The stereoselective Pictet-Spengler reaction and studies towards the total synthesis of ajmaline

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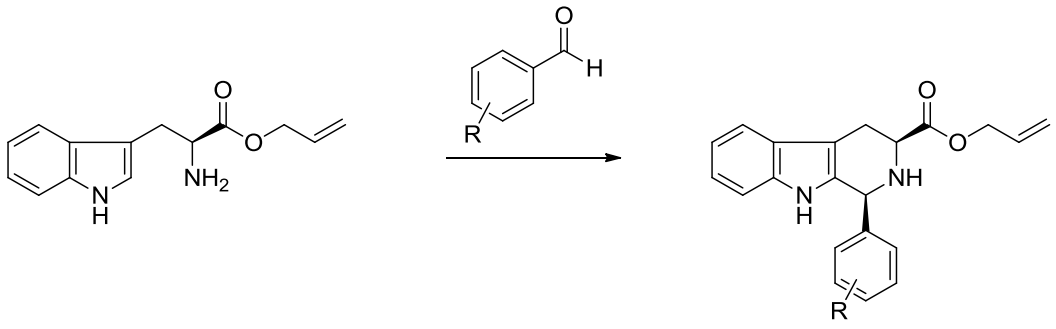
Abstract

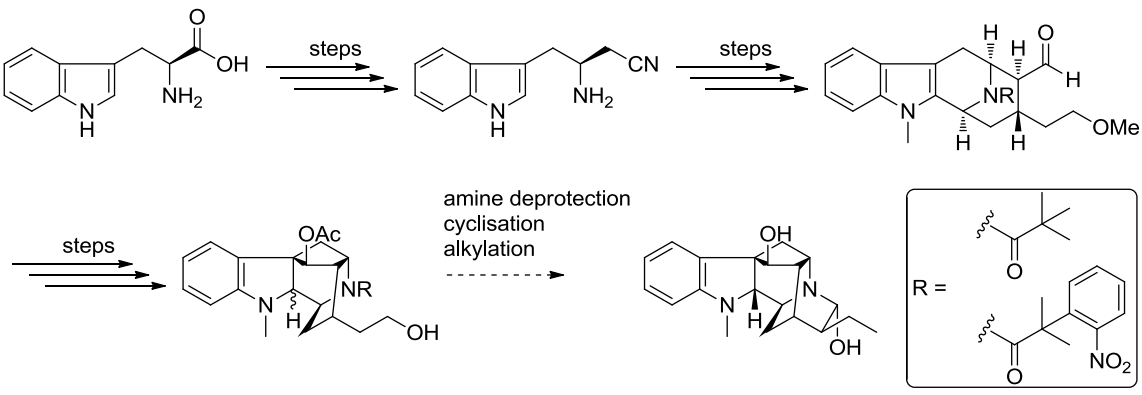
Due to their extensive and important medicinal properties, the indole alkaloids are an important class of natural products. A key step towards the total synthesis of indole alkaloids is the diastereoselective Pictet-Spengler reaction, which has enabled the total syntheses of a number of these natural products to be reported, one of which is the medicinally-important alkaloid ajmaline. Ajmaline is well-studied and the previous attempts towards its synthetic preparation are described.

During our investigations towards the asymmetric syntheses of ajmaline and other related indole alkaloids, it was found that the kinetically-controlled Pictet-Spengler cyclisations of L-tryptophan allyl ester gave *cis*-3,5-disubstituted tetrahydro-β-carbolines with enhanced stereoselectivities of up to 20:1. The Pictet-Spengler reaction of L-tryptophanamide was also studied and the *cis/trans* tetrahydro-β-carbolines were formed in a ratio of 3:1, typical of that for other kinetically-controlled Pictet-Spengler cyclisations reported previously.



Scheme 1 – Kinetically-controlled Pictet-Spengler reactions of L-tryptophan allyl ester

Studies towards our total synthesis of ajmaline are also described. The synthesis features the kinetically-controlled Pictet-Spengler reaction, a highly stereoselective intramolecular Michael cyclisation and a one-pot indole cyclisation/reduction procedure, which was used to introduce three stereocentres simultaneously. It was found that the nitrogen protecting group has a defining role to play in both the indole cyclisation step, and during reduction of the subsequent iminium ion through remote steric induction. Despite installing seven of the nine stereocentres with high levels of stereocontrol, an inability to remove the robust nitrogen amide protecting group prevented completion of a total synthesis. The final ring-closing protocol could be carried out using semi-synthetic material derived from ajmaline. Cyclisation was achieved by the selective oxidation of a primary alcohol to the aldehyde, which spontaneously ring closed under the conditions of the reaction to complete the ajmaline framework.



Scheme 2 – Key intermediates towards our synthesis of ajmaline

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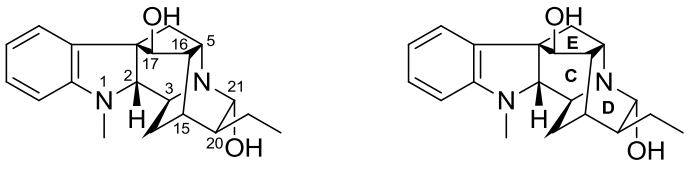
Abbreviations

Ac	acetyl
Ada	adamantoyl
aq.	aqueous
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	*n*-butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
COSY	correlated spectroscopy
d	doublet
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	dicyclohexylurea
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMNA	2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl
DMSO	dimethyl sulfoxide
d.r.	diastereoisomeric ratio
ECG	electrocardiography

eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
et al.	*et alia* (and others)
HRMS	high resolution mass spectrometry
IBX	*ortho*-iodoxybenzoic acid
IR	infrared
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
m	multiplet
Me	methyl
MeCN	acetonitrile
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl
p-TsOH	*para*-toluenesulfonic acid
PVPCC	poly(vinylpyridinium chlorochromate)
py.	pyridine
q	quartet
rt	room temperature
s	singlet
t	triplet
TBAF	tetra-*N*-butylammonium fluoride

TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMB	2,4,6-trimethylbenzoyl
Ts	*para*-toluenesulfonyl

Ajmaline framework numbering and ring lettering



Numbering of key atoms is shown[1] as well as non-indole derived ring lettering. N_a is defined as the aromatic nitrogen atom adjacent to the benzene ring, whilst N_b is defined as the basic nitrogen within the quinuclidine ring of ajmaline.

Chapter 1

The total synthesis of (+)-ajmaline and related indole alkaloids

1.1 Introduction and background

1.1.1 Isolation of (+)-ajmaline

Of the many and varied members of the *Rauwolfia* genus, *Rauwolfia serpentina* is one of the few to have long been recognised as containing a number of medicinally-important alkaloids. Indian literature refers to extracts of the plant as being used as antipyretics, as remedies for snake-bites and also as a cure for dysentery,[2] though its most important action in reducing blood pressure was identified by Mukherjee.[3] Subsequent studies of the extracts of *Rauwolfia serpentina* led to the isolation of a number of alkaloid bases including reserpine,[4] responsible for the hypertensive effects already noted, yohimbine[5] and ajmaline.[6]

1.1.2 Medicinal application of (+)-ajmaline

Soon after its isolation and identification, ajmaline was recognised as a potent antiarrhythmic agent[7] and its use as such was trialled with various cardiac conditions.[8,9] Most notable of these was Wolff-Parkinson-White syndrome, for which ajmaline was found to be effective in the treatment of atrial fibrillation.[10]

During 1991 and 1992, Josep and Pedro Brugada reported the sudden deaths of eight otherwise healthy patients in whom they found right bundle branch block, a defect in the heart's electrical conduction system, and persistent ST segment elevation in leads v_1-v_3.[11] This condition was named Brugada Syndrome after the physicians who first identified it. The use of class Ia sodium channel blockers

(Singh and Vaughan-Williams classification) such as ajmaline and procainamide was first described by Miyazaki in 1996 to unmask ECG patterns associated with Brugada Syndrome.[12] As a result, ajmaline, as well as procainamide and flecainide, went on to be used as diagnostic agents for Brugada Syndrome in patients where a familial history of sudden cardiac death was prevalent, and in cases where an episode of sudden cardiac arrest had proved not to be fatal.

According to the Monthly Index of Medical Specialities USA (MIMS), the mode of action of ajmaline is described as preventing depolarisation of the cell membrane by blocking the inward flow of sodium ions into cardiac cells. It is this interference with the rate of depolarisation of cardiac cells which causes the irregularities in the ECG scans of people suffering from undiagnosed tachycardia.

1.1.3 Structural elucidation of (+)-ajmaline

Elegant degradation and chemical transformation experiments carried out by Sir Robert Robinson led to the isolation and identification of a number of ajmaline derivatives, which eventually enabled Robinson to propose that ajmaline had the structure **1** (Figure 1.1).[2] Further degradation studies carried out by Woodward soon after led to the revised correct structure **2** for ajmaline,[13] which differed only in the connections of the carbon-carbon bond framework, C15 being joined to C16 and not C17 as proposed by Robinson. Robinson had noted during his original proposal his uncertainty with regard to the tertiary nature of the alcohol at C17.

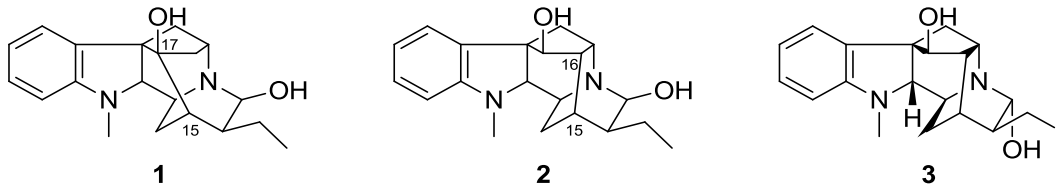


Figure 1.1 – Key structures towards elucidation of ajmaline framework and stereochemistry

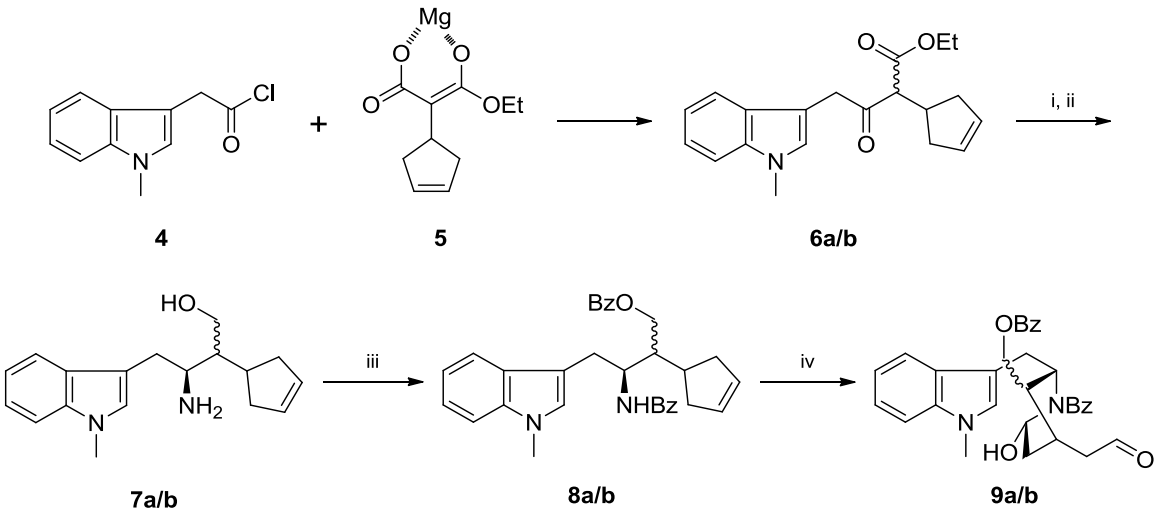
Any stereochemical assignments suggested at this stage were speculative. Progress in elucidating the stereochemistry of ajmaline was made by Bartlett through a range of stereospecific degradation studies and comparison of the resulting products with compounds of known structure.[14] In this way, Bartlett was able to assign successfully the stereochemistry of ajmaline, as shown by structure **3** (Figure 1.1), and this was confirmed by X-ray crystallography in 1978.[15]

1.2 Previous formal syntheses of (+)-ajmaline

1.2.1 Masamune's formal synthesis[16]

Given the continued interest in ajmaline's biological properties, and its potential use as a medicinally-important compound, it is unsurprising that many groups were interested in its synthetic preparation. A synthetic method of obtaining ajmaline became more important when the natural source, *Rauwolfia serpentina,* was placed on the Convention on International Trade in Endangered Species of Wild Fauna and Flora list in 1990.[17] Masamune's synthesis of ajmaline was the first to be published and laid down many of the foundations for subsequent synthetic attempts.

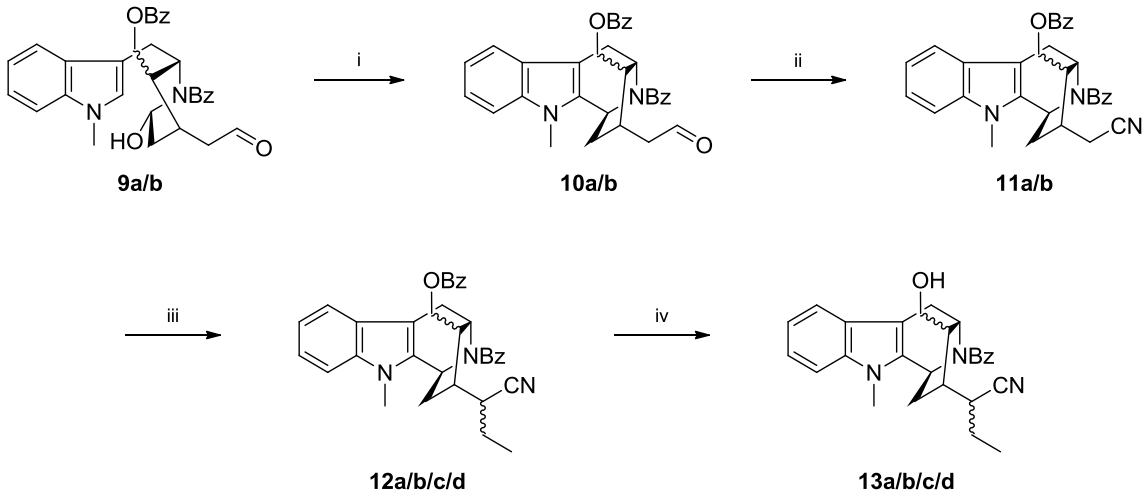
The synthesis began with the condensation of the magnesium chelate of ethyl hydrogen cyclopentenylmalonate with *N*-methyl-3-indolacetyl chloride **4** to give the corresponding indolyl ketoesters **6a/b** in a yield of 80%. Amination of the ketone carbonyl using methoxyamine was followed by lithium aluminium hydride-mediated reduction of the ethyl ester to give the primary alcohol as a 2:1 mixture of epimeric α,γ-amino alcohols in 70% yield (Scheme 1.1).



