (2 × C*Me*$_3$), 33.0 (*C*(4)), 44.6 (*C*(5)), 64.8 (*C*(2)), 72.8 (*C*(3)), 79.6, 81.4 (2 × *C*Me$_3$), 154.3 (N*C*O), 169.7 (*C*O_2^{t}Bu); *m/z* (ESI$^+$) 310 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{25}NNaO_5^+$ ([M+Na]$^+$) requires 310.1625; found 310.1622.

Method B: ^{n}BuLi (2.5 M in hexanes, 10.0 mL, 24.9 mmol) was added to a stirred solution of **187** (11.3 g, 22.7 mmol) in THF (227 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 mins then at rt for 2 h. Satd aq NH_4Cl (150 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with brine (250 mL) then dried, filtered and concentrated *in vacuo*. Purification via flash column

chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave **188** as a colourless oil (5.48 g, 84%, >95:5 dr).

(2*R*,3*S*)-3-Hydroxyproline 131



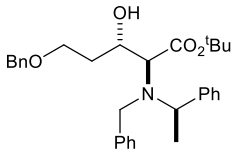
Method A: A solution of **188** (93 mg, 0.32 mmol) in 6.0 M aq HCl (1.00 mL) was stirred at rt for 16 h, then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX® 50WX8-200, eluent 1.0 M aq NH_4OH) gave **131** as a white solid (41 mg, 96%, >95:5 dr); mp 217–223 °C (dec.); {lit.[8] mp 210–217 °C (dec.)}; $[\alpha]_D^{25}$ +80.9 (*c* 1.0 in H_2O); {lit.[8] $[\alpha]_D^{25}$ +96.3 (*c* 0.9 in H_2O)}; ν_{max} 3310 (N−H), 2945 (C−H), 1587 (C=O); δ_H (400 MHz, D_2O) 2.10–2.30 (2H, m, C(4)H_2), 3.45–3.64 (2H, m, C(5)H_2), 4.15 (1H, d, *J* 4.0, C(2)*H*), 4.73 (1H, td, *J* 4.1, 1.4, C(3)*H*); δ_C (101 MHz, D_2O) 36.0 (*C*(4)), 46.6 (*C*(5)), 70.3 (*C*(2)), 73.7 (*C*(3)), 173.4 (CO_2H); *m/z* (ESI^+) 132 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_5H_{10}NO_3^+$ ($[M+H]^+$) requires 132.0655; found 132.0654.

Method B – Step 1: $Pd(OH)_2/C$ (58.0 mg, 25% w/w) was added to a degassed solution of **220** (233 mg, 0.727 mmol) in MeOH/H_2O/AcOH (1.00 mL, 40:4:1) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and was stirred at rt for 16 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL), and the resultant solution was washed with 2.0 M aq NaOH (20 mL) and the aqueous washings were extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL) then dried, filtered and concentrated *in vacuo* to give (2*R*,3*S*)-2-(*tert*-butoxycarbonyl)-3-acetoxypyrrolidine as a colourless oil (140 mg, 84%, >95:5 dr); $[\alpha]_D^{25}$ +2.9 (*c* 1.0 in $CHCl_3$); ν_{max} 2978 (C−H), 1719 (C=O); δ_H 1.38 (9H, s, CMe_3), 1.79–

1.89 (1H, m, C(4)H_A), 1.95 (3H, s, CO*Me*), 2.00–2.11 (1H, m, C(4)H_B), 2.46 (1H, s, N*H*), 2.89 (1H, ddd, *J* 10.5, 8.7, 4.2, C(5)H_A), 3.18 (1H, app dt, *J* 10.5, 7.8, C(5)H_B), 3.69 (1H, d, *J* 4.9, C(2)*H*), 5.40 (1H, app td, *J* 4.9, 1.9, C(3)*H*); δ_C (101 MHz, $CDCl_3$) 21.0 (CO*Me*), 28.0 (CMe_3), 33.4 (*C*(4)), 44.6 (*C*(5)), 65.0 (*C*(2)), 75.8 (*C*(3)), 81.7 (*C*Me_3), 169.2, 169.9 (*C*OMe, *C*$O_2{}^t$Bu); *m/z* (ESI$^+$) 230 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{20}NO_4^+$ ([M+H]$^+$) requires 230.1387; found 230.1387.

Method B – Step 2: A solution of (2*R*,3*S*)-2-(*tert*-butoxycarbonyl)-3-acetoxypyrrolidine (139 mg, 0.484 mmol) in 6.0 M aq HCl (1.00 mL) was stirred at rt for 16 h, then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX® 50WX8-200, eluent 1.0 M aq NH_4OH) gave **131** as a white solid (54 mg, 85% (from (2*R*,3*S*)-2-(*tert*-butoxycarbonyl)-3-acetoxypyrrolidine), >95:5 dr); mp 218–222 °C (dec.); {lit.[8] mp 210–217 °C (dec.)}; $[\alpha]_D^{25}$ +80.4 (*c* 1.0 in H_2O); {lit.[8] $[\alpha]_D^{25}$ +96.3 (*c* 0.9 in H_2O)}.

tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)]-3-hydroxy-5-benzyloxy pentanoate 190

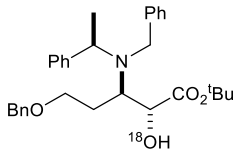


190

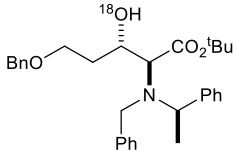
Tf_2O (12.9 mL, 45.9 mmol) was added to a stirred solution of **171** (15.0 g, 30.6 mmol) and DTBMP (18.9 g, 91.8 mmol) in CH_2Cl_2 (153 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h then at rt for 5 h. H_2O (30.0 mL) was added and the resultant mixture was stirred at rt for 24 h. H_2O (250 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were then dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (250 mL), and the resultant suspension was filtered and

concentrated *in vacuo* to give a 58:42 mixture of **171** and **190**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **171** as a colourless oil (8.13 g, 55%, >95:5 dr). Further elution (eluent Et_2O) gave **190** as a colourless oil (6.21 g, 42%, >95:5 dr); $[\alpha]_D^{25}$ −30.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3503 (O−H), 2973 (C−H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20–1.27 (1H, m, C(4)H_A), 1.36 (3H, d, *J* 7.2, C(α)*Me*), 1.49 (9H, s, CMe_3), 1.87–1.96 (1H, m, C(4)H_B), 3.01 (1H, d, *J* 4.5, O*H*), 3.11 (1H, d, *J* 9.2, C(2)*H*), 3.19–3.33 (2H, m, C(5)H_2), 3.79 (1H, d, *J* 14.3, NCH_AH_BPh), 3.90–3.95 (1H, m, C(3)*H*), 3.97 (1H, q, *J* 7.2, C(α)*H*), 4.11 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 4.25 (1H, d, *J* 11.9, OCH_AH_BPh), 4.31 (1H, d, *J* 11.9, OCH$_A$$H_B$Ph), 7.08–7.29 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 13.2 (C(α)*Me*), 28.2 (CMe_3), 32.8 (*C*(4)), 51.9 (N*C*H_2Ph), 56.7 (*C*(α)), 63.6 (*C*(2)), 68.7 (*C*(5)), 70.6 (*C*(3)), 73.1 (O*C*H_2Ph), 81.2 (*C*Me_3), 126.9, 127.0, 127.6, 128.0, 128.1, 128.2, 128.3, 128.4, 129.1 (*o,m,p-Ph*), 138.1, 140.4, 143.4 (*i-Ph*), 173.2 (*C*(1)); *m/z* (ESI$^+$) 490 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_4^+$ ([M+H]$^+$) requires 490.2952; found 490.2945.

***tert*-butyl (*R,R,R*)-2-(^{18}O-hydroxy)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-benzyloxypentanoate ^{18}O-171 and *tert*-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)]-3-(^{18}O-hydroxy)-5-benzyloxypentanoate ^{18}O-190**



^{18}O-171



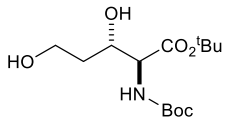
^{18}O-190

Tf_2O (100 μL, 613 μmol) was added to a stirred solution of **171** (200 mg, 408 μmol) and DTBMP (251 mg, 1.22 mmol) in CH_2Cl_2 (2.04 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h then at rt for 5 h. $H_2{}^{18}O$ (0.40 mL, ≥98% ^{18}O) was added and the resultant mixture was stirred at rt for 24 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL),

and the combined organic extracts were dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (220 mL), and the resultant suspension was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave ^{18}O-**171** as a colourless oil (83 mg, 36%, >95:5 dr, 96% ^{18}O); $[\alpha]_D^{25}$ –33.7 (*c* 1.0 in $CHCl_3$); ν_{max} 3490 (O−H), 2854 (C−H), 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 7.0, C(α)*Me*), 1.29 (9H, s, C*Me*$_3$), 1.35–1.42 (1H, m, C(4)*H*$_A$), 1.68–1.79 (1H, m, C(4)*H*$_B$), 2.86 (1H, d, *J* 5.8, O*H*), 3.48–3.69 (5H, m, C(2)*H*, C(3)*H*, C(5)*H*$_2$, NC*H*$_A$H$_B$Ph), 3.84 (1H, q, *J* 7.1, C(α)*H*), 4.21 (1H, d, *J* 15.5, NCH$_A$*H*$_B$Ph), 4.35 (1H, d, *J* 11.5, OC*H*$_A$H$_B$Ph), 4.40 (1H, d, *J* 11.5, OCH$_A$*H*$_B$Ph), 7.10–7.38 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 27.9 (C*Me*$_3$), 28.0 (*C*(4)), 50.9 (N*C*H$_2$Ph), 55.3 (*C*(3)), 58.0 (*C*(α)), 67.5 (*C*(5)), 71.4 (*C*(2)), 72.9 (O*C*H$_2$Ph), 82.6 (*C*Me$_3$), 126.5, 127.1, 127.4, 127.8, 128.1, 128.2, 128.3, 128.3 (*o,m,p-Ph*), 138.7, 142.3, 142.6 (*i-Ph*), 174.4 (*C*(1)); *m/z* (ESI$^+$) 492 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_3{}^{18}O^+$ ([M+H]$^+$) requires 492.2994; found 492.2990.

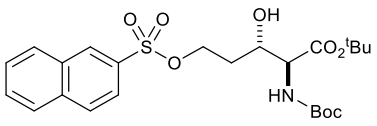
Further elution (eluent Et_2O) gave ^{18}O-**190** as a colourless oil (71 mg, 32%, >95:5 dr, 96% ^{18}O); $[\alpha]_D^{25}$ –29.5 (*c* 1.0 in $CHCl_3$); ν_{max} 3503 (O−H), 2923 (C−H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22–1.31 (1H, m, C(4)*H*$_A$), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.52 (9H, s, C*Me*$_3$), 1.89–2.00 (1H, m, C(4)*H*$_B$), 3.01 (1H, d, *J* 4.4, O*H*), 3.14 (1H, d, *J* 9.2, C(2)*H*), 3.21–3.37 (2H, m, C(5)*H*$_2$), 3.82 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 3.94–4.06 (2H, m, C(3)*H*, C(α)*H*), 4.14 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 4.28 (1H, d, *J* 11.9, OC*H*$_A$H$_B$Ph), 4.33 (1H, d, *J* 11.9, OCH$_A$*H*$_B$Ph), 7.12–7.34 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 13.3 (C(α)*Me*), 28.3 (C*Me*$_3$), 32.8 (*C*(4)), 51.9 (N*C*H$_2$Ph), 56.7 (*C*(α)), 63.6 (*C*(2)), 68.7 (*C*(5)), 70.6 (*C*(3)), 73.1 (O*C*H$_2$Ph), 81.2 (*C*Me$_3$), 126.9, 127.0, 127.6, 128.1, 128.3, 128.4, 128.4, 129.1 (*o,m,p-Ph*), 138.1, 140.5, 143.4 (*i-Ph*), 173.2 (*C*(1)); *m/z* (ESI$^+$) 492 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_3{}^{18}O^+$ ([M+H]$^+$) requires 492.2994; found 492.2985.

tert-Butyl (*S*,*S*)-2-[(*N*-_tert_-butoxycarbonyl)amino]-3,5-dihydroxypentanoate 195



$Pd(OH)_2/C$ (310 mg, 10% w/w) was added to a degassed solution of **190** (3.10 g, 6.33 mmol,) and Boc_2O (2.07 g, 9.50 mmol) in MeOH (4.0 mL), and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and was stirred at rt for 65 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1 increased to 0:1) gave **195** as a white solid (2.61 g, 67%, >95:5 dr); mp 80–82 °C; $[\alpha]_D^{25}$ +28.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3419 (O−H), 1697 (C=O); δ_H (400 MHz, MeOH-d_4) 1.47 (9H, s, CMe_3), 1.50 (9H, s, CMe_3), 1.70–1.82 (2H, m, C(4)H_2), 3.66–3.76 (2H, m, C(5)H_2), 3.99 (1H, ddd, *J* 9.0, 5.3, 3.7, C(3)*H*), 4.08 (1H, d, *J* 5.3, C(2)*H*); δ_C (101 MHz, MeOH-d_4) 27.0, 27.3 (2 × CMe_3), 35.7 (*C*(4)), 58.4 (*C*(5)), 59.5 (*C*(2)), 68.9 (*C*(3)), 79.3, 81.5 (2 × *C*Me_3), 156.5 (N*C*O), 170.2 (*C*(1)); *m/z* (ESI^+) 328 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{28}NO_6^+$ ($[M+H]^+$) requires 306.1911; found 306.1207.

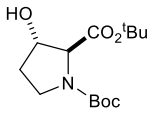
tert-Butyl (*S*,*S*)-2-(_tert_-butoxycarbonylamino)-3-hydroxy-5-(naphthalen-2-ylsulfonyloxy) pentanoate 196



2-$NapSO_2Cl$ (2.23 g, 9.82 mmol) was added to a stirred solution of **195** (2.00 g, 6.55 mmol) in pyridine (13.2 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 5 h. EtOAc (30 mL) was added and the resultant mixture was washed with satd aq $CuSO_4$ (3 × 30 mL). The combined aqueous extracts were extracted with EtOAc (2 × 50 mL) then the combined organic

extracts were washed sequentially with H_2O (5 × 50 mL), satd aq $NaHCO_3$ (3 × 50 mL) and brine (2 × 50 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **196** as a colourless oil (2.54 g, 78%, >95:5 dr); $[\alpha]_D^{25}$ −12.1 (*c* 1.0 in MeOH); ν_{max} 3728 (N−H), 3391 (O−H), 2361 (C−H), 1710 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 1.43 (9H, s, C*Me*$_3$), 1.73–1.83 (2H, m, C(4)*H*$_2$), 3.56 (1H, br s, O*H*), 4.08 (1H, dt, *J* 9.4, 4.1, C(3)*H*), 4.20–4.32 (3H, m, C(2)*H*, C(5)*H*$_2$), 5.44 (1H, d, *J* 6.5, N*H*), 7.59–7.70 (2H, m, C(6′)*H*, C(7′)*H*), 7.81–8.00 (4H, m, C(3′)*H*, C(4′)*H*, C(5′)*H*, C(8′)*H*), 8.48 (1H, d, *J* 2.1, C(1′)*H*); δ_C (101 MHz, $CDCl_3$) 27.9, 28.2 (C*Me*$_3$), 32.3 (*C*(4)), 59.0 (*C*(2)), 67.7 (*C*(5)), 69.4 (*C*(3)), 80.7, 83.4 (*C*Me$_3$), 122.5 (*C*(3′)), 127.8, 128.0, 129.3, 129.7, 129.7, 129.8 (*C*(1′), *C*(4′)–*C*(8′)), 132.0, 132.8 (*C*(4a′), *C*(8a′)), 135.3 (*C*(2′)), 156.6 (N*C*O), 168.9 (*C*(1)); *m/z* (ESI$^+$) 518 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}NNaO_8S^+$ ([M+Na]$^+$) requires 518.1819; found 518.1820.

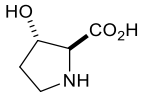
***di-tert*-Butyl (*S*,*S*)-*N*-1,2-dicarboxylate-3-hydroxypyrrolidine 189**



A solution of **196** (500 mg, 1.01 mmol) in THF (5.0 mL) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 44 mg, 1.11 mmol) in THF (5.0 mL) at rt, and the resultant mixture was stirred at rt for 2 h. H_2O (5 mL) was added and the resultant mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave **189** as a white solid (177 mg, 61%, >95:5 dr); mp 103–105 °C; $[\alpha]_D^{25}$ −16.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3430 (O−H), 1740 (C=O); δ_H (500 MHz, PhMe-*d*$_8$, 363 K) 1.38 (9H, s, C*Me*$_3$), 1.45 (9H, s, C*Me*$_3$), 1.51–1.61 (1H, m, C(4)*H*$_A$), 1.81–1.96 (2H, m,

C(4)H_B, O*H*), 3.53 (2H, br s, C(5)H_2), 4.10–4.22 (2H, m, C(2)*H*, C(3)*H*); δ_C (125 MHz, PhMe-d_8, 363 K) 28.4, 28.9 (2 × CMe_3), 33.0 (*C*(4)), 45.1 (*C*(5)), 69.9 (*C*(2)), 75.7 (*C*(3)), 79.7, 81.1 (2 × *C*Me$_3$), 154.7 (N*C*O), 170.7 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 310 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{26}NO_5^+$ ([M+H]$^+$) requires 288.1805; found 288.1806.

(2*S*,3*S*)-3-Hydroxyproline 136



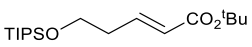
Method A: A solution of **189** (130 mg, 0.457 mmol) in 6.0 M aq HCl (1.0 mL) was stirred at rt for 16 h, then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX® 50WX8-200, eluent 1.0 M aq NH_4OH) gave **136** as a white solid (52 mg, 87%, >95:5 dr); mp 231 °C (dec.); {lit.[8] mp 231–234 °C (dec.)}; $[\alpha]_D^{25}$ −15.8 (*c* 1.0 in H_2O); {lit.[8] $[\alpha]_D^{25}$ −18.8 (*c* 1.0 in H_2O)}; ν_{max} 3222 (N−H), 3062 (O−H), 1627 (C=O); δ_H (400 MHz, D_2O) 2.01–2.11 (2H, m, C(4)H_2), 3.46–3.56 (1H, m, C(5)H_A), 3.56–3.65 (1H, m, C(5)H_B), 4.08 (1H, *J* 1.5, C(2)*H*), 4.69 (1H, q, *J* 3.3, 1.5, C(3)*H*); δ_C (101 MHz, D_2O) 34.3 (*C*(4)), 47.0 (*C*(5)), 71.7 (*C*(2)), 76.65 (*C*(3)), 174.4 (*C*O$_2$H); *m/z* (ESI$^+$) 132 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_5H_{10}NO_3^+$ ([M+H]$^+$) requires 132.0655; found 132.0655.

Method B – Step 1: $Pd(OH)_2$/C (49.0 mg, 25% w/w) was added to a degassed solution of **211** (196 mg, 0.612 mmol) in MeOH/H_2O/AcOH (1.00 mL, 40:4:1) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and was stirred at rt for 16 h. The resultant mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL), and the resultant solution was washed with 2.0 M aq NaOH (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine

(20 mL), then dried, filtered and concentrated *in vacuo* to give (*S*,*S*)-2-(*tert*-butoxycarbonyl)-3-acetoxypyrrolidine as a colourless oil (114 mg, 82%, >95:5 dr); $[\alpha]_D^{25}$ +3.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3349 (N−H), 2978 (C−H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.77–1.86 (1H, m, C(4)*H*$_A$), 1.92–2.03 (1H, m, C(4)*H*$_B$), 2.04 (3H, s, CO*Me*), 2.29 (1H, s, N(1)*H*), 3.01 (1H, ddd, *J* 10.6, 8.1, 7.0, C(5)*H*$_A$), 3.12 (1H, ddd, *J* 10.6, 8.1, 4.5, C(5)*H*$_B$), 3.62 (1H, d, *J* 2.9, C(2)*H*), 5.30 (1H, app dt, *J* 6.1, 2.9, C(3)*H*); δ_C (101 MHz, $CDCl_3$) 21.1 (CO*Me*), 27.9 (C*Me*$_3$), 32.6 (*C*(4)), 45.3 (*C*(5)), 66.7 (*C*(3)), 77.7 (*C*(2)), 82.0 (*C*Me$_3$), 170.3, 171.7 (*C*OMe, *C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 230 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{20}NO_4^+$ ([M+H]$^+$) requires 230.1387; found 230.1387

Method B – Step 2: A solution of (*S*,*S*)-2-(*tert*-butoxycarbonyl)-3-acetoxypyrrolidine (100 mg, 0.43 mmol) in 6.0 M aq HCl (0.50 mL) was stirred at rt for 16 h, then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX® 50WX8-200, eluent 1.0 M aq NH_4OH) gave **136** as a white solid (50 mg, 89%, >95:5 dr); mp 230–234 °C (dec.); {lit.[8] mp 231–234 °C (dec.)}; $[\alpha]_D^{25}$ −12.4 (*c* 1.0 in H_2O); {lit.[9] $[\alpha]_D^{25}$ −18.8 (*c* 1.0 in H_2O)}.

tert-Butyl (*E*)-5-(triisopropylsilyloxy)pent-2-enoate 203[9]

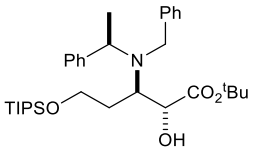


Step 1: **178** (30.0 g, 394 mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 15.8 g, 394 mmol) in THF (788 mL) at 0 °C, and the resultant mixture was stirred at rt for 45 min. TIPSCl (84.3 mL, 394 mmol) was added at 0 °C and the resultant mixture was stirred at rt for 6 h. H_2O (500 mL) was added and the reaction mixture was extracted with Et_2O (3 × 500 mL). The combined organic extracts were washed with brine (500 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1 to 0:1) gave **202** as a colourless oil (68.8 g, 75%); δ_H (400 MHz, $CDCl_3$)

1.03–1.17 (21H, m, Si(C*HMe*$_2$)$_3$), 1.80 (2H, app q, *J* 5.5, C(2)*H*$_2$), 2.74 (1H, t, *J* 5.4, O*H*), 3.84 (2H, q, *J* 5.4, C(1)*H*$_2$), 3.94 (2H, t, *J* 5.5, C(3)*H*$_2$).

Step 2: DMSO (24.6 mL, 344 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (14.0 mL, 172 mmol) in CH_2Cl_2 (300 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min. A solution of **202** (20.0 g, 86.0 mmol) in CH_2Cl_2 (130 mL) was added dropwise and the resultant mixture was stirred at –78 °C for 30 min. Et_3N (72.3 mL, 516 mmol) was added and stirring was continued at –78 °C for 30 min. The reaction mixture was allowed to warm to rt and stirred at rt for 30 min. **177** (32.4 g, 86.0 mmol) was added to the resultant mixture was stirred at rt for 16 h. H_2O (1.0 L) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (500 mL) and brine (500 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1 increased to 5:1) gave **203** as a colourless oil (24.8 g, 99%, >95:5 dr [(*E*):(*Z*)]); ν_{max} 2943 (C−H), 2867 (C−H), 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 1.00–1.12 (21H, m, Si(C*HMe*$_2$)$_3$), 1.47 (9H, s, C*Me*$_3$), 2.41 (2H, app qd, *J* 6.7, 1.5, C(4)*H*$_2$), 3.79 (2H, t, *J* 6.7, C(5)*H*$_2$), 5.79 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 6.88 (1H, dt, *J* 15.7, 7.1, C(3)*H*); δ_C (101 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$, 18.0 (Si(CH*Me*$_2$)$_3$), 28.1 (C*Me*$_3$), 35.7 (*C*(4)), 62.0 (*C*(5)), 80.0 (*C*Me$_3$), 124.6 (*C*(2)), 144.7 (*C*(3)), 165.9 (*C*(1)); *m/z* (ESI$^+$) 351 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{36}NaO_3Si^+$ ([M+Na]$^+$) requires 351.2326; found 351.2327.

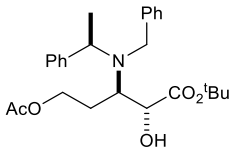
tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-triisopropyl silyloxypentanoate 204



^{n}BuLi (2.5 M in hexanes, 17.4 mL, 43.5 mmol) was added dropwise to a stirred solution of (*R*)-**41** (9.51 g, 45.0 mmol, >99.0% ee) in THF (156 mL) at –78 °C, and the resultant mixture was stirred at –78 °C for 30 min. A solution of **203** (9.24 g, 28.1 mmol) in THF (78 mL) was added via cannula and the resultant mixture was stirred at –78 °C for 2 h. (–)-**183** (10.9 g, 47.8 mmol) was added and the resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. Satd aq NH_4Cl (70 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (70 mL) and 10% aq citric acid (70 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 70 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (70 mL) and brine (70 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **204** as a white solid (14.1 g, 91%, >95:5 dr); mp 86–88 °C; $[\alpha]_D^{25}$ −17.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3500 (O−H), 2942 (C−H), 2867 (C–H), 1719 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99–1.04 (21H, m, Si(C*H*M*e*$_2$)$_3$), 1.30 (3H, d, *J* 7.0, C(α)*Me*), 1.31–1.36 (1H, m, C(4)H_A), 1.39 (9H, s, C*Me*$_3$), 1.76–1.86 (1H, m, C(4)H_B), 2.90 (1H, d, *J* 6.2, O*H*), 3.50 (1H, ddd, *J* 9.2, 4.7, 1.9, C(3)*H*), 3.61 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.65 (1H, dd, *J* 6.2, 1.9, C(2)*H*), 3.72–3.82 (2H, m, C(5)H_2), 3.85 (1H, q, *J* 7.0, C(α)*H*), 4.14 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 7.09–7.45 (10H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.2 (Si(CH*Me*$_2$)$_3$), 18.5 (C(α)*Me*), 28.0 (C*Me*$_3$), 30.8 (*C*(4)), 51.0 (N*C*H$_2$Ph), 54.9 (*C*(3)), 57.5 (*C*(α)), 60.7 (*C*(5)), 71.4 (*C*(2)), 82.4 (*C*Me$_3$), 126.5, 127.0, 128.1, 128.3, 128.3 (*o*,*m*,*p*-*Ph*), 141.9, 142.5 (*i*-*Ph*), 174.3

(*C*(1)); *m/z* (ESI$^+$) 556 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{54}NO_4Si^+$ ([M+H]$^+$) requires 556.3817; found 556.3809.

tert-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-acetoxy pentanoate 197

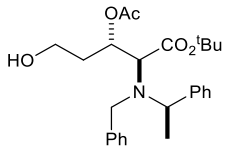


Step 1: Ac_2O (1.79 mL, 19.0 mmol) was added to a stirred solution of **204** (7.04 g, 12.7 mmol, DMAP (30.0 mg, 0.250 mmol) and pyridine (1.53 mL, 19.0 mmol) in THF (25.3 mL), and the resultant mixture was stirred at rt for 18 h. 1.0 M aq HCl (100 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried, filtered and concentrated *in vacuo* to give **205** as a colourless oil (9.13 g).

Step 2: TBAF (1.0 M in THF, 60.9 mL, 60.9 mmol) was added to a solution of **205** (9.13 g) from the previous step in THF (76 mL), and the resultant mixture was stirred at rt for 24 h. H_2O (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1 to 1:1) gave **197** as a colourless oil (5.15 g, 92%, >95:5 dr); mp 77–80 °C; $[\alpha]_D^{25}$ −19.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3496 (O−H), 2976 (C−H), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 7.0, C(α)*Me*), 1.22–1.35 (1H, m, C(4)H_A), 1.38 (9H, s, CMe_3), 1.73–1.82 (1H, m, C(4)H_B), 1.85 (3H, s, CO*Me*), 2.85 (1H, d, *J* 5.3, O*H*), 3.33–3.42 (1H, m, C(3)*H*), 3.58 (1H, d, *J* 15.8, NCH_AH_BPh), 3.82–3.90 (2H, m, C(2)*H*, C(α)*H*), 4.00–4.08 (1H, m, C(5)H_A), 4.23–4.32 (2H, m, C(5)H_B, NCH_AH_BPh), 7.12–7.39 (10H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 20.7,

21.0 (CO*Me*, C(α)*Me*), 26.3 (*C*(4)), 28.0 (C*Me*$_3$), 50.9 (NCH_2Ph), 55.6 (*C*(3)), 59.2 (*C*(α)), 62.0 (*C*(5)), 70.7 (*C*(2)), 82.8 (*C*Me$_3$), 126.4, 127.1, 127.8, 128.1, 128.2, 128.4 (*o,m,p-Ph*), 142.4, 143.2 (*i-Ph*), 170.9, 174.3 (*C*(1), *C*OMe); *m/z* (ESI$^+$) 442 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO_5^+$ ([M+H]$^+$) requires 442.2588; found 442.2583.