4 **5** **6a/b** **7a/b** **8a/b** **9a/b**

Scheme 1.1 – i) NH_2OMe; ii) $LiAlH_4$; iii) BzCl, py.; iv) OsO_4, $NaIO_4$

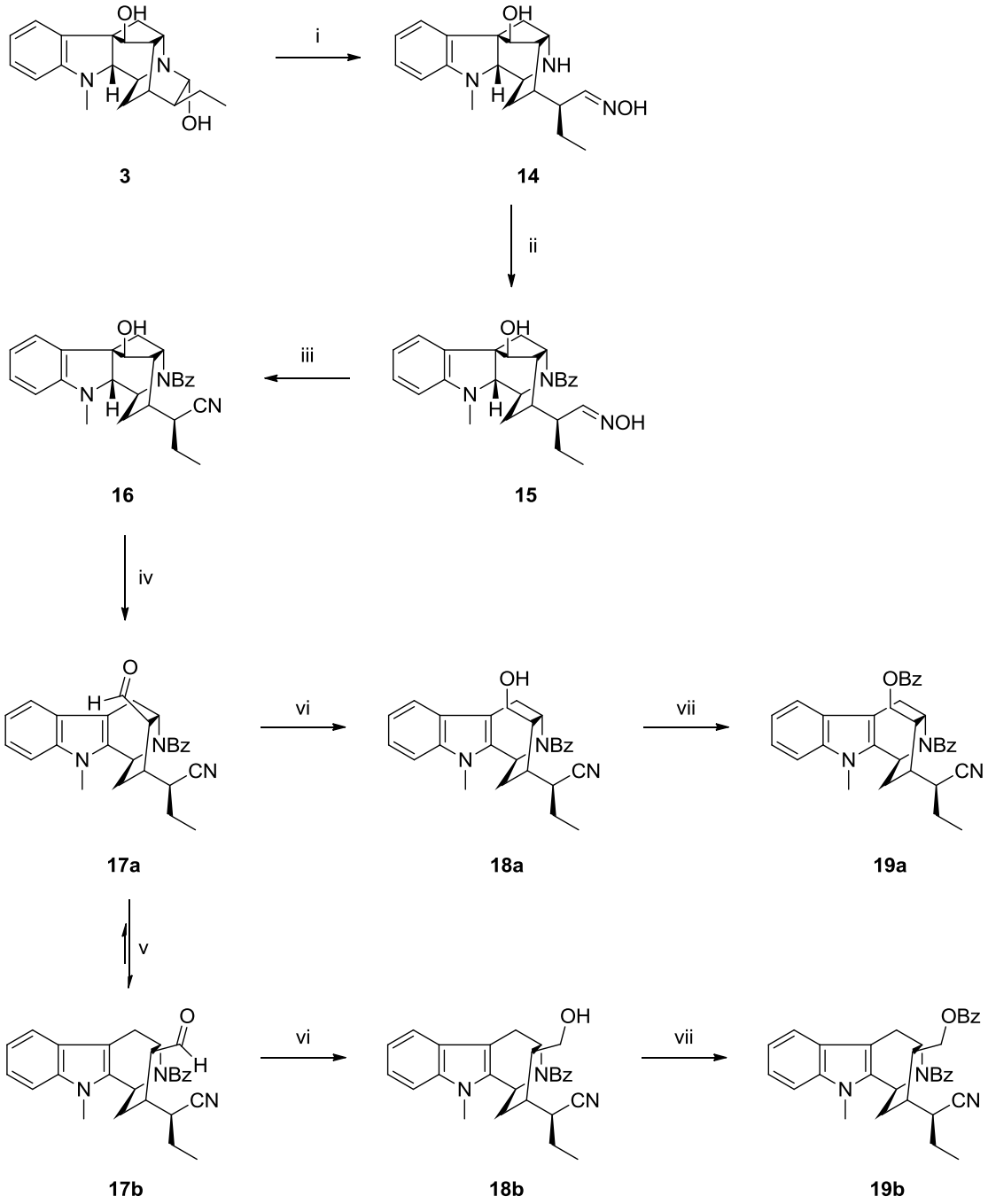
These two epimers were carried through the synthesis since they were interconvertible at a later point. Conversion to the dibenzoyl compound then took place, followed by oxidative cleavage of the cylcopentenyl ring using osmium tetroxide and sodium metaperiodate. Under the reaction conditions, one of the newly-formed aldehydes cyclised to give the benzoyl-protected piperidine ring system **9a/b** (Scheme 1.1).



Scheme 1.2 – i) AcOH, 50 °C; ii) NH_2OH, BzCl, py.; iii) $Na^+[(Ph)_3C]^-$, EtI; iv) NaOMe

In one of the key carbon-carbon bond forming steps of the synthesis, stirring the hydroxy aldehyde **9a/b** in acetic acid at 50 °C initiated alkylation from the indole 2-position giving the corresponding tetrahydro-β-carboline aldehydes **10a** and **10b** in 40% and 50% yield, respectively. Conversion of the aldehyde functionality to the corresponding nitrile then took place using hydroxylamine and benzoyl chloride in warm pyridine. Deprotonation at the α-position to the nitrile using triphenylmethyl sodium, in the presence of an excess of ethyl iodide, gave the monoethylated compound as a mixture of diastereoisomers, typically yielding in the range of 60-70%. Brief treatment of this compound with sodium methoxide removed the benzoyl ester to give the resulting primary alcohol as a mixture of diastereoisomers **13a-d** (Scheme 1.2).

At this point Masamune compares the spectroscopic data of **12a-d** and **13a-d** with those of products obtained from the degradation of naturally-sourced ajmaline, which were formed as follows (Scheme 1.3).

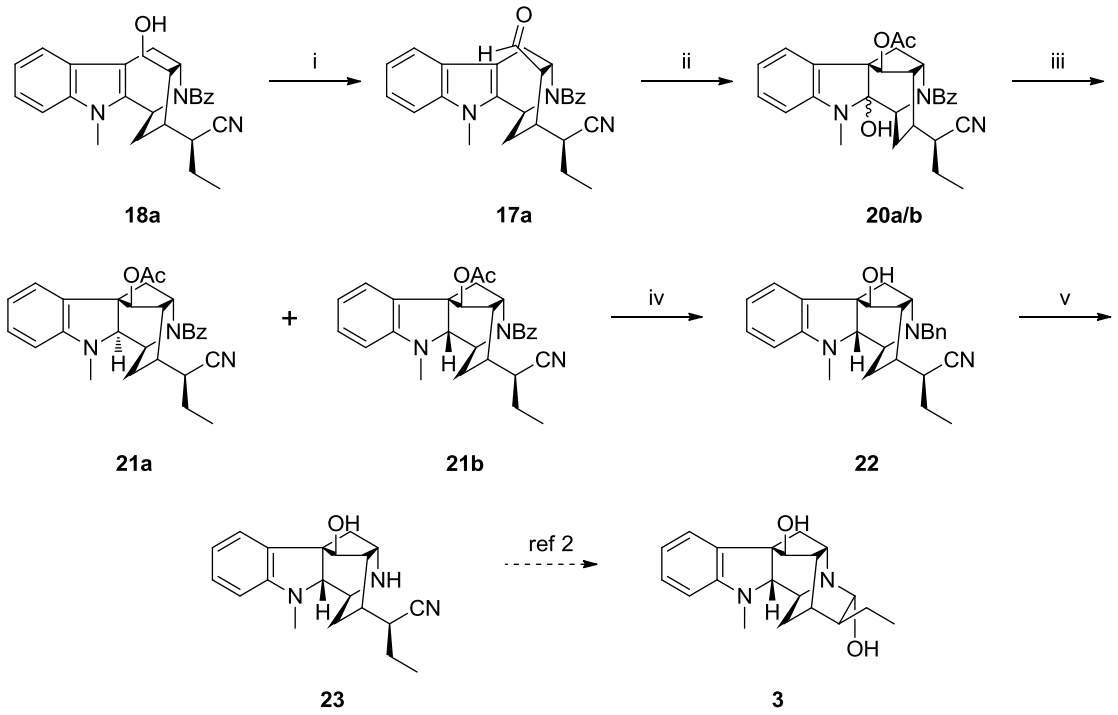


Scheme 1.3 – i) NH_2OH, H_2O, heat; ii) BzCl, py.; iii) NaOH; iv) $Pb(OAc)_4$; v) Alumina; vi) $NaBH_4$; vii) BzCl

Conversion of ajmaline **3** to ajmaline oxime **14** by Robinson's method[2] first took place, followed by selective benzoylation of the free amine using benzoyl chloride in warm pyridine. Treatment of oxime **15** with sodium hydroxide resulted in

dehydration of the oxime to the desired cyano compound **16**. Oxidative cleavage of the ajmaline framework (C7-C17 bond) using lead tetraacetate followed by neutral work-up provided the aldehyde **17a,** which Masamune showed could be epimerised in the presence of alumina providing access to both C16 epimers. The two aldehydes **17a** and **17b** could then be reduced to the primary alcohols **18a** and **18b** using sodium borohydride and the benzoate esters **19a** and **19b** prepared using benzoyl chloride (Scheme 1.3).

Masamune then states that the two C16 epimeric alcohols **18a** and **18b** and the corresponding *O*-benzoate esters **19a** and **19b** formed *via* this degradative pathway are spectroscopically identical to those compounds formed during the forward synthetic route (Scheme 1.2).

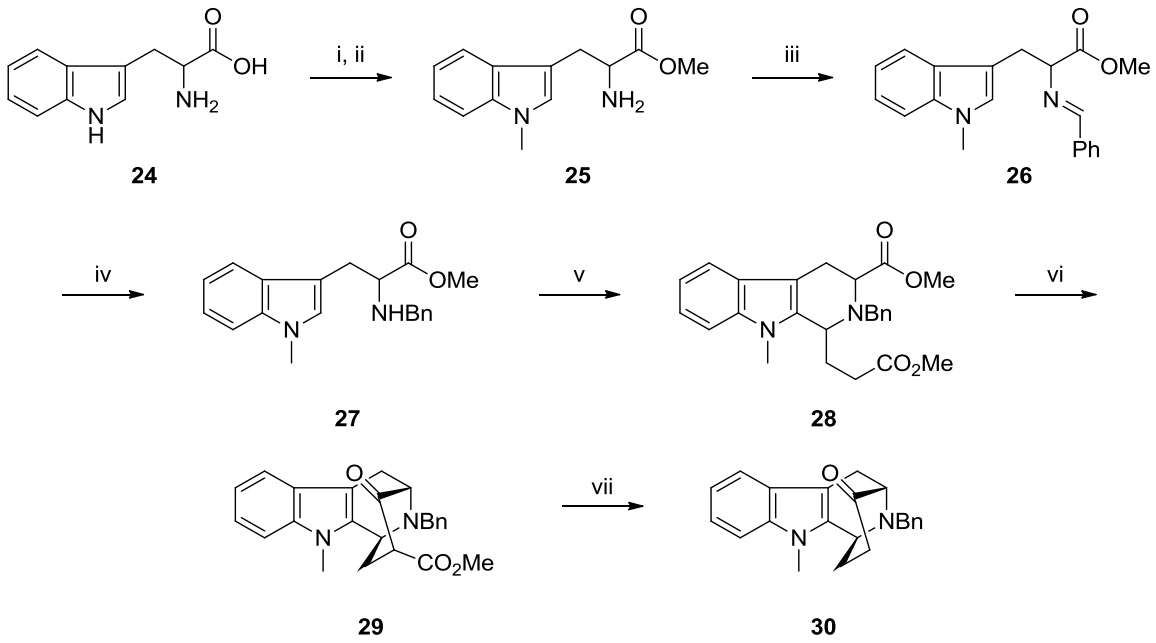


Scheme 1.4 – i) DMSO, Ac_2O; ii) AcOH, Ac_2O, HCl; iii) Pt, H_2, 6 M HCl; iv) $Li(OEt)_3AlH$; v) H_2

Treatment of alcohol **18a**, obtained from ajmaline **3**, with DMSO in the presence of acetic anhydride formed aldehyde **17a,** which when stirred in acetic acid, acetic anhydride and hydrochloric acid underwent cyclisation from the indole 3-position in 65% yield. Carbinolamine **20a/b** was then hydrogenated over a platinum catalyst in 6 M hydrochloric acid to provide the desired C2 epimer **21b** in a yield of 60% and the opposite epimer **21a** in 30% yield. The benzoyl group was removed firstly by reduction of the carbonyl functionality using lithiumtriethoxy aluminium hydride, followed by hydrogenolysis, which gave the corresponding secondary amine **23**. Finally, Masamune cites Robinson's cyclisation of nitrile amine **23** using lithium aluminium hydride to complete the first formal synthesis of ajmaline (Scheme 1.4).[2]

Whilst Masamune's synthesis was racemic and didn't feature any stereocontrol as such, it remains to this day, a remarkable synthetic achievement for its time. However, the decision to compare racemic intermediates **12a-d** and **13a-d** with the ajmaline degradation compounds **19a/b** and **18a/b** respectively appears tenuous given the level of detailed stereochemical assignment available at the time.