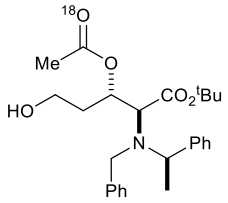
***tert*-Butyl (2*S*,3*S*,*αR*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-acetoxy-5-hydroxy pentanoate 201**



Tf_2O (0.210 mL, 1.22 mmol) was added to a stirred solution of **197** (360 mg, 0.815 mmol) and DTBMP (503 mg, 2.45 mmol) in CH_2Cl_2 (4.1 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min then at rt for 30 min. H_2O (10 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (20 mL), and the resultant suspension was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **201** as a colourless oil (301 mg, 84%, >95:5 dr); $[\alpha]_D^{25}$ −43.4 (*c* 1.0 in $CHCl_3$); ν_{max} 3500 (O−H), 2974 (C−H), 1742 (C=O), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.85–0.95 (1H, m, C(4)H_A), 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 1.90 (3H, s, CO*Me*), 1.96–2.06 (1H, m, C(4)H_B), 2.07–2.22 (1H, m, O*H*), 3.18 (1H, ddd, *J* 11.8, 10.2, 3.8, C(5)H_A), 3.24–3.33 (2H, m, C(2)*H*, C(5)H_B), 3.72 (1H, d, *J* 14.0, NCH_AH$_B$Ph), 4.01 (1H, q, *J* 7.0, C(α)*H*), 4.11 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 5.22 (1H, app td, *J* 9.9, 2.6, C(3)*H*), 7.10–7.35 (10H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 12.7 (C(α)*Me*), 20.9 (CO*Me*), 28.1 (C*Me*$_3$), 34.2 (*C*(4)), 51.6 (NCH_2Ph), 56.1 (*C*(α)), 57.9 (*C*(5)), 62.4 (*C*(2)), 70.2 (*C*(3)), 81.4 (*C*Me$_3$), 127.1, 127.2, 128.1, 128.3, 128.4, 129.3 (*o,m,p-Ph*), 139.6, 142.8 (*i-Ph*), 171.3,

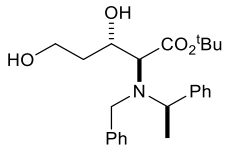
171.4 (*C*(1), *C*OMe); *m/z* (ESI$^+$) 442 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO_5^+$ ([M+H]$^+$) requires 442.2588; found 442.2589.

tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(^{18}O-acetoxy)-5-hydroxy pentanoate ^{18}O-201



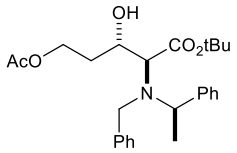
Tf_2O (30.0 μL, 165 μmol) was added to a stirred solution of **197** (50 mg, 110 μmol) and DTBMP (68 mg, 330 μmol) in CH_2Cl_2 (0.55 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min then at rt for 30 min. $H_2{}^{18}O$ (0.99 mL, ≥98% ^{18}O) was added and the resultant mixture was allowed to stir at rt for 1 h. The resultant mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were then dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (10 mL), and the resultant suspension was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave ^{18}O-**201** as a colourless oil (27 mg, 55%, >95:5 dr, 90% ^{18}O); ν_{max} 3430 (O−H), 2974 (C−H), 1726 (C=O), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 0.86–0.96 (1H, m, C(4)H_A), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.47 (9H, s, CMe_3), 1.90 (3H, s, C^{18}O*Me*), 1.94–2.06 (1H, m, C(4)H_B), 2.09–2.20 (1H, m, O*H*), 3.18 (1H, ddd, *J* 11.8, 10.1, 3.9, C(5)H_A), 3.24–3.32 (2H, m, C(2)*H*, C(5)H_B), 3.72 (1H, d, *J* 14.0, NCH_AH_BPh), 4.01 (1H, q, *J* 7.0, C(α)*H*), 4.14 (1H, d, *J* 14.0, N*C*H$_A$$H_B$Ph), 5.22 (1H, app td, *J* 9.9, 2.6, C(3)*H*), 7.12–7.31 (10H, m, *Ph*); *m/z* (ESI$^+$) 444 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO_4{}^{18}O^+$ ([M+H]$^+$) requires 444.2630; found 444.2625.

tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3,5-dihydroxypentanoate 208



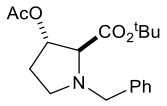
K_2CO_3 (28 mg, 204 μmol) was added to a stirred solution of ^{18}O-**201** (30 mg, 67 μmol, 90% ^{18}O) in MeOH (0.34 mL) and the resultant mixture was stirred at rt for 2 h. The reaction mixture was then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave **208** as a colourless oil (14 mg, 52%, >95:5 dr); $[\alpha]_D^{25}$ −50.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3412 (O−H), 2972 (C−H), 1723 (C=O), 1144; δ_H (400 MHz, $CDCl_3$) 1.12–1.23 (1H, m, C(4)H_A), 1.37 (3H, d, *J* 6.9, C(α)*Me*), 1.51 (9 H, s, CMe_3), 1.75–1.84 (1H, m, C(4)H_B), 2.20 (1H, br s, O*H*), 2.85 (1H, br s, O*H*), 3.19 (1H, d, *J* 9.0, C(2)*H*), 3.38–3.49 (2H, m, C(5)H_2), 3.78 (1H, d, *J* 14.1, NCH_AH_BPh), 3.85–3.91 (1H, m, C(3)*H*), 3.93 (1H, d, *J* 14.1, NCH_AH_BPh), 4.00 (1H, q, *J* 6.9, C(α)*H*), 7.13–7.27 (10H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 14.8 (C(α)*Me*), 28.3 (CMe_3), 34.6 (*C*(4)), 52.3 (N*C*H_2Ph), 57.6 (*C*(α)), 61.5 (*C*(5)), 64.3 (*C*(2)), 71.4 (*C*(3), 81.9 (*C*Me_3), 127.1, 127.2, 128.0, 128.2, 128.3, 129.1 (*o*,*m*,*p*-*Ph*), 140.0, 143.7 (*i*-*Ph*), 173.3 (*C*(1)); *m/z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{34}NO_4^+$ ([M+H]$^+$) requires 400.2482; found 400.2474.

tert-Butyl (2S,3S,αR)-2-[*N*-benzyl-*N*-(α-methyl-benzyl)amino]-3-hydroxy-5-acetoxy pentanoate 200



TBAF (1.0 M in THF, 2.26 mL, 2.26 mmol) was added to a solution of **201** (250 mg, 0.566 mmol) THF (2.80 mL), and the resultant mixture was stirred at rt for 24 h. H_2O (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1 to 1:1) gave **200** as a colourless oil (225 mg, 90%, >95:5 dr); $[\alpha]_D^{25}$−41.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3657 (O−H), 2979 (C−H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.12 (1H, ddt, *J* 14.7, 9.7, 4.6, C(4)H_A), 1.46 (3H, d, *J* 6.9, C(α)*Me*), 1.60 (9H, s, CMe_3), 2.02 (3H, s, C(O)*Me*), 2.03–2.09 (1H, m, C(4)H_B), 2.46 (1H, d, *J* 5.3, O*H*), 3.20 (1H, d, *J* 8.8, C(2)*H*), 3.84–3.92 (2H, m, C(3)H, NC$H_A$$H_B$Ph), 4.01 (1H, ddd, *J* 10.8, 5.9, 4.6, C(5)H_A), 4.05–4.14 (3H, m, C(5)H_B, C(α)*H*, NC$H_A$$H_B$Ph), 7.20–7.39 (10H, m, *Ph*); δ_C (126 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 21.0 (C(O)*Me*), 28.3 (C*Me*$_3$), 32.5 (*C*(4)), 52.1 (N*C*H_2Ph), 57.0 (*C*(α)H), 61.5 (*C*(5)), 64.2 (*C*(2)), 68.0 (*C*(3)), 81.8 (*C*Me_3), 127.1, 127.1, 128.1, 128.1, 128.3, 129.1 (*o,m,p-Ph*), 140.0, 143.4 (*i-Ph*), 171.2 (*C*(O)Me), 173.1 (*C*(1)); HRMS (ESI^+) $C_{26}H_{36}NO_5^+$ ($[M+H]^+$) requires 442.2588; found 442.2586. Further elution gave **201** as a colourless oil (23 mg, 9%, >95:5 dr).

(*S*,*S*)-*N*-1-Benzyl-2-(*tert*-butoxycarbonyl)-3-acetoxypyrrolidine-2-carboxylate 211

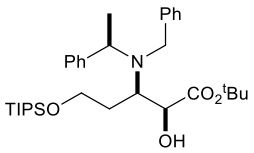


Step 1: TsCl (259 mg, 1.36 mmol) was added to a stirred solution of **201** (200 mg, 0.450 mmol) in pyridine (0.90 mL) and the resultant mixture was stirred at rt for 2 h. EtOAc (10 mL) was added and the resultant mixture was washed with satd aq $CuSO_4$ (3 × 10 mL). The combined aqueous washings were extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed sequentially with H_2O (5 × 20 mL), satd aq $NaHCO_3$ (3 × 20 mL) and brine (2 × 20 mL), then dried, filtered and concentrated *in vacuo* to give **209** as a colourless oil (390 mg).

Step 2: A solution of **209** (390 mg) from the previous step in MeCN (4.5 mL) was heated at 70 °C for 1 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL), and the resultant solution was washed with 2.0 M aq NaOH (20 mL). The aqueous washings were extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts were washed with brine (20 mL) then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1 to 1:1) gave **211** as a white solid (113 mg, 78%, >95:5 dr); mp 50–52 °C; $[\alpha]_D^{25}$ −26.3 (*c* 1.0 in $CHCl_3$); ν_{max} 2978 (C−H), 1741 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, C*Me*$_3$), 1.73 (1H, app ddt, *J* 13.8, 6.7, 2.5, C(4)H_A), 1.98 (3H, s, CO*Me*), 2.16 (1H, app ddt, *J* 13.8, 9.8, 7.7, C(4)H_B), 2.52 (1H, ddd, *J* 9.8, 8.8, 6.7, C(5)H_A), 2.90 (1H, ddd, *J* 8.8, 7.7, 2.5, C(5)H_B), 3.12 (1H, d, *J* 3.1, C(2)*H*), 3.54 (1H, d, *J* 13.0, NCH_AH$_B$Ph), 3.93 (1H, d, *J* 13.0, NCH$_A$$H_B$Ph), 5.22 (1H, ddd, *J* 7.1, 3.1, 2.0, C(3)*H*), 7.14–7.29 (5H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 21.2 (CO*Me*), 28.0 (C*Me*$_3$), 31.3 (*C*(4)), 51.3 (*C*(5)), 58.2 (N*C*H$_2$Ph), 72.0 (*C*(2)), 77.2 (*C*(3)), 81.4 (*C*Me$_3$), 127.1, 128.3, 129.0 (*o*,*m*,*p*-*Ph*), 138.3 (*i*-*Ph*), 170.4, 170.9 (*C*OMe, *C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 342

($[M+Na)^+$, 100%), 320 ($[M+H]^+$, 60%); HRMS (ESI^+) $C_{18}H_{26}NO_4^+$ ($[M+H]^+$) requires 320.1856; found 320.1853.

tert-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-triisopropyl silyloxypentanoate 212

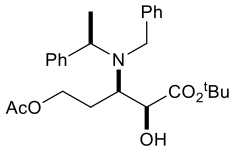


Step 1: DMSO (2.57 mL, 36.0 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.46 mL, 18.0 mmol) in CH_2Cl_2 (30.0 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min. A solution of **204** (5.00 g, 8.99 mmol) in CH_2Cl_2 (15.0 mL) was added dropwise and the resultant mixture was stirred at –78 °C for 30 min. Et_3N (7.56 mL, 54.0 mmol) was added and the resultant mixture was stirred –78 °C for 30 min. The reaction mixture was allowed to warm to rt and was stirred at rt for 30 min. H_2O (50 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were then dried, filtered and concentrated *in vacuo* to give a yellow oil; δ_H (400 MHz, $CDCl_3$) 0.89–1.05 (21H, m, Si(C*HMe*$_2$)$_3$, 1.37 (3H, d, *J* 6.9, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 1.78 (1H, dddd, *J* 13.9, 8.4, 6.1, 3.8, C(4)H_A), 2.03 (1H, ddt, *J* 13.9, 9.6, 5.0, C(4)H_B), 3.49 (1H, ddd, *J* 10.1, 8.4, 5.0, C(5)H_A), 3.65–3.74 (3H, m, NCH_2Ph, C(5)H_B), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.44 (1H, dd, *J* 9.3, 3.8, C(3)*H*), 7.09–7.30 (10H, m, *Ph*).

Step 2: $NaBH_4$ (340 mg, 8.99 mmol) was added to a stirred solution of the residue from the previous step in MeOH (440 mL) at –20 °C, and the resultant mixture was stirred at –20 °C for 2 h. The reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were then dried, filtered

and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **212** as a colourless oil (4.75 g, 95%, >95:5 dr); $[\alpha]_D^{25}$ −3.4 (*c* 1.0 in $CHCl_3$); ν_{max} 3657 (O−H), 2970 (C−H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97–1.07 (21H, m, Si(C*HMe*$_2$)$_3$, 1.31 (3H, d, *J* 7.0, C(α)*Me*), 1.37 (9H, s, C*Me*$_3$), 1.79 (2H, app q, *J* 6.5, C(4)*H*$_2$), 3.10 (1H, s, O*H*), 3.42 (1H, dd, *J* 6.6, 5.0, C(3)*H*), 3.62–3.72 (3H, m, C(5)*H*$_2$, NC*H*$_A$H$_B$Ph), 3.85–3.93 (2H, m, C(2)*H*, NCH$_A$*H*$_B$Ph) 4.02 (1H, q, *J* 7.0, C(α)*H*), 7.03–7.28 (10H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 18.3 (C(α)*Me*), 28.0 (C*Me*$_3$), 31.1 (*C*(4)), 50.8 (N*C*H$_2$Ph), 57.4 (*C*(3)), 60.8 (*C*(α)), 61.2 (*C*(5)), 73.6 (*C*(2)), 81.9 (*C*Me$_3$), 126.5, 127.0, 128.1, 128.1, 128.2, 128.5 (*o,m,p-Ph*), 141.7, 143.4 (*i-Ph*), 173.4 (*C*(1)); *m/z* (ESI$^+$) 556 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{54}NO_4Si^+$ ([M+H]$^+$) requires 556.3817; found 556.3825.

tert-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-acetoxy pentanoate 214



Method A – Step 1: DMSO (0.19 mL, 2.70 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.11 mL, 1.40 mmol) in CH_2Cl_2 (2.4 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min. A solution of **197** (300 mg, 0.679 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise and the resultant mixture was stirred at –78 °C for 30 min. Et_3N (0.57 mL, 4.1 mmol) was added and the resultant mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to rt and was stirred at rt for 30 min. H_2O (10 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were then dried, filtered and concentrated *in vacuo* to give a yellow oil;

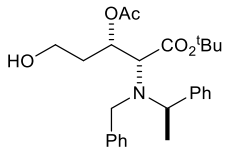
Method A – Step 2: $NaBH_4$ (25 mg, 0.680 mmol) was added to a stirred solution of the residue from the previous step in MeOH (34 mL) at –20 °C and the resultant mixture was stirred at –20 °C for 2 h. The reaction mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1 to 1:1) gave **214** as a colourless oil (122 mg, 41% from **197**, >95:5 dr); $[\alpha]_D^{25}$ +6.1 (*c* 1.0 in $CHCl_3$); ν_{max} 3493 (O−H), 2977 (C−H), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 7.0, C(α)*Me*), 1.36 (9H, s, C*Me*$_3$), 1.74–1.87 (2H, m, C(4)*H*$_2$), 1.94 (3H, s, CO*Me*), 3.07 (1H, d, *J* 4.5, O*H*), 3.14 (1H, app dt, *J* 7.0, 6.0, C(3)*H*), 3.77 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 3.82 (1H, dd, *J* 6.0, 4.2, C(2)*H*), 3.86 (1H, d, *J* 14.9, NCH$_A$*H*$_B$Ph), 3.96–4.10 (3H, m, C(5)*H*$_2$, C(α)*H*), 7.07–7.34 (10H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 18.5 (C(α)*Me*), 21.0 (CO*Me*), 27.9 (*C*(4)), 28.0 (C*Me*$_3$), 50.6 (N*C*H$_2$Ph), 57.2 (*C*(3)), 60.4 (*C*(α)), 62.3 (*C*(5)), 73.7 (*C*(2)), 82.4 (*C*Me$_3$), 126.8, 127.2, 128.0, 128.3, 128.4 (*o*,*m*,*p*-*Ph*), 141.4, 143.4 (*i*-*Ph*), 170.9, 173.0 (*C*(1), *C*OMe); *m/z* (ESI$^+$) 442 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO_5^+$ ([M+H]$^+$) requires 442.2588; found 442.2592.

Method B – Step 1: Ac_2O (1.21 mL, 12.8 mmol) was added to a stirred solution of **212** (4.75 g, 8.54 mmol, >95:5 dr), DMAP (21 mg, 0.170 mmol) and pyridine (1.04 mL, 12.8 mmol) in THF (17 mL) and the resultant mixture was stirred at rt for 18 h. 1.0 M aq HCl (80 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (80 mL) and brine (80 mL), then dried, filtered and concentrated *in vacuo* to give a colourless oil.

Method B – Step 2: TBAF (1.0 M in THF, 34.2 mL, 34.2 mmol) was added to a stirred solution of the residue from the previous step in THF (42.7 mL) and the resultant mixture was stirred at

rt for 20 h. H_2O (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1 to 1:1) gave **214** as a colourless oil (2.22 g, 58% from **212**, >95:51 dr).

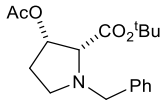
***tert*-Butyl (2*R*,3*S*,*αR*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-acetoxy-5-hydroxy pentanoate 217**



Tf_2O (1.27 mL, 7.54 mmol) was added to a stirred solution of **214** (2.22 g, 5.02 mmol) and DTBMP (3.09 g, 15.1 mmol) in CH_2Cl_2 (25.1 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min, then at rt for 1.5 h. H_2O (60 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (100 mL), and the resultant suspension was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **217** as a colourless oil (1.71 g, 77%, >95:5 dr); $[\alpha]_D^{25}$ +1.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3459 (O−H), 2980 (C−H), 1726 (C=O); δ_H (500 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 1.79 (1H, dddd, *J* 14.3, 10.3, 5.5, 2.9, C(4)H_A), 1.92 (1H, app ddt, *J* 14.3, 10.3, 3.5, C(4)H_B), 2.06 (3H, s, CO*Me*), 2.53 (1H, s, O*H*), 3.42 (1H, t, *J* 10.7, C(5)H_A), 3.58–3.66 (2H, m, C(2)*H*, C(5)H_B), 4.10 (1H, q, *J* 6.9, C(α)*H*), 4.16 (1H, d, *J* 16.4, NCH_AH$_B$Ph), 4.42 (1H, d, *J* 16.4, NCH$_A$$H_B$Ph), 5.44 (1H, ddd, *J* 10.3, 5.8, 2.9, C(3)*H*), 7.17–7.59 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.1 (CO*Me*), 21.5 (C(α)*Me*), 28.0 (C*Me*$_3$), 35.1 (*C*(4)), 53.3 (N*C*H$_2$Ph), 58.2 (*C*(5)), 60.9 (*C*(α)), 64.2 (*C*(2)), 71.5 (*C*(3)), 81.5 (*C*Me$_3$), 126.4, 127.3, 127.5, 127.9, 128.2, 128.4 (*o,m,p-Ph*), 142.3, 143.4 (*i-Ph*),

170.0 (*C*(1)), 171.7 (*C*OMe); *m/z* (ESI$^+$) 442 ([M+H]$^+$, 60%), 464 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO_5^+$ ([M+H]$^+$) requires 442.2588; found 442.2594.

(2*R*,3*S*)-*N*-1-Benzyl-2-(*tert*-butoxycarbonyl)-3-acetoxypyrrolidine 220



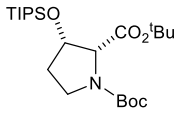
Step 1: TsCl (259 mg, 1.36 mmol) was added to a solution of **217** (200 mg, 0.450 mmol) in pyridine (0.910 mL), and the resultant mixture was stirred at rt for 2 h. EtOAc (10 mL) was added and the resultant mixture was washed with satd aq $CuSO_4$ (3 × 10 mL). The combined aqueous washings were extracted with EtOAc (2 × 20 mL) and the combined organic extracts were washed sequentially with H_2O (5 × 20 mL), satd aq $NaHCO_3$ (3 × 20 mL) and brine (2 × 20 mL), then dried, filtered and concentrated *in vacuo* to give **218** as a colourless oil.

Step 2: A solution of **218** from the previous step in MeCN (4.5 mL) was heated at 70 °C for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL), and the resultant solution was washed with 2.0 M aq NaOH (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1 to 1:1) gave **220** as a white solid (96 mg, 66%, >95:5 dr); mp 74–76 °C; $[\alpha]_D^{25}$ +51.0 (*c* 1.0 in $CHCl_3$); ν_{max} 2976 (C−H), 1742 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.79 (1H, app dtd, *J* 13.6, 8.5, 4.7, C(4)*H*$_A$), 1.96 (3H, s, CO*Me*), 2.21 (1H, dtd, *J* 13.6, 7.8, 2.6, C(4)*H*$_B$), 2.30 (1H, app q, *J* 8.4, C(5)*H*$_A$), 3.04 (1H, app td, *J* 8.8, 2.7, C(5)*H*$_B$), 3.23 (1H, d, *J* 6.8, C(2)*H*), 3.49 (1H, d, *J* 13.0, NC*H*$_A$H$_B$Ph), 3.93 (1H, d, *J* 13.0, NCH$_A$*H*$_B$Ph), 5.32 (1H, app td, *J* 7.3, 4.8, C(3)*H*), 7.09–7.38 (5H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 21.1 (CO*Me*), 28.2 (C*Me*$_3$), 30.8 (*C*(4)), 50.4 (*C*(5)), 57.5 (N*C*H$_2$Ph),

68.4 (*C*(2)), 74.4 (*C*(3)), 81.2 (*C*Me$_3$), 127.2, 128.2, 129.4 (*o,m,p-Ph*), 137.3 (*i-Ph*), 168.6, 170.3 (*C*OMe, *C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 320 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{26}NO_4^+$ ([M+H]$^+$) requires 320.1856; found 320.1853.

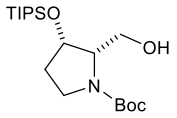
7.3 Experimental Data for Chapter 3

di-tert-Butyl (2*R*,3*S*)-*N*-1,2-dicarboxylate-3-triisopropylsilyloxypyrrolidine 222



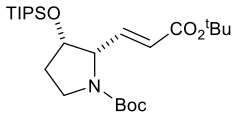
188 (1.32 g, 4.59 mmol) in THF (11 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 183 mg, 4.59 mmol) in THF (12 mL) at rt, and the resultant mixture was stirred at rt for 15 min. TIPSCl (1.96 mL, 9.18 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (50 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 10:1) gave **222** as a yellow oil (2.16 g, quant, >95:5 dr); $[\alpha]_D^{25}$ −12.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2944 (C−H), 2868 (C−H), 1740 (C=O), 1706 (C=O), 1392; δ_H (400 MHz, $CDCl_3$, rotameric) 1.08 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.44 (6H, s, C*Me*$_3$ major), 1.45 (3H, s, C*Me*$_3$ minor), 1.46 (3H, s, C*Me*$_3$ minor), 1.47 (6H, s, C*Me*$_3$ major), 2.02–2.22 (2H, m, C(4)*H*$_2$), 3.26 (1H, m, C(5)*H*$_A$), 3.55–3.69 (1H, m, C(5)*H*$_B$), 4.13 (0.7H, d, *J* 7.7, C(2)*H* major), 4.24 (0.3H, d, *J* 7.7 C(2)*H* minor), 4.55 (1H, dq, *J* 10.1, 7.1, C(3)*H*; δ_C (101 MHz, $CDCl_3$, rotameric) 12.2, 12.3, 12.4 (Si(*C*H(Me$_2$)$_3$), 17.8, 18.0, 18.1 (Si(C*H*(*Me*$_2$)$_3$), 28.2, 28.3, 28.5 (C*Me*$_3$), 31.8, 32.6 (*C*(4)), 43.4, 43.9 (*C*(5)), 63.3, 63.7 (*C*(2)), 72.4, 73.1 (*C*(3)), 79.7, 80.1, 81.0, 81.1 (2 x *C*Me$_3$), 154.1, 154.4 (N*C*O), 169.5, 169.9 (*C*(O)^{t}Bu); *m/z* (ESI$^+$) 466 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{46}NO_5Si^+$ ([M+H]$^+$) requires 444.3140; found 444.3135.

(2*S*,3*S*)-*N*-1-(*tert*-Butoxycarbonyl)-2-hydroxymethyl-3-triisopropylsilyloxypyrrolidine 227



DIBAL-H (1.0 M in CH_2Cl_2, 1.35 mL, 1.35 mmol) was added dropwise to a solution of **222** (150 mg, 0.338 mmol) in CH_2Cl_2 (1.69 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 10 min. The reaction mixture was then allowed to warm to rt and was stirred at rt for 4 h. Satd aq NH_4Cl (0.5 mL) and satd aq Rochelle′s salt (2 mL) were added and the mixture was stirred at rt for 2 h. H_2O (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1 increased to 5:1) gave **227** as a colourless oil (42 mg, 33%, >95:5 dr); $[\alpha]_D^{25}$ +16.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3421 (O−H), 2943 (C−H), 1697 (C=O); δ_H (400 MHz, $CDCl_3$, rotameric) 1.01–1.15 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.45 (9H, s, C*Me*$_3$), 1.86–2.18 (2H, m, C(4)*H*$_2$), 2.69 (1H, t, *J* 6.6, O*H*), 3.21–3.34 (1H, m, C(5)*H*$_A$), 3.45 (1H, ddd, *J* 12.0, 8.5, 3.8, C(5)*H*$_B$), 3.67–3.77 (1H, m, C*H*$_A$OH), 3.83 (0.4H, td, *J* 9.7, 8.9, 4.0, C(2)*H* minor), 3.90–3.99 (1.6H, m, C(2)*H* major, C*H*$_B$OH), 4.47–4.61 (1H, m); δ_C (101 MHz, $CDCl_3$ rotameric) 12.1 (Si(*C*H(Me$_2$)$_3$), 17.9, 18.0 (Si(CH(*Me*$_2$)$_3$), 28.5 (C*Me*$_3$), 32.0, 33.3 (*C*(4)), 42.9, 43.9 (*C*(5)), 59.6, 62.0 (*C*H$_2$OH), 62.3, 63.7 (*C*(2)), 72.7, 73.7 (*C*(3)), 80.1 (*C*Me$_3$), 154.4, 156.3 (N*C*O); *m/z* (ESI$^+$) 396 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{39}NNaO_4^+$ ([M+H]$^+$) requires 396.2541; found 396.2538

tert-Butyl (_E_)-3-[(2′_S_,3′S)-N-1′-(_tert_-butoxycarbonyl)-3′-triisopropylsilyloxypyrrolidin-2′-yl]prop-2-enoate 223

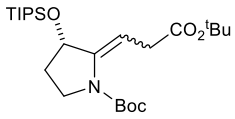


Step 1: DMSO (0.12 mL, 1.68 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (70.0 μL, 0.840 mmol) in CH_2Cl_2 (1.10 mL) and the resultant mixture was stirred at –78 °C for 20 min. A solution of **227** (157 mg, 0.420 mmol) in CH_2Cl_2 (1.00 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 30 min. Et_3N (0.350 mL, 2.52 mmol) was added and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to rt was stirred at rt for 16 h. H_2O (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1 increasing to 5:1) gave **228** as a colourless oil (33 mg, 21%, >95:5 dr).

Step 2: **177** (38 mg, 0.100 mmol) was added to a stirred solution of **228** (31 mg, 83.0 μmol) from the previous step in CH_2Cl_2 (0.42 mL) and the mixture was stirred at rt for 16 h. The reaction mixture was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **223** as a colourless oil (36 mg, 92%, >95:5 dr); $[\alpha]_D^{25}$ −9.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2944 (C−H), 2867 (C−H), 1701 (C=O); δ_H (400 MHz, $CDCl_3$, rotameric) 1.01–1.11 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.41 (5H, s, C*Me*$_3$ major), 1.45 (9H, s, C*Me*$_3$), 1.46 (4H, s, C*Me*$_3$ minor), 1.80–1.92 (1H, m, C(4′)H_A), 1.99–2.07 (1H, m, C(4′)H_B), 3.25–3.54 (2H, m, C(5′)H_2), 4.31 (0.6H, t, *J* 6.6, C(2′)*H* major), 4.42–4.54 (1.4H, m, C(2′)*H* minor, C(3′)*H*), 5.73 (1H, dd, *J* 15.7, 5.3, C(2)*H*), 6.85 (1H, ddd, *J* 26.7, 15.7, 5.5, C(3)*H*); δ_C (101 MHz, $CDCl_3$, rotameric) 12.2 (Si(*C*H(Me$_2$)$_3$), 18.1, 18.1 (Si(CH(*Me*$_2$)$_3$), 28.2, 28.5, 28.6 (2 x C*Me*$_3$), 31.9, 32.3 (*C*(4′)), 43.0, 43.2 (*C*(5′)), 60.4, 61.5 (*C*(2′)), 72.8, 73.8 (*C*(3′)), 79.9, 80.0,

80.13, 80.2 (2 x *C*Me_3), 123.9, 124.2 (*C*(2)), 143.9, 144.3 (*C*(3)), 154.5, 154.6 (N*C*O), 165.6 (*C*(1)); *m/z* (ESI^+) 492 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{47}NNaO_5Si^+$ ($[M+H]^+$) requires 492.3116; found 492.3113.

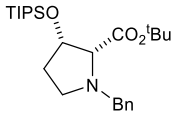
tert-Butyl (*EZ*)-3-[(3′*S*)-N-1′-tertbutoxycarbonyl-3′-triisopropylsilyloxypyrrolidin-2′-yl] propene-1-carboxylate 229



^{n}BuLi (2.5 M in hexanes, 80.0 μL, 0.198 mmol) was added dropwise to a stirred solution of (*R*)-**41** (43.0 mg, 0.204 mmol, >99.0% ee) in THF (0.45 mL) at –78 °C, and the resultant mixture was stirred at –78 °C for 30 min. A solution of **223** (60 mg, 0.128 mmol) in THF (0.40 mL) was added via cannula and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (1 mL) was added and the resultant mixture was allowed to warm to rt. The resultant mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 10% aq citric acid (20 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **229** as a colourless oil (20 mg, 33%, >95:5 dr); $[\alpha]_D^{25}$ +17.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2967 (C−H), 2867 (C−H), 1727 (C=O), 1142; δ_H (400 MHz, $CDCl_3$) 1.00–1.13 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.44 (9H, s, C*Me*$_3$), 1.47 (9H, s, C*Me*$_3$), 1.75 (1H, ddt, *J* 12.2, 8.2, 5.6, C(4′)H_A), 1.97 (1H, ddd, *J* 11.9, 8.1, 6.0, C(4′)H_B), 2.95–3.13 (2H, m, C(2)H_2), 3.47 (1H, ddd, *J* 10.6, 8.2, 5.7, C(5′)H_A), 3.65 (1H, ddd, *J* 10.6, 8.2, 6.1, C(5′)H_B), 4.42–4.52 (1H, m, C(3′)*H*), 5.27 (1H, td, *J* 6.7, 1.1, C(3)*H*); δ_C (101 MHz, $CDCl_3$) 12.2 (Si(*C*H(Me$_2$)$_3$), 18.1 (Si(CH(*Me*$_2$)$_3$), 28.1, 28.4 (C*Me*$_3$), 31.6 (*C*(4′)), 35.7 (*C*(2)), 45.9 (*C*(5′)), 72.5 (*C*(3)), 80.2 (*C*Me$_3$), 104.6 (*C*(3)), 141.3 (N*C*O), 171.8 (*C*(1)); *m/z* (ESI^+) 492

([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{47}NNaO_5^+$ ([M+Na]$^+$) requires 492.3116; found 492.3108.

tert-Butyl (2*R*,3*S*)-1-*N*-benzyl-3-triisopropylsiloxypyrrolidine-2-carboxylate 236



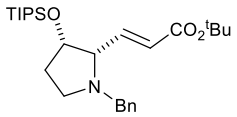
Step 1: **188** (2.48 g, 8.64 mmol) in THF (28 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 345 mg, 8.64 mmol) in THF (15 mL) at rt, and the resultant mixture was stirred at rt for 15 min. TIPSCl (3.70 mL, 17.3 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (50 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo* to give **222** as a yellow oil (4.96 g).