1.2.2 Sato's formal synthesis

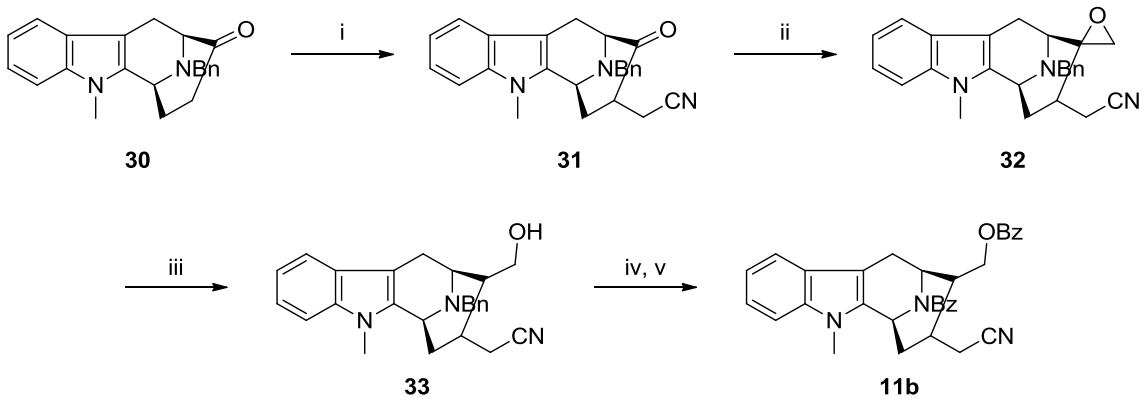


Scheme 1.5 – i) Na/NH_3, MeI; ii) MeOH, HCl; iii) PhCHO; iv) $NaBH_4$, MeOH; v) methyl 3-formylpropionate, MeOH, reflux; vi) NaH, PhMe, MeOH, reflux; vii) AcOH, HCl

The next major contribution to the synthesis of ajmaline came from Sato.[18,19] An alternative approach to Masamune's key intermediate **11b** was published beginning from the readily available tetracyclic ketone intermediate **30**, the preparation of which was also published from the same laboratory by Yoneda.[20]

The synthesis reported by Yoneda (Scheme 1.5) began with the indole methylation and methyl esterification of tryptophan **24** according to Yamada's method.[21] A reductive amination with benzaldehyde and sodium borohydride then followed to give the N_b-benzyl derivative **27**. Pictet-Spengler reaction of this compound with methyl 3-formylpropionate in refluxing aqueous methanol gave the

tetrahydro-β-carboline diester as a mixture of diastereoisomers which were separable by chromatography. This mixture of diastereoisomers was then treated with sodium hydride in refluxing toluene to initiate Dieckmann cyclisation, giving the tetracyclic product **29**. The presence of a small amount of methanol proved to be essential in providing the desired product in good yield. Stirring this compound in acetic acid and hydrochloric acid with heating resulted in hydrolysis and decarboxylation of the ester side chain to give racemic N_b-benzyl-protected tetracyclic ketone **30**.

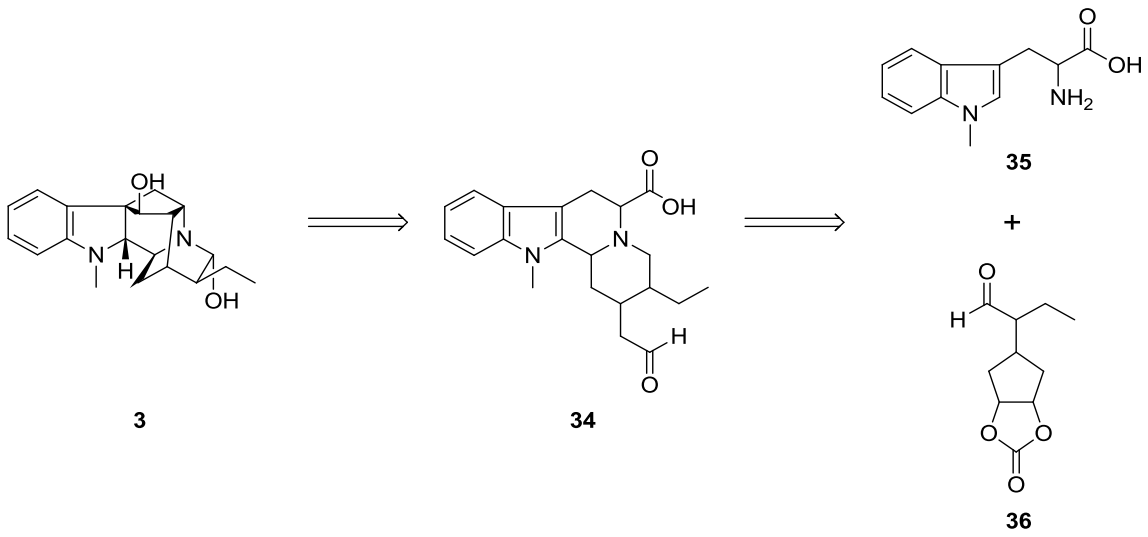


Scheme 1.6 – i) Pyrrolidine, PhH, dioxane, $ClCH_2CN$, reflux; ii) $(CH_3)_2SOCH_2$, NaH, DMSO; iii) $HAlCl_2$, $LiAlH_4$, Et_2O; iv) Pd/C, H_2, HCl, EtOH; v) BzCl, py.

Proceeding from Yoneda's tetracyclic ketone **30**, Sato alkylated at the α-position to the carbonyl *via* the pyrrolidine enamine using chloroacetonitrile. Treatment of the ketone **31** with an oxosulfonium ylid transformed the carbonyl to the epoxide **32** according to Corey's method.[22] This was then regioselectively ring opened using dichloro(hydrido)aluminium to give the corresponding primary alcohol **33** as the only product. Hydrogenolysis of the benzyl protecting group was then carried out, followed by benzoylation of both the alcohol and secondary amine, to give Masamune's late-stage intermediate **11b** (Scheme 1.6).

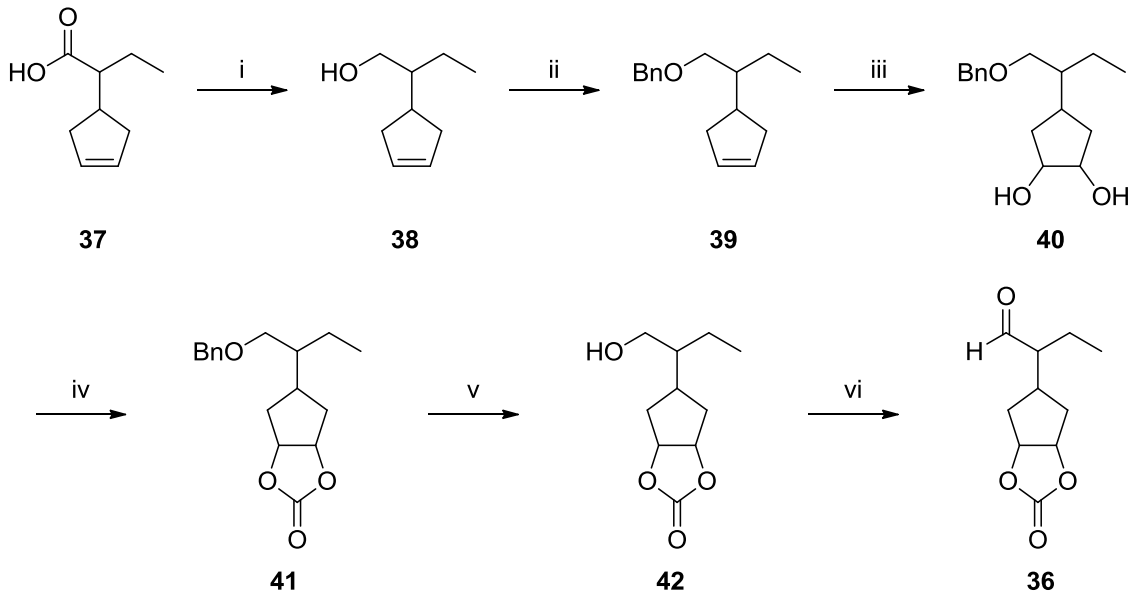
1.2.3 Van Tamelen's biogenetic-inspired synthesis[23,24]

In a slight departure from the previous syntheses of Masamune and Sato, Van Tamelen modelled the synthesis of ajmaline on the proposed biogenetic pathway.



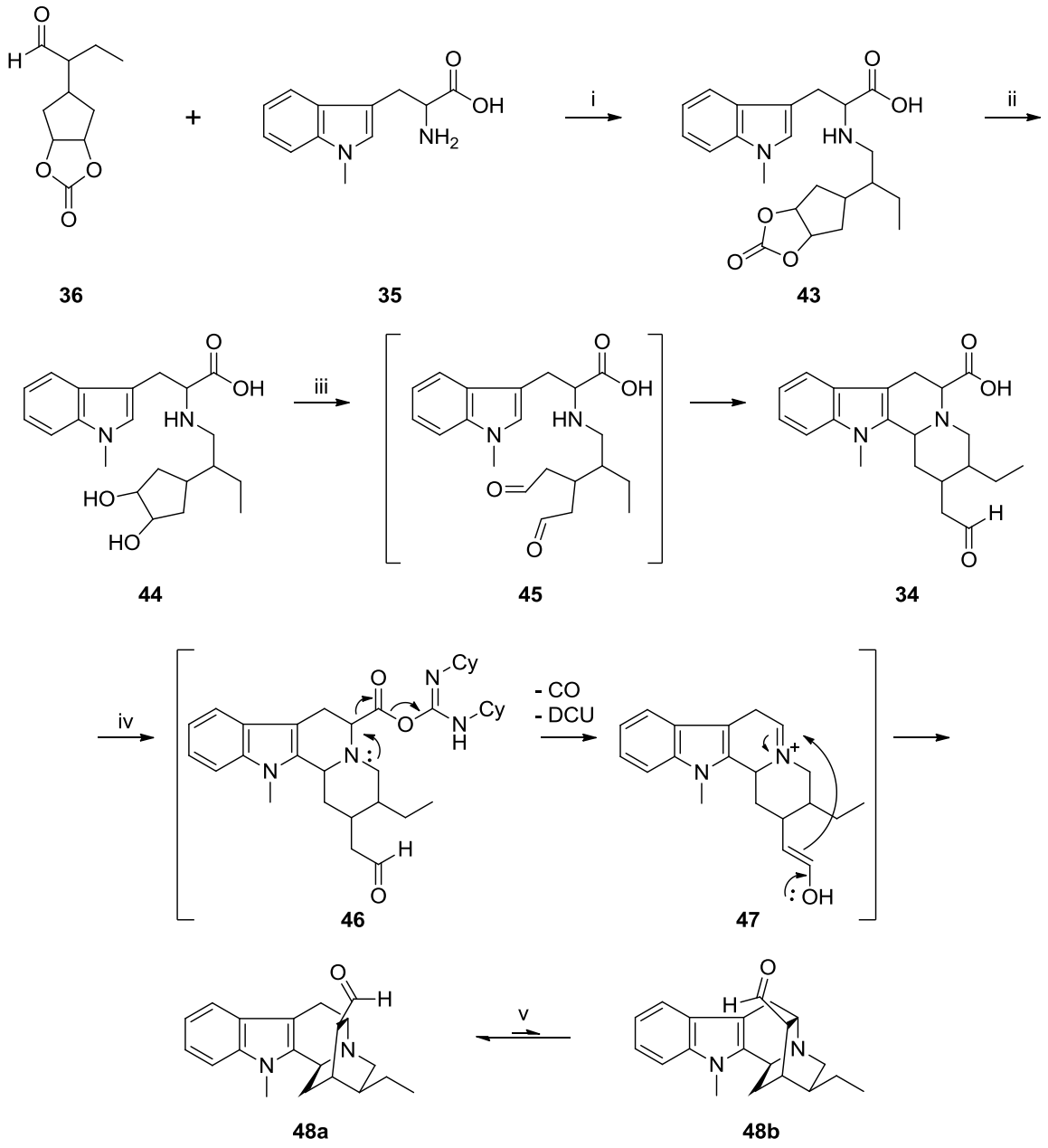
Scheme 1.7 – Ajmaline retrosynthesis *via* a biogenetic-inspired route

Van Tamelen envisioned a reductive alkylation of *N*-methyl tryptophan **35** with an appropriate nine-carbon alkyl fragment **36** as an early key step (Scheme 1.7). The nine-carbon alkylation fragment was prepared as shown in scheme 1.8.