Step 2: TFA (6.6 mL, 86.4 mmol) was added dropwise to a stirred solution of **222** (4.96 g) in CH_2Cl_2 (43 mL) and the reaction mixture was stirred at rt for 2 h. H_2O (50 mL) was added and the resultant mixture was basified with 2.0 M aq NaOH (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (50 mL), then dried, filtered and concentrated *in vacuo* to give a colourless oil (3.78 g).

Step 3: Et_3N (6.00 mL, 43.2 mmol) was added to a solution of the residue from the previous step (3.78 g) in CH_2Cl_2 (43.0 mL) at rt, and the resultant mixture was stirred at rt for 15 min. BnBr (2.60 mL, 21.6 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (50 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **236** as a colourless oil (1.90 g, 51%, >95:5 dr); $[\alpha]_D^{25}$ +0.9 (*c* 1.0 in

$CHCl_3$); ν_{max} (film) 2943 (C−H), 2867 (C−H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.00–1.07 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.45 (9H, s, C*Me*$_3$), 2.00–2.20 (2H, m, C(4)*H*$_2$), 2.75 (1H, td, *J* 8.2, 6.7, C(5)*H*$_A$), 3.08 (1H, ddd, *J* 10.1, 8.6, 3.9, C(5)*H*$_B$), 3.54 (1H, d, *J* 7.0, C(2)*H*), 3.66 (1H, d, *J* 13.1, NC*H*$_A$H$_B$Ph), 3.79 (1H, d, *J* 13.1, NCH$_A$*H*$_B$Ph), 4.59 (1H, td, *J* 8.2, 7.0, C(3)*H*), 7.16–7.29 (5H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 12.2 (Si(*C*H(Me$_2$)$_3$), 18.0, 18.0 (Si(C*H*(*Me*$_2$)$_3$), 28.4 (C*Me*$_3$), 33.0 (*C*(4)), 50.1 (*C*(5)), 56.6 (NC*H*$_2$Ph), 70.0 (*C*(2)), 73.4 (*C*(3)), 80.5 (*C*Me$_3$), 127.0, 128.2, 128.8 (*o*,*m*,*p*-*Ph*), 138.9 (*i*-*Ph*), 170.8 (*C*(O)); *m/z* (ESI^+) 434 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{44}NO_3Si^+$ ($[M+H]^+$) requires 434.3085; found 434.3087.

tert-Butyl (*E*)-3-[(2′*S*,3′*S*)-*N*-1′-benzyl-3′-triisopropylsilyloxypyrrolidin-2′-yl]prop-2-enoate 231



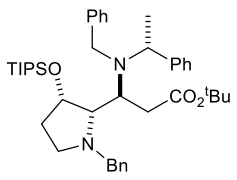
Step 1: DIBAL-H (1.0 M in CH_2Cl_2, 4.60 mL, 4.60 mmol) was added dropwise to a solution of **236** (500 mg, 1.15 mmol) in CH_2Cl_2 (5.76 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 15 min. The reaction mixture was then allowed to warm to rt and was stirred at rt for 2 h. Satd aq NH_4Cl (1.5 mL) and satd aq Rochelle′s salt (6.5 mL) were added and the mixture was stirred at rt for 2 h. The resultant mixture was filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo* to give **237** as a colourless oil (474 mg).

Step 2: DMSO (0.33 mL, 4.60 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.19 mL, 2.30 mmol) in CH_2Cl_2 (1.80 mL) and the resultant mixture was stirred at –78 °C for 20 min. A solution of **237** (474 mg) in CH_2Cl_2 (4.00 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 30 min. Et_3N (0.97 mL, 6.90 mmol) was added and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to rt and

was stirred at rt for 16 h. H_2O (20 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and concentrated *in vacuo* to give **238** as a yellow oil.

Step 3: **177** (952 mg, 2.53 mmol) was added to a stirred solution of **238** in CH_2Cl_2 (11.5 mL) and the mixture was stirred at 45 °C for 16 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **231** as a colourless oil (402 mg, 76%, >95:5 dr, [(*E*):(*Z*)]); $[\alpha]_D^{25}$ +25.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2941 (C−H), 2866 (C−H), 1713 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97–1.09 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.48 (9H, s, C*Me*$_3$), 1.77–1.90 (1H, m, C(4′)H_A), 2.09–2.24 (2H, m, C(4′)H_B, C(5′)H_A), 2.94–3.01 (1H, m, C(5′)H_B), 3.06–3.15 (1H, m, C(2′)*H*), 3.28 (1H, d, *J* 13.3, NCH_AH$_B$Ph), 3.85 (1H, d, *J* 13.3, NCH$_A$$H_B$Ph), 4.53 (1H, td, *J* 6.9, 5.7, C(3′)*H*), 5.88 (1H, dd, *J* 15.7, 0.9, C(2)*H*), 6.92 (1H, dd, *J* 15.7, 8.3, C(3)*H*), 7.19–7.34 (5H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 12.3 (Si(*C*H(Me$_2$)$_3$), 18.2, 18.2 (Si(C*H*(*Me*$_2$)$_3$), 28.2 (C*Me*$_3$), 35.2 (*C*(4′)), 51.0 (*C*(5′)), 58.4 (NC*H*$_2$Ph), 70.1 (*C*(2′)), 74.9 (*C*(3′)), 80.1 (*C*Me$_3$), 125.4 (*C*(2)), 127.0, 128.3, 128.3, 129.0, 129.0 (*o,m,p-Ph*), 138.9 (*i-Ph*), 146.4 (*C*(3)), 165.7 (*C*(1)); *m/z* (ESI$^+$) 460 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{46}NO_3Si^+$ ([M+H]$^+$) requires 460.3242; found 460.3236.

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-[(2′*S*,3′*S*)-*N*-1′-benzyl-3′-triisopropylsilyloxypyrrolidin-2′-yl]proponoate 239



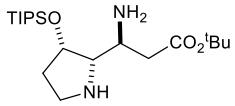
Method A: ^{n}BuLi (2.5 M in hexanes, 0.14 mL, 0.338 mmol) was added dropwise to a stirred solution of (*R*)-**41** (74 mg, 0.348 mmol, >99.0% ee) in THF (0.95 mL) at –78 °C, and the

resultant mixture was stirred at –78 °C for 30 min. A solution of **231** (100 mg, 0.218 mmol) in THF (0.5 mL) was added via cannula and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (1 mL) was added and the resultant mixture was allowed to warm to rt. The resultant mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 10% aq citric acid (20 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **239** as a colourless oil (59 mg, 40%, >95:5 dr); $[\alpha]_D^{25}$ +0.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2842 (C−H), 2866 (C−H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.91–1.10 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.33 (3H, d, *J* 6.9, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 1.63–1.74 (1H, m, C(4′)H_A), 1.78–1.88 (1H, m, C(4′)H_B), 2.08–2.19 (1H, m, C(5′)H_A), 2.30–2.43 (1H, m, C(2)H_A), 2.49 (1H, dd, *J* 16.5, 5.0, C(2)H_B), 2.73 (1H, ddd, *J* 10.8, 7.2, 3.9, C(5′)H_B), 3.01 (1H, dd, *J* 7.9, 2.3, C(2′)*H*), 3.29 (1H, d, *J* 13.5, N(1′)CH_AH$_B$Ph), 3.77 (1H, d, *J* 16.0, NCH_AH$_B$Ph), 3.92–4.05 (4H, m, C(3)*H*, C(α)*H*, N(1′)CH$_A$*H*$_B$Ph, NCH$_A$*H*$_B$Ph), 4.35 (1H, td, *J* 8.0, 6.5, C(3′)*H*), 6.93–7.31 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 12.6 (Si(*C*H(Me$_2$)$_3$), 18.2, 18.4 (Si(C*H*(*Me*$_2$)$_3$), 19.2 (C(α)*Me*), 28.3 (C*Me*$_3$), 34.0 (*C*(4′)), 36.7 (*C*(2)), 50.2, 50.4 (*C*(5′)), (N*C*H$_2$Ph), 55.8 (*C*(3)), 60.8 (C(α)*H*), 61.9 (N(1′)*C*H$_2$Ph), 70.1 (*C*(2′)), 74.2 (*C*(3′)), 79.5 (*C*Me$_3$), 125.9, 126.6, 126.6, 127.8, 127.8, 128.0, 128.0, 128.4, 128.4 (*o,m,p-Ph*), 140.0, 143.0, 144.1 (*i-Ph*), 172.6 (*C*(1)); *m/z* (ESI$^+$) 672 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{42}H_{63}N_2O_3Si^+$ ([M+H]$^+$) requires 671.4603; found 671.4596. Further elution (eluent 30–40 °C petrol/Et_2O, 10:1) gave **231** as a colourless oil (21 mg, 21%, >95:5 dr).

Method B: ^{n}BuLi (2.5 M in hexanes, 8.40 mL, 21.1 mmol) was added dropwise to a stirred solution of (*R*)-**41** (4.59 g, 21.7 mmol, >99.0% ee) in THF (28 mL) at –78 °C, and the resultant mixture was stirred at –78 °C for 30 min. A solution of **231** (1.00 g, 2.17 mmol) in THF (10 mL) was added via cannula and the resultant mixture was stirred at –78 °C for 2 h. Satd aq

NH_4Cl (50 mL) was added and the resultant mixture was allowed to warm to rt. The resultant mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (100 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **239** as a colourless oil (936 mg, 64%, >95:5 dr). Further elution (eluent 30–40 °C petrol/Et_2O, 10:1) gave **231** as a colourless oil (131 mg, 13%, >95:5 dr).

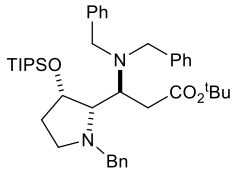
***tert*-Butyl (3*S*)-3-amino-3-[(2′*S*,3′*S*)-*N*-1′-amino-3′-triisopropylsilyloxypyrrolidin-2′-yl] propanoate 241**



$Pd(OH)_2/C$ (100 mg, 100% w/w) was added to a degassed solution of **239** (100 mg, 0.148 mmol) in MeOH (1 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and the mixture was stirred at rt for 2 days. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C CH_2Cl_2/MeOH, 100:1) gave **241** as a colourless oil (34 mg, 59%, >95:5 dr); $[\alpha]_D^{25}$ +15.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3653 (C−H), 2978 (C−H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.05–1.11 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.43 (9H, s, C*Me*$_3$), 1.84 (1H, dddd, *J* 13.5, 7.9, 5.1, 2.7, C(4′)H_A), 1.97 (1H, dddd, *J* 13.5, 9.0, 7.1, 5.0, C(4′)H_B), 2.28–2.38 (4H, m, C(2)H_A, NH_2, N*H*), 2.72 (1H, dd, *J* 15.8, 3.6, C(2)H_B), 2.77 (1H, dd, *J* 7.9, 4.1, C(2′)*H*), 2.94 (1H, ddd, *J* 11.1, 9.0, 5.1, C(5′)H_A), 3.15 (1H, ddd, *J* 11.1, 7.9, 7.1, C(5′)H_B), 3.38 (1H, ddd, *J* 9.3, 7.9, 3.6, C(3)*H*), 4.53–4.58 (1H, m, C(3′)*H*); δ_C (101 MHz, $CDCl_3$) 12.7 (Si(*C*H(Me$_2$)$_3$), 18.1, 18.2 (Si(C*H*(*Me*$_2$)$_3$), 28.1 (C*Me*$_3$), 35.8 (*C*(4′)), 41.5 (*C*(2)), 44.3 (*C*(5′)),

48.4 (*C*(3)), 68.5 (*C*(2′)), 73.8 (*C*(3′)), 80.5 (*C*Me$_3$), 172.1 (*C*(1)); *m/z* (ESI$^+$) 387 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{43}N_2O_3Si^+$ ([M+H]$^+$) requires 387.3038; found 387.3034.

tert-Butyl (3*S*)-3-(*N*,*N*-dibenzyl)-3-[(2′*S*,3′*S*)-*N*-1′-benzyl-3′-triisopropylsilyloxy pyrrolidin-2′-yl]proponoate 240

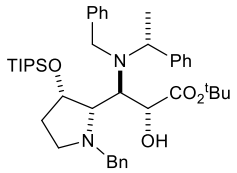


Method A: ^{n}BuLi (2.5 M in hexanes, 0.14 mL, 0.351 mmol) was added dropwise to a stirred solution of dibenzylamine (71 mg, 0.361 mmol) in THF (0.4 mL) at –78 °C, and the resultant mixture was stirred at –78 °C for 30 min. A solution of **231** (83 mg, 0.180 mmol) in THF (0.6 mL) was added via cannula and the resultant mixture was stirred at –78 °C for 2 h. Satd aq NH_4Cl (1 mL) was added and the resultant mixture was allowed to warm to rt. The resultant mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 mL) and 10% aq citric acid (20 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave **240** as a colourless oil (34 mg, 29%, >95:5 dr); $[\alpha]_D^{25}$ +1.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2942 (C−H), 2866 (C−H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (21H, s, Si(C*H*(*Me*$_2$)$_3$), 1.55 (9H, s, C*Me*$_3$), 1.73–1.83 (1H, m, C(4′)H_A), 1.91–2.01 (1H, m, C(4′)H_B), 2.28 (1H, ddd, *J* 10.3, 9.2, 6.6, C(5′)H_A), 2.69 (1 H, dd, *J* 15.0, 5.1, C(2)H_A), 2.78–2.92 (2H, m, C(2)H_B, C(5′)H_B), 3.27 (1H, dd, *J* 8.2, 2.6, C(2′)*H*), 3.53 (1H, d, *J* 13.6, N(1′)CH_AH$_B$Ph), 3.81–3.90 (3H, m, C(3)*H*, N(CH_AH$_B$Ph)$_2$), 3.99 (2H, d, *J* 14.3, N(CH$_A$$H_B$Ph)$_2$), 4.26 (1H, d, *J* 13.6, N(1′)CH$_A$$H_B$Ph), 4.44 (1H, td, *J* 8.3, 6.7, C(3′)*H*), 7.14–7.44 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 12.4 (Si(*C*H(Me$_2$)$_3$), 18.1, 18.2 (Si(C*H*(*Me*$_2$)$_3$),

28.3 (C*Me*$_3$), 34.1 (*C*(4′)), 36.6 (*C*(2)), 50.4 (*C*(5′)), 54.9 (N(*C*H$_2$Ph)$_2$), 56.4 (*C*(3)), 62.2 (N(1′)*C*H$_2$Ph), 68.5 (*C*(2′)), 73.6 (*C*(3′)), 79.7 (*C*Me$_3$), 126.5, 126.7, 128.0, 128.2, 128.3, 128.8 (*o,m,p-Ph*), 140.0, 140.4 (*i-Ph*), 172.7 (*C*(1)); *m/z* (ESI$^+$) 657 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{41}H_{61}N_2O_3Si^+$ ([M+H]$^+$) requires 657.4446; found 657.4431.

Method B: BnBr (60 μL, 0.528 mmol), Et$_3$N (80 μL, 1.06 mmol) and TBAI (10 mg, 26.4 μmol) were added to a solution of **241** (34 mg, 87.9 μmol) in CH_2Cl_2 (0.90 mL) and the resultant mixture was stirred at rt for 16 h. H_2O (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), brine (2 x 20 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et$_2$O, 20:1) gave **240** as a white reside (8 mg, 14%, >95:5 dr).

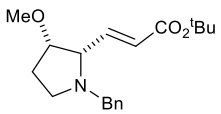
tert-Butyl (2*R*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-[(2′*S*,3′*S*)-*N*-1′-benzyl-3′-triisopropylsilyloxypyrrolidin-2′-yl]proponoate 232



^{n}BuLi (2.5 M in hexanes, 0.16 mL, 0.405 mmol) was added dropwise to a stirred solution of (*R*)-**41** (88.3 mg, 0.418 mmol, >99.0% ee) in THF (1.00 mL) at –78 °C, and the resultant mixture was stirred at –78 °C for 30 min. A solution of **231** (120 mg, 0.261 mmol) in THF (0.75 mL) was added via cannula and the resultant mixture was stirred at –78 °C for 2 h. (−)-**183** (102 mg, 0.444 mmol) was added and the resultant mixture was allowed to warm to rt and was stirred at rt for 16 h. Satd aq NH_4Cl (70 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (70 mL) and 10% aq citric acid (70 mL),

the aqueous layer was extracted with CH_2Cl_2 (2 × 70 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (70 mL) and brine (70 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **239** as a colourless oil (61 mg, 35%, >95:5 dr); further elution (eluent 30–40 °C petrol/Et_2O, 10:1) gave **231** as a colourless oil (35 mg, 29%, >95:5 dr); further elution (eluent 30–40 °C petrol/Et_2O, 5:1) gave **232** as a colourless oil (20 mg, 11%, >95:5 dr); $[\alpha]_D^{25}$ −2.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2942 (C−H), 2867 (C−H), 1734 (C=O); δ_H (400 MHz, $CDCl_3$) 1.11–1.16 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.46 (3H, d, *J* 7.1, C(α)*Me*), 1.54 (9H, s, C*Me*$_3$), 1.72–1.79 (1H, m, C(4′)H_A), 1.87–1.95 (1H, m, C(4′)H_B), 2.17 (1H, s, O*H*), 2.37 (1H, ddd, *J* 11.0, 9.1, 7.2, C(5′)H_A), 2.97 (1H, ddd, *J* 11.0, 7.8, 3.4, C(5′)H_B), 3.35 (1H, dd, *J* 7.3, 3.1, C(2′)*H*), 3.46 (1H, d, *J* 13.4, N(1′)CH_AH$_B$Ph), 3.84 (1H, d, *J* 13.4, N(1′)CH$_A$$H_B$Ph), 3.98–4.07 (2H, m, C(α)*H*, NCH_AH$_B$Ph), 4.13–4.17 (2H, m, C(2)*H*, C(3)*H*), 4.22 (1H, d, *J* 15.9, NCH$_A$$H_B$Ph), 4.28 (1H, dt, *J* 9.0, 6.5, C(3′)*H*), 7.15–7.46 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 12.7 (Si(*C*H(Me$_2$)$_3$), 18.2, 18.4 (Si(C*H*(*Me*$_2$)$_3$), 19.4 (C(α)*Me*), 28.2 (C*Me*$_3$), 33.3 (*C*(4′)), 49.1 (*C*(5′), 51.7 (N*C*H$_2$Ph)), 56.5 (*C*(3)), 59.1 (*C*(α)H), 61.9 (N(1′)*C*H$_2$Ph), 71.9 (*C*(2′)), 73.3 (*C*(3′)), 75.0 (*C*(2)), 81.0 (*C*Me$_3$), 126.3, 126.9, 127.2, 127.8, 128.0, 128.2, 128.4, 128.7, 128.8 (*o,m,p-Ph*), 137.9 (N(1′)CH$_2$*i-Ph*), 142.1, 142.4 (*i-Ph*), 173.7 (*C*(1)); *m/z* (ESI$^+$) 687 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{42}H_{63}N_2O_4Si^+$ ([M+H]$^+$) requires 687.4552; found 687.4544.

tert-Butyl (*E*)-3-[(2′*S*,3′*S*)-*N*-1′-benzyl-3′-methoxypyrrolidin-2′-yl]prop-2-enoate 243



Step 1: **188** (500 mg, 1.74 mmol) in THF (5.00 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 69 mg, 3.70 mmol) in THF (3.70 mL) at rt, and the resultant mixture was stirred at 0 °C for 15 min. MeI (0.54 mL, 8.70 mmol) was added and the resultant

mixture was stirred at 0 °C for 15 min then rt for 1.5 h. H_2O (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), then dried, filtered and concentrated *in vacuo* to give a colourless oil (520 mg).

Step 2: TFA (1.33 mL, 17.4 mmol) was added dropwise to a stirred solution of the oil from from the previous step (520 mg) in CH_2Cl_2 (8.70 mL) and the reaction mixture was stirred at rt for 2 h. H_2O (25 mL) was added and the resultant mixture was basified with 2.0 M aq NaOH (25 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (50 mL), then dried, filtered and concentrated *in vacuo* to give colourless oil (306 mg).

Step 3: Et_3N (1.21 mL, 8.70 mmol) was added to a solution of the oil from the previous step (306 mg) in CH_2Cl_2 (8.70 mL) at rt, and the resultant mixture was stirred at rt for 15 min. BnBr (0.520 mL, 4.35 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), then dried, filtered and concentrated *in vacuo* to give a yellow oil (351 mg).

Step 4: DIBAL-H (1.0 M in CH_2Cl_2, 6.96 mL, 6.96 mmol) was added dropwise to a solution of the oil from the previous step (351 mg) in CH_2Cl_2 (8.70 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 15 min. The reaction mixture was allowed to warm to rt and stirred at rt for 2 h. Satd aq NH_4Cl (2.0 mL) and satd aq Rochelle′s salt (5.0 mL) were added and the mixture was stirred at rt for 2 h. The resultant mixture was filtered through Celite® and $MgSO_4$ (eluent CH_2Cl_2) and concentrated *in vacuo* to give a colourless oil (220 mg).

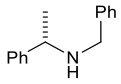
Step 5: DMSO (0.500 mL, 6.96 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.28 mL, 3.48 mmol) in CH_2Cl_2 (3.70 mL) and the resultant mixture was stirred at –78 °C for

20 min. A solution of the oil from the previous step (220 mg) in CH_2Cl_2 (5.00 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 30 min. Et_3N (1.46 mL, 10.4 mmol) was added and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to rt and was stirred at rt for 16 h. H_2O (20 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and concentrated *in vacuo* to give a yellow oil (312 mg).

Step 6: **177** (1.44 g, 3.83 mmol) was added to a stirred solution of the oil from the previous step in CH_2Cl_2 (17.4 mL) and the mixture was stirred at 45 °C for 16 h. The reaction mixture was cooled to rt and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **243** as a pink oil (179 mg, 32% (from **188**), >95:5 dr); $[\alpha]_D^{25}$ +40.4 (*c* 1.0 in $CHCl_3$); ν_{max} 2977 (C−H), 1711 (C=O); δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.85 (1H, ddt, *J* 12.8, 8.7, 4.2, C(4′)*H*$_A$), 2.08–2.15 (1H, m, C(4′)*H*$_B$), 2.15–2.23 (1H, m, C(5′)*H*$_A$), 3.02 (1H, td, *J* 8.7, 2.7, C(5′)*H*$_B$), 3.07–3.12 (1H, m, C(2′)*H*), 3.21 (1H, d, *J* 13.2, NC*H*$_A$H$_B$Ph), 3.27 (3H, s, O*Me*), 3.85–3.92 (2H, m, C(3′)*H*, NC*H*$_A$H$_B$Ph), 5.94 (1H, dd, *J* 15.8, 1.0, C(2)*H*), 6.91 (1H, dd, *J* 15.8, 8.4, C(3)*H*), 7.19–7.34 (5H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 30.4 (*C*(4′)), 51.1 (*C*(5′)), 57.5 (O*Me*), 58.3 (N*C*H$_2$Ph), 69.4 (*C*(2′)), 80.3 (*C*Me$_3$), 83.4 (*C*(3′)), 125.7 (*C*(2)), 126.9, 128.1, 128.9 (*o,m,p-Ph*), 138.6 (*i-Ph*), 144.9 (*C*(3)), 165.5 (*C*(1)); *m/z* (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{28}NO_3^+$ ([M+H]$^+$) requires 318.2064; found 318.2060.

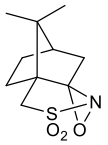
7.4 Experimental Data for Chapter 4

(*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (*S*)-41[5]



Benzaldehyde (83.8 mL, 826 mmol) was added to a stirred solution of (*S*)-**47** (100 mL, 786 mmol, 99.9% ee) in EtOH (500 mL) at rt and the reaction mixture was heated at reflux for 3 h before being cooled to 0 °C. $NaBH_4$ (29.7 g, 786 mmol) was added portionwise and the resultant suspension was stirred at rt for 48 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (500 mL) and CH_2Cl_2 (750 mL). The organic layer was washed with brine (400 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (150 mL) and the resultant suspension was added dropwise to a flask containing 10 M aq HCl (100 mL) and Et_2O (1.0 L) at 0 °C. The white precipitate was collected by filtration, washed with Et_2O (250 mL) and dissolved in CH_2Cl_2 (1.0 L). The resultant solution was dried, filtered and concentrated *in vacuo* to give (*S*)-**41**·HCl as a white solid (175 g). The free amine was regenerated by treatment of (*S*)-**41**·HCl with 2.0 M aq NaOH, followed by extraction with CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give (*S*)-**41** as a pale yellow oil (149 g, 89%, >99.0% ee[10]); $[\alpha]_D^{25}$ −52.5 (*c* 2.0 in EtOH); {lit.[5] for (*R*)-**41** $[\alpha]_D^{25}$ +53.3 (*c* 2.0 in EtOH)}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.6, C(α)*Me*), 1.64 (1H, br s, N*H*), 3.64 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.71 (1H, d, *J* 13.2, NC$H_A$$H_B$Ph), 3.86 (1H, q, *J* 6.6, C(α)*H*), 7.25−7.43 (10H, m, *Ph*).

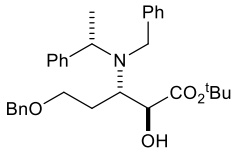
(+)-Camphorsulfonyloxaziridine [(+)-CSO] (+)-183[7]



$SOCl_2$ (252 mmol, 3.45 mmol) was added dropwise to a stirred solution on (+)-**180** (200 g, 861 mmol) in $CHCl_3$ (1.00 L) and the resultant mixture was heated at reflux for 12 h. The volatiles were then removed *in vacuo*, the residue was dissolved in $CHCl_3$ (1.00 L) and the resultant solution was added dropwise to a stirred solution of 35% aq NH_3 (2.00 L) at 0 °C. The resultant mixture was stirred for 4 h at 0 °C then the aqueous layer was extracted with CH_2Cl_2 (2 x 800 mL). The combined organics were dried, filtered and concentrated *in vacuo*. The residue was dissolved in PhMe (1.00 L) and Amberlyst® 15 (wet) ion exchange resin (12.0 g) was added to the resultant solution. A Dean-Stark apparatus was fitted and the resultant mixture heated to reflux for 12 h. After cooling to room temperature, the mixture was filtered through Celite® and the solvent removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.50 L) and Aliquat 336 (17.0 g, 42.1 mmol) was added. 2.0 M aq K_2CO_3 (750 mL, 1.43 mol) was added dropwise at 0 °C, maintaining the reaction temperature below 5 °C. Peracetic acid solution (39% in AcOH, 217 mL, 1.31 mol) was added dropwise, maintaining the reaction temperature below 5 °C and the resultant mixture was allowed to warm to rt over 8 h. The resultant mixture was quenched with Na_2SO_3 (1.0 equiv) and 1.0 M aq NaOH (800 mL) added. The aqueous layer was extracted with CH_2Cl_2 (3 x 800 mL) and the combined organic extracts were washed sequentially with H_2O (200 mL) and satd aq $NaHCO_3$ (400 mL) before being dried, filtered and concentrated *in vacuo*. Purification via recrystallisation (CH_2Cl_2/30−40 °C petroleum ether) gave (+)-**183** as a white amorphous solid (148 g, 75%); mp 169–172 °C {lit.[7] mp 165–167 °C}; $[\alpha]_D^{25}$ +40.3 (*c* 1.0 in $CHCl_3$); {lit.[7] for (−)-**183** $[\alpha]_D^{22}$ −44.9 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, s, *Me*), 1.18 (3H, s, *Me*), 1.46–1.58 (1H, m, C*H*), 1.78 (1H, d, *J* 15.5,

CH_ACN), 1.89–2.14 (5H, m, CH_BCN, CH_2CH_2), 2.60–2.67 (1H, m, C*H*), 3.10 (1H, d, *J* 14.0, CH_ASO$_2$), 3.27 (1H, d, *J* 14.0, CH_BSO$_2$).

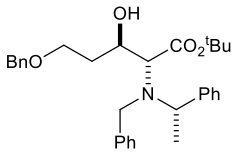
tert-Butyl (*S*,*S*,*S*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-benzyloxy pentanoate _ent_-171



^{n}BuLi (2.5 M in hexanes, 118 mL, 296 mmol) was added dropwise to a stirred solution of (*S*)-**41** (64.4 g, 305 mmol, >99.0% ee) in THF (663 mL) at –78 °C, and the resultant mixture was stirred at –78 °C for 30 min. A solution of **170** (50.0 g, 191 mmol) in THF (532 mL) was added via cannula and the resultant mixture was stirred at –78 °C for 2 h. (+)-**183** (75.0 g, 325 mmol) was added and the reaction mixture was allowed to warm to rt and was stirred at rt for 12 h. Satd aq NH_4Cl (250 mL) was added, and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (250 mL) and 10% aq citric acid (250 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 250 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (250 mL) and brine (250 mL), then dried, filtered and concentrated *in vacuo.* Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1 to 7.5:1) gave *ent*-**171** as a colourless oil (57.4 g, 62%, >95:5 dr); $[\alpha]_D^{25}$ +30.6 (*c* 1.0 in $CHCl_3$); ν_{max} 3497 (O−H), 2975 (C−H), 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 7.1, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 1.39–1.52 (1H, m, C(4)H_A), 1.83 (1H, td, *J* 9.7, 4.8, C(4)H_B), 2.94 (1H, d, *J* 5.8, O*H*), 3.58–3.65 (2H, m, C(3)*H*, C(5)H_A), 3.67 (1H, d, *J* 15.6, NCH_AH$_B$Ph), 3.70–3.76 (2H, m, C(2)*H*, C(5)H_B), 3.93 (1H, q, *J* 7.0, C(α)*H*), 4.29 (1H, d, *J* 15.6, NCH$_A$$H_B$Ph), 4.44 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 4.49 (1H, d, *J* 11.5, OCH$_A$$H_B$Ph), 7.19–7.46 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 27.9 (C*Me*$_3$), 28.0 (*C*(4)), 50.9

(NCH_2Ph), 55.3 (*C*(3)), 58.0 (C(α)*H*), 67.5 (*C*(5)), 71.5 (*C*(2)), 72.9 (OCH_2Ph), 82.6 (*C*Me$_3$), 126.4, 127.0, 127.4, 127.7, 128.0, 128.1, 128.2, 128.2, 128.3 (*o,m,p-Ph*), 138.7, 142.3, 142.6 (*i-Ph*), 174.4 (*C*(1)); *m/z* (ESI$^+$) 490 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_4^+$ ([M+H]$^+$) requires 490.2952; found 490.2951.