Scheme 1.8 – i) $LiAlH_4$, THF, reflux; ii) BnCl, KOH, 100 °C; iii) OsO_4, THF, py., H_2S; iv) $CO(OCH_3)_2$, NaOMe, reflux; v) Pd/C, H_2, EtOH; vi) CrO_3.py., DCM

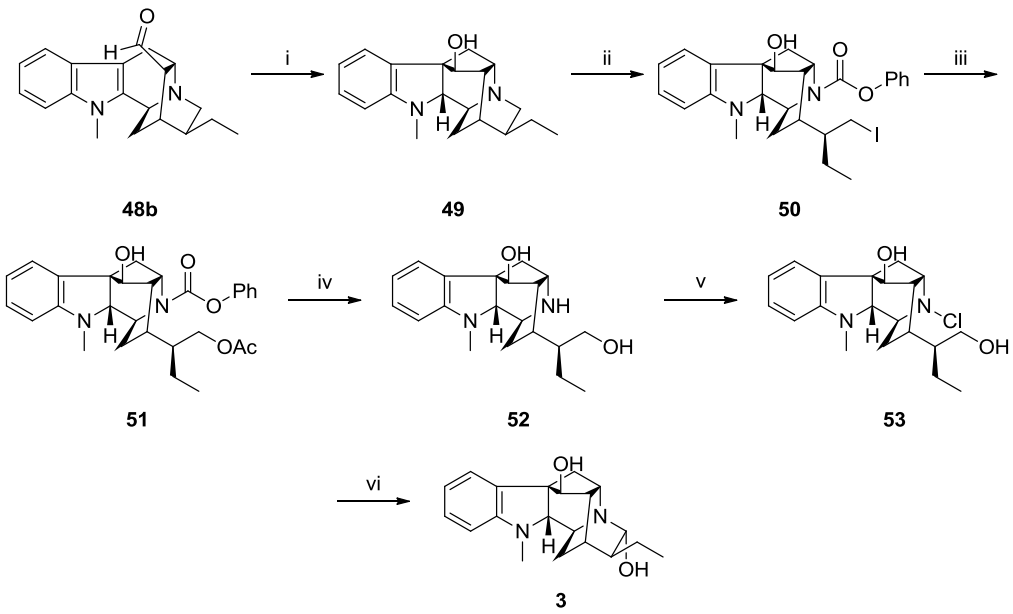
The synthesis of aldehyde **36** began with the cyclopentenyl acid **37**, which in turn was prepared by a known sequence developed previously by Van Tamelen.[25] Lithium aluminium hydride reduction of the acid was followed by protection of the resulting alcohol as the benzyl ether. Dihydroxylation of the alkene was then carried out using osmium tetroxide to give the racemic diol **40**. The diol was protected as the cyclic carbonate, which was followed by catalytic hydrogenolysis of the benzyl ether and chromium-mediated oxidation of the resulting alcohol to the required aldehyde **36** (Scheme 1.8).



Scheme 1.9 – i) Pd/C, H_2, EtOH; ii) KOH, reflux; iii) NaOAc, HIO_4, H_2O; iv) DCC, *p*-TsOH.H_2O, dioxane, 80 °C; v) AcOH, NaOAc or alumina, PhH, reflux

With aldehyde **36** prepared, reductive alkylation with N_a-methyl tryptophan then took place, followed by hydrolysis of the carbonate functionality to give the diol **44**. The subsequent one-pot 1,2-glycol cleavage and Pictet-Spengler cyclisation is reminiscent of the sequence employed by Masamune during his synthesis of

ajmaline,[16] but was in fact first employed by Van Tamelen during the synthesis of the related alkaloid yohimbine.[26] Activation of the acid using DCC, in the presence of *para*-toluenesulfonic acid, resulted in decarbonylation to give the iminium ion intermediate **47**. Intramolecular cyclisation then took place *via* the enol tautomer of the remote aldehyde onto the iminium ion. Given the non-stereoselective nature of the synthesis up to this point, only a small proportion of the product aldehyde with the necessary ajmaline framework was isolated. To compound the issue of low yield, no material was isolated with the required relative stereochemistry at C16 for the subsequent cyclisation onto the indole 3-position. Equilibration of the wrong aldehyde **48a** to the necessary aldehyde **48b**, could take place using acetic acid and sodium acetate at room temperature, or with alumina in refluxing benzene, to give approximately 15% of the required C16 aldehyde – deoxyajmalal A (Scheme 1.9).

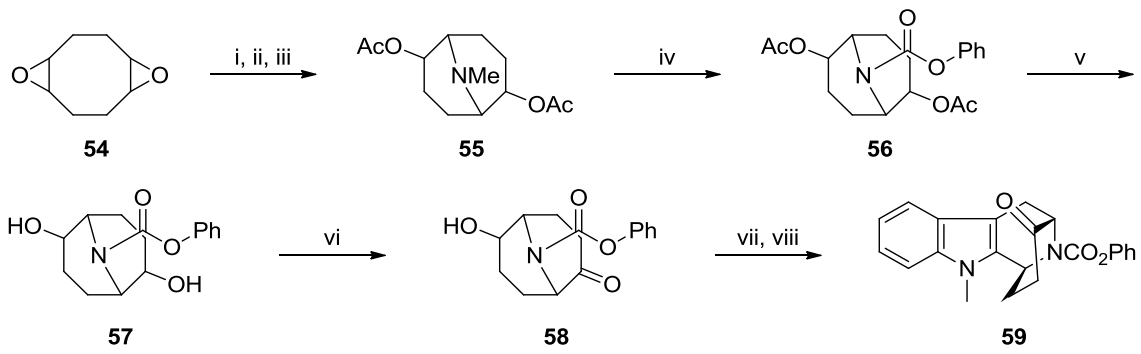


Scheme 1.10 – i) $HClO_4$, Zn; ii) PhOCOCl, LiI, acetone; iii) NaOAc, DMF, heat; iv) KOH, digol, 150 °C; v) *N*-chlorosuccinimide, DCM; vi) KO^tBu

Reductive cyclisation of deoxyajmalal A **48b** was carried out using perchloric acid and zinc dust, as demonstrated by Bartlett, to give deoxyajmaline **49**.[27] The C21 hydroxyl group was then introduced using a ring-opening oxidative ring-closing procedure as developed by Hobson and McCloskey.[28] Opening of the tertiary amine took place using phenyl chloroformate to give the carbamate and the alkyl chloride which, in the presence of lithium iodide, was replaced to give the iodo compound **50**. Displacement of iodine with acetate anion was then carried out with sodium acetate in hot DMF followed by base-catalysed hydrolysis of both the acetate ester and the carbamate. Halogenation of the secondary amine was carried out using *N*-chlorosuccinimide in DCM and treatment of the resulting chloroamine with potassium *tert*-butoxide led to cyclisation, yielding racemic ajmaline (Scheme 1.10).

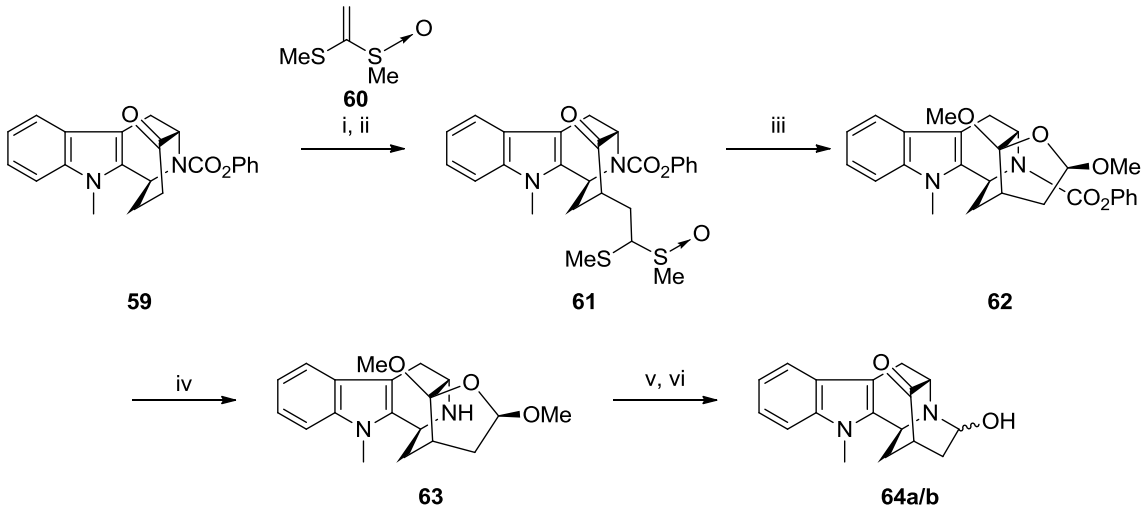
1.2.4 A Fischer indole synthesis approach to (+)-ajmaline[29]

The next contribution towards the total synthesis of ajmaline came from Kluge *et al*., published in 1981. Up to this point, all previous attempts had featured indolic starting materials and had utilised a Pictet-Spengler reaction as one of the key ring-forming reactions. Retrosynthetic analysis of ajmaline led Kluge to a tetracyclic ketone, similar to many of the previous syntheses, as an advanced intermediate. In contrast though, the ketone's synthesis was planned *via* an *in situ* indole ring formation.



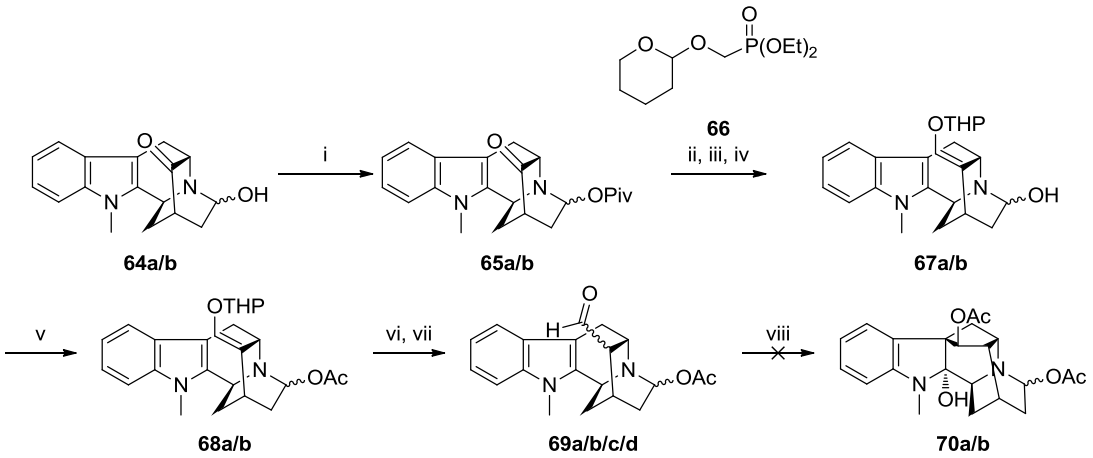
Scheme 1.11 – i) CH_3NH_2, MeOH, H_2O, 85 °C; ii) Ac_2O, py.; iii) 300 °C; iv) PhOCOCl, LiI, acetone; v) K_2CO_3, MeOH, H_2O; vi) PVPCC, DCM; vii) $PhN(CH_3)NH_3^+Cl^-$, DMF, 95 °C; viii) $(COCl)_2$, DMSO, NEt_3, −78 °C

Beginning with the diepoxide **54**, diacetate **55** was formed efficiently using a previously reported three step sequence.[30] The *N*-methyl group was then converted to the carbophenoxy carbamate and the two acetate groups removed using aqueous potassium carbonate. Formation of the monoketone using poly(vinylpyridinium chlorochromate) (PVPCC) proved to be the best way to differentiate the two alcohols.[31] Fischer indole synthesis gave the tetracyclic alcohol, which was then oxidised using Swern[32] conditions to give the amine-protected tetracyclic ketone **59** (Scheme 1.11).



Scheme 1.12 – i) LiHMDS, THF; ii) **60**; iii) 3% methanolic HCl; iv) LiOH, H_2O, dioxane; v) HCl, H_2O, THF, reflux; vi) 3 M NaOH

The lithium enolate of ketone **59** was generated using LiHMDS and alkylation took place using a ketene thioacetal monoxide to give tetracycle **61**, treatment of which with methanolic hydrochloric acid gave the acetal **62**. Hydrolysis of the carbamate first and then the acetal with lithium hydroxide and hydrochloric acid respectively preceded base-catalysed quinuclidinol formation (Scheme 1.12).



Scheme 1.13 – i) $(Piv)_2O$, DMAP, NEt_3, THF; ii) **66**, LiHMDS, THF, −78 °C; iii) H_2O; iv) KO^tBu, THF; v) Ac_2O, DMAP, NEt_3, THF; vi) HCl, H_2O, THF; vii) pH 9 buffer; viii) AcOH, Ac_2O, HCl

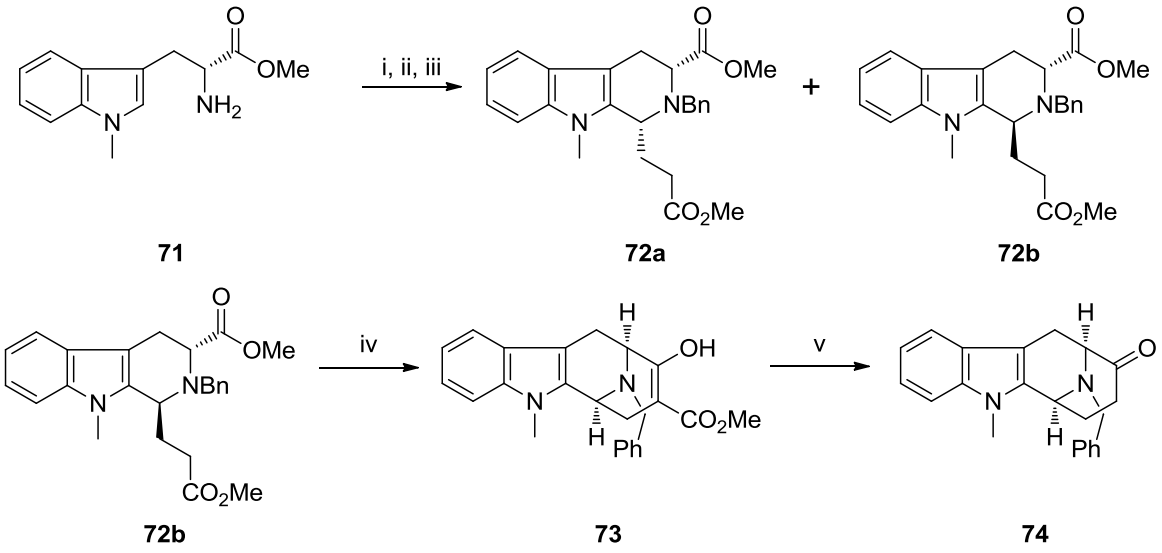
Acylation of alcohols **64a/b** with pivalic anhydride gave the pivaloate esters **65a** and **65b**. Condensation of these pivaloate esters with the lithiated phosphonate **66**, followed by treatment with potassium *tert*-butoxide gave the THP enol ethers, which unfortunately also proceeded with concurrent cleavage of the pivaloate groups. Reacylation with acetic anhydride was followed by acidic hydrolysis of the enol ether to give a mixture of C16 aldehyde epimers **69a/b**. Despite the similarity of this compound with that of Masamune's synthesis, treatment of this mixture with acetic acid, acetic anhydride and hydrochloric acid failed to produce any of the desired indole C3-cyclised product, ending synthetic efforts towards ajmaline (Scheme 1.13).