***tert*-Butyl (2*R*,3*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)]-3-hydroxy-5-benzyloxy pentanoate *ent*-190**



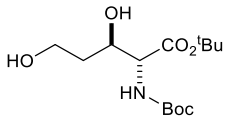
Iteration 1: Tf_2O (49.7 g, 176 mmol) was added to a stirred solution of *ent*-**171** (57.4 g, 117 mmol) and DTBMP (72.0 g, 351 mmol) in CH_2Cl_2 (585 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h then at rt for 5 h. H_2O (115 mL) was added and the resultant mixture was stirred at rt for 24 h. H_2O (1.00 L) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (750 mL), and the resultant suspension was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave *ent*-**171** as a colourless oil (32.2 g, 56%, >95:5 dr); further elution gave *ent*-**190** as a colourless oil (25.2 g, 44%, >95:5 dr); $[\alpha]_D^{25}$ +36.0 (*c* 1.0 in $CHCl_3$); ν_{max} 3503 (O−H), 2974 (C−H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (1H, dddd, *J* 15.0, 8.8, 6.7, 4.6, C(4)H_A), 1.44 (3H, d, *J* 6.9, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 2.01 (1H, dddd, *J* 15.0, 7.2, 4.9, 2.3, C(4)H_B), 3.07 (1H, d, *J* 4.6, O*H*), 3.21 (1H, d, *J* 9.1, C(2)*H*), 3.36 (2H, dddd, *J* 22.9, 9.4, 6.7, 4.9, C(5)H_2), 3.89 (1H, d, *J* 14.3, NCH_AH$_B$Ph), 3.98–4.11 (2H, m, C(3)*H*, C(α)*H*), 4.21 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 4.35 (1H, d, *J* 11.9, OCH_AH$_B$Ph), 4.40 (1H, d, *J* 11.9, OCH$_A$$H_B$Ph), 7.18–7.39 (15H, m, *Ph*); δ_C (101 MHz, $CDCl_3$)

13.3 (C(α)*Me*), 28.3 (C*Me*$_3$), 32.9 (*C*(4)), 52.0 (NC*H*$_2$Ph), 56.8 (*C*(α)H), 63.7 (*C*(2)), 68.6 (*C*(5)), 70.6 (*C*(3)), 73.1 (OC*H*$_2$Ph), 81.1 (*C*Me$_3$), 126.9, 127.0, 127.6, 128.0, 128.1, 128.2, 128.3, 128.4, 129.1 (*o,m,p-Ph*), 138.1, 140.5, 143.4 (*i-Ph*), 173.2 (*C*(1)); *m/z* (ESI$^+$) 490 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_4^+$ ([M+H]$^+$) requires 490.2952; found 490.2949.

Iteration 2: Tf_2O (27.6 g, 98.1 mmol) was added to a stirred solution of *ent*-**171** (32.0 g, 65.4 mmol) and DTBMP (40.3 g, 196 mmol) in CH_2Cl_2 (327 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h then at rt for 5 h. H_2O (64.0 mL) was added and the resultant mixture was stirred at rt for 24 h. H_2O (500 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (500 mL), and the resultant suspension was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave *ent*-**171** as a colourless oil (17.6 g, 31% (overall from *ent*-**171**), >95:5 dr); further elution gave *ent*-**190** as a colourless oil (14.1 g, 68% (overall from *ent*-**171**), >95:5 dr).

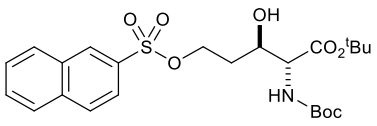
Iteration 3: Tf_2O (15.2 g, 53.9 mmol) was added to a stirred solution of *ent*-**171** (17.6 g, 35.9 mmol) and DTBMP (22.1 g, 108 mmol) in CH_2Cl_2 (179 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h then at rt for 5 h. H_2O (35.0 mL) was added and the resultant mixture was stirred at rt for 24 h. H_2O (250 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. The residue was suspended in Et_2O (250 mL), and the resultant suspension was filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave *ent*-**171** as a colourless oil (9.55g, 17% (overall from *ent*-**171**), >95:5 dr); further elution gave *ent*-**190** as a colourless oil (6.80 g, 80% (overall from *ent*-**171**), >95:5 dr).

tert-Butyl (2*R*,3*S*)-2-[(_tert_-butoxycarbonyl)amino]-3,5-dihydroxypentanoate _ent_-195



$Pd(OH)_2/C$ (8.80 g, 20% w/w) was added to a degassed solution of *ent*-**190** (44.0 g, 90.0 mmol) and Boc_2O (39.0 g, 180 mmol) in MeOH (300 mL) and the resultant mixture was placed under an atmosphere of H_2 (5 atm) and stirred at rt for 4 days. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1 increased to 0:1) gave *ent*-**195** as a white solid (31.1 g, quant, >95:5 dr); $[\alpha]_D^{25}$ −30.0 (*c* 1.0 in MeOH); ν_{max} 3390 (O−H), 2979 (C−H), 1697 (C=O); δ_H (400 MHz, MeOH-d_4) 1.50 (9H, s, CMe_3), 1.53 (9H, s, CMe_3), 1.71–1.86 (2H, m, C(4)H_2), 3.36 (1H, br s, N*H*), 3.70–3.80 (2H, m, C(5)H_2), 4.02 (1H, ddd, *J* 9.0, 5.2, 3.7, C(3)*H*), 4.12 (1H, d, *J* 5.3, C(2)*H*); δ_C (101 MHz, MeOH-d_4) 28.3, 28.7 (CMe_3), 37.1 (*C*(4)), 59.8 (*C*(5)), 60.9 (*C*(2)), 70.3 (*C*(3)), 80.7, 82.9 (*C*Me$_3$), 157.9 (N*C*O), 171.5 (*C*(1)); *m/z* (ESI^+) 306 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{27}NNaO_6^+$ ($[M+Na]^+$) requires 328.1731; found 328.1230.

tert-Butyl (_R_,_R_)-2-(_tert_-butoxycarbonylamino)-3-hydroxy-5-(naphthalen-2-ylsulfonyloxy) pentanoate _ent_-196

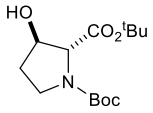


2-NapSO_2Cl (33.4 g, 147 mmol) was added to a stirred solution of *ent*-**195** (30.0 g, 98.2 mmol) in pyridine (196 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. EtOAc (500 mL) was added and the resultant mixture was washed with satd aq $CuSO_4$ (3 × 400 mL).

The combined aqueous extracts were extracted with EtOAc (2 × 400 mL) then the combined organic extracts were washed sequentially with H_2O (5 × 400 mL), satd aq $NaHCO_3$ (3 × 400 mL) and brine (2 × 400 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave *ent*-**196** as a colourless oil (37.0 g, 82%, >95:5 dr); $[\alpha]_D^{25}$ +12.8 (*c* 1.0 in MeOH); ν_{max} 3396 (O−H), 2978 (C−H), 1734 (C=O);

δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 1.43 (9H, s, CMe$_3$), 1.70–1.84 (2H, m, C(4)*H*$_2$), 3.57 (1H, brs, O*H*), 4.08 (1H, dt, *J* 9.3, 4.2, C(3)*H*), 4.19–4.32 (3H, m, C(2)*H*, C(5)*H*$_2$), 5.44 (1H, d, *J* 7.3, N*H*), 7.58–7.70 (2H, m, C(6′)*H*, C(7′)*H*), 7.82–8.00 (4H, m, C(3′)*H*, C(4′)*H*) C(5′)*H*, C(8′)*H*), 8.48 (1H, d, *J* 1.8, C(1′)*H*); δ_C (101 MHz, $CDCl_3$) 27.9, 28.2 (C*Me*$_3$), 32.3 (*C*(4)), 59.0 (*C*(2)), 67.7 (*C*(5)), 69.4 (*C*(3)), 80.7, 83.4 (*C*Me$_3$), 122.5 (*C*(3′)), 127.8, 128.0, 129.3, 129.4, 129.7, 129.7 (*C*(1′, 4′, 5′, 6′, 7′, 8′)), 132.0, 132.8, 135.3 (*C*(4a′, 8a′)), 156.6 (N*C*(O)), 168.9 (*C*(1)); *m/z* (ESI$^+$) 496 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}NO_8SNa^+$ ([M+H]$^+$) requires 496.2000; found 496.1995.

***di-tert*-Butyl (*R*,*R*)-*N*-1,2-dicarboxylate-3-hydroxypyrrolidine *ent*-189**

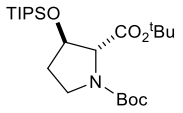


^{n}BuLi (2.5 M in hexanes, 32.4 mL, 81.0 mmol) was added dropwise to a stirred solution of *ent*-**196** (36.5 g, 73.7 mmol) in THF (737 mL) at –78 °C, and the resultant mixture was stirred at –78 °C for 30 min then rt for 2 hours. Satd aq NH_4Cl (200 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave *ent*-**189** as a white solid (16.5

g, 78%, >95:5 dr); mp 100–102 °C; $[\alpha]_D^{25}$ +20.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3431 (O−H), 1678 (C=O);

δ_H (500 MHz, PhMe-d_8, 363 K) 1.38 (9H, s, CMe_3), 1.45 (9H, s, CMe_3), 1.50–1.64 (1H, m, C(4)H_A), 1.81–1.97 (2H, m, C(4)H_B, O*H*), 3.53 (2H, s, C(5)H_2), 4.08–4.25 (2H, m, C(2)*H*, C(3)*H*); δ_C (125 MHz, PhMe-d_8, 363 K) 27.6, 28.1 (2 × CMe_3), 32.2 (*C*(4)), 44.3 (*C*(5)), 69.1 (*C*(2)), 75.0 (*C*(3)), 78.9, 80.3 (2 × *C*Me_3), 137.0 (N*C*O), 169.8 (*C*$O_2{}^t$Bu); *m/z* (ESI^+) 288 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{26}NO_5^+$ ($[M+H]^+$) requires 288.1806; found 288.1811.

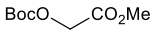
di-tert-Butyl (_R_,_R_)-_N_-1,2-dicarboxylate-3-triisopropylsilyloxypyrrolidine 266



ent-**189** (4.86 g, 16.9 mmol) in THF (40.0 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 676 mg, 16.9 mmol) in THF (45.0 mL) at rt, and the resultant mixture was stirred at rt for 15 min. TIPSCl (7.20 mL, 33.8 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **266** as a colourless oil (7.78 g, quant, >95:5 dr); $[\alpha]_D^{25}$ +20.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3431 (O−H), 1678 (C=O); δ_H (400 MHz, $CDCl_3$, rotameric) 1.04–1.10 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.43–1.46 (18H, m, 2 x CMe_3), 1.80–1.88 (1H, m, C(4)H_A), 1.91–2.02 (1H, m, C(4)H_B), 3.46–3.69 (2H, m, C(5)H_2), 4.04 (1H, s, C(2)*H major*), 4.17 (1H, s, C(2)*H minor*), 4.44 (1H, app t, *J* 4.7, C(3)*H*); δ_C (101 MHz, $CDCl_3$, rotameric) 12.1 (Si(*C*H(Me$_2$)$_3$, 17.9, 17.9 (Si(C*H*(*Me*$_2$)$_3$), 28.0, 28.2, 28.4, 28.4 (2 x CMe_3), 33.0, 33.8 (*C*(4)), 44.4, 44.8 (*C*(5)), 69.3, 69.6 (*C*(2)), 75.1, 76.1 (*C*(3)), 79.6, 81.2 (2 x *C*Me$_3$),

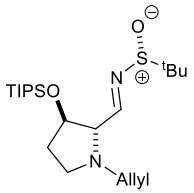
135.6 (N*C*O), 170.2 (*C*O_2^{t}Bu)); *m/z* (ESI$^+$) 466 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{45}NO_5Si^+$ ([M+H]$^+$) requires 444.2959; found 444.2956.

Methyl 2-((*tert*-butoxycarbonyl)oxy)acetate 250[11]



DMAP (1.35 g, 11.1 mmol) and Boc_2O (36.0 g, 166 mmol) were added to a solution of **270** (10.0 g, 111 mmol) in MeCN (444 mL) and the resultant mixture was stirred at rt for 3 days. Brine (100 mL) was added and the resultant mixture was extracted with Et_2O (2 x 400 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1 to 0:1) gave **250** as a colourless oil (20.1 g, 99%); δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, C*Me*$_3$), 3.78 (3H, s, O*Me*), 4.57 (2H, s, C*H*$_2$).

(*R*s)-[(2′*S*,3′*R*)-*N*-1′-allyl-3′-triisopropylsilyloxypyrrolidin-2′-yl]*tert*-butyl-1-sulfinamide (*R*s)-269



Step 1: TFA (4.00 mL, 52.3 mmol) was added dropwise to a stirred solution of **266** (2.31 g, 5.22 mmol) in CH_2Cl_2 (26.1 mL) and the reaction mixture was stirred at rt for 2 h. H_2O (100 mL) was added and the resultant mixture was basified with 2.0 M aq NaOH (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo* to give a colourless oil (1.47 g).

Step 2: Et_3N (3.63 mL, 26.1 mmol) was added to the oil from the previous step (1.47 g) in CH_2Cl_2 (26.1 mL) at rt, and the resultant mixture was stirred at rt for 15 min. Allyl bromide (1.12 mL, 13.1 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo* to give **267** as a colourless oil (1.59 g, 79%, >95:5 dr); δ_H (400 MHz, $CDCl_3$) 1.05–1.07 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.45 (9H, s, OC*Me*$_3$), 1.74 (1H, ddt, *J* 12.7, 6.1, 1.9, C(4)*H*$_A$), 2.04 (1H, dddd, *J* 12.7, 10.8, 7.0, 5.6, C(4)*H*$_B$), 2.72 (1H, ddd, *J* 10.8, 8.5, 6.1, C(5)*H*$_A$), 3.01–3.13 (2H, m, C(5)*H*$_B$, C(2)*H*), 3.23–3.38 (2H, m, NC*H*$_2$), 4.46 (1H, dt, *J* 5.6, 2.0, C(3)*H*), 5.08 (1H, ddt, *J* 10.1, 2.1, 1.3, CHC*H*$_A$), 5.19 (1H, dq, *J* 17.0, 1.3, CHC*H*$_B$), 5.91 (1H, ddt, *J* 17.0, 10.1, 6.6, C*H*CH_2).

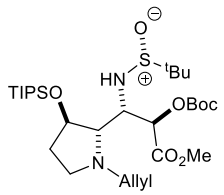
Step 3: DIBAL-H (1.0 M in CH_2Cl_2, 20.9 mL, 20.9 mmol) was added dropwise to a solution of **267** (1.59 g) from the previous step in CH_2Cl_2 (26.1 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 15 min. The reaction mixture was allowed to warm to rt and was stirred at rt for 2 h. Satd aq NH_4Cl (20 mL) and satd aq Rochelle′s salt (50 mL) were added and the mixture was stirred at rt for 2 h. The resultant mixture was filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo* to give a colourless oil (1.22 g)

Step 4: DMSO (1.49 mL, 20.9 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.840 mL, 10.4 mmol) in CH_2Cl_2 (10.3 mL) and the resultant mixture was stirred at –78 °C for 20 min. A solution of the oil from the previous step (1.22 g) in CH_2Cl_2 (16.0 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 30 min. Et_3N (4.40 mL, 31.3 mmol) was added and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to rt and was stirred at rt for 16 h. H_2O (100 mL) was added and the resultant

mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and concentrated *in vacuo* to give **268** as a yellow residue.

Step 5: (*R*)-*tert*-butanesulfinamide (1.14 g, 9.40 mmol) and $Ti(OEt)_4$ (2.38 g, 10.4 mmol) were added to a solution of **268** from the previous step in THF (26.1 mL) and the resultant mixture was stirred at rt for 24 h. H_2O (15 mL) was added and the resultant suspension was filtered through Celite® (eluent CH_2Cl_2). The combined filtrate was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL), the organic layer was extracted with 10% aq citric acid (50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL), and were washed sequentially with satd aq $NaHCO_3$ (2 x 50 mL) and brine (50 mL), then dried, filtered and concentrated *in vacuo* to give (R_S)-**269** as an orange oil (1.28 g, 59% from **266**); δ_H (400 MHz, $CDCl_3$) 1.01–1.07 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.20 (9H, s, SC*Me*$_3$), 1.78–1.88 (1H, m, C(4)H_A), 2.70 (1H, ddd, *J* 10.7, 8.7, 6.6, C(4)H_B), 3.05–3.17 (2H, m, C(2)*H*, C(5)H_A), 3.29–3.37 (2H, m, C(5)H_B, NCH_ACH$_B$), 4.16–4.29 (1H, m, NCH$_A$$H_B$), 4.46 (1H, dt, *J* 5.7, 2.7, C(3)*H*), 5.09 (1H, ddt, *J* 10.0, 2.0, 1.2, CHCH_A), 5.18 (1H, dq, *J* 17.1, 1.6, CHCH_B), 5.85 (1H, dddd, *J* 17.1, 10.1, 7.0, 6.0, C*H*CH$_2$), 7.88 (1H, d, *J* 5.8, C(N)*H*).

Methyl (2*R*,3*S*,*R*S)-2-[(*tert*-butoxycarbonyl)oxy]-3-[(*tert*-butylsulfinyl)amido]-3-[(2′*S*,3′*R*)-*N*-1′-allyl-3′-triisopropylsilyloxypyrrolidin-2′-yl]propanoate 271

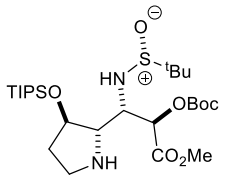


LiHMDS (1 M in THF, 17.8 mL, 17.8 mmol) was added to a solution of **250** (1.48 g, 17.8 mmol) in THF (64.0 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 hour. A solution of (R_S)-**269** (1.48 g, 3.57 mmol) in THF (15.8 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 3 hours. Satd aq NH_4Cl (50 mL) was added and

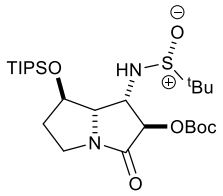
the resultant mixture was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1 to 1:1) gave **271** as a yellow oil

(1.79 g, 83%, >95:5 dr); $[\alpha]_D^{25}$ −63.1 (*c* 1.0 in $CHCl_3$); ν_{max} 2945 (C−H), 2867 (C−H), 1748 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99–1.08 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.18 (9H, s, SC*Me*$_3$), 1.45 (9H, s, OC*Me*$_3$), 1.70 (1H, ddd, *J* 12.8, 6.1, 2.8, C(4′)H_A), 1.90 (1H, dddd, *J* 12.8, 10.3, 7.4, 4.4, C(4′)H_B), 2.73 (1H, ddd, *J* 10.3, 9.4, 6.1, C(5′)H_A), 2.89–2.93 (1H, m, C(2′)*H*), 3.03 (1H, ddd, *J* 9.4, 7.4, 2.9, C(5′)H_B), 3.21 (1H, ddt, *J* 14.1, 7.2, 1.1, NCH_AH_B), 3.47 (1H, ddt, *J* 14.1, 5.4, 1.7, NCH$_A$$H_B$), 3.59 (1H, dt, *J* 5.6, 4.0, C(3)*H*), 3.72 (3H, s, O*Me*), 4.33 (1H, dt, *J* 4.4, 2.0, C(3′)*H*), 4.87 (1H, d, *J* 4.0, C(2)*H*), 5.03–5.21 (3H, m, CHCH_2, N*H*), 5.84 (1H, dddd, *J* 17.3, 10.2, 7.2, 5.4, C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) 12.1 (Si(*C*H(Me$_2$)$_3$), 18.1, 18.1 (Si(C*H*(*Me*$_2$)$_3$), 22.7 (SC*Me*$_3$), 27.6 (OC*Me*$_3$), 34.3 (*C*(4′)), 51.6 (*C*(5′)), 52.2 (O*Me*), 56.0 (S*C*Me$_3$), 56.8 (*C*(3)), 59.1 (N*C*H$_2$), 72.8 (*C*(2′)), 76.2 (*C*(2)), 77.8 (*C*(3′)), 83.0 (O*C*Me$_3$), 116.6 (CH*C*H$_2$), 136.0 (*C*HCH$_2$), 152.8 (O*C*O), 168.6 (*C*(1)); *m/z* (ESI$^+$) 605 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{57}N_2O_7SSi^+$ ([M+H]$^+$) requires 605.3650; found 605.3640.

Methyl (2*R*,3*S*,*R*S)-2-[(*tert*-butoxycarbonyl)oxy]-3-[(*tert*-butylsulfinyl)amido]-3-[(2′*S*,3′*R*)-3′-triisopropylsilyloxypyrrolidin-2′-yl]propanoate 273 and (1*S*,2*R*,7*R*,7a*S*,*R*S)-1-[(*tert*-butylsulfinyl)amido]-2-[(*tert*-butoxycarbonyl)oxy]-7-triisopropylsilyloxy-pyrrolizin-3-one 274



273



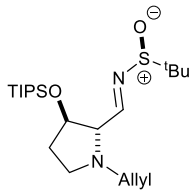
274

$Pd(PPh_3)_4$ (152 mg, 0.132 mmol) was added to a degassed solution of **271** (400 mg, 0.661 mmol) and DMBA (309 mg, 1.98 mmol) in CH_2Cl_2 (6.60 mL) under an argon atmosphere and the mixture was stirred at rt for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between Et_2O (25 mL) and water (25 mL), the aqueous layer was extracted with Et_2O (2 x 25 mL), and the combined organic extracts were washed sequentially with satd aq K_2CO_3 (2 x 25 mL) and brine (50 mL), then dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:2) gave **273** as a yellow oil (167 mg, 45%, >95:5 dr); $[\alpha]_D^{25}$ −38.5 (*c* 1.0 in $CHCl_3$); ν_{max} 3237 (N−H), 2945 (C−H), 2867 (C−H), 1749 (C=O), 1703 (C=O), 1675 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02–1.09 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.20 (9H, s, SC*Me*$_3$), 1.47 (9H, s, OC*Me*$_3$), 1.72 (1H, ddt, *J* 11.1, 7.4, 3.9, C(4′)H_A), 1.95 (1H, dddd, *J* 13.0, 8.7, 7.4, 5.8, C(4′)H_B), 2.99 (1H, ddd, *J* 9.6, 7.3, 4.3, C(5′)H_A), 3.14 (1H, td, *J* 9.1, 7.1, C(5′)H_B), 3.27 (1H, d, *J* 3.4, C(2′)*H*), 3.72–3.75 (4H, m, O*Me*, N*H*), 3.76–3.81 (1H, m, C(3)*H*), 4.42 (1H, dt, *J* 5.8, 3.4, C(3′)*H*), 4.82 (1H, d, *J* 4.1, C(2)*H*), 5.11 (1H, s, N*H*); δ_C (101 MHz, $CDCl_3$) 12.3 (Si(*C*H(Me$_2$)$_3$), 18.1, 18.2 (Si(C*H*(*Me*$_2$)$_3$), 22.9 (SCMe$_3$), 27.8 (OCMe$_3$), 35.6 (C(4′)), 44.8 (C(5′)), 52.3 (S*C*Me$_3$), 56.4 (OMe), 57.9 (C(3)), 66.9 (C(2′)), 76.4 (C(3′)), 77.6 (C(2)), 83.4 (O*C*Me$_3$), 152.9 (OCO), 168.7 (C(1)); *m/z* (ESI+)

565 ([M+H]+, 100%); HRMS (ESI$^+$) $C_{26}H_{53}N_2O_7SSi^+$ ([M+H]$^+$) requires 565.3337; found 565.3330.

Further elution gave **274** as colourless crystals (59 mg, 17%, >95:5 dr); mp 170–173 °C; $[\alpha]_D^{25}$ −11.7 (*c* 1.0 in $CHCl_3$); ν_{max} 2943 (C−H), 1749 (C=O), 1703 (C=O); δ_H (400 MHz, $CDCl_3$) 1.04–1.10 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.20 (9H, s, SC*Me*$_3$), 1.50 (9H, s, OC*Me*$_3$), 1.99–2.06 (2H, m, C(6)*H*$_2$), 3.19–3.27 (1H, m, C(5)*H*$_A$), 3.41 (1H, d, *J* 4.6, N*H*), 3.74 (1H, dd, *J* 12.0, 6.1, C(5)*H*$_B$), 4.11–4.19 (2H, m, C(1)*H*, C(7a)*H*), 4.52 (1H, td, *J* 5.2, 4.2, C(7)*H*), 4.97 (1H, d, *J* 1.8, C(2)*H*); δ_C (101 MHz, $CDCl_3$) 12.2 (Si(*C*H(Me$_2$)$_3$), 18.1 (Si(C*H*(*Me*$_2$)$_3$), 22.4 (SC*Me*$_3$), 27.7 (OC*Me*$_3$), 36.9 (*C*(6)), 40.8 (*C*(5)), 56.4, 56.5 (*C*(1), S*C*Me$_3$), 70.6 (*C*(7a)), 70.8 (*C*(7)), 81.8 (*C*(2)), 83.8 (O*C*Me$_3$), 152.1 (O*C*O), 168.1 (*C*(3)); HRMS (ESI$^+$) $C_{25}H_{49}N_2O_6SSi^+$ ([M+H]$^+$) requires 533.3075; found 533.3073.

(*S*S)-[(2′*S*,3′*R*)-*N*-1′-allyl-3′-triisopropylsilyloxypyrrolidin-2′-yl]*tert*-butyl-1-sulfinamide (*S*S)-260



Step 1: TFA (4.81 mL, 62.8 mmol) was added dropwise to a stirred solution of **266** (2.79 g, 6.28 mmol) in CH_2Cl_2 (31.4 mL) and the reaction mixture was stirred at rt for 2 h. H_2O (100 mL) was added and the resultant mixture was basified with 2.0 M aq NaOH (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organics were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo* to give a colourless oil (2.01 g).

Step 2: Et_3N (4.40 mL, 31.4 mmol) was added to the oil from the previous step (2.01 g) in CH_2Cl_2 (31.4 mL) at rt, and the resultant mixture was stirred at rt for 15 min. AllylBr (1.35 mL,

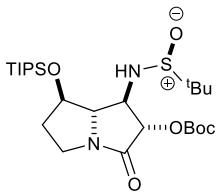
15.7 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried, filtered and concentrated *in vacuo* to give **267** as a white residue (2.28 g, 94%, >95:5 dr); δ_H (400 MHz, $CDCl_3$) 1.05–1.07 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.45 (9H, s, OC*Me*$_3$), 1.74 (1H, ddt, *J* 12.7, 6.1, 1.9, C(4)*H*$_A$), 2.04 (1H, dddd, *J* 12.7, 10.8, 7.0, 5.6, C(4)*H*$_B$), 2.72 (1H, ddd, *J* 10.8, 8.5, 6.1, C(5)*H*$_A$), 3.01–3.13 (2H, m, C(5)*H*$_B$, C(2)*H*), 3.23–3.38 (2H, m, NC*H*$_2$), 4.46 (1H, dt, *J* 5.6, 2.0, C(3)*H*), 5.08 (1H, ddt, *J* 10.1, 2.1, 1.3, CHC*H*$_A$), 5.19 (1H, dq, *J* 17.0, 1.3, CHC*H*$_B$), 5.91 (1H, ddt, *J* 17.0, 10.1, 6.6, C*H*CH_2).

Step 3: DIBAL-H (1.0 M in CH_2Cl_2, 25.1 mL, 25.1 mmol) was added dropwise to a solution of **267** (2.28 g) in CH_2Cl_2 (31.4 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 15 min. The reaction mixture was allowed to warm to rt and was stirred at rt for 2 h. Satd aq NH_4Cl (20 mL) and satd aq Rochelle′s salt (50 mL) were added and the mixture was stirred at rt for 2 h. The resultant mixture was filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo* to give a colourless oil (1.79 g).

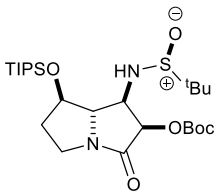
Step 4: DMSO (1.80 mL, 25.1 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (1.02 mL, 12.6 mmol) in CH_2Cl_2 (20.4 mL) and the resultant mixture was stirred at –78 °C for 20 min. A solution of the oil from the previous step (1.79 g) in CH_2Cl_2 (11.0 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 30 min. Et_3N (5.30 mL, 37.7 mmol) was added and the reaction mixture was stirred at –78 °C for 30 min. The reaction mixture was allowed to warm to rt and was stirred at rt for 16 h. H_2O (100 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and concentrated *in vacuo* to give **268** as a yellow residue.

Step 5: (*S*)-*tert*-butanesulfinamide (1.37 g, 11.3 mmol) and $Ti(OEt)_4$ (2.88 g, 12.6 mmol) were added to a solution of **268** (1.95 g) from the previous step in THF (31.4 mL) and the resultant mixture was stirred at rt for 24 h. H_2O (15 mL) was added and the resultant suspension was filtered through Celite® (eluent CH_2Cl_2). The combined filtrate was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL), the organic layer was extracted with 10% aq citric acid (50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 x 50 mL), and were washed sequentially with satd aq $NaHCO_3$ (2 x 50 mL) and brine (50 mL), then dried, filtered and concentrated *in vacuo* to give (S_S)-**260** as an orange oil (1.73 g, 67%); δ_H (400 MHz, $CDCl_3$) 1.03–1.08 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.20 (9H, s, SC*Me*$_3$), 1.77–1.87 (1H, m, C(4)H_A), 1.96 (1H, dddd, *J* 12.8, 11.0, 7.3, 5.5, C(4)H_B), 3.08–3.19 (2H, m, C(2)*H*, C(5)H_A), 3.39–3.46 (2H, m, C(5)H_B, NCH_ACH_B), 4.16–4.29 (1H, m, NC$H_A H_B$), 4.43 (1H, dt, *J* 5.1, 2.3, C(3)*H*), 5.10 (1H, ddt, *J* 10.1, 2.1, 1.1, CHCH_A), 5.19 (1H, dq, *J* 17.1, 1.6, CHCH_B), 5.88 (1H, dddd, *J* 17.2, 10.1, 7.1, 5.9, C*H*CH_2), 7.91 (1H, d, *J* 5.0, C(N)*H*).

(1*R*,2*S*,7*R*,7aS,*S*S)-1-[(*tert*-butylsulfinyl)amido]-2-[(*tert*-butoxycarbonyl)oxy]-7-triisopropylsilyloxy-pyrrolizin-3-one 262 and (1*R*,2*R*,7*R*,7a*S*,S*S*)-1-[(*tert*-butylsulfinyl) amido]-2-[(*tert*-butoxycarbonyl)oxy]-7-triisopropylsilyloxy-pyrrolizin-3-one 275



262



275

Method A − Step 1: LiHMDS (1 M in THF, 15.9 mL, 15.9 mmol) was added to a solution of **250** (3.02 g, 15.9 mmol) in THF (57.1 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 hour. A solution of (S_S)-**260** (1.78 g) in THF (18.9 mL) was added dropwise and

the reaction mixture was stirred at –78 °C for 3 hours. Satd aq NH_4Cl soln (50 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1 to 1:1) gave a mixture of **261** and **272** as a yellow oil (2.12 g, 82%, 50:50 dr); δ_H (400 MHz, $CDCl_3$, selected peaks) 1.09 (9H, s, SC*Me*$_3$), 1.21 (9H, s, SC*Me*$_3$), 1.43 (9H, s, OC*Me*$_3$), 1.44 (9H, s, OC*Me*$_3$), 3.64 (3H, s, O*Me*), 3.65 (3H, s, O*Me*).