1.3 Cook's total asymmetric synthesis[33,34]

It took until 1999 for the first total asymmetric synthesis of ajmaline to be published. That it took over forty years from structural assignment to total synthesis could perhaps be attributed to the significant challenge which a total synthesis of ajmaline represents. The long lead-time could also be credited to the time required for the development of reliable asymmetric synthetic methodology. In either case, Cook's development of a *trans*-selective Pictet-Spengler reaction gave his group stereoselective access to a late-stage intermediate which could be further elaborated into a number of mono and bisindolic alkaloid natural products, including ajmaline.

1.3.1 Synthesis of tetracyclic ketone 74

The key late-stage intermediate was the tetracyclic ketone **74,** first prepared in racemic form by Yoneda.[20] An enantioselective route to this ketone was the initial target towards Cook's total synthesis of ajmaline.[35]



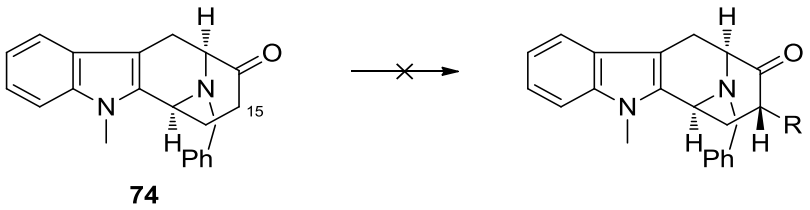
Scheme 1.14 – i) PhCHO, MeOH; ii) $NaBH_4$; iii) methyl 4,4-dimethoxybutyrate, TFA, $CHCl_3$, reflux; iv) NaH, MeOH, PhMe, reflux; v) AcOH, HCl, reflux

The synthesis of ketone **74** began with *N*-methyl D-tryptophan methyl ester **71**. Reductive alkylation of the amino group using a slight excess of benzaldehyde, followed by sodium borohydride reduction of the imine, provided the N_b-benzyl-protected tryptophan ester. Pictet-Spengler reaction with methyl 4,4-dimethoxybutyrate with an excess of trifluoroacetic acid in refluxing chloroform gave the *trans*- and *cis*-3,5-diesters **72b** and **72a** in a ratio of 10:1 respectively. The *trans*-diester was then subject to strongly basic conditions in order to first cause epimerisation at the 5-position and then initiate Dieckmann cyclisation to

give enol **73**. Treatment of this tetracyclic enol with acetic acid and hydrochloric acid caused hydrolysis and decarboxylation of the ester group to give the desired tetracyclic ketone **74** (Scheme 1.14).

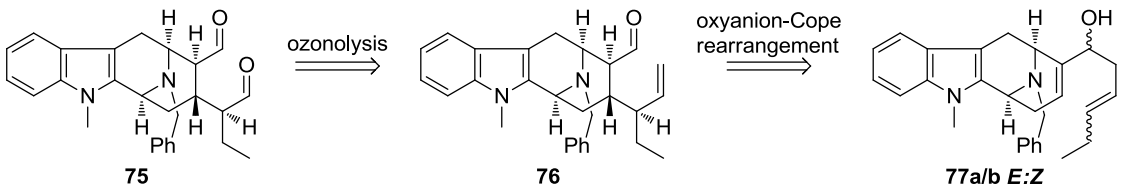
1.3.2 Alkylation of C15

Initially, Cook intended to elaborate ketone **74** further towards ajmaline *via* intermolecular alkylation at C15, α to the ketone carbonyl. However, despite numerous attempts,[29,36-40] Cook was unable to alkylate ketone **74** directly at C15.



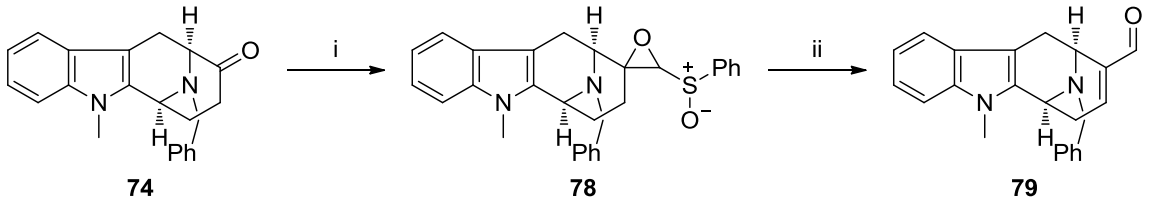
Scheme 1.15 – Failed attempts at C15 alkylation

Retrosynthetic analysis of ajmaline by Cook led to the dialdehyde **75**, which he envisioned could be prepared *via* an oxyanion-Cope rearrangement of the allylic alcohol **77** (Scheme 1.16).



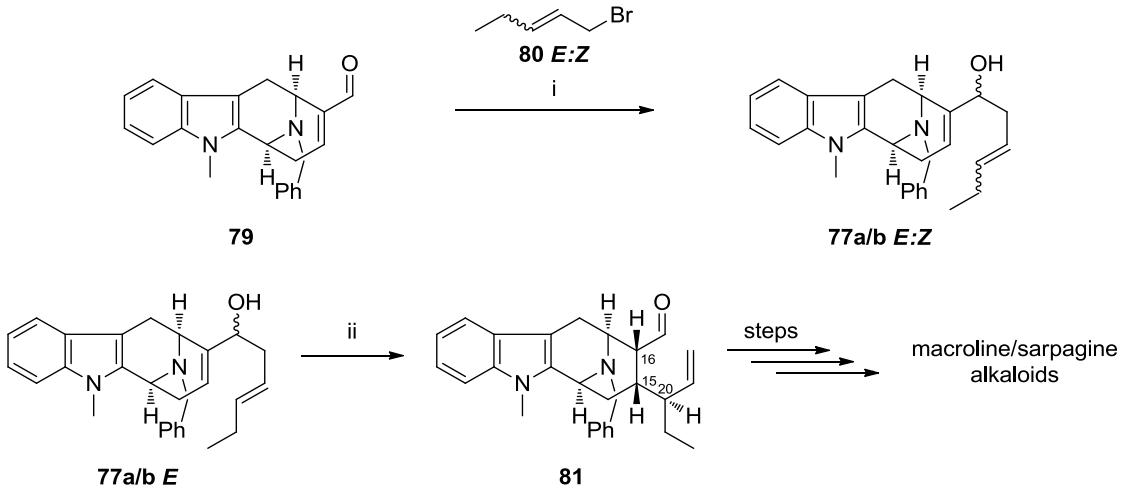
Scheme 1.16 – C15 elaboration strategy

In order to generate the desired allylic alcohol, a one-carbon homologation of the ketone group was required. Using the chemistry of Reutrakul,[41,42] the anion of chloromethyl phenyl sulfoxide was added to the ketone, forming a phenylsulfinyl epoxide intermediate **78**. Pyrolysis of this epoxide in the presence of lithium perchlorate generated the α,β-unsaturated aldehyde **79** (Scheme 1.17).



Scheme 1.17 – i) LDA, $ClCH_2SOPh$, KOH, TFA; ii) $LiClO_4$, *n*-Bu_3PO, PhMe, reflux

To add the necessary five-carbon unit, Cook planned to use barium chemistry developed by Yamamoto to add regioselectively the appropriate carbanion to the carbonyl group.[43]



Scheme 1.18 – i) **80**, Li, biphenyl, BaI_2, THF, −78 °C; ii) KH, 18-crown-6, dioxane, reflux, MeOH, rt

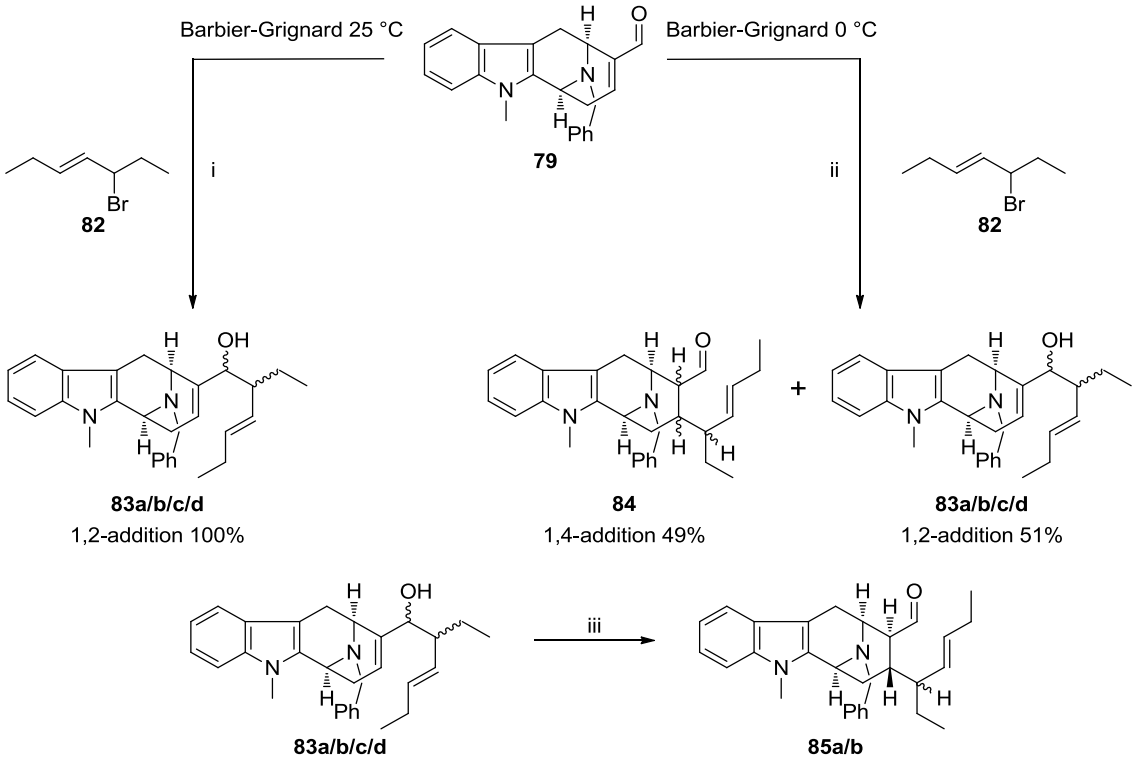
Addition of *cis/trans*-1-bromo-2-pentene to the unsaturated aldehyde **79** took place to obtain the 1,2-addition product in high yield (85-90%). Oxyanion-Cope rearrangement of the *E*-allylic alcohol using potassium hydride at 100 °C then generated the desired aldehyde as a mixture of diastereoisomers at C16 in favour of the (*R*)-epimer. This epimeric mixture of C16 aldehydes could be converted exclusively to the C16 (*R*)-isomer by the addition of DBU or sodium methoxide. Cook then went on to streamline this two-step rearrangement epimerisation to a one-pot process by adding methanol at room temperature following the oxyanion-Cope rearrangement (Scheme 1.18).

This two-step sequence was significant in that it generated the desired chirality at C15 and C20 for ajmaline with high selectivity. Whilst formation of the C16 (*R*)-stereocentre also went with high selectivity, it gave the opposite stereochemistry necessary to proceed towards the synthesis of ajmaline. However, the chirality formed at C16 is that required for the macroline/sarpagine family of compounds and Cook exploited this process to provide stereoselective syntheses of a number of these alkaloids.[40,44,45]

1.3.3 Alkylation of C15 – a modified Barbier-Grignard approach

Having provided a highly selective route towards the macroline and sarpagine families of alkaloids (Scheme 1.18), Cook then strived to modify alkylation of the unsaturated aldehyde **79** in order to obtain the necessary (*S*) configuration at C16.

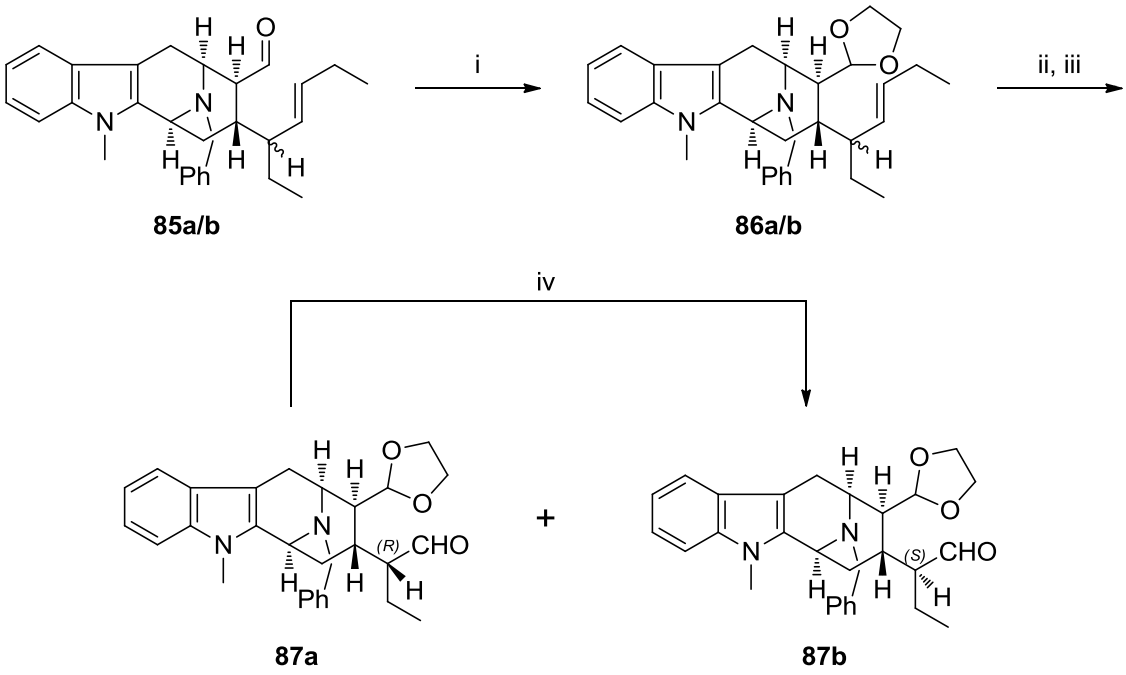
Addition of the bromoheptenyl fragment **82** under standard Barbier-Grignard conditions (0 °C) gave a mixture of the 1,2-addition products (51%) and the 1,4-addition products (49%). A modified Barbier-Grignard addition at 25 °C however gave the 1,2-addition products exclusively. Exposure of the 1,2-addition products to the oxy-Cope rearrangement conditions then led to the formation of the aldehydes **85a** and **85b** with the desired C16 (*S*)-stereocentre required for ajmaline with 64% selectivity. Under these conditions, Cook was able to obtain the desired ajmaline stereochemistry at C16 but not at C20, in contrast to the Yamamoto conditions used previously, where the necessary chirality could be generated at C20 but not at C16.