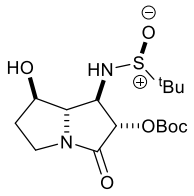
Method A − Step 2: Polymer supported $Pd(PPh_3)_4$ (550 mg, 0.06 mmol/g, 0.033 mmol) was added to a degassed solution of **261** and **272** (50:50 dr, 100 mg, 0.661 mmol) and DMBA (77 mg, 0.496 mmol) in CH_2Cl_2 (1.65 mL) under an argon atmosphere and the mixture was stirred at rt for 18 h. The resultant suspension was filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 5:1 then 3:1) gave **262** as a colourless oil (31 mg, 35%, >95:5 dr); $[\alpha]_D^{25}$ −18.9 (*c* 1.0 in $CHCl_3$); ν_{max} 2944 (C−H), 2866 (C−H), 1732 (C=O); δ_H (500 MHz, $CDCl_3$) 1.03–1.07 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.20 (9H, s, SC*Me*$_3$), 1.48 (9H, s, OC*Me*$_3$), 1.89–1.95 (2H, m, C(6)H_2), 3.20 (1H, dtd, *J* 11.8, 7.6, 1.3, C(5)H_A), 3.53 (1H, dd, *J* 8.0, 3.5, C(7a)*H*), 3.69 (1H, d, *J* 4.8, N*H*), 3.78 (1H, ddd, *J* 8.9, 8.0, 4.8, C(1)*H*), 3.85 (1H, ddd, *J* 11.8, 7.1, 5.1, C(5)H_B), 4.43 (1H, td, *J* 4.8, 3.5, C(7)*H*), 5.41 (1H, dd, *J* 8.9, 1.2, C(2)*H*); δ_C (126 MHz, $CDCl_3$) 12.1 (Si(*C*H(Me$_2$)$_3$), 18.0, 18.2 (Si(C*H*(*Me*$_2$)$_3$), 22.4 (SC*Me*$_3$), 27.7 (OC*Me*$_3$), 35.3 (*C*(6)), 42.0 (*C*(5)), 56.2 (S*C*Me$_3$), 62.4 (*C*(1)), 69.6 (*C*(7a)), 74.9 (*C*(7)), 79.6 (*C*(2)), 83.3 (O*C*Me$_3$), 152.4 (O*C*O), 168.2 (*C*(3)); *m/z* (ESI+) 533 ([M+H]+, 100%); HRMS (ESI^+) $C_{25}H_{49}N_2O_6SSi^+$ ($[M+H]^+$) requires 533.3075; found 533.3076.

Further elution gave **275** as a white residue (40 mg, 46%, >95:5 dr); $[\alpha]_D^{25}$ −38.7 (*c* 1.0 in $CHCl_3$); ν_{max} 2944 (C−H), 2867 (C–O), 1707 (C=O); δ_H (500 MHz, $CDCl_3$) 1.01 (21H, s,

Si(C*H*(*Me*$_2$)$_3$), 1.25 (9H, s, SC*Me*$_3$), 1.46 (9H, s, OC*Me*$_3$), 1.82–1.98 (2H, m, C(6)*H*$_2$), 3.09–3.16 (1H, m, C(5)*H*$_A$), 3.73–3.80 (2H, m, C(1)*H*, N*H*), 3.87 (1H, ddd, *J* 11.9, 7.4, 4.5, C(5)*H*$_B$), 4.28–4.36 (2H, m, C(7)*H*, C(7a)*H*), 4.80 (1H, dd, *J* 8.0, 2.9, C(2)*H*); δ_C (126 MHz, $CDCl_3$) 12.7 (Si(*C*H(Me$_2$)$_3$), 18.0, 18.1 (Si(C*H*(*Me*$_2$)$_3$), 22.7 (SC*Me*$_3$), 28.2 (OC*Me*$_3$), 34.9 (*C*(6)), 41.1 (*C*(5)), 59.9 (S*C*Me$_3$), 60.9 (*C*(1)), 66.7 (*C*(7a)), 73.3 (*C*(2)), 75.7 (*C*(7)), 84.5 (O*C*Me$_3$), 153.4 (O*C*O), 172.2 (*C*(3)); *m/z* (ESI$^+$) 533 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{49}N_2O_6SSi^+$ ([M+H]$^+$) requires 533.3075; found 533.3073.

Method B: $Pd(PPh_3)_4$ (2.02 g, 1.75 mmol) was added to a degassed solution of **261** (4.23 g, 6.99 mmol, >95:5 dr) and DMBA (3.27 g, 20.1 mmol) in CH_2Cl_2 (70 mL) under an argon atmosphere and the mixture was stirred in the dark at rt for 18 h. The resultant suspension was filtered through Celite® (eluent CH_2Cl_2). The combined filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 7.5:1 the 5:1) gave **262** yellow oil (3.89 g, quant, >95:5 dr).

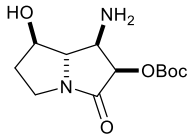
(1*R*,2*S*,7*R*,7a*S*,*S*$_S$)-1-[(*tert*-butylsulfinyl)amido]-2-[(*tert*-butoxycarbonyl)oxy]-7-hydroxy-pyrrolizin-3-one 276



TBAF (1.0 M in THF, 3.30 mL, 3.30 mmol) was added to a solution of **262** (440 mg, 0.828 mmol) in THF (4.1 mL), and the resultant mixture was stirred at rt for 2 h. The resultant solution was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 3:1 to 1:1) gave **276** as colourless crystals (299 mg, 96% , >95:5 dr); mp 184–188 °C; $[\alpha]_D^{25}$ −21.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3237 (O−H), 2981 (C−H), 1750 (C=O),

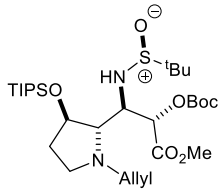
1716 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, SC*Me*$_3$), 1.48 (9H, s, OC*Me*$_3$), 2.01–2.14 (1H, m, C(6)*H*$_A$), 2.44 (1H, dtd, *J* 13.3, 7.7, 3.1, C(6)*H*$_B$), 3.31 (1H, dddd, *J* 11.4, 9.6, 3.1, 1.4, C(5)*H*$_A$), 3.41 (1H, dd, *J* 7.7, 6.4, C(7a)*H*), 3.54–3.63 (1H, m, C(5)*H*$_B$), 3.72 (1H, ddd, *J* 11.2, 10.0, 7.7, C(1)*H*), 3.88 (1H, d, *J* 11.2, N*H*), 4.20 (1H, app q, *J* 7.2, C(7)*H*), 5.16 (1H, d, *J* 1.5, O*H*), 5.40 (1H, dt, *J* 10.0, 1.1, C(2)*H*); δ_C (101 MHz, $CDCl_3$) 22.5 (SC*Me*$_3$), 27.6 (OC*Me*$_3$), 33.7 (*C*(6)), 40.2 (*C*(5)), 56.7 S*C*Me$_3$, 66.2 (*C*(1), 69.5 (*C*(7a)), 74.5 (*C*(7)), 78.3 (*C*(2)), 83.6 (O*C*Me$_3$), 152.6 (O*C*O), 165.6 (*C*(3)); HRMS (ESI$^+$) $C_{16}H_{29}N_2O_6S^+$ ([M+H]$^+$) requires 377.1741; found 377.1737.

(1*R*,2*R*,7*R*,7a*S*)-1-amino-2-[(*tert*-butoxycarbonyl)oxy]-7-hydroxy-pyrrolizin-3-one 277



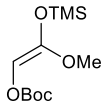
TBAF (1.0 M in THF, 0.88 mL, 0.880 mmol) was added to a solution of **275** (117 mg, 0.220 mmol) in THF (1.1 mL), and the resultant mixture was stirred at rt for 10 h. The resultant solution was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 1:1 to 1:2) gave **277** as a white residue (31 mg, 52%, >95:5 dr); $[\alpha]_D^{25}$ +24.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3289 (O−H), 3289 (C−H), 1676 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, OC*Me*$_3$), 1.90–2.04 (1H, m, C(6)*H*$_A$), 2.28–2.40 (1H, m, C(6)*H*$_B$), 3.20–3.31 (2H, m, C(5)*H*$_A$, C(7a)*H*), 3.50–3.62 (2H, m, C(1)*H*, C(5)*H*$_B$), 3.96 (1H, dt, *J* 9.5, 7.3, C(7)*H*), 4.68 (1H, dd, *J* 10.2, 2.9, C(2)*H*), 5.06 (1H, d, *J* 1.4, N*H*), 5.63–5.70 (1H, m, N*H*), 6.60 (1H, d, *J* 2.8, O*H*); δ_C (101 MHz, $CDCl_3$) 28.3 (OC*Me*$_3$), 32.3 (*C*(6)), 40.2 (*C*(5)), 62.1 (*C*(1)), 70.6 (*C*(7a)), 74.8 (*C*(7)), 75.7 (*C*(2)), 81.0 (O*C*Me$_3$), 157.7 (O*C*O), 171.7 (*C*(3)); HRMS (ESI$^+$) $C_{12}H_{20}N_2O_5Na^+$ ([M+H]$^+$) requires 295.1264; found 295.1264.

Methyl (2*S*,3*R*,*S*S)-2-[(*tert*-butoxycarbonyl)oxy]-3-[(*tert*-butylsulfinyl)amido]-3-[(2′*S*,3′*R*)-*N*-1′-allyl-3′-triisopropylsilyloxypyrrolidin-2′-yl]propanoate 261

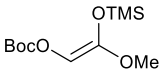


NaHMDS (2 M in THF, 8.8 mL, 17.6 mmol) was added to a solution of **250** (3.35 g, 17.6 mmol) in THF (64 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 hour. A solution of (*S*S)-**260** (1.46 g, 3.52 mmol) in THF (12.6 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 3 hours. Satd aq NH_4Cl (50 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 250 mL). The combined organic extracts were washed with brine (250 mL), dried, filtered and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1 to 1:1) gave **261** as a yellow oil (2.69 g, quant, >95:5 dr); $[\alpha]_D^{25}$ +22.2 (*c* 1.0 in $CHCl_3$); ν_{max} 2947 (C−H), 2865 (C−H), 1753 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02–1.07 (21H, m, Si(C*H*(*Me*$_2$)$_3$), 1.14 (9H, s, SC*Me*$_3$), 1.48 (9H, s, OC*Me*$_3$), 1.80–1.98 (2H, m, C(4′)H_2), 2.70–2.78 (2H, m, C(2′)*H*, C(5′)H_A), 3.07 (1H, ddd, *J* 8.8, 7.6, 1.2, C(5′)H_B), 3.12–3.20 (1H, m, NCH_AH$_B$), 3.29–3.41 (3H, m, C(3)*H*, N*H*, NCH$_A$$H_B$), 3.70 (3H, s, O*Me*), 4.79 (1H, d, *J* 3.0, C(3′)*H*), 5.00 (1H, dq, *J* 10.5, 1.2, CHCH_A), 5.11 (1H, dq, *J* 17.2, 1.6, CHCH_B), 5.48 (1H, d, *J* 1.7, C(2)*H*), 5.80 (1H, dddd, *J* 17.4, 10.1, 7.5, 5.0, C*H*CH$_2$); δ_C (101 MHz, $CDCl_3$) 12.0 (Si(*C*H(Me$_2$)$_3$), 18.1, 18.3 (Si(C*H*(*Me*$_2$)$_3$), 22.7 (SC*Me*$_3$), 27.7 (OC*Me*$_3$), 33.8 (*C*(4′)), 52.0, 52.1 (*C*(5′), (O*Me*)), 56.3 (S*C*Me$_3$), 61.0 (NCH$_2$), 61.7 (*C*(3)), 74.0, 74.3 (*C*(2′), (*C*(3′)), 75.0 (*C*(2)), 83.1 (O*C*Me$_3$), 116.0 (CH*C*H$_2$), 136.6 (*C*HCH$_2$), 152.5 (O*C*O), 169.6 (*C*(1)); *m/z* (ESI$^+$) 605 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{57}N_2O_7SSi^+$ ([M+H]$^+$) requires 605.3650; found 605.3663.

(*E*)- and (*Z*)-1-Methoxy-2-[(*tert*-butoxycarbonyl)oxy]-ethenoltrimethylsilane (*E*)-278 and (*Z*)-279[12]



(*E*)-**278**

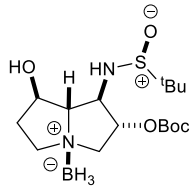


(*Z*)-**279**

Method A: TMSCl (90 μL, 0.70 mmol) was added to LiHMDS (1.0 M in THF, 0.75 mL, 0.75 mmol) at −78 °C and the resultant solution was stirred for 5 min. A solution of **250** (95 mg, 0.500 mmol) in THF (1.8 mL) was added and the resultant solution was stirred at −78 °C for 2 h. The reaction mixture was stirred at rt for 30 mins then 30–40 °C petrol (3 mL) was added. The resultant suspension was filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo* to give a 10:90 mixture of (*E*)-**278** and (*Z*)-**279**; δ_H (500 MHz, $CDCl_3$)[13] 3.52 (2.7H, s, (*Z*)-O*Me*), 3.62 (0.3H, s, (*E*)-O*Me*), 5.98 (0.9H, s, (*Z*)-C*H*), 6.00 (0.1H, s, (*E*)-C*H*).

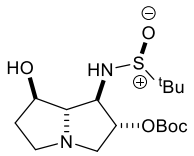
Method B: TMSCl (90 μL, 0.70 mmol) was added to NaHMDS (2.0 M in THF, 0.38 mL, 0.75 mmol) at −78 °C and the resultant solution was stirred for 5 min. A solution of **250** (95 mg, 0.500 mmol) in THF (1.8 mL) was added and the resultant solution was stirred at −78 °C for 2 h. The reaction mixture was stirred at rt for 30 mins then 30–40 °C petrol (3 mL) was added. The resultant suspension was filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo* to give a 25:75 mixture of (*E*)-**278** and (*Z*)-**279**; δ_H (500 MHz, $CDCl_3$)[13] 3.52 (2.25H, s, (*Z*)-O*Me*), 3.62 (0.75H, s, (*E*)-O*Me*), 5.98 (0.75H, s, (*Z*)-C*H*), 6.00 (0.25H, s, (*E*)-C*H*).

(1*R*,2*R*,4*S*,7*R*,7a*S*,S$_S$)-1-[(*tert*-butylsulfinyl)amido]-2-[(*tert*-butoxycarbonyl)oxy]-7-hydroxy-pyrrolizine borane complex 263·BH$_3$



BH_3·Me_2S (0.25 mL, 2.65 mmol) was added to a solution of **276** (100 mg, 0.265 mmol) in THF (2.7 mL) and the mixture was stirred at rt for 16 h. MeOH (1 mL) was added and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/acetone, 3:1) gave **263**·BH_3 as a colourless crystaline solid (49 mg, 51%, >95:5 dr); mp 196–197 °C (dec); $[\alpha]_D^{25}$ −2.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3221 (O−H), 2980 (C−H), 2378 (B−H), 1747 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, SC*Me*$_3$), 1.45 (9H, s, OC*Me*$_3$), 2.11–2.22 (2H, m, C(6)*H*$_2$), 2.86 (1H, dd, *J* 11.6, 7.8, C(3)*H*$_A$), 2.98–3.07 (1H, m, C(5)*H*$_A$), 3.50–3.69 (4H, m, C(1)*H*, C(3)*H*$_B$, C(5)*H*$_B$, C(7a)*H*), 4.41 (1H, td, *J* 5.4, 3.6, C(7)*H*), 4.65 (1H, d, *J* 9.2, N*H*), 4.93 (1H, brs, O*H*), 5.28 (1H, dt, *J* 7.7, 6.4, C(2)*H*); δ_C (101 MHz, $CDCl_3$) 22.7 (SC*Me*$_3$), 27.7 (OC*Me*$_3$), 32.4 (*C*(6)), 56.7 (S*C*Me$_3$), 63.0 (*C*(5)), 63.5 (*C*(3)), 65.4 (*C*(1)), 75.4 (*C*(7)), 78.1 (*C*(2)), 83.4 (O*C*Me$_3$), 83.9 (*C*(7a)), 152.0 (O*C*O); $\delta^{11}{}_B$ (160 MHz, $CDCl_3$) -6.2 (N*B*H$_3$); *m/z* (ESI$^+$) 363 ([M+H]$^+$, 25%), 399 ([M·BH_3+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{33}N_2O_5{}^{11}BSNa^+$ ([M+Na]$^+$) requires 398.2096; found 398.2093

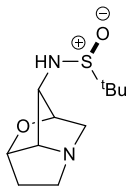
(1*R*,2*R*,7*R*,7a*S*,*S*S)-1-[(*tert*-butylsulfinyl)amido]-2-[(*tert*-butoxycarbonyl)oxy]-7-hydroxy-pyrrolizine borane complex 263



Method A: BH_3·THF solution (1.0 M in THF, 72.5 mL, 72.5 mmol) was added to a solution of **276** (2.73 g, 7.25 mmol) in THF (72.5 mL) and the mixture was stirred at rt for 2 h. MeOH (145 mL) was added heated to 70 °C for 16 h. The resultant solution was concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH,[14] 20:1:0.1) gave **263** as colourless crystals (2.07 g, 79%, >95:5 dr); mp 161–164 °C; $[\alpha]_D^{25}$ +23.1(*c* 1.0 in $CHCl_3$); ν_{max} 3656 (O−H), 2980 (C−H), 1744 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, SC*Me*$_3$), 1.45 (9H, s, OC*Me*$_3$), 1.97 (1H, dddd, *J* 12.5, 10.2, 8.4, 6.9, C(6)H_A), 2.19–2.29 (1H, m, C(6)H_B), 2.53–2.63 (2H, m C(3)H_A, C(5)H_A), 3.06 (1H, dd, *J* 8.5, 5.3 C(7a)*H*), 3.20 (1H, ddd, *J* 9.8, 6.8, 3.0, C(5)H_A), 3.39–3.50 (2H, m C(1)*H*, C(3)H_B), 3.68 (1H, d, *J* 10.2, N*H*), 4.31 (1H, dt, *J* 8.4, 5.9, C(7)*H*), 5.11 (1H, td, *J* 8.8, 6.6, C(2)*H*); δ_C (101 MHz, $CDCl_3$) 22.6 (SC*Me*$_3$), 27.7 (OC*Me*$_3$), 35.1 (*C*(6)), 53.8 (*C*(5)), 55.9 (*C*(3)), 56.3 (S*C*Me$_3$), 66.1 (*C*(1)), 75.7 (*C*(7a)), 76.1 (*C*(7)), 79.3 (*C*(2)), 82.8 (O*C*Me$_3$), 152.8 (O*C*O); *m/z* (ESI$^+$) 363 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{31}N_2O_5S^+$ ([M+Na]$^+$) requires 363.1948; found 363.1949.

Method B: A solution of **263**·BH_3 (18 mg, 50 μmol) in MeOH-d_4 (0.50 mL) was heated to 60 °C for 16 h. The resultant solution was concentrated *in vacuo* to give **263** as a white residue (17 mg, quant, >95:5 dr).

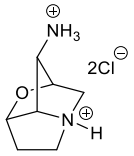
(1*R*,2*R*,7*S*,8*S*,*S*S)-1-[(*tert*-butylsulfinyl)amido]-2,7-epoxypyrrolizidine 265



Step 1: Et_3N (0.460 mL, 3.31 mmol) was added to a solution of **263** (300 mg, 0.828 mmol) and Ms_2O (289 mg, 1.66 mmol) in CH_2Cl_2 (8.3 mL) and the mixture was stirred at 0 °C for 1 h. H_2O (10 mL) was added and the resultant solution was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried, filtered and concentrated *in vacuo* (at 0 °C) to give **282** as a yellow oil (528 mg).

Step 2: K_2CO_3 (686 mg, 4.97 mmol) was added to a solution of **282** (528 mg) from the previous step in MeOH (16.6 mL) and heated to 70 °C for 20 h. The resultant suspension was concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH,[14] 20:1:0.1) gave **265** as a yellow oil (136 mg, 67%, >95:5 dr); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, SC*Me*$_3$), 1.94 (1H, ddt, *J* 14.0, 9.5, 3.8, C(6)*H*$_A$), 2.06 (1H, ddd, *J* 14.0, 8.6, 7.1, C(6)*H*$_B$), 2.42 (1H, d, *J* 11.5, C(3)*H*$_A$), 3.00 (1H, ddd, *J* 12.8, 9.5, 7.1, C(5)*H*$_A$), 3.10 (1H, ddd, *J* 12.8, 8.6, 3.8, C(5)*H*$_B$), 3.39–3.44 (1H, m, C(8)*H*), 3.51–3.58 (1H, m, C(3)*H*$_B$), 3.88 (1H, dd, *J* 2.2, 1.0, C(1)*H*), 4.38 (1H, dd, *J* 4.5, 1.9, C(7)*H*), 4.42 (1H, d, *J* 2.2, C(2)*H*).

(1*R*,2*R*,7*S*,8*S*)-1-amino-2,7-epoxypyrrolizidine dihydrochloride [Norloline dihydrochloride] 2·2HCl



Step 1: Et_3N (1.25 mL, 9.00 mmol) was added to a solution of **263** (817 mg, 2.25 mmol) and Ms_2O (786 mg, 4.51 mmol) in CH_2Cl_2 (22.5 mL) and the mixture was stirred at 0 °C for 1 h. H_2O (50 mL) was added and the resultant solution was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried, filtered and concentrated *in vacuo* (at 0 °C) to give **282** as a yellow oil (1.56 g).

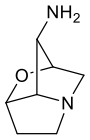
Step 2: K_2CO_3 (622 mg, 4.50 mmol) was added to a solution of **282** (427 mg) from the previous step in MeOH (15.0 mL) and heated to 70 °C in three sealed vials for 20 h. Silica gel (2.0 g) was added to each vial and the resultant suspension was concentrated *in vacuo*. Filtration of the combined resultant solid through a pad of silica gel (eluent $CHCl_3$/MeOH/NH_4OH,[14] 10:1:0.1) gave **265** as an orange oil (680 mg).

Step 3: HCl (1.25 M in MeOH, 12.0 mL, 9.60 mmol) was added to **265** (227 mg) from the previous step and heated to 70 °C in three sealed vials for 20 h. The resultant suspensions were combined and concentrated *in* vacuo. H_2O (10 mL) was added and the resultant solution was extracted with CH_2Cl_2 (3 x 10 mL). The combined aqeuous extracts were concentrated *in vacuo* to give **2**·2HCl as a brown solid (407 mg, 85%, >95:5 dr); mp 168–171 °C (dec); $[\alpha]_D^{25}$ +7.0 (*c* 1.0 in H_2O); δ_H (400 MHz, D_2O) 2.39–2.49 (1H, m, C(6)H_A), 2.55 (1H, dddd, *J* 15.1, 9.2, 6.0, 4.9, C(6)H_B), 3.71 (1H, d, *J* 13.8, C(3)H_A), 3.82–3.97 (2H, m, C(5)H_2), 4.29 (1H, dd, *J* 13.8, 1.2, C(3)H_B), 4.40 (1H, d, *J* 2.6, C(1)*H*), 4.85–4.91 (3H, m, C(2)*H*, C(7)*H*, C(8)*H*); δ_C (101 MHz, D_2O) 31.9 (*C*(6)), 58.2 (*C*(5)), 58.2 (*C*(1)), 64.4 (*C*(3)), 73.7 (*C*(8)), 75.1 (*C*(2)), 83.4

(*C*(7)); *m/z* (ESI$^+$) 141 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{13}N_2O^+$ ([M+H]$^+$) requires 141.1022; found 141.1021.

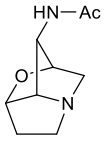
7.5 Experimental Data for Chapter 5

(1*R*,2*R*,7*S*,8*S*)-1-amino-2,7-epoxypyrrolizidine [(*N*)-norloline] 2



NaOH (88 mg, 2.20 mmol) was added to a suspension of **2**·2HCl (43 mg, 0.202 mmol) in $CDCl_3$ (2.0 mL) and the mixture was stirred at rt for 30 min. The resultant solution was filtered to give **2**; δ_H (400 MHz, $CDCl_3$) 1.96 (1H, dddd, *J* 14.2, 9.5, 4.5, 3.4, C(6)H_A), 2.05 (1H, ddd, *J* 14.2, 8.4, 7.3, C(6)H_B), 2.41 (1H, dt, *J* 11.7, 1.6, C(3)H_B), 2.92 (1H, dddd, *J* 12.6, 9.5, 7.3, 0.8, C(5)H_A), 3.03 (1H, dd, *J* 1.8, 1.6 C(8)*H*), 3.09 (1H, ddd, *J* 12.6, 8.4, 3.4, C(5)H_B), 3.48 (1H, d, *J* 11.7, C(3)H_A), 3.55–3.60 (1H, m, C(1)*H*), 3.83 (1H, dd, *J* 2.6, 1.1, C(2)*H*), 4.40 (1H, dd, *J* 4.5, 1.8, C(7)*H*); δ_C (101 MHz, $CDCl_3$) 34.2 (*C*(6)), 54.6 (*C*(5)), 60.3 (*C*(1)), 60.8 (*C*(3)), 71.9 (*C*(8)), 76.2 (*C*(2)), 81.7 (*C*(7)).

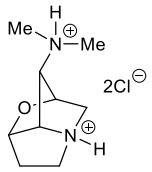
(1*R*,2*R*,7*S*,8*S*)-1-acetamide-2,7-epoxypyrrolizidine [(+)-(*N*)-acetyl norloline] (+)-4



Et_3N (0.157 mL, 1.13 mmol) and Ac_2O (50.0 μL, 0.563 mmol) were added to a suspension of **2**·2HCl (43 mg, 0.202 mmol) in CH_2Cl_2 (2.8 mL) and the mixture was stirred at rt for 2 h. The resultant solution was concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH,[14] 15:1:0.1) gave a yellow oil. 2.0 M aq NaOH (5 mL) was added and the resultant solution was extracted with $CHCl_3$ (5 x 5 mL). The combined organic extracts

were washed with brine (50 mL), dried, filtered and concentrated *in vacuo* to give **4** as a colourless oil (34 mg, 67%, >95:5 dr); $[\alpha]_D^{25}$ +40.0 (*c* 1.0 in $CDCl_3$), $[\alpha]_D^{20}$ +54.6 (*c* 0.5 in $CDCl_3$); {lit.[15] $[\alpha]_D^{20}$+49.8 (*c* 0.5 in $CHCl_3$), lit.[16] $[\alpha]_D^{20}$+49.8 (*c* 2.23 in $CHCl_3$)}; ν_{max} 3434 (N−H), 2918 (C−H), 1661 (C=O); δ_H (400 MHz, $CDCl_3$) 1.99 (3 H, s, CO*Me*), 2.01–2.06 (1H, m, C(6)H_A), 2.10 (1H, ddd, *J* 14.3, 8.6, 7.6, C(6)H_B), 2.45 (1H, d, *J* 11.9, C(3)H_A), 2.93 (1H, ddd, *J* 12.9, 9.4, 7.3, C(5)H_A), 3.10 (1H, dd, *J* 8.6, 3.7, C(8)*H*), 3.12–3.16 (1H, m, C(5)H_B), 3.32 (1H, dd, *J* 11.9, 1.3, C(3)H_A), 4.19 (1H, d, *J* 1.4, C(2)*H*), 4.41–4.47 (1H, m, C(1)*H*), 4.46 (1H, dd, *J* 4.6, 1.9, C(7)*H*), 6.30 (1H, brs, N*H*); δ_C (101 MHz, $CDCl_3$) 23.2 (C(O)*Me*), 33.8 (*C*(6)), 54.6 (*C*(5)), 57.6 (*C*(1)), 60.9 (*C*(3)), 69.6 (*C*(8)), 73.8 (*C*(2)), 80.9 (*C*(7)), 170.4 (*C*(O)Me); *m/z* (ESI$^+$) 183 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{15}N_2O_2^+$ ([M+H]$^+$) requires 183.1128; found 183.1130.

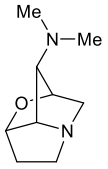
(1*R*,2*R*,7*S*,8*S*)-1-(*N*,*N*-dimethylamino)-2,7-epoxypyrrolizidine·dihydrochloride [(*N*)-methyl loline dihydrochloride] 283·2HCl



Formaldehyde (35% in H_2O, 0.26 mL, 3.00 mmol) was added to a solution of **2**·2HCl (40 mg, 0.188 mmol) in MeCN (6.3 mL) and the mixture was stirred at 0 °C for 10 min. $NaCNBH_3$ (24 mg, 0.376 mmol) was added at 0 °C and the resultant mixture was stirred at rt for 16 h. The resultant solution was concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH 5:1) followed by addition of HCl (1.25 M in MeOH, 12 mL) gave **283**·2HCl as a colourless oil (30 mg, 66%, >95:5 dr); $[\alpha]_D^{25}$ +7.2 (*c* 1.0 in H_2O); ν_{max} 3381 (N−H), 2989 (C−H); δ_H (400 MHz, D_2O) 2.41 (1H, ddd, *J* 15.3, 8.9, 7.4, C(6)H_A), 2.52 (1H, ddt, *J* 15.3, 9.9, 4.8, C(6)H_B), 3.11 (6H, s, NMe_2), 3.73 (1H, d, *J* 14.2, C(3)H_A), 3.78–3.96 (2H,

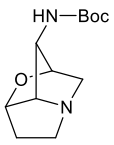
m, C(5)H_2), 4.29 (1H, dd, *J* 14.2, 1.2, C(3)H_B), 4.45–4.50 (1H, m, C(1)*H*), 4.89 (1H, dd, *J* 4.8, 2.2, C(7)*H*), 4.96–5.03 (2H, m, C(2)*H*, C(8)*H*); δ_C (101 MHz, D_2O) 31.8 (*C*(6)), 47.3, (N*Me*$_2$), 58.6 (*C*(5)), 64.3 (*C*(3)), 72.2 (*C*(8)), 73.8 (*C*(1)), 74.1 (*C*(2)), 84.0 (*C*(7)); *m/z* (ESI^+) 169 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{17}N_2O^+$ ($[M+H]^+$) requires 169.1335; found 169.1336.