Scheme 1.19 – i) **82**, Mg, THF, 25 °C; ii) **82**, Mg, THF, 0 °C; iii) KH, dioxane, cumene, 150 °C

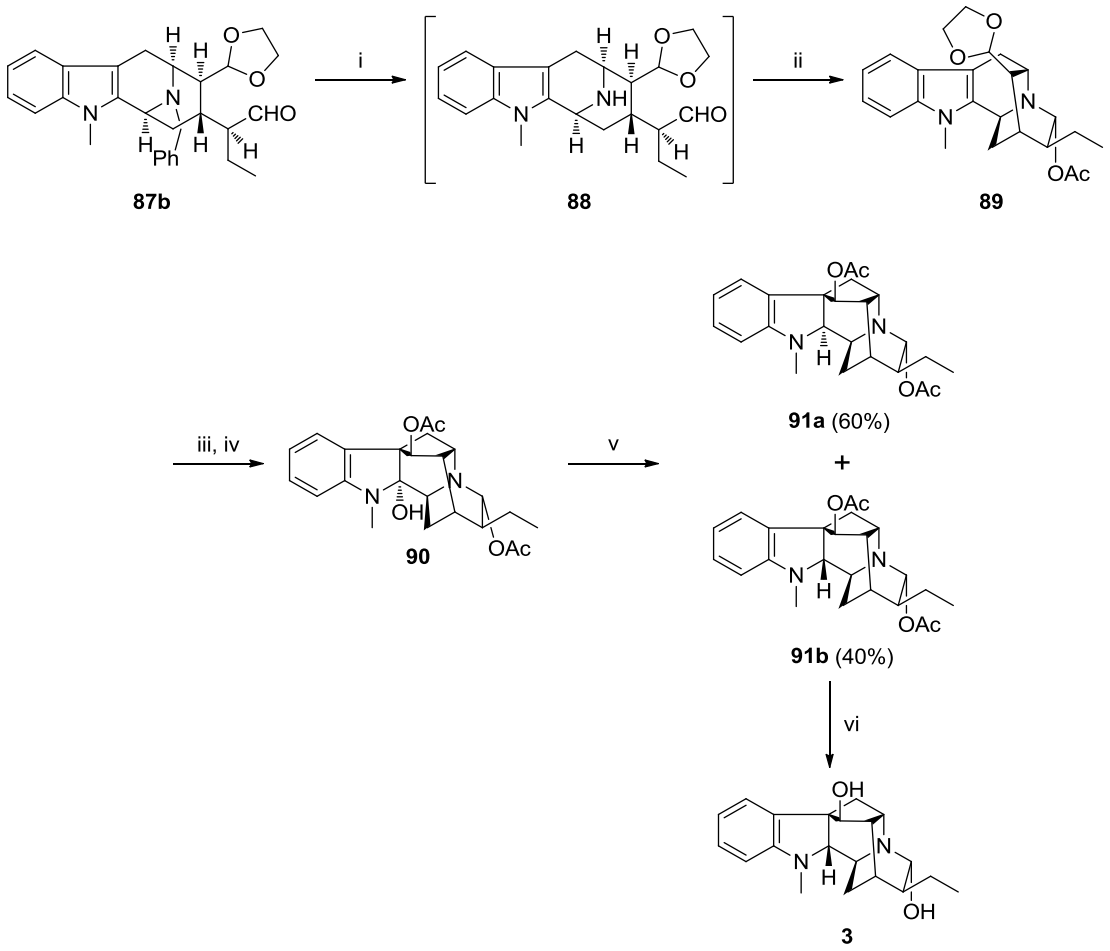
Cook's modified Barbier-Grignard conditions represented a significant breakthrough in the control of the stereochemistry at C16. Many groups had previously reported that the aldehyde group was prone to epimerisation to give the thermodynamically more stable C16 (*R*) configuration.[16,24] By the results found with the addition of the pentenyl group under Yamamoto conditions, and later by computational methods, Cook reasoned that the presence of the extra ethyl group in allylic alcohol **83** was critical in preventing epimerisation of the (*S*)-C16 centre to the (*R*)-stereocentre. The extra steric hindrance provided by the ethyl group also encouraged protonation of the desired face of the enol form of the aldehyde under the oxy-Cope rearrangement conditions.

1.3.4 D- and E-ring closures – ajmaline end-game



Scheme 1.20 – i) ethylene glycol, *p*-TsOH, PhMe, reflux; ii) OsO_4, THF, py., $NaHSO_3$; iii) $NaIO_4$, MeOH; iv) NaOMe, MeOH

Having generated the necessary chiral centres at C3, C5, C15 and C16, Cook proceeded with the C20 epimers **85a** and **85b**. Protection of the C16 aldehyde as the ethylene cyclic acetal first took place, followed by oxidative cleavage of the alkene using osmium tetroxide and sodium periodate, to give the two new aldehydes **87a** and **87b**. At this point, separation of the two aldehydes and treatment of the (*R*)-aldehyde with sodium methoxide generated an equilibrium mixture of the (*R/S*)-aldehydes. Repetition of this sequence allowed isolation of the (*S*)-aldehyde in greater than 80% yield (Scheme 1.20).

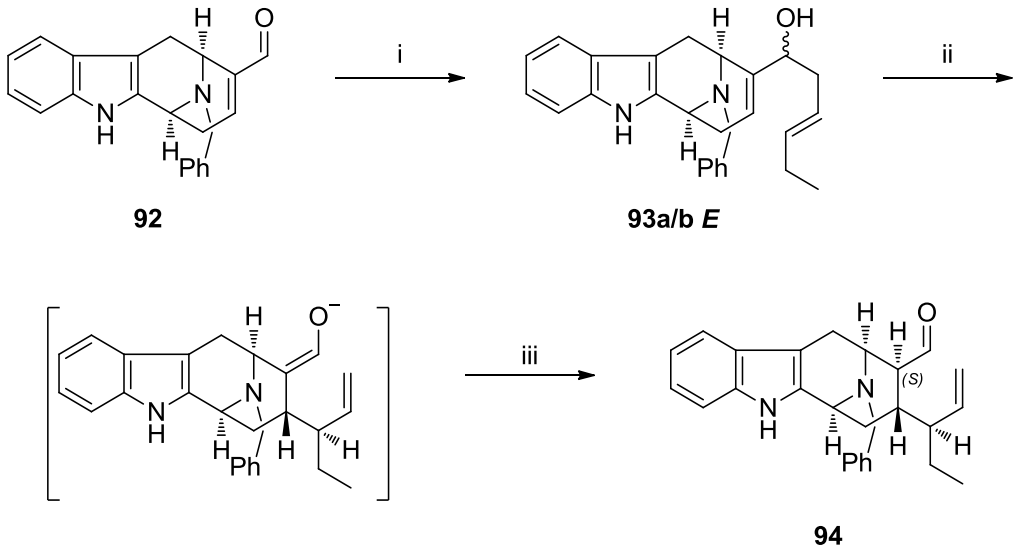


Scheme 1.21 – i) Pd/C, H_2, DME; ii) Ac_2O, DMAP; iii) AcOH, HCl; iv) Ac_2O, $HCl_{(g)}$, $NaHCO_3$; v) $BF_3.OEt_2$, PtO_2, H_2; vi) aq. K_2CO_3, MeOH

Catalytic hydrogenolysis of the benzyl protecting group provided the free amine **88,** which was followed by the addition of acetic anhydride to give the new D-ring closed, acetate-protected compound **89** in an efficient one-pot process. In a further example of multiple transformations, acetal hydrolysis took place using acetic acid and concentrated hydrochloric acid, followed by the addition of acetic anhydride and HCl gas to cause cyclisation from the indole 3-position onto the newly revealed aldehyde, giving the C2-hydroxyajmaline diacetate **90**. After numerous conditions were attempted, it was found that in the presence of boron trifluoride etherate, to generate the intermediate iminium ion, reduction took place to give C2-*epi*diacetylajmaline **91a** and diacetylajmaline **91b** in a ratio of 3:2 respectively. Finally, hydrolysis of the acetate protecting groups took place with aqueous potassium carbonate to give synthetic ajmaline which was identical to that of naturally-sourced ajmaline.

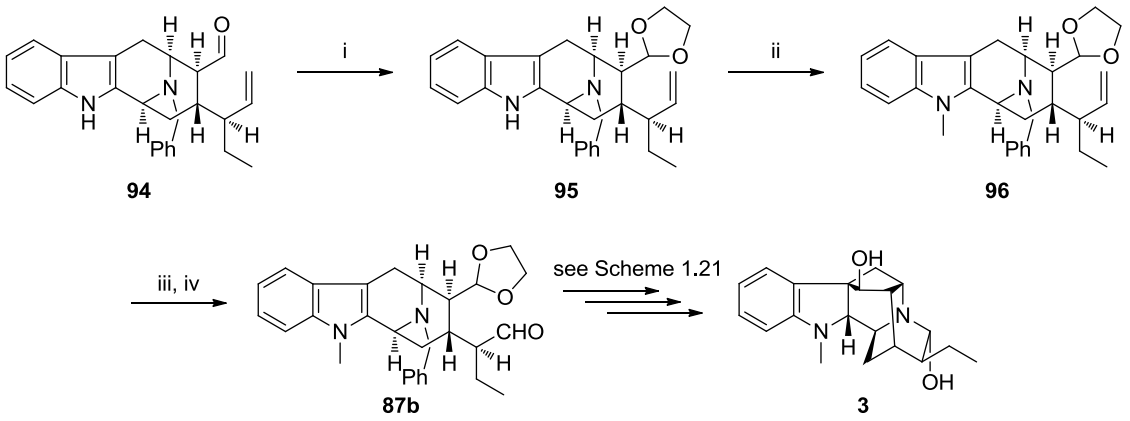
1.3.5 Alkylation of C15 – modified Yamamoto conditions[46]

Despite the fact that Cook was able to generate the stereocentres at C15 and C16 with good selectivity, he sought to improve the control during the formation of the chiral centre at C20. Soon after, Cook reported a modified procedure for the alkylation of the unsaturated aldehyde **92**.



Scheme 1.22 – i) Li, biphenyl, BaI_2, THF, −78 °C, **80*E***; ii) KH, 18-crown-6, dioxane, 100 °C; iii) 1 M TFA in THF, −100 °C

Reverting back to Yamamoto barium chemistry in order to obtain C20 selectively, *trans*-1-bromo-2-pentene was premixed with unsaturated aldehyde **92** and added to a solution of barium metal at −78 °C, giving the allylic alcohol in 90% yield. Based on previous observations and modelling work, Cook reasoned that in order to generate the necessary stereochemistry at C16, the enolate formed during the oxyanion-Cope rearrangement must be protonated from the least-hindered face to give the kinetically-favoured product aldehyde. As such, the allylic alcohols **93a/b *E*** were subject to rearrangement conditions used previously but then quenched with a 1 M TFA/THF solution at −100 °C to give the C16 (*S*)-epimer **94** with a selectivity of 43:1. In this way, Cook was able to generate the chiral centres at C15, C16 and C20 in two steps with exceptional stereocontrol (Scheme 1.22). It is worth noting that this selectivity was only reported for the non-indole-methylated compounds. With this in mind, steps to ajmaline were modified as follows.



Scheme 1.23 – i) ethylene glycol, *p*-TsOH, PhH, reflux; ii) MeI, NaH, THF; iii) OsO_4, py., THF, $NaHSO_3$; iv) $NaIO_4$, MeOH, H_2O

The aldehyde at C16 was acetal-protected as before and, having neutralised the labile proton at C16, the indole nitrogen could then be methylated using methyl iodide and sodium hydride. Oxidative cleavage of the alkene and the subsequent final steps towards ajmaline also took place as previously shown (Scheme 1.23).