(1*R*,2*R*,7*S*,8*S*)-1-(*N*,*N*-dimethylamino)-2,7-epoxypyrrolizidine·[(*N*)-methyl loline] 283



NaOH (100 mg, 2.50 mmol) was added to a suspension of **283**·2HCl (30 mg, 0.125 mmol) in $CDCl_3$ (2.0 mL) and the mixture was stirred at rt for 30 min. The resultant solution was filtered to give **283**; δ_H (400 MHz, $CDCl_3$) 1.88–1.96 (1H, m, C(6)H_A), 2.03 (1H, ddd, *J* 14.2, 8.6, 7.1, C(6)H_B), 2.29 (6H, s, N*Me*$_2$), 2.36 (1H, d, *J* 11.0, C(3)H_A), 2.70 (1H, d, *J* 1.5, C(1)*H*), 2.91–2.99 (1H, m, C(5)H_A), 3.06 (1H, ddd, *J* 12.4, 8.6, 3.6, C(5)H_B), 3.18 (1H, t, *J* 1.5, C(8)*H*), 3.54 (1H, dt, *J* 11.0, 0.8, C(3)H_B), 4.00 (1H, d, *J* 1.3, C(2)*H*), 4.42 (1H, dd, *J* 4.5, 1.9, C(7)*H*); δ_C (101 MHz, $CDCl_3$) 33.8 (*C*(6)), 44.8 (N*Me*$_2$), 54.7 (*C*(5)), 61.6 (*C*(3)), 69.7 (*C*(8)), 74.5 (*C*(1)), 74.7 (*C*(2)), 82.4 (*C*(7)).

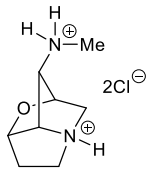
(1*R*,2*R*,7*S*,8*S*)-1-[(*tert*-butoxycarbonyl)amino]-2,7-epoxypyrrolizidine [(*N*)-Boc norloline] (+)-98



Boc_2O (102 mg, 0.469 mmol) and K_2CO_3 (129 mg, 0.940 mmol) were added to a suspension of **2**·2HCl (40 mg, 0.188 mmol) in MeOH (3.8 mL) and the mixture was stirred at rt for 24 h.

The resultant solution was concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH,[14] 20:1:0.1) gave a **98** as a colourless oil (15 mg, 33%, >95:5 dr); $[\alpha]_D^{25}$ +24.3 (*c* 1.0 in $CHCl_3$), $[\alpha]_D^{25}$ +20.1 (*c* 0.35 in $CHCl_3$); {lit.[17] $[\alpha]_D^{20}$+38.7 (*c* 0.5 in $CHCl_3$)}; ν_{max} 2973 (C−H), 1706 (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.91–2.12 (2H, m, C(6)*H*$_2$), 2.40 (1H, d, *J* 11.8, C(3)*H*$_A$), 2.92 (1H, ddd, *J* 12.9, 9.4, 7.2, C(5)*H*$_A$), 3.03–3.14 (2H, m, C(5)*H*$_B$, C(8)*H*), 3.35 (1H, d, *J* 11.8, C(3)*H*$_B$), 4.11–4.16 (1H, m, C(2)*H*), 4.21 (1H, d, *J* 7.2, C(1)*H*), 4.44 (1H, dd, *J* 4.5, 1.9, C(7)*H*), 5.87 (1H, brs, N*H*); δ_C (101 MHz, $CDCl_3$) 28.4 (C*Me*$_3$), 33.8 (*C*(6)), 54.6 (*C*(5)), 58.5 (*C*(1)), 61.0 (*C*(3)), 69.6 (*C*(8)), 74.1 (*C*(2)), 79.5 (*C*Me$_3$), 81.1 (*C*(7)), 155.6 (N*C*O); *m/z* (ESI$^+$) 241 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{21}N_2O_3^+$ ([M+H]$^+$) requires 241.1547; found 241.1546.

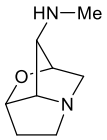
(1*R*,2*R*,7*S*,8*S*)-1-[*N*-methylamino]-2,7-epoxypyrrolizidine dihydrochloride [(+)-loline dihydrochloride] (+)-1·2HCl



$LiAlH_4$ (2.0 M in THF, 0.19 mL, 0.375 mmol) was added to a solution of **98** (15 mg, 62.4 μmol) in THF (1.25 mL) and heated at 70 °C for 4 h. 2.0 M aq NaOH (0.5 mL) was added and the resultant mixture was stirred at rt for 30 min. The resultant mixture was filtered through Celite® (eluent CH_2Cl_2), then silica gel (500 mg) was added and the resultant solution was concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH 4:1) followed by addition of HCl (1.25 M in MeOH, 5 mL) gave **1**·2HCl as a colourless oil (5 mg, 35%, >95:5 dr); $[\alpha]_D^{25}$ +3.3 (*c* 0.31 in H_2O); {lit.[17] $[\alpha]_D^{25}$ +5.4 (*c* 0.31 in H_2O), lit[18] {$[\alpha]_D^{19}$ +6.2 (*c* 9.7 in H_2O)}; ν_{max} 2965 (C−H), 2924 (C−H); δ_H (400 MHz, D_2O) 2.39–2.51 (1H, m, C(6)*H*$_A$), 2.56 (1H, ddt, *J* 15.0, 10.0, 4.9, C(6)*H*$_A$), 2.97 (3H, s, N*Me*), 3.74 (1H, d, *J* 14.0,

C(3)H_A), 3.82–3.98 (2H, m, C(5)H_2), 4.30 (1H, dd, *J* 14.0, 1.2, C(3)H_B), 4.40 (1H, d, *J* 2.5, C(1)*H*), 4.90 (1H, dd, *J* 4.9, 2.3, C(7)*H*), 4.96 (2H, app dd, *J* 5.5, 2.4, C(2)*H*, C(8)*H*); δ_C (101 MHz, D_2O) 31.9 (*C*(6)), 36.7 (N*Me*), 58.5 (*C*(5)), 64.5 (*C*(3)), 66.3 (*C*(1)), 72.5 (*C*(8)), 74.3 (*C*(2)), 83.6 (*C*(7)); *m/z* (ESI^+) 155 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{15}N_2O^+$ ($[M+H]^+$) requires 155.1179; found 155.1178.

(1*R*,2*R*,7*S*,8*S*)-1-[*N*-methylamino]-2,7-epoxypyrrolizidine [Loline] 1



NaOH (18 mg, 0.440 mmol) was added to a suspension of **1**·2HCl (5 mg, 22.0 μmol) in $CDCl_3$ (1.0 mL) and the suspension was stirred at rt for 30 min. The resultant solution was filtered to give **1**; δ_H (500 MHz, $CDCl_3$) 1.91–2.01 (1H, m, C(6)H_A), 2.05 (1H, ddd, *J* 14.2, 8.5, 7.2, C(6)H_B), 2.42 (1H, d, *J* 11.6, C(3)H_A), 2.49 (3H, s, N*Me*), 2.93 (1H, ddd, *J* 12.6, 9.5, 7.2, C(5)H_A), 3.08 (1H, ddd, *J* 12.6, 8.5, 3.4, C(5)H_B), 3.15 (1H, dd, *J* 1.7, 1.5, C(8)*H*), 3.32–3.36 (1H, m, C(1)*H*), 3.41 (1H, d, *J* 11.6, C(3)H_B), 4.03 (1H, app t, *J* 1.8, C(2)*H*), 4.41 (1H, dd, *J* 4.5, 1.7, C(7)*H*); (126 MHz, $CDCl_3$) 34.1 (*C*(6)), 35.2 (N*Me*)54.7 (*C*(5)), 68.3 (*C*(1)), 61.2 (*C*(3)), 69.6 (*C*(8)), 74.1 (*C*(2)), 81.8 (*C*(7)).

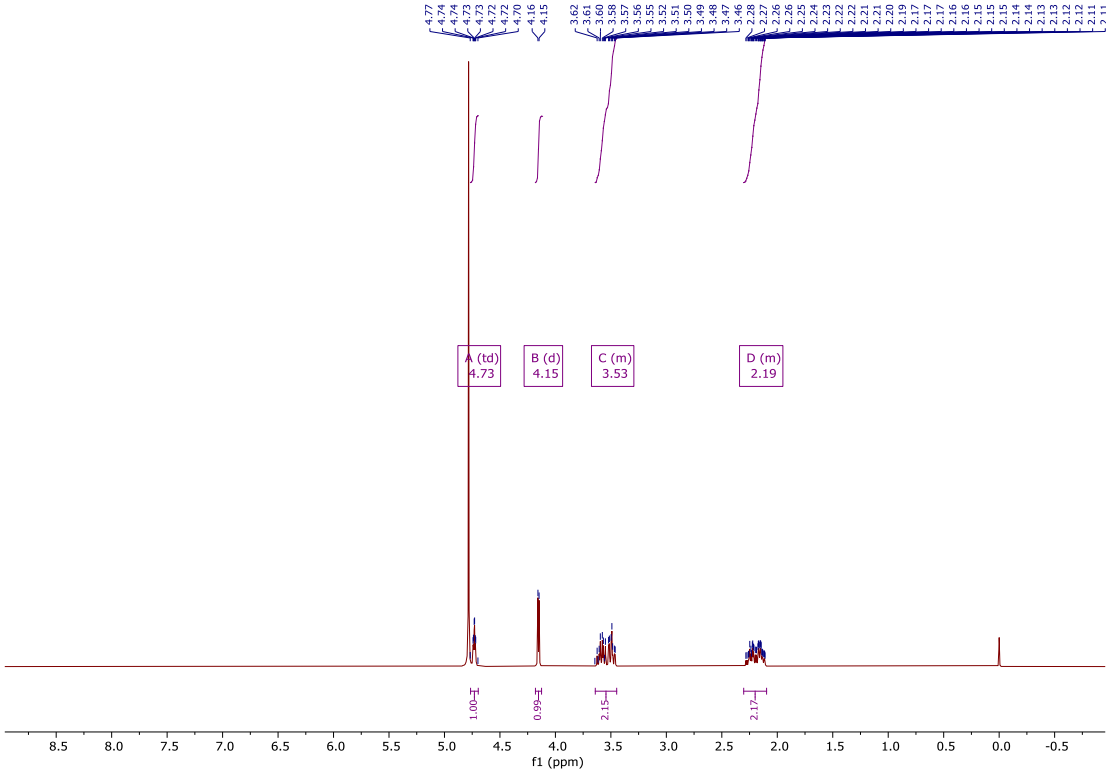
7.6 References and Notes

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(6) The enantiomeric purity of (*R*)-**41** was confirmed as >99.0% ee by ^1H NMR spectroscopic analyses in the presence of (*S*)-*O*-acetylmandelic acid and (*RS*)-*O*-acetylmandelic acid.
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(10) The enantiomeric purity of (*S*)-**41** was confirmed as >99.0% ee by ^1H NMR spectroscopic analyses in the presence of (*R*)-*O*-acetylmandelic acid and (*RS*)-*O*-acetylmandelic acid.

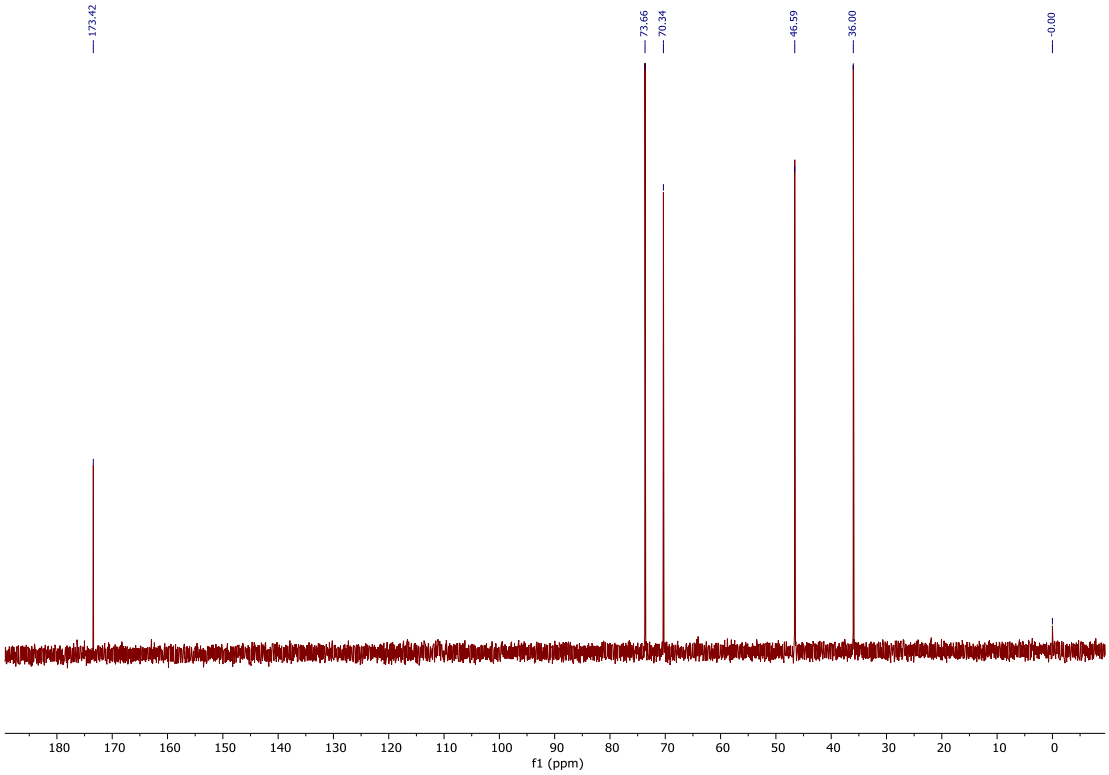
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(13) OTMS and OBoc ^{1}H NMR chemical shifts are not reported due to them being obscured by residual reagent chemical shifts.
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Appendix 1: 3-Hydroxyproline NMR Data

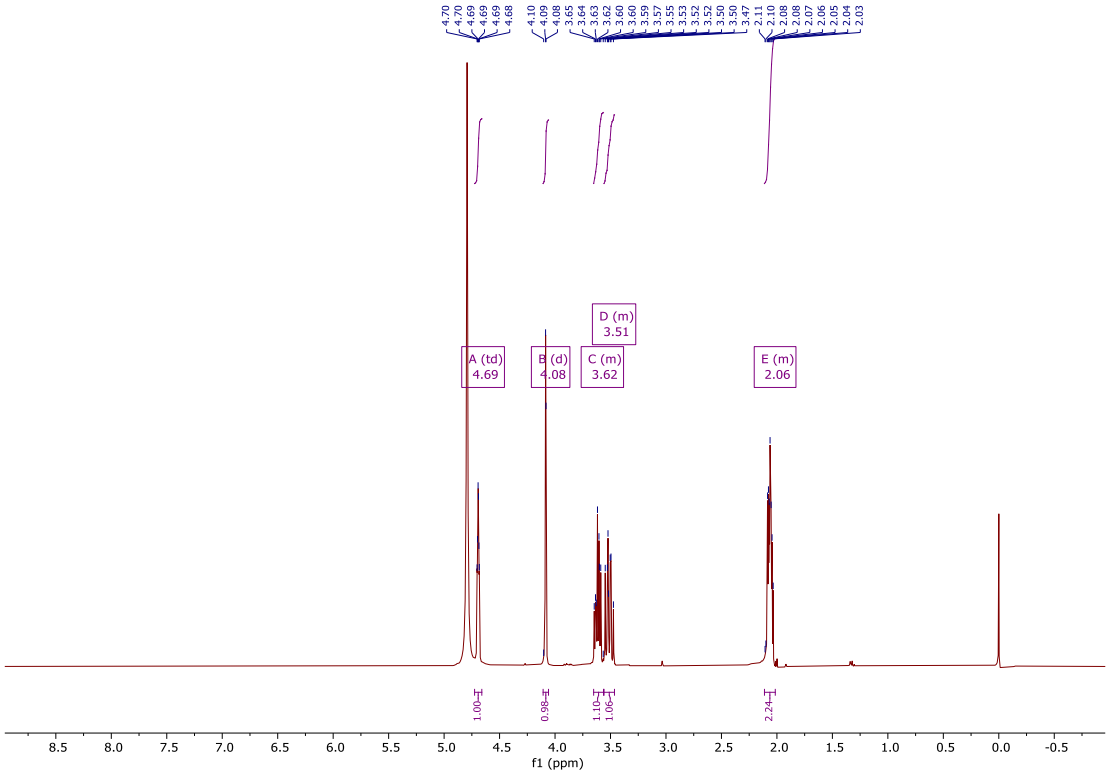
(2*R*,3S)-*cis*-3-Hydroxyproline 131 (400 MHz, ^{1}H, D_2O)



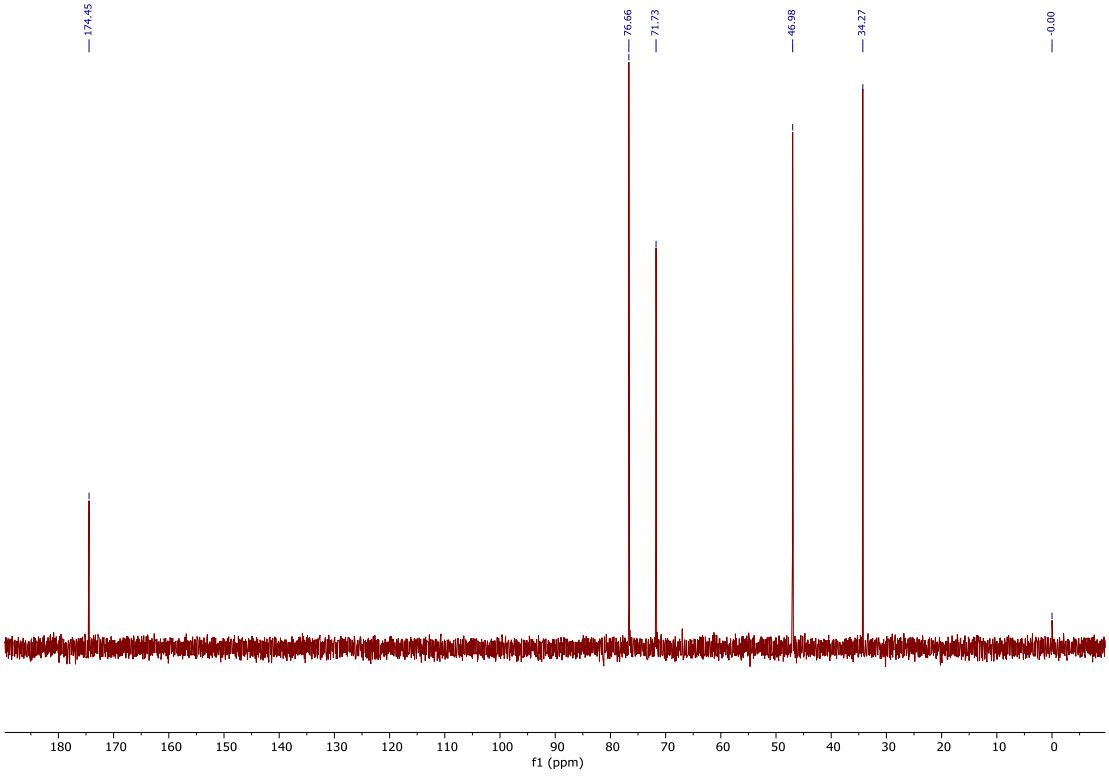
(2*R*,3*S*)-*cis*-3-Hydroxyproline 131 (101 MHz, ^{13}C, D_2O)



(2*S*,3*S*)-3-*trans*-Hydroxyproline 136 (400 MHz, ^{1}H, D_2O)



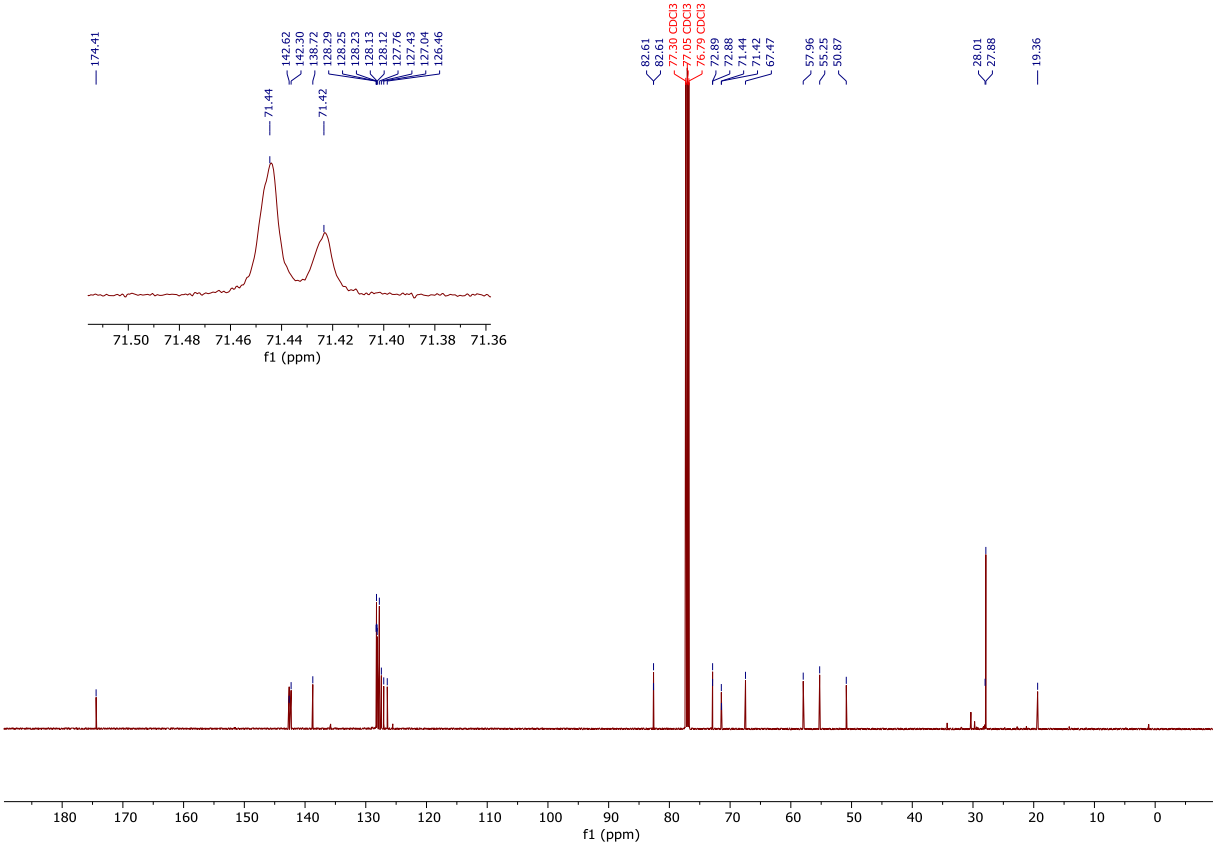
(2*S*,3*S*)-3-*trans*-Hydroxyproline 136 (101 MHz, ^{13}C, D_2O)



Appendix 2: ^{18}O isotopic Shift NMR Data

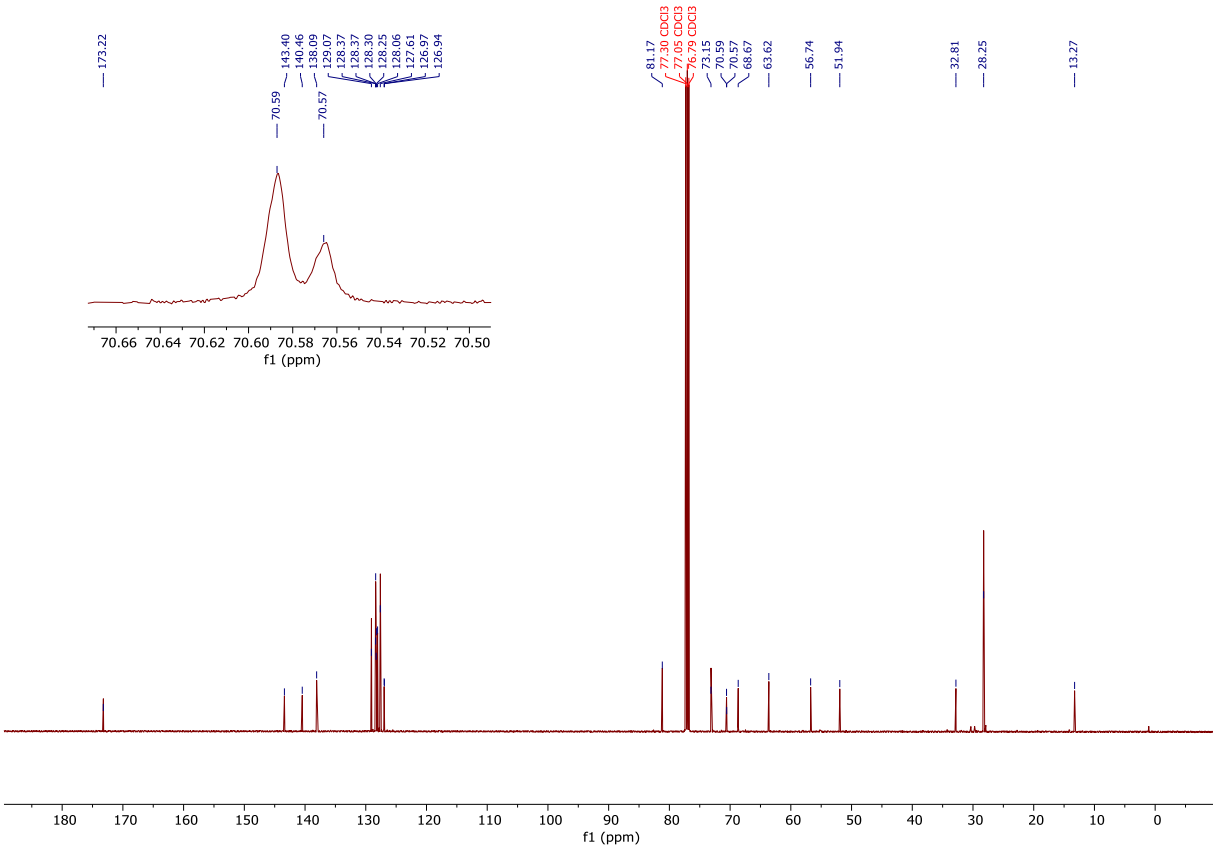
tert-butyl (_R_,_R_,_R_)-2-(hydroxy)-3-[_N_-benzyl-_N_-(α-methylbenzyl)amino]-5-benzyloxypentanoate 171 and _tert_-butyl (_R_,_R_,_R_)-2-(^{18}O-hydroxy)-3-[_N_-benzyl-_N_-(α-methylbenzyl)amino]-5-benzyloxypentanoate ^{18}O-171

(126 MHz, ^{13}C, $CDCl_3$)



tert-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)]-3-(hydroxy)-5-benzyloxypentanoate 190 and _tert_-Butyl (2*S*,3*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)]-3-(^{18}O-hydroxy)-5-benzyloxypentanoate ^{18}O-190

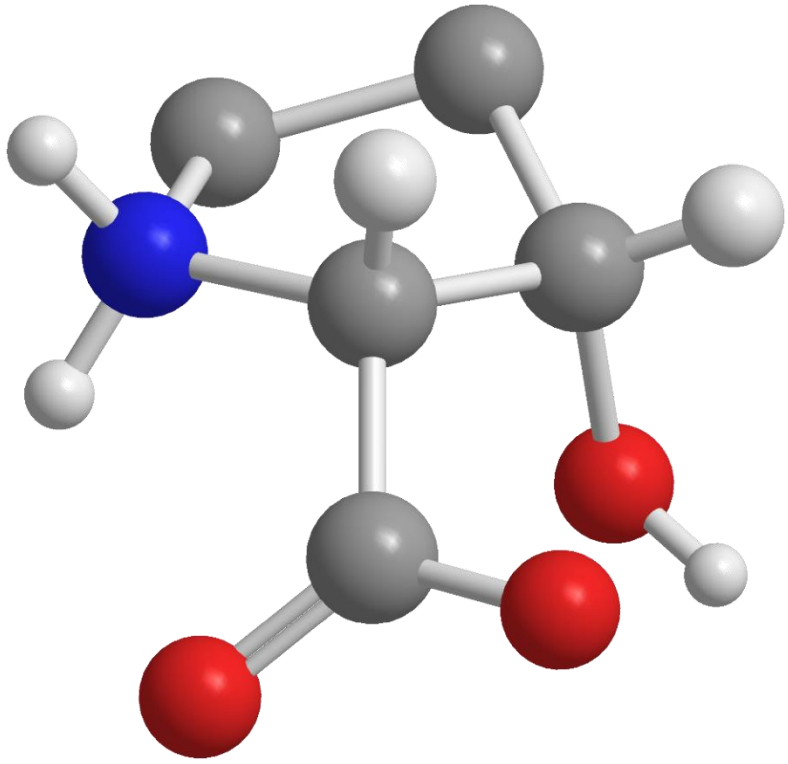
(126 MHz, ^{13}C, $CDCl_3$)



Appendix 3: X-Ray Crystal Structure Data

X-Ray crystal structure data for (2*R*,3*S*)-131

(selected H atoms are omitted for clarity)



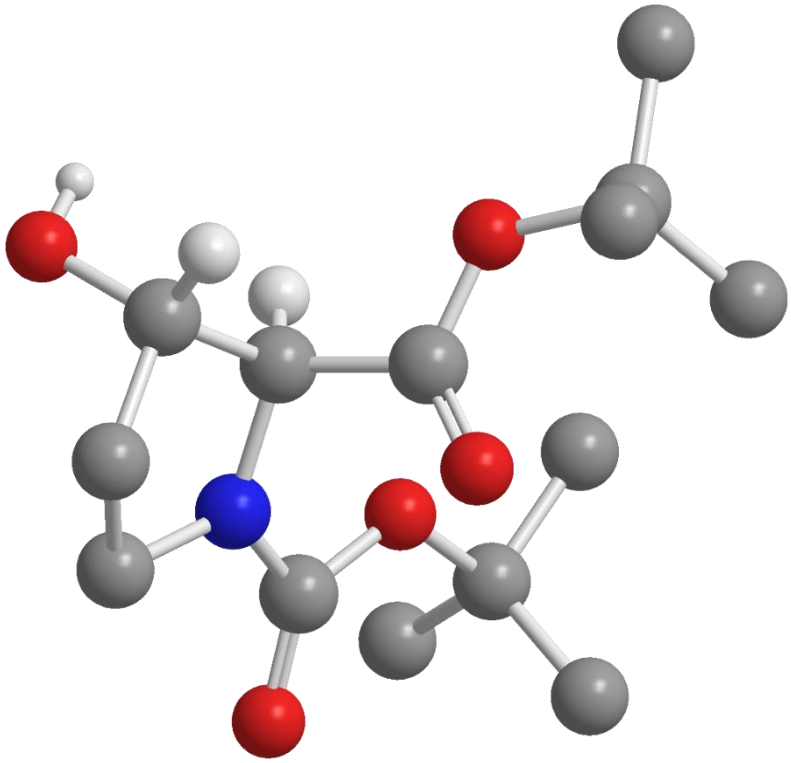
X-ray crystal structure determination for 131

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 **131** [$C_5H_9NO_3$]: M = 131.13, monoclinic, space group $P2_1$, a = 4.7164(2) Å, b = 8.5266(4) Å, c = 7.4048(3) Å, β = 91.454(4)°, V = 297.13(2) Å^3, Z = 2, μ = 1.037 mm^{-1}, colourless plate, crystal dimensions = 0.12 × 0.19 × 0.20 mm^3. A total of 920 unique reflections were measured for $6 < \theta < 76$ and 819 reflections were used in the refinement. The final parameters were wR_2 = 0.0542 and R_1 = 0.0220 [$I > -3.0\sigma(I)$], with Flack enantiopole = 0.2(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.