These modifications meant that the stereocentres at C15, C16 and C20 could be generated with a high level of control. The necessity for the indole nitrogen to be non-methylated meant that cheaper D-tryptophan methyl ester could be used during the early Pictet-Spengler step instead of N_a-methyl D-tryptophan methyl ester. Finally, since the stereochemistry at C20 was formed selectively, the previously laborious and inefficient base equilibration of that centre in compound **87** was rendered unnecessary. Despite the significant synthetic achievement, Cook had to use D-tryptophan as the initial source of chirality, the stereochemistry of which was reversed during the early Dieckmann cyclisation. A more direct approach should be readily achievable. The major failing of this total synthesis

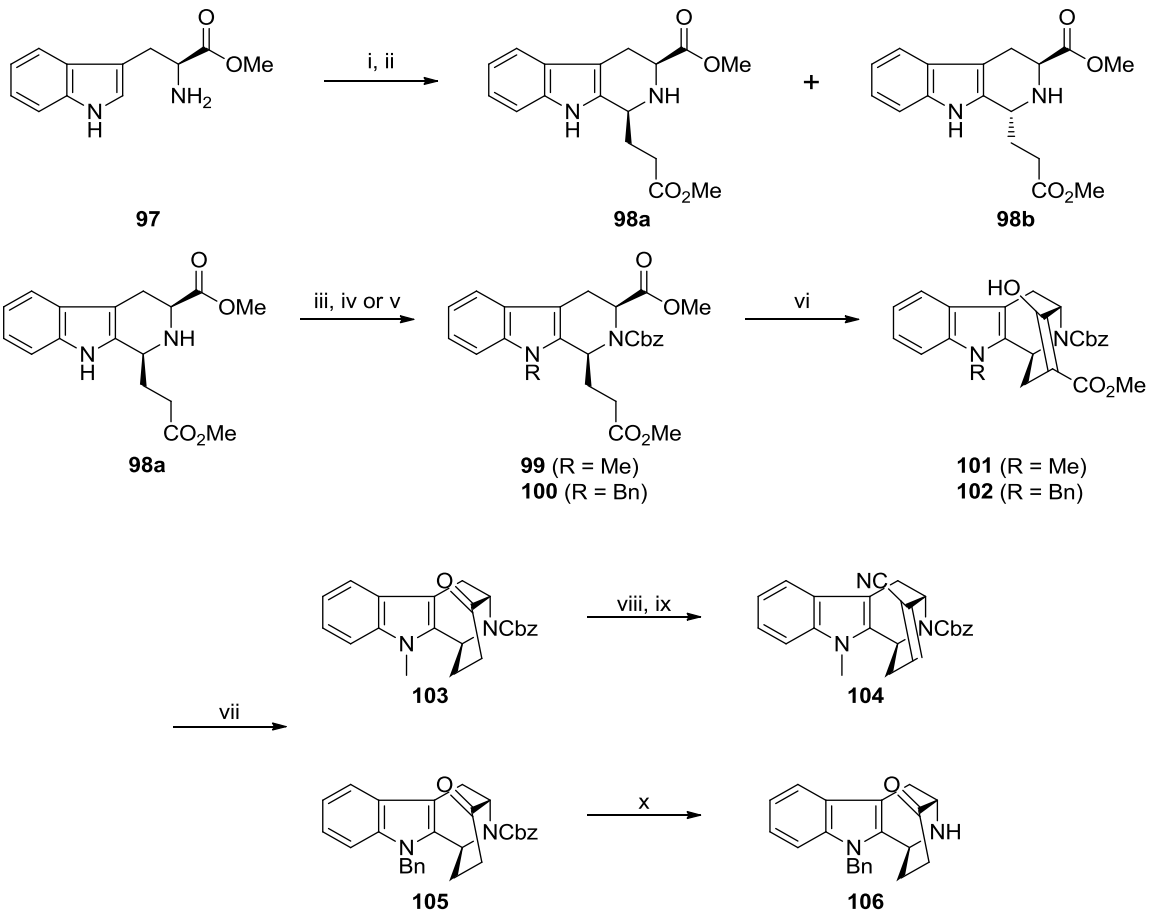
however, was the inability to generate any preference for the ajmaline C2 stereochemistry during reduction of carbinolamine **90**. An investigation into the selectivity of this particular step is described in chapter 3.

1.4 Bailey's approach to bridged indole alkaloids

1.4.1 Formal syntheses of (−)-koumine, (−)-taberpsychine, (−)-koumidine,[47] (+)-ajmaline and (−)-suaveoline[48]

Through the development of a kinetically-controlled Pictet-Spengler reaction to give *cis*-3,5-disubstituted tetrahydro-β-carbolines selectively,[49] Bailey has managed to complete a number of total and formal syntheses of a range of indole alkaloids.

One of the earliest of these was the development of a route to the tetracyclic ketone **106**, similar to those developed by Yoneda[20] and Cook.[35] Bailey's (−)-ketone was enantiomeric to the ketone prepared by Magnus, which was used during the total synthesis of the gelsemium alkaloids (+)-koumine, (+)-taberpsychine and (+)-koumidine.[50] Bailey's preparation of ketone **106** therefore represented formal syntheses of the gelsemium alkaloids with the natural absolute stereochemistry.

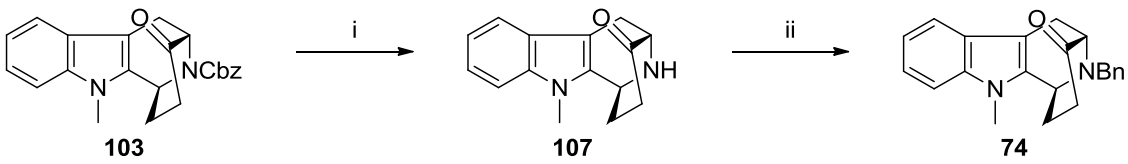


Scheme 1.24 – i) $MeO_2C(CH_2)_2CHO$, PhH, reflux; ii) 2 eq. TFA, DCM, 0 °C; iii) $PhCH_2OCOCl$, $NaHCO_3$, DCM; iv) MeI, NaH, DMF; v) BnBr, NaH, DMF; vi) NaH, MeOH, DMF; vii) NaCl, H_2O, DMF, 130 °C; viii) $(CF_3SO_2)_2NPh$, NaH, THF; ix) LiCN, $Pd(PPh_3)_4$, 12-crown-4, PhH; x) Pd/C, H_2, MeOH

Beginning from L-tryptophan methyl ester **97**, formation of the corresponding imine from methyl 4-oxobutanoate, followed by acid-catalysed Pictet-Spengler cyclisation at 0 °C, led to the formation of the *cis*- and *trans*-3,5-disubstituted tetrahydro-β-carbolines in a ratio of 4:1 respectively. Protection of the aliphatic N_b nitrogen with benzyl chloroformate gave the corresponding Cbz-protected compound.

Methylation of the indolic nitrogen with methyl iodide and sodium hydride was followed by sodium hydride-induced Dieckmann cyclisation to give the indole-methylated tetracycle **101** predominantly as the enol tautomer. A source of protons was essential to ensure successful Dieckmann cyclisation, the use of sodium hydride alone led only to epimerisation at the C5 position. Ester hydrolysis and decarboxylation was then carried out using Krapcho's method to give the tetracyclic ketone **103**.[51] As others had reported, alkylation of the α-position to the ketone proved to be problematic.[29,34] Formation of the enol triflate was first required, followed by palladium catalysed displacement with cyanide which gave the α,β-unsaturated nitrile **104**. Bailey states that this compound is suitable for further elaboration by Michael addition to give late-stage intermediates for the ajmaline and sarpagine family of natural products (Scheme 1.24).

Alternatively, protection of the indole nitrogen with benzyl bromide was followed by Dieckmann cyclisation, ester hydrolysis and decarboxylation to give the N_a-benzyl-protected tetracyclic ketone **105**. Catalytic hydrogenolysis of the N_b-Cbz group was then carried out to give tetracyclic ketone **106** completing the formal syntheses of (−)-koumine, (−)-taberpsychine and (−)-koumidine (Scheme 1.24).



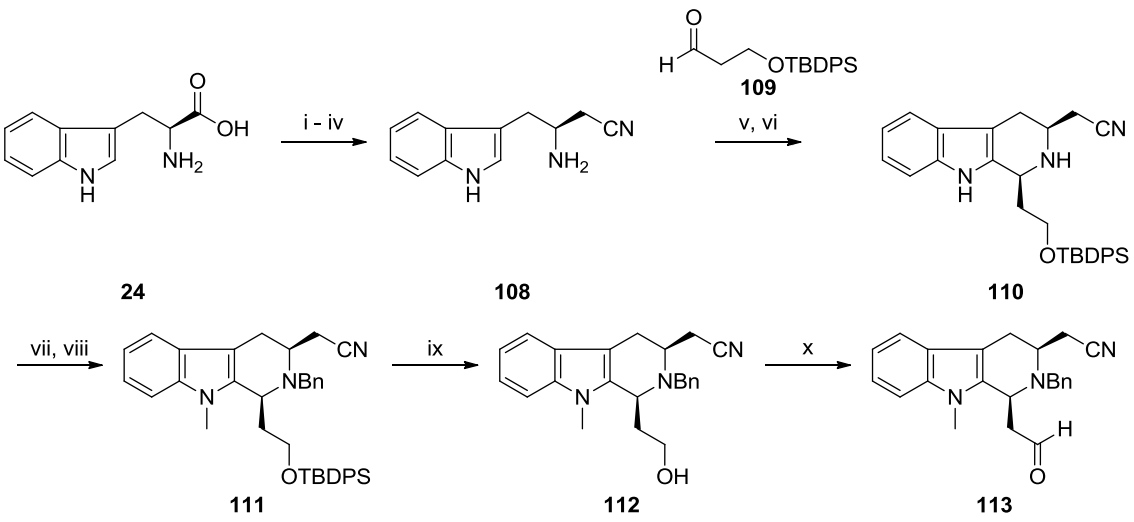
103 **107** **74**

Scheme 1.25 – i) Pd/C (10%), H_2, MeOH; ii) BnBr, $NaHCO_3$, DCM, reflux

Catalytic deprotection of the Cbz group of tetracycle **103**, followed by benzylation, gave the N_b-benzyl-protected tetracycle **74** the racemate of which was used by Mashimo and Sato to synthesise racemic ajmaline,[18] and also by Cook to prepare racemic suaveoline (Scheme 1.25).[40] Generation of enantiomerically pure ketone **74** therefore represented further formal syntheses of (+)-ajmaline and (−)-suaveoline.

1.4.2 The *cis*-selective Pictet-Spengler reaction

Bailey had previously used a kinetically-controlled Pictet-Spengler reaction employing tryptophan alkyl esters to give *cis*-3,5-disubstituted tetrahydro-β-carbolines, typically with 80% selectivity (*cis/trans* ratio 4:1).[52] The next major development in the synthesis of bridged indole alkaloids by Bailey, was the application of an amino nitrile compound in the kinetically-controlled Pictet-Spengler reaction, which gave the *cis* tetrahydro-β-carboline exclusively (Scheme 1.26).[49] The ability to prepare this compound in an enantiospecific manner, on a multigram scale, enabled the total asymmetric syntheses of (−)-suaveoline and (−)-raumacline to be carried out.

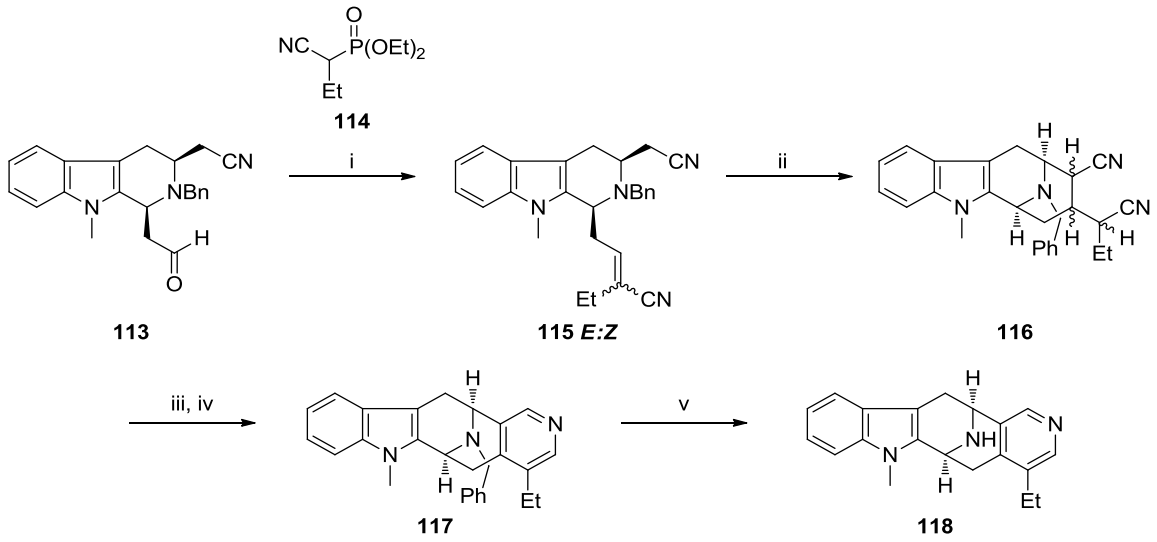


Scheme 1.26 – i) $LiAlH_4$, THF; ii) TsCl, py.; iii) KCN, MeOH, reflux; iv) Na, NH_3, THF, −78 °C; v) **109**, 3 Å MS, DCM, 0 °C; vi) 2 eq. TFA, −78 °C to rt; vii) BnBr, 70 °C; viii) MeI, NaH, DMF; ix) TBAF, THF; x) $(COCl)_2$, DMSO, NEt_3, DCM, −60 °C

Both suaveoline and raumacline were prepared *via* the nitrile aldehyde **113**. Starting from L-tryptophan **24**, the amino nitrile **108** was prepared in similar fashion to Kutney's procedure.[53] Reduction of tryptophan was carried out using lithium aluminium hydride, followed by tosylation of the alcohol and amino groups. Displacement of the *O*-tosyl group with cyanide was followed by single-electron-mediated reduction of the amino tosyl group to give the free amine. The kinetically-controlled Pictet-Spengler reaction *via* the corresponding imine, from TBDPS-protected aldehyde **109**, gave the *cis* carboline **110** in a highly stereoselective manner. Bailey found that the aromatic groups inherent with the silyl protecting group proved to be essential for the selectivity during the kinetically-controlled Pictet-Spengler cyclisation step. A non-aromatic silyl protecting group when similarly employed, resulted in reduced selectivity, typical of that found during other kinetically-controlled Pictet-Spengler cyclisations (~4:1 *cis/trans*).[54]

Protection of the potentially reactive nitrogen centres then took place, firstly the N_b nitrogen with a benzyl group and the N_a nitrogen next with a methyl group. The silyl protecting group was removed using TBAF and a Swern oxidation of the resulting alcohol provided the aldehyde necessary for both the suaveoline and raumacline syntheses.