X-Ray crystal structure data for (2*S*,3*S*)-189·$CHCl_3$

(selected H atoms and $CHCl_3$ are omitted for clarity)



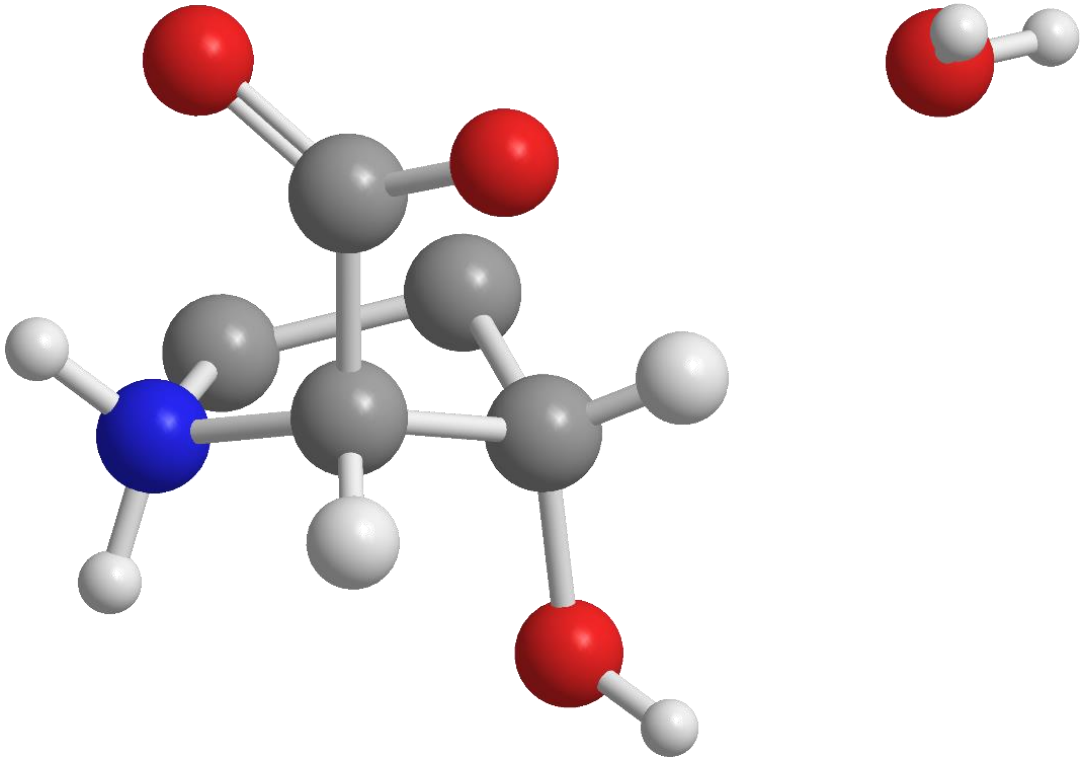
X-ray crystal structure determination for 189·$CHCl_3$

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 **189**·$CHCl_3$ [$C_{15}H_{26}Cl_3NO_5$]: M = 406.73, monoclinic, space group $P\,2_1$, a = 9.2897(2) Å, b = 10.4221(3) Å, c = 10.2261(3) Å, β = 91.806(2)°, V = 989.57(4) $Å^3$, Z = 2, μ = 4.402 mm^{-1}, colourless prism, crystal dimensions = 0.11 × 0.12 × 0.28 mm^3. A total of 3637 unique reflections were measured for $4 < \theta < 76$ and 3416 reflections were used in the refinement. The final parameters were wR_2 = 0.072 and R_1 = 0.023 [I>–3.0$\sigma(I)$], with Flack enantiopole =–0.015(10).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*S*,3*S*)-136

(selected H atoms are omitted for clarity)



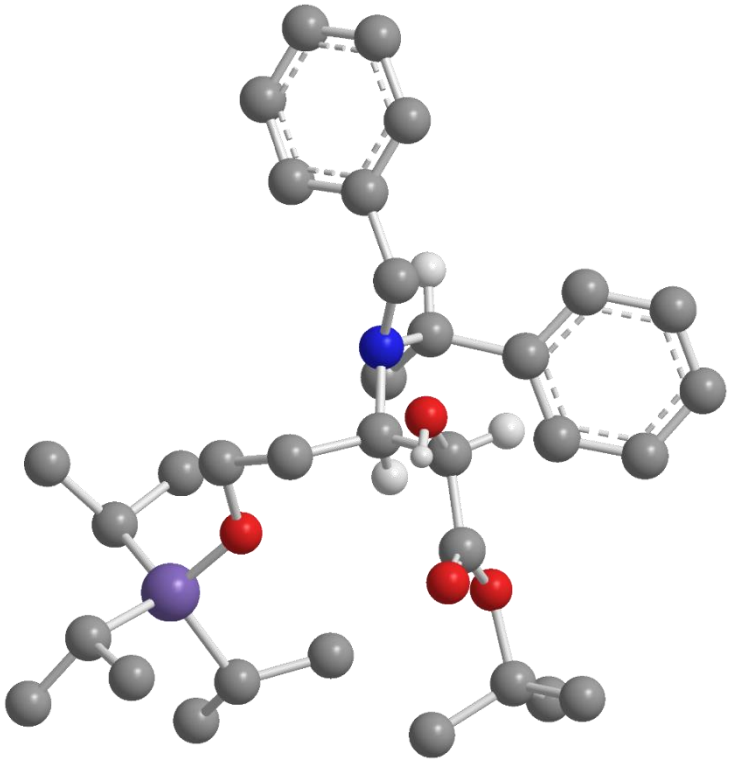
X-ray crystal structure determination for 136

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 **136** [$C_5H_{11}NO_4$]: M = 149.15, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.8676(3) Å, b = 9.7916(4) Å, c = 11.9349(6) Å, V = 685.70(6) Å^3, Z = 4, μ = 1.077 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.19 × 0.20 mm^3. A total of 1405 unique reflections were measured for 6 < θ < 76 and 1068 reflections were used in the refinement. The final parameters were wR_2 = 0.0649 and R_1 = 0.0262 [I>–3.0σ(I)], with Flack enantiopole = –0.1(3).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*R*,3*R*,α*R*)-204

(selected H atoms are omitted for clarity)



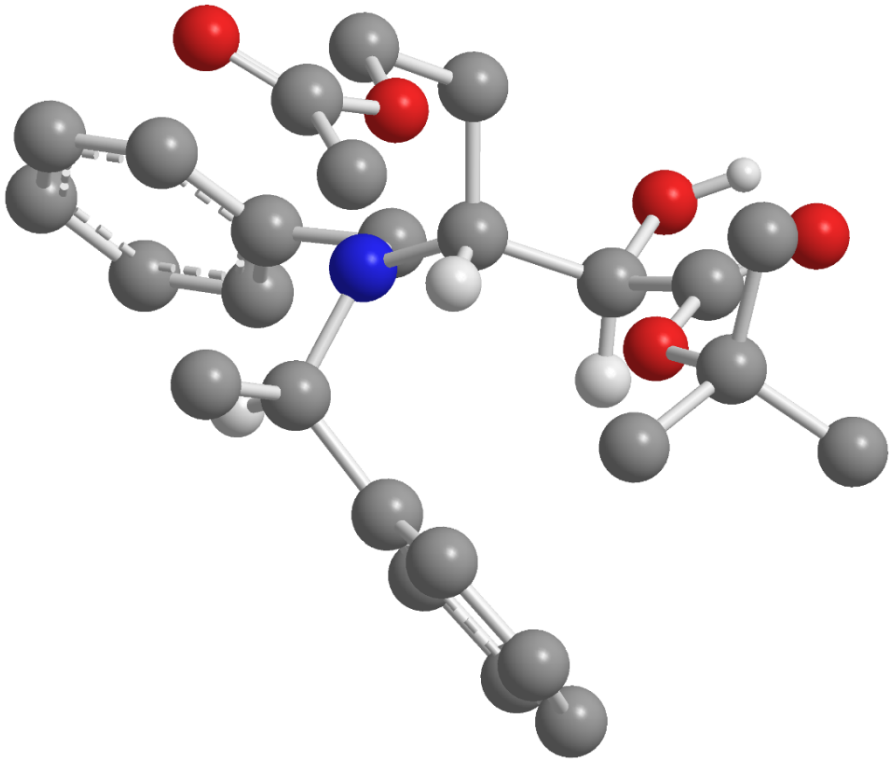
X-ray crystal structure determination for 204

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 **204** [$C_{33}H_{53}NO_4Si$]: M = 555.87, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 9.1679(1) Å, b = 18.3380(2) Å, c = 20.1595(2) Å, V = 3389.23(6) Å^3, Z = 4, μ = 0.869 mm^{-1}, colourless block, crystal dimensions = 0.15 × 0.18 × 0.20 mm^3. A total of 7034 unique reflections were measured for 3 < θ < 76 and 7007 reflections were used in the refinement. The final parameters were wR_2 = 0.107 and R_1 = 0.042 [I>–3.0σ(I)], with Flack enantiopole = –0.01(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.

X-Ray crystal structure data for (2*R*,3*R*,*αR*)-197

(selected H atoms are omitted for clarity)



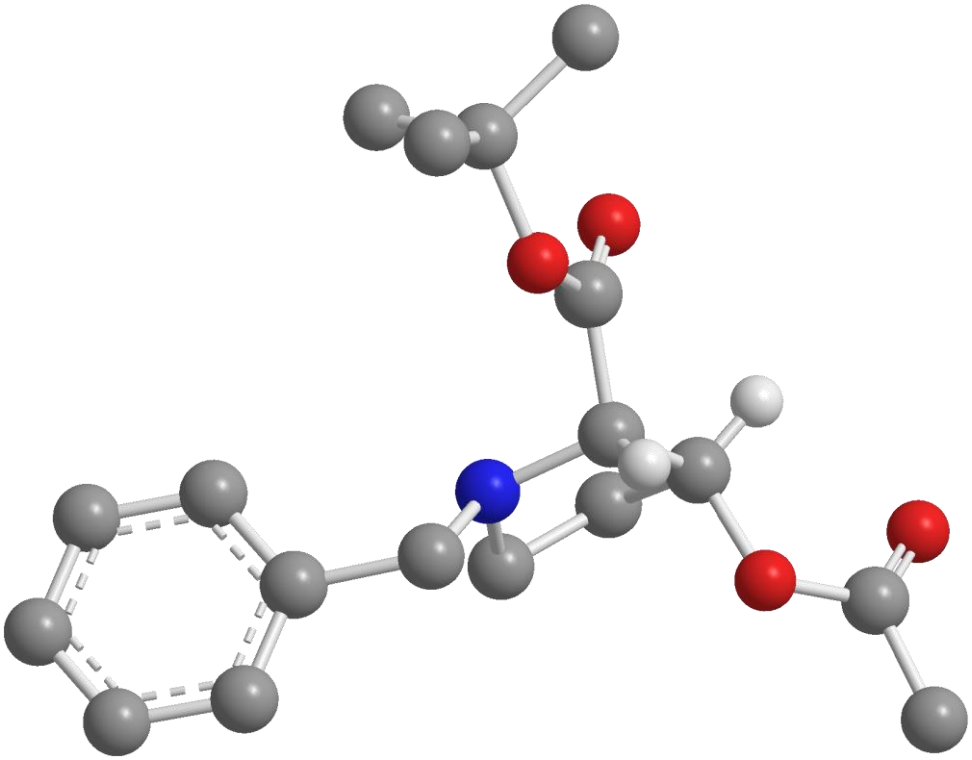
X-ray crystal structure determination for 197

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 **197** [$C_{26}H_{35}NO_5$]: M = 441.57, monoclinic, space group $P\ 2_1$, a = 8.6403(2) Å, b = 15.7274(3) Å, c = 9.35062(19) Å, β = 102.006(2)°, V = 1242.86(5) Å^3, Z = 2, μ = 0.652 mm^{-1}, colourless block, crystal dimensions = 0.26 × 0.29 × 0.33 mm^3. A total of 5033 unique reflections were measured for 5 < θ < 76 and 4407 reflections were used in the refinement. The final parameters were wR_2 = 0.068 and R_1 = 0.026 [I>–3.0σ(I)], with Flack enantiopole = 0.00(11).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*S*,3*S*)-211

(selected H atoms are omitted for clarity)



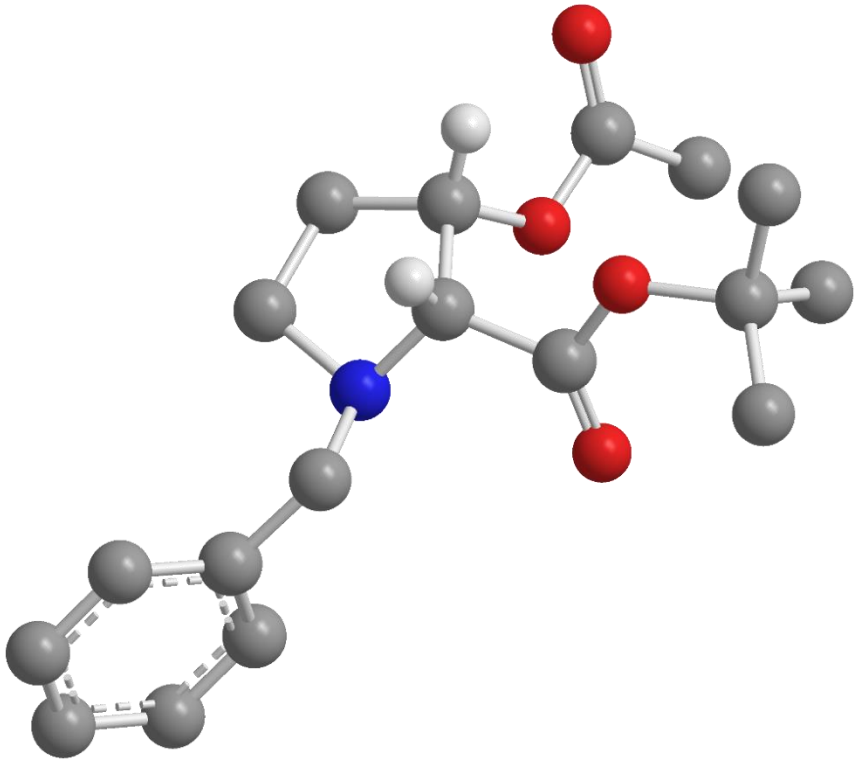
X-ray crystal structure determination for 211

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.[1]

X-ray crystal structure data for **211** [$C_{18}H_{25}NO_4$]: M = 638.80, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 5.58602(7) Å, b = 10.01796(14) Å, c = 62.2675(7) Å, V = 3484.52(8) Å^3, Z = 8, μ = 0.694 mm^{-1}, colourless prism, crystal dimensions = 0.11 × 0.12 × 0.29 mm^3. A total of 7194 unique reflections were measured for 3 < θ < 76 and 6352 reflections were used in the refinement. The final parameters were wR_2 = 0.105 and R_1 = 0.043 [I>–3.0σ(I)], with Flack enantiopole = –0.03(15).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*R*,3*S*)-221

(selected H atoms are omitted for clarity)



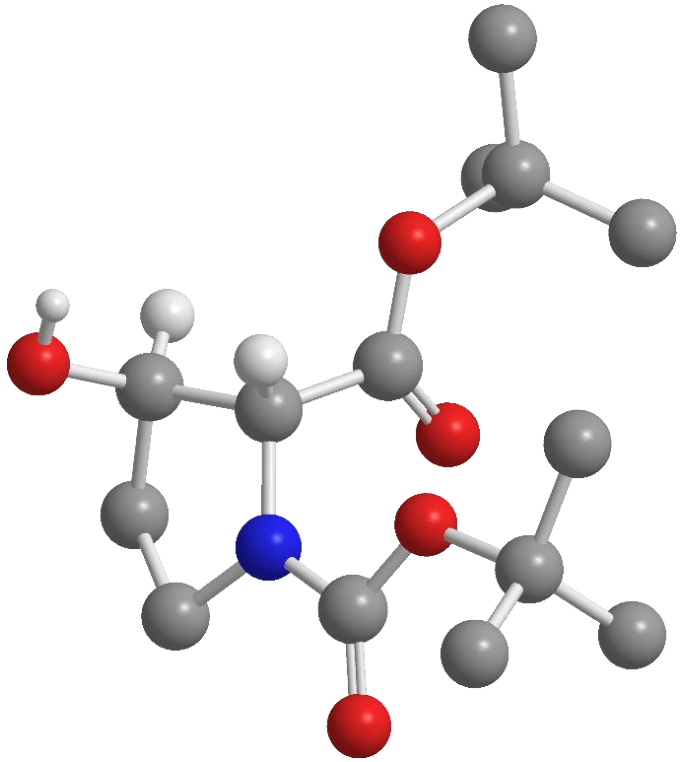
X-ray crystal structure determination for 221

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 **221** [$C_{18}H_{25}NO_4$]: M = 319.40, monoclinic, space group $P\,2_1$, a = 5.61627(17) Å, b = 17.6769(5) Å, c = 18.0379(5) Å, β = 92.977(3)°, V = 1788.36(9) Å^3, Z = 4, μ = 0.676 mm^{-1}, colourless prism, crystal dimensions = 0.09 × 0.11 × 0.26 mm^3. A total of 7130 unique reflections were measured for 4 < θ < 76 and 7106 reflections were used in the refinement. The final parameters were wR_2 = 0.0975 and R_1 = 0.0467 [I>–3.0σ(I)], with Flack enantiopole = –0.09(15).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*R*,3*R*)-*ent*-189

(selected H atoms are omitted for clarity)



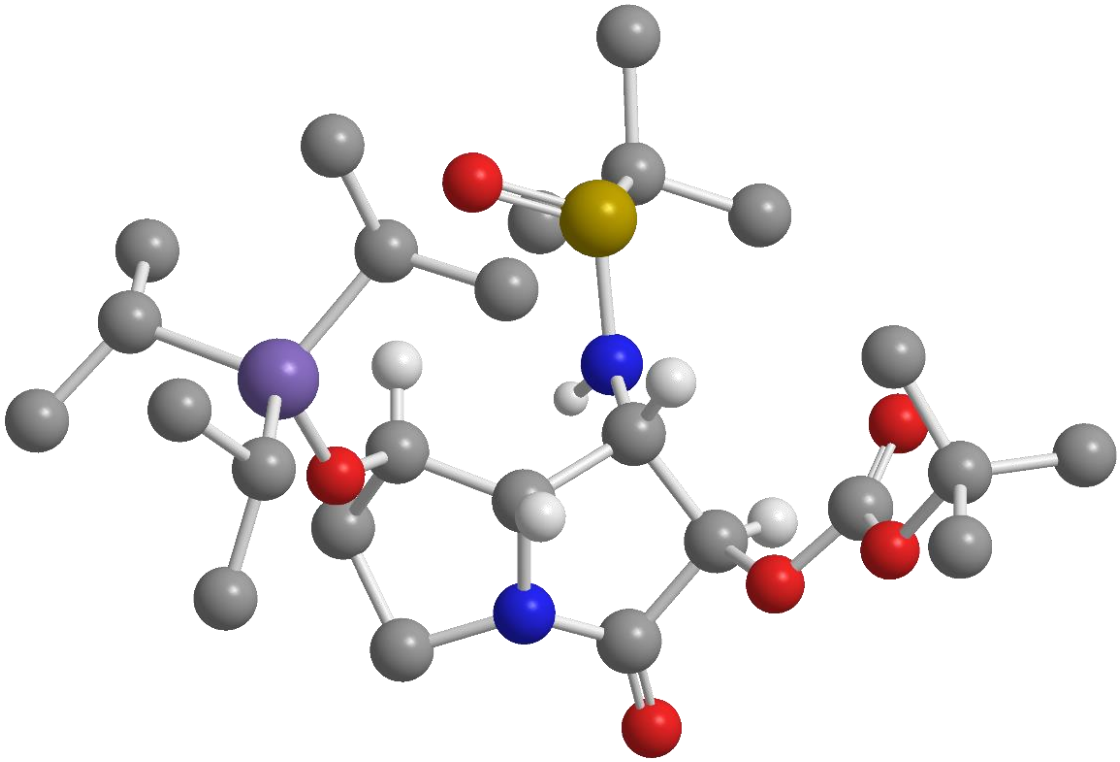
X-ray crystal structure determination for *ent*-189·$CHCl_3$

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 *ent*-**189**·$CHCl_3$ [$C_{15}H_{26}Cl_3NO_5$]: M = 406.74, monoclinic, space group $P\,2_1$, a = 9.29029(11) Å, b = 10.42733(14) Å, c = 10.22998(14) Å, β = 91.7833(11)°, V = 990.53(2) Å^3, Z = 4, μ = 4.397 mm^{-1}, colourless block, crystal dimensions = 0.13 × 0.22 × 0.22 mm^3. A total of 4079 unique reflections were measured for $4 < \theta < 76$ and 3810 reflections were used in the refinement. The final parameters were wR_2 = 0.0570 and R_1 = 0.0224 [I>–3.0σ(I)], with Flack enantiopole = –0.009(8).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (1*S*,2*R*,7*R*,7a*S*,R_S)-274

(selected H atoms are omitted for clarity)



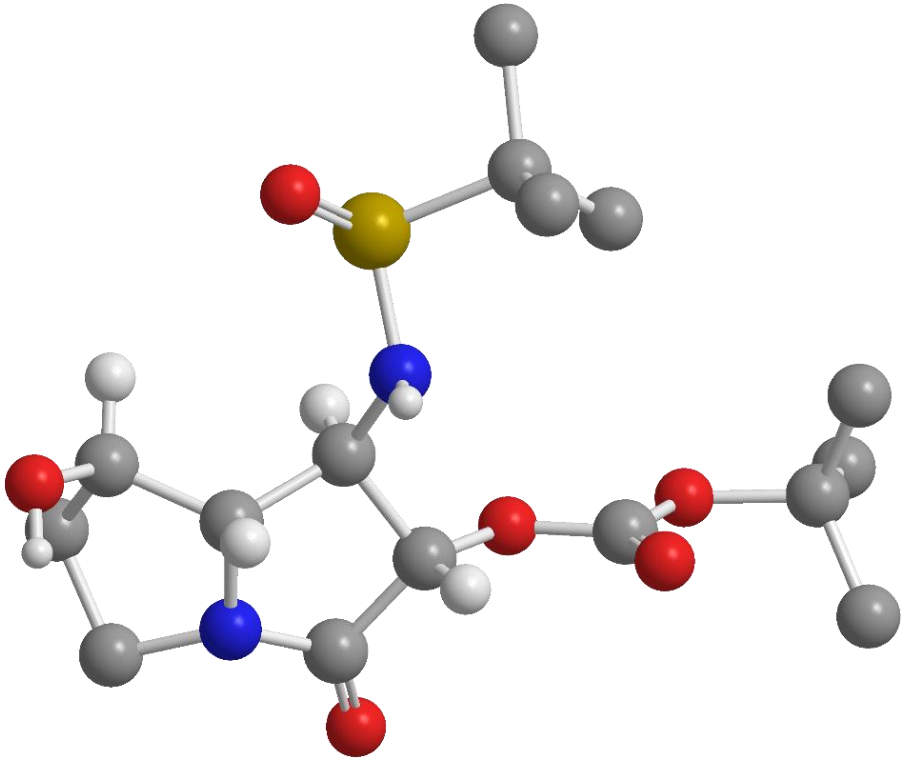
X-ray crystal structure determination for 274

Data were collected using n 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 274 [$C_{25}H_{48}N_2O_6SSi$]: M = 532.825, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 16.832(2) Å, b = 19.6714(13) Å, c = 56.6846(6) Å, V = 18602.9(4) Å^3, Z = 30, μ = 1.598 mm^{-1}, colourless prism, crystal dimensions = 0.16 × 0.18 × 0.27 mm^3. A total of 34696 unique reflections were measured for 3 < θ < 76 and 33354 reflections were used in the refinement. The final parameters were wR_2 = 0.1636 and R_1 = 0.075 [I>–3.0σ(I)], with Flack enantiopole = –007(16).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (1*R*,2*S*,7*R*,7a*S*,S_S)-276

(selected H atoms are omitted for clarity)



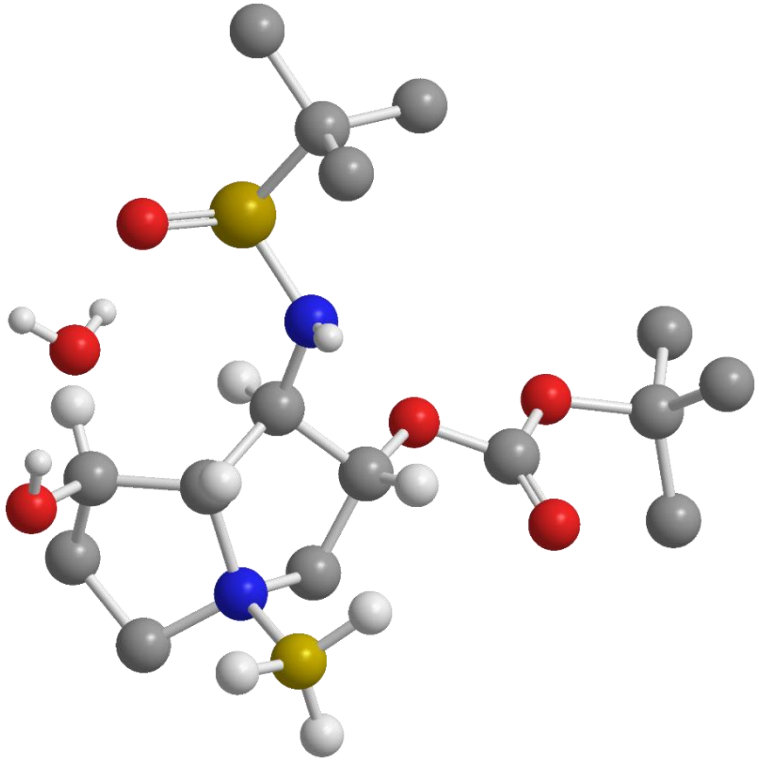
X-ray crystal structure determination for 276

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 **276** [$C_{16}H_{28}N_2O_6Si$]: M = 376.47, orthorhombic, space group $P2_12_12_1$, a = 5.96864(11) Å, b = 15.6792(3) Å, c = 20.5546(3) Å, V = 1923.57(6) Å^3, Z = 4, μ = 1.788 mm^{-1}, colourless block, crystal dimensions = 0.12 × 0.13 × 0.20 mm^3. A total of 3978 unique reflections were measured for 4 < θ < 76 and 3473 reflections were used in the refinement. The final parameters were wR_2 = 0.0812 and R_1 = 0.0347 [I>–3.0σ(I)], with Flack enantiopole = –0.011(17).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (1*R*,2*R*,4*S*,7*R*,7a*S*,S_S)-263·BH_3·H_2O

(selected H atoms are omitted for clarity)



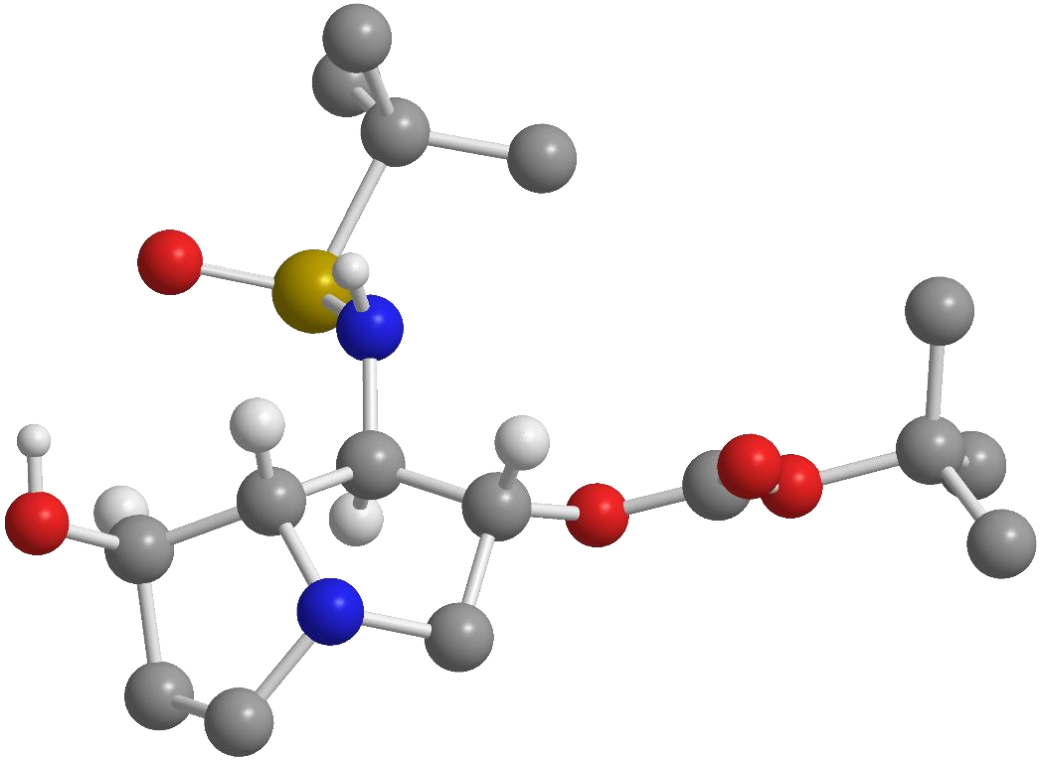
X-ray crystal structure determination for 263·BH_3·H_2O

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

X-ray crystal structure data for 263·BH_3·H_2O [$C_{16}H_{35}N_2O_6Si$]: M = 394.34, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 5.99365(14) Å, b = 11.5309(2) Å, c = 30.9703(6) Å, V = 2140.43(8) Å^3, Z = 4, μ = 1.675 mm^{-1}, colourless prism, crystal dimensions = 0.06 × 0.09 × 0.19 mm^3. A total of 4497 unique reflections were measured for $3 < \theta < 7$ and 3791 reflections were used in the refinement. The final parameters were wR_2 = 0.1163 and R_1 = 0.0832 [I>–3.0σ(I)], with Flack enantiopole = –0.02(3).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (1*R*,2*R*,7*R*,7a*S*,S_S)-263·0.5H_2O

(selected H atoms are omitted for clarity)



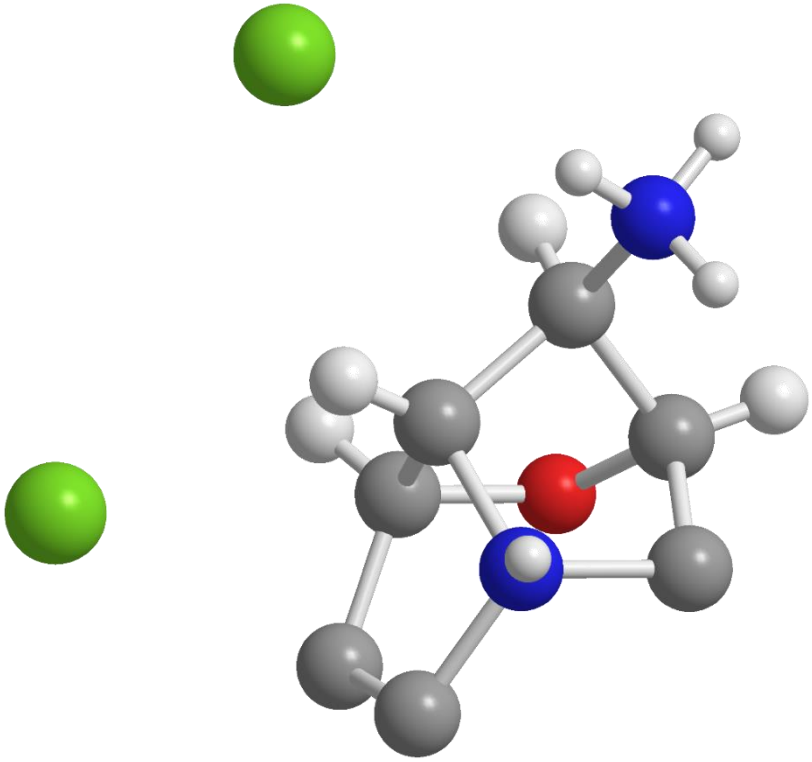
X-ray crystal structure determination for 263·0.5H_2O

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

X-ray crystal structure data for **263**·0.5H_2O [$C_{16}H_{31}N_2O_{0.5}S$]: M = 371.50, monoclinic, space group $P\ 2_1$, a = 6.14973(17) Å, b = 16.2619(3) Å, c = 20.3467(6) Å, β = 90.138(3)°, V = 2034.80(9) Å^3, Z = 4, μ = 1.660 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.20 × 0.31 mm^3. A total of 8251 unique reflections were measured for 2 < θ < 76 and 7765 reflections were used in the refinement. The final parameters were wR_2 = 0.1086 and R_1 = 0.0501 [I>–3.0σ(I)], with Flack enantiopole = –0.016(14).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (1*R*,2*R*,7*S*,8*S*)-2·HCl

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 2·HCl

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]

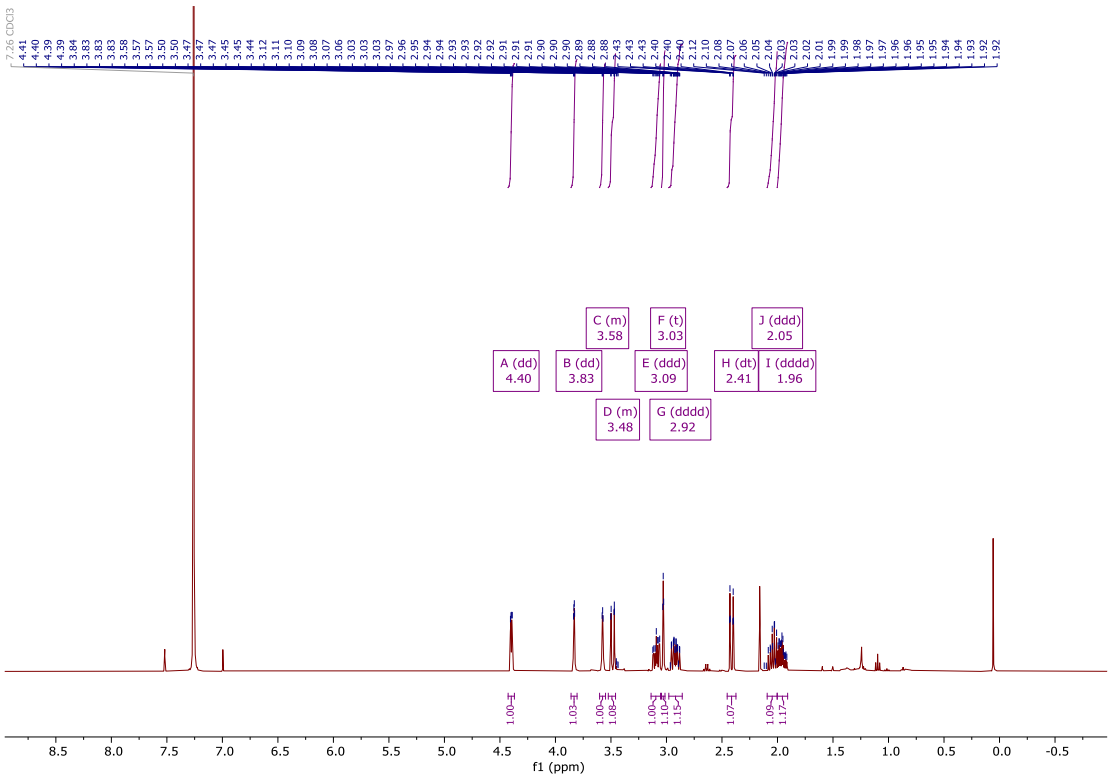
X-ray crystal structure data for 2·HCl [$C_7H_{14}Cl_2N2O$]: M = 213.11, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.29038(10) Å, b = 6.50236(12) Å, c = 22.0613(3) Å, V = 902.36(3) Å^3, Z = 4, μ = 6.103 mm^{-1}, colourless prism, crystal dimensions = 0.10 × 0.12 × 0.27 mm^3. A total of 1901 unique reflections were measured for 4 < θ < 77 and 1690 reflections were used in the refinement. The final parameters were wR_2 = 0.0749 and R_1 = 0.0292 [I>–3.0σ(I)], with Flack enantiopole = –0.016(19).[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.

References and Notes

(1) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487–1487.
(2) Flack, H. D.; Bernardinelli, G. *Acta Crystallogr. Sect. A* **1999**, *55*, 908–915.

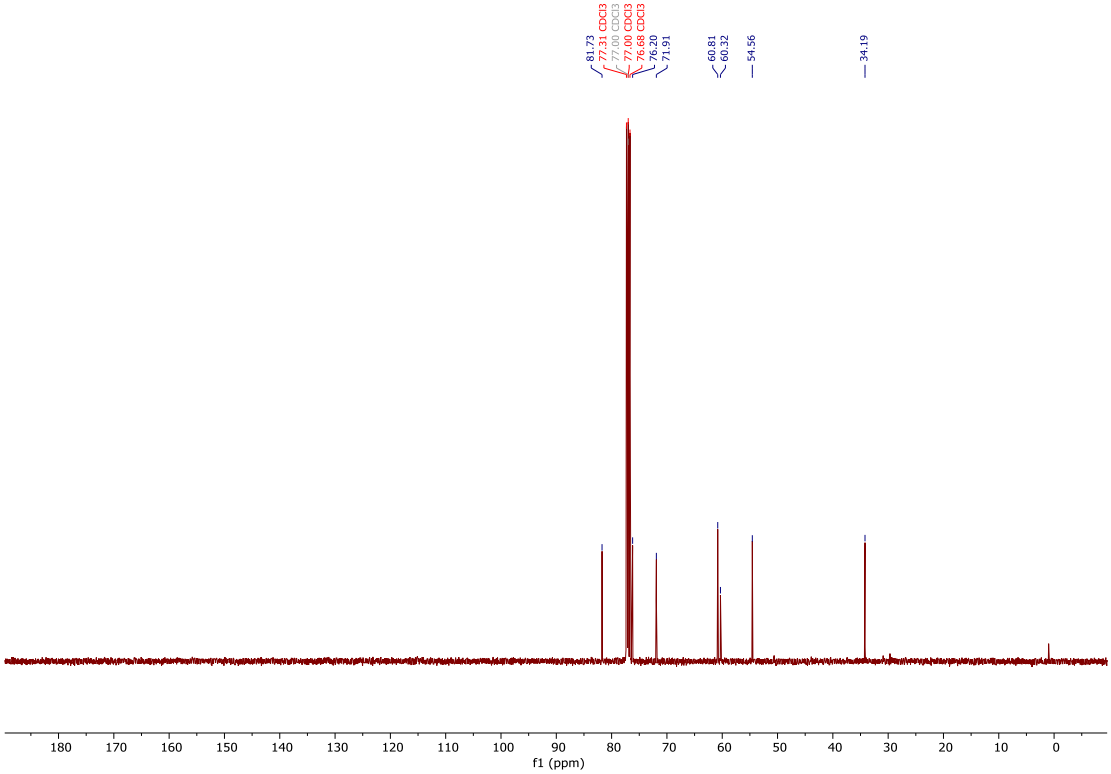
Appendix 4: Loline Alkaloid NMR Data

(1*R*,2*R*,7*S*,8*S*)-1-amino-2,7-epoxypyrrolizidine [norloline] 2 (400 MHz, ^{1}H, $CDCl_3$)



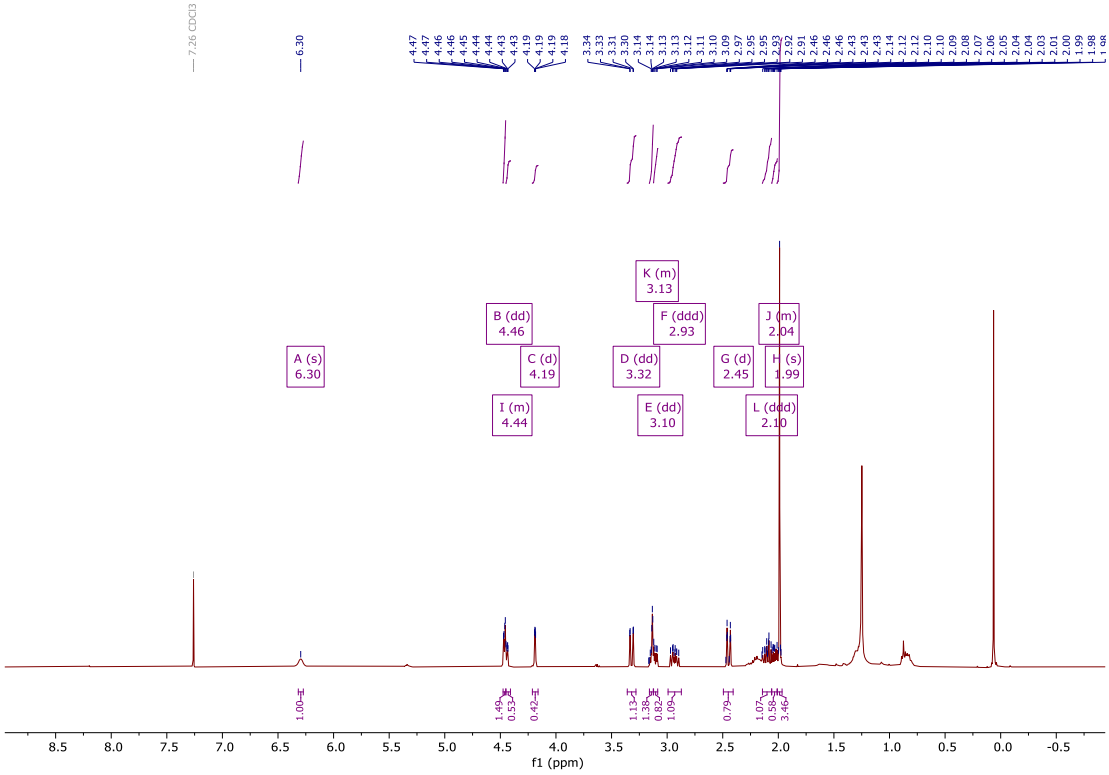
(1*R*,2*R*,7*S*,8*S*)-1-amino-2,7-epoxypyrrolizidine [norloline] 2

(101 MHz, ^{13}C, $CDCl_3$)



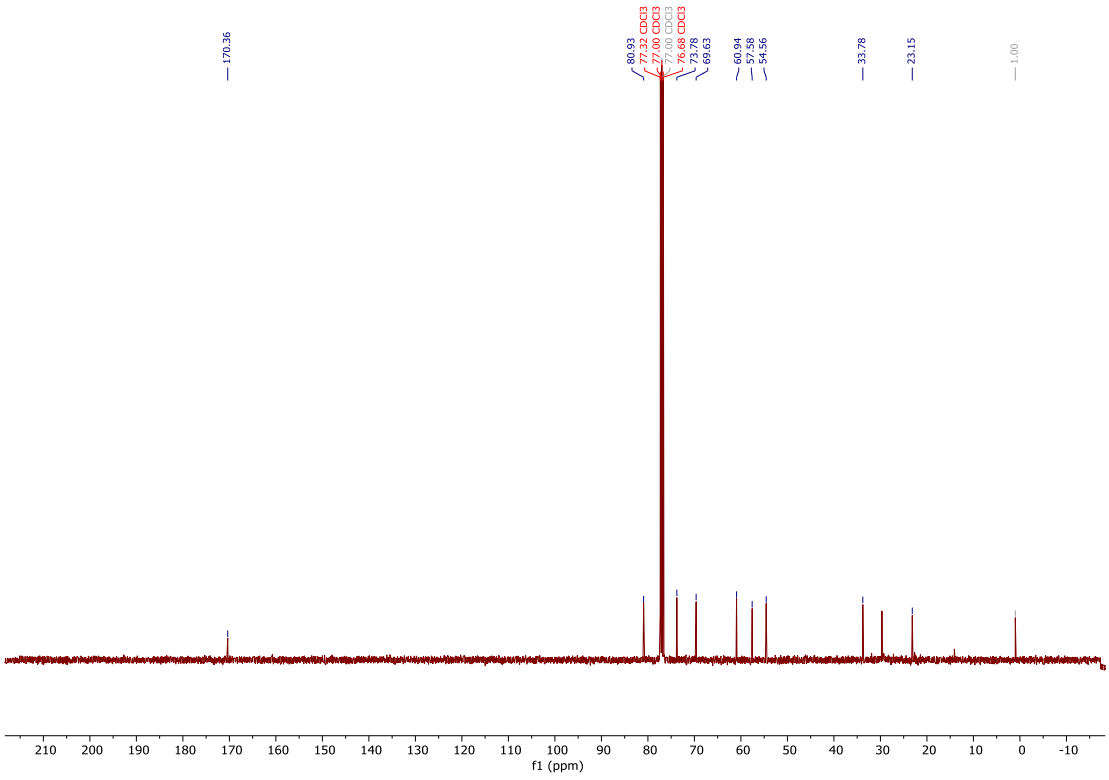
(1*R*,2*R*,7*S*,8*S*)-1-acetamide-2,7-epoxypyrrolizidine [(*N*)-acetyl norloline] (+)-4

(400 MHz, ^{1}H, $CDCl_3$)



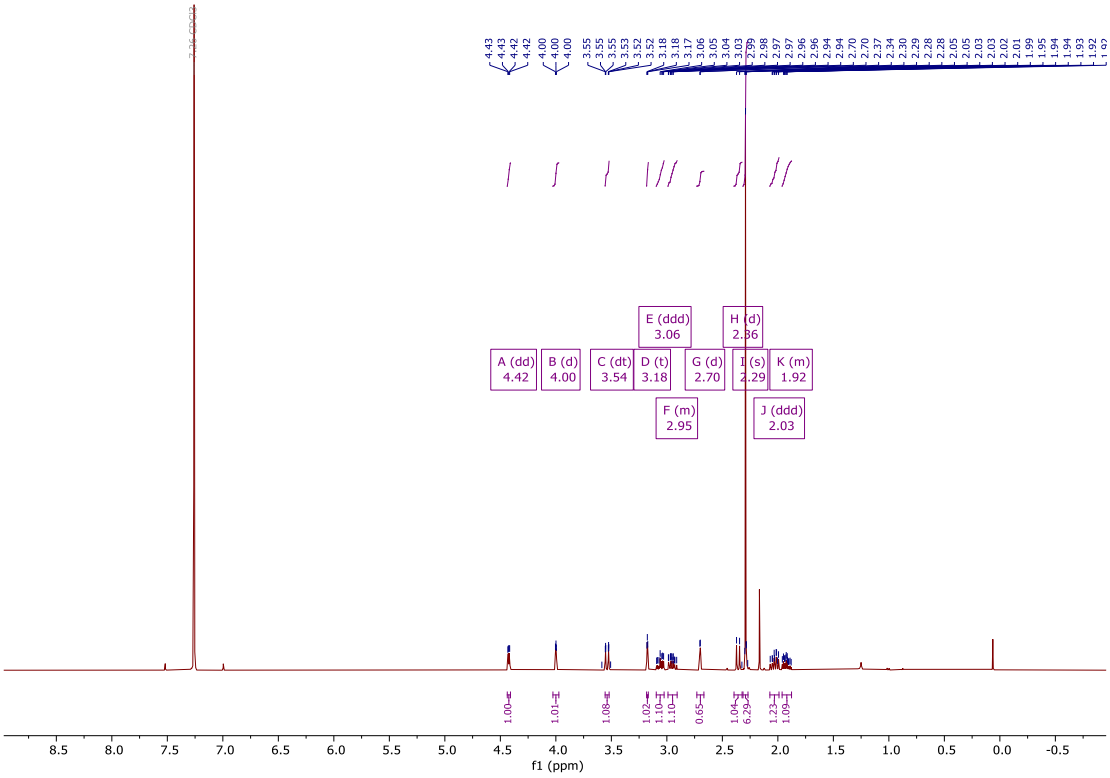
(1*R*,2*R*,7*S*,8*S*)-1-acetamide-2,7-epoxypyrrolizidine [(*N*)-acetyl norloline] (+)-4

(101 MHz, ^{13}C, $CDCl_3$)



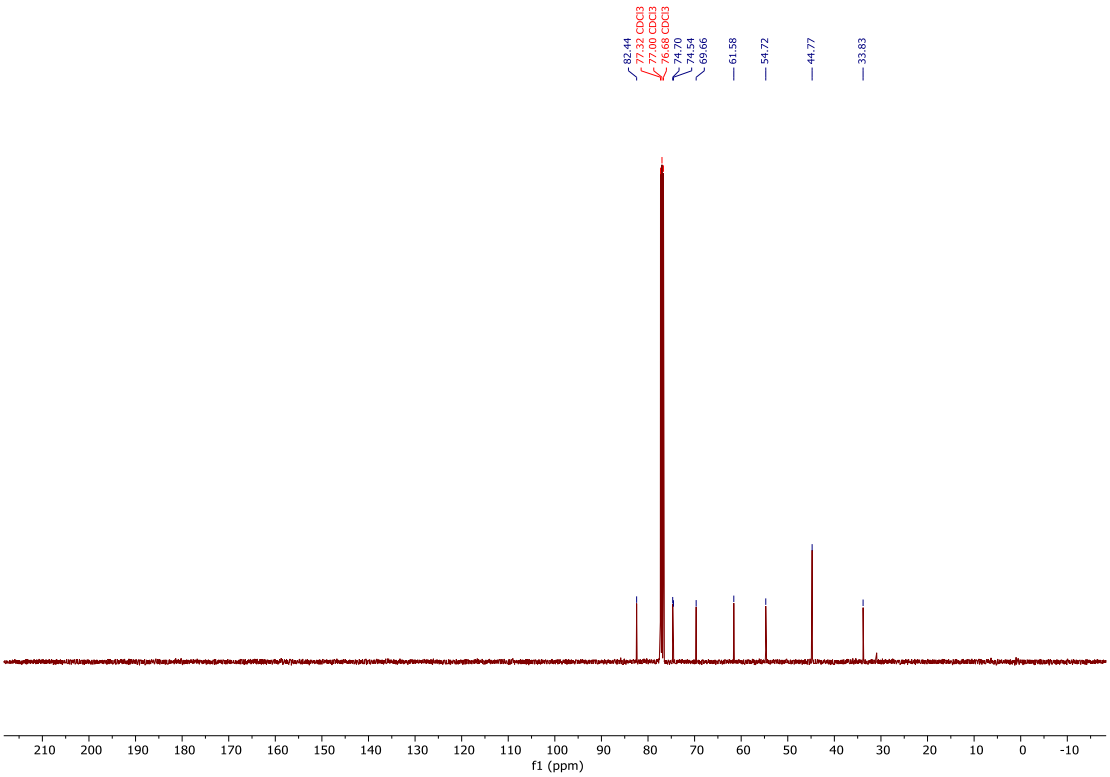
(1*R*,2*R*,7*S*,8*S*)-1-(*N*,*N*-dimethylamino)-2,7-epoxypyrrolizidine [(*N*)-methyl loline] 283

(400 MHz, ^{1}H, $CDCl_3$)



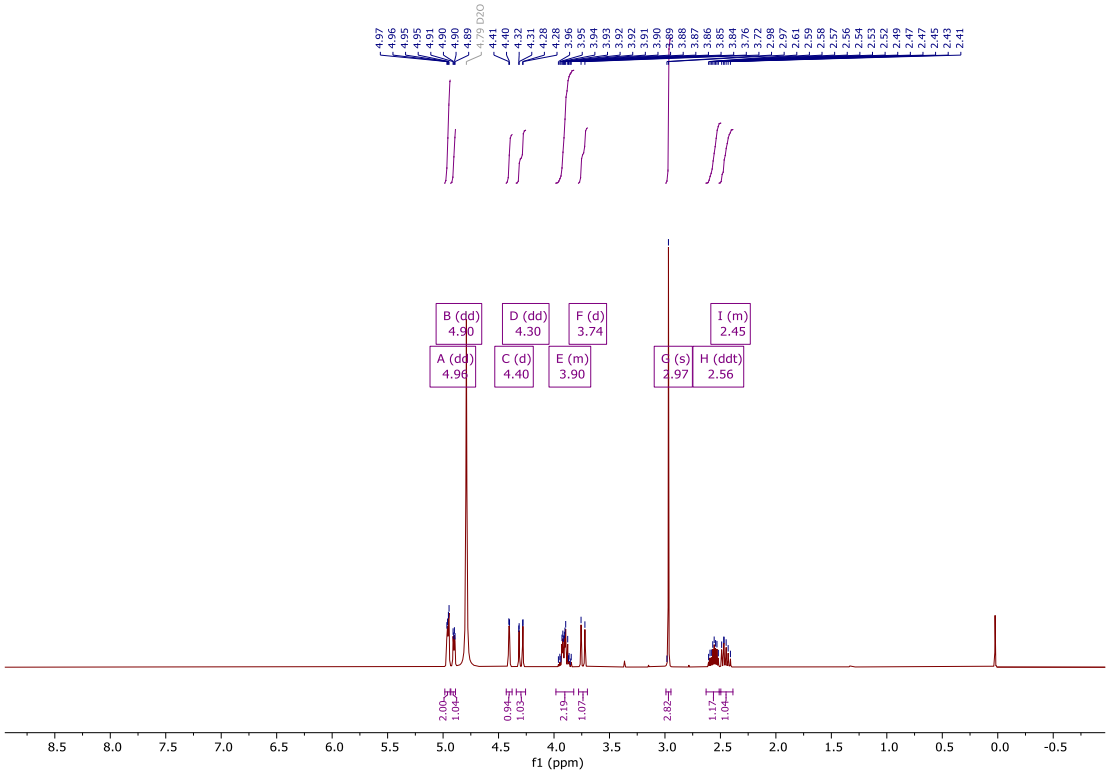
(1*R*,2*R*,7*S*,8*S*)-1-(*N*,*N*-dimethylamino)-2,7-epoxypyrrolizidine [(*N*)-methyl loline] 283

(101 MHz, ^{13}C, $CDCl_3$)



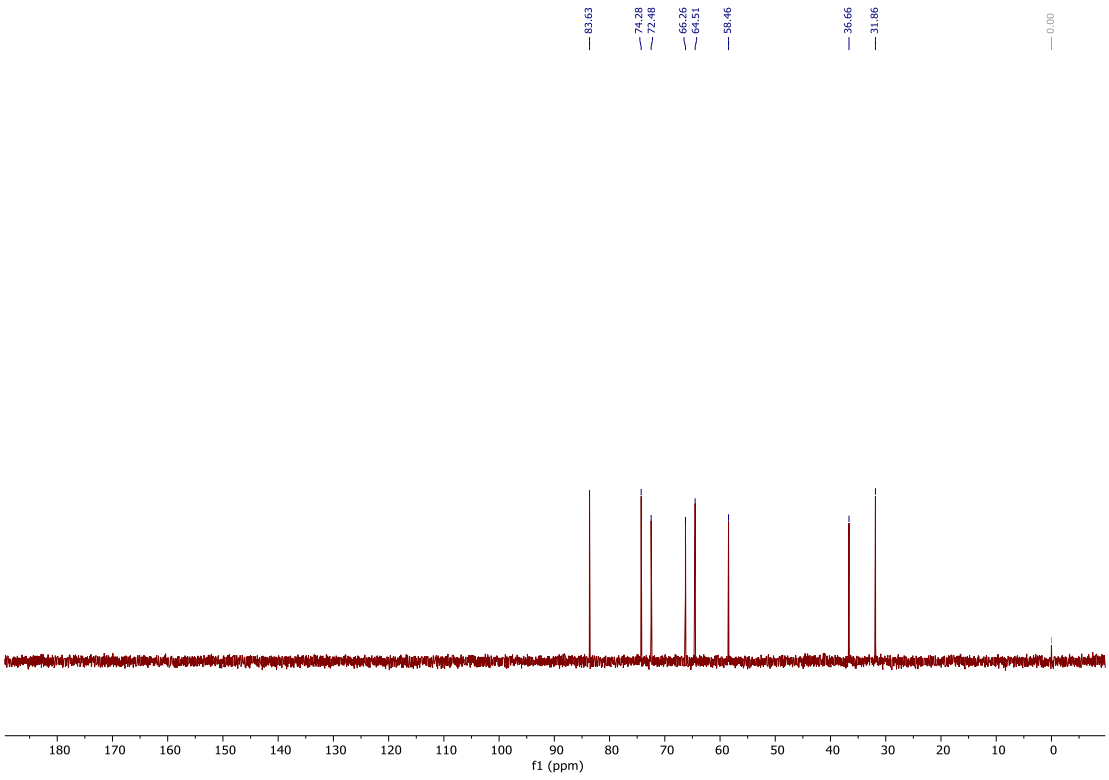
(1*R*,2*R*,7*S*,8*S*)-1-(*N*-methylamino)-2,7-epoxypyrrolizidine hydrochloride [(+)-loline·HCl]

(+)-1·HCl (400 MHz, ^{1}H, D_2O)



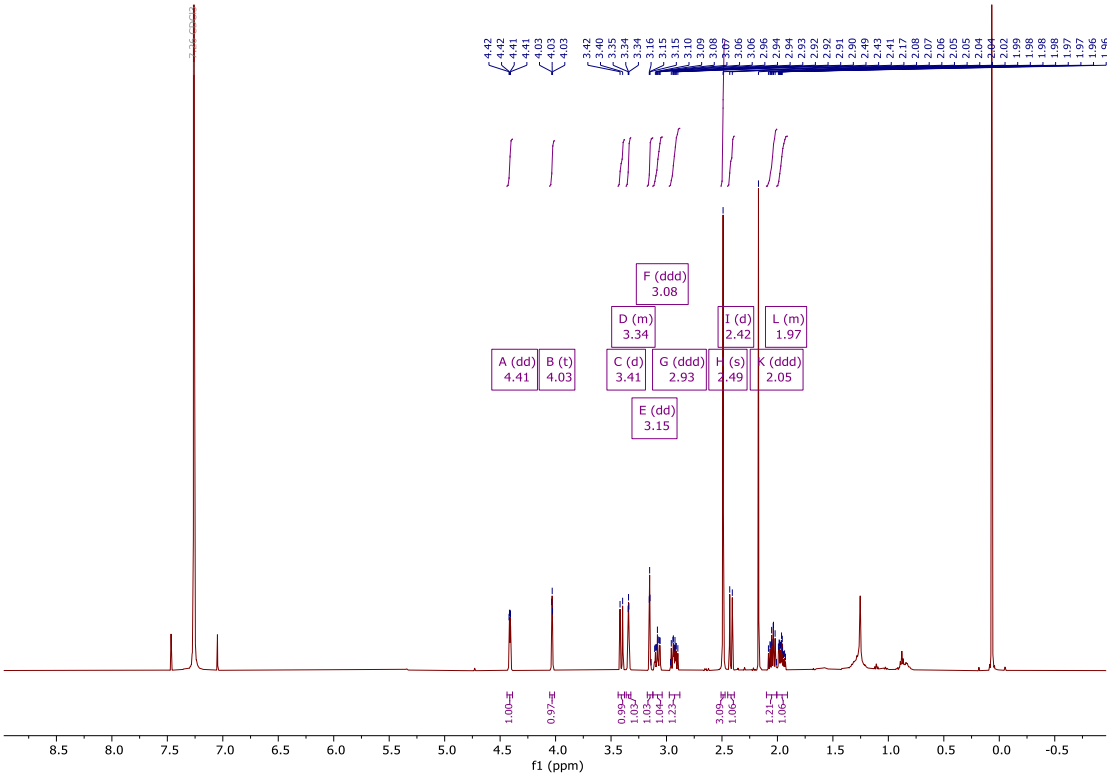
(1*R*,2*R*,7*S*,8*S*)-1-(*N*-methylamino)-2,7-epoxypyrrolizidine hydrochloride [(+)-loline·HCl]

(+)-1·HCl (101 MHz, ^{13}C, D_2O)



(1*R*,2*R*,7*S*,8*S*)-1-(*N*-methylamino)-2,7-epoxypyrrolizidine [loline]

1 (500 MHz, ^{1}H, $CDCl_3$)



(1*R*,2*R*,7*S*,8*S*)-1-(*N*-methylamino)-2,7-epoxypyrrolizidine [loline]

1 (126 MHz, ^{13}C, $CDCl_3$)