1.4.3 The total synthesis of (−)-suaveoline[49,55]



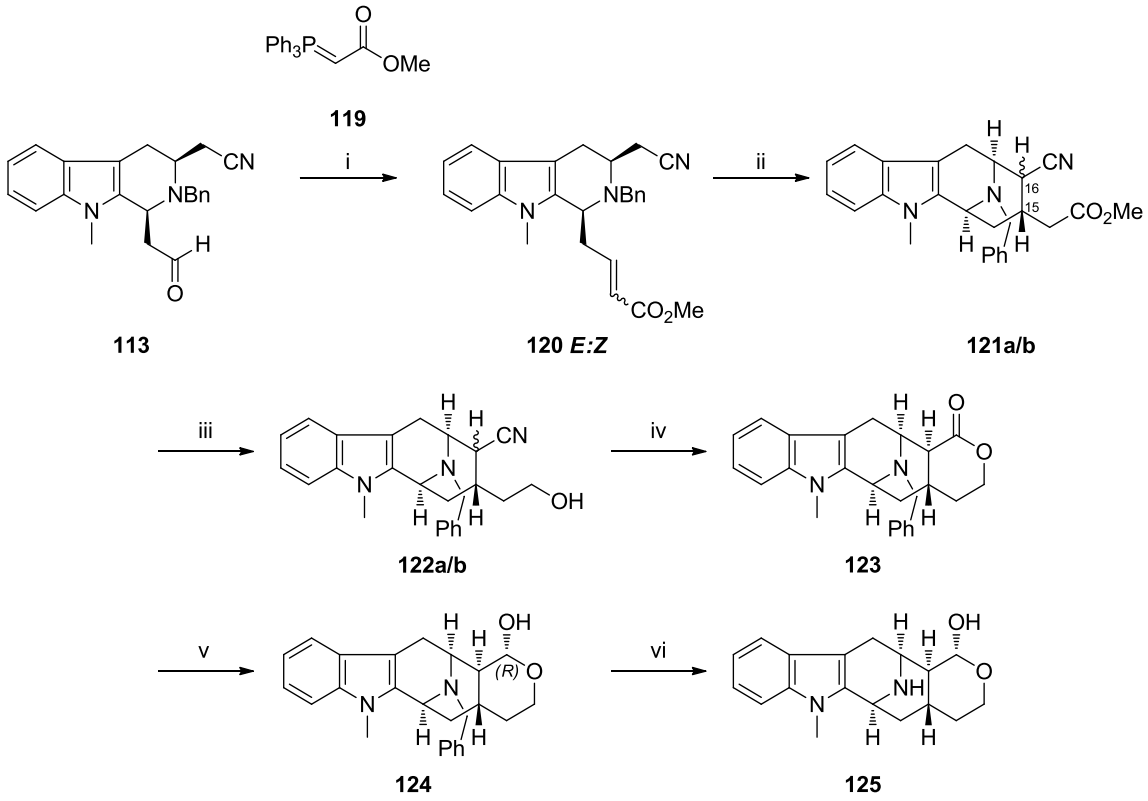
Scheme 1.27 – i) **114**, DMF; ii) KO^{t}Bu, THF; iii) DIBAL, DCM, −78 °C to rt; iv) $NH_2OH.HCl$, EtOH, reflux; v) Pd/C, H_2, EtOH

Bailey generated the Horner-Wadsworth-Emmons reagent **114** by ethylation of the corresponding nitrile phosphonate, which was then added to aldehyde **113** to give the unsaturated dinitrile **115** as a mixture of geometric isomers. The use of potassium *tert*-butoxide then initiated a vinylogous Thorpe cyclisation to form the tetracyclic dinitrile as a mixture of diastereoisomers. DIBAL reduction of the dinitrile, followed by the addition of hydroxylamine hydrochloride at reflux in

ethanol, gave the pyridine ring system, which was then subject to catalytic hydrogenation to remove the N_b-benzyl protecting group. (−)-Suaveoline **118** was formed in 14% overall yield from L-tryptophan (Scheme 1.27).

1.4.4 The total synthesis of (−)-raumacline[56,57]

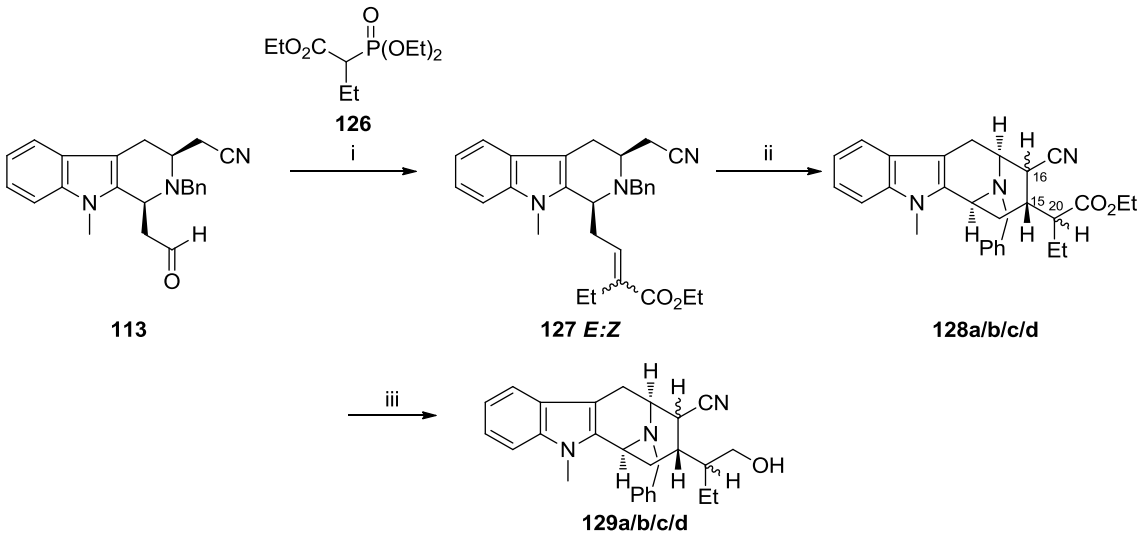
Raumacline represented a slightly more challenging prospect in that it contains four extra stereocentres as compared to suaveoline. As such, Bailey decided to attempt a total synthesis of a de-ethyl derivative of raumacline in an attempt to simplify the synthesis as a first proof of concept.



Scheme 1.28 – i) **119**, DCM, 0 °C to rt, 4 hrs; ii) $LiNEt_2$, THF, −78 °C to 0 °C, 3 hrs; iii) $LiBH_4$, THF, reflux, 3 hrs; iv) *p*-TsOH.H_2O, THF, reflux, 16 hrs; v) DIBAL, DCM, −78 °C, 1 hr; vi) 20% $Pd(OH)_2$/C, H_2, EtOH, rt, 3 hrs

Beginning from aldehyde **113**, Wittig alkylation using the phosphorus ylid methyl (triphenylphosphoranylidene)acetate **119** gave the *E*- and *Z*-unsaturated esters in a ratio of 4:1. An intramolecular Michael reaction from the α-position to the nitrile was initiated using lithium diethylamide giving the tetracycles **121a** and **121b** as a 2:1 mixture of diastereoisomers. Given the likelihood of the methyl ester group wanting to adopt an equatorial position in the ring forming transition state, it was postulated that the stereochemistry at C15 would be fixed, however it would be harder to predict whether the less sterically demanding nitrile group would adopt either an axial or equatorial position in the new ring. Subsequent NMR studies proved the above statement to be true; the stereochemistry at C15 was found to be exclusively (*S*)-configured and the C16 stereocentre found as a 2:1 mix of epimers in favour of the (*S*)-stereocentre. Lithium borohydride reduction of both C16 epimers gave the corresponding cyano alcohols **122a** and **122b**. In quite an elegant resolution, treatment of both C16 epimeric alcohols with *para*-toluenesulfonic acid in refluxing tetrahydrofuran gave just the *trans*-decalin pentacycle **123**. It was assumed that any *cis*-decalin product that formed epimerised under the reaction conditions to the more thermodynamically stable *trans*-decalin. The resultant lactone was then reduced stereoselectively with DIBAL to give the desired (*R*)-lactol only, catalytic debenzylation of which gave de-ethyl raumacline **125**. The debenzylation step was carried out in trifluoroethanol, as the use of conventional hydrogenation solvents, such as methanol and ethanol, led to the formation of small amounts of the respective N_b-methyl and N_b-ethyl amines *via* catalytic alkylation.[58]

Having established a stereoselective route to de-ethyl raumacline, the next challenge was to decide when and how to introduce the extra C20 ethyl group.

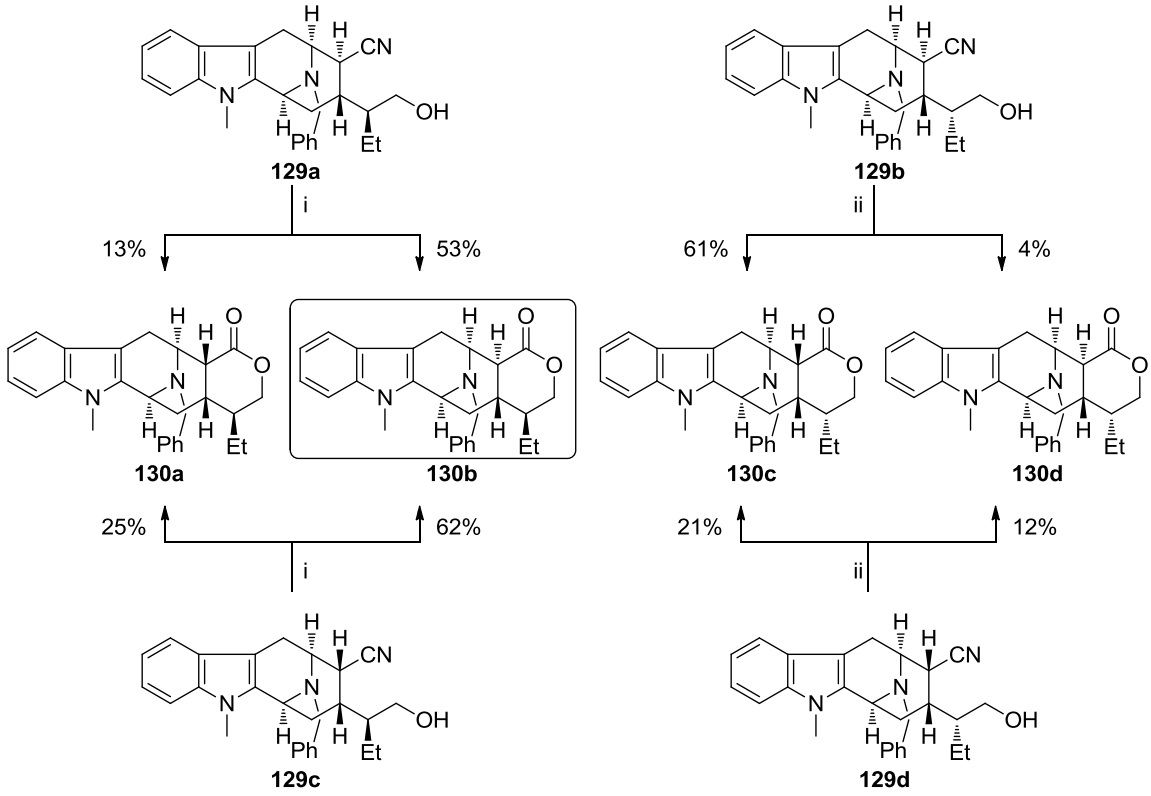


Scheme 1.29 – i) **126**, NaH, DMF, −20 °C; ii) $LiNEt_2$, THF, −78 °C; iii) $LiBH_4$, THF, reflux

Horner-Wadsworth-Emmons alkylation of aldehyde **113** using phosphonate **126** provided the perfect opportunity for introducing the required ethyl group; 5:3 *E/Z*-geometric isomers were formed. Michael reaction gave the tetracycle as previously, forming the new stereocentre at C15 selectively. The stereocentre at C16 was found to be formed as a mixture of 2:1 epimers in favour of the undesired (*R*)-diastereoisomer, whilst the stereocentre at C20 was formed as a mixture of epimers with no apparent stereocontrol. The mixture of C16 and C20 diastereoisomers was then reduced using lithium borohydride to give the corresponding alcohols **129a-d** (Scheme 1.29).

At this point, all four stereoisomers resulting from the lithium borohydride reduction were separated and elaborated individually to the benzyl-protected lactone, in

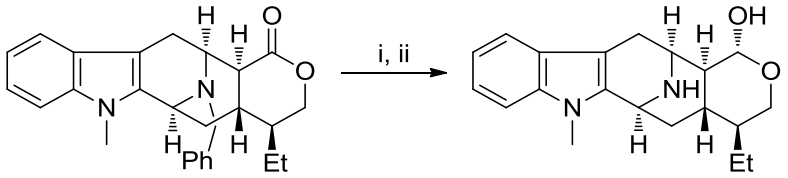
order to investigate the stereoselectivity of the lactonisation step, and how the presence of the C20 ethyl group might affect that cyclisation.



Scheme 1.30 – i) *p*-TsOH, THF, reflux, 22 hrs; ii) *p*-TsOH, THF, reflux, 48 hrs

As can be seen in scheme 1.30, all four cyano alcohol diastereoisomers underwent epimerisation at C16 to a certain degree during lactone formation, which was in contrast to the results found during the synthesis of de-ethyl raumacline, where the two C16 epimers **122a** and **122b** converged to the one desired lactone **123**. In all cases the major product was the one in which the C16 proton and the C20 ethyl group were arranged antiperiplanar, which can be explained by considering the available conformations of the pentacyclic lactone. A 1,3-diaxial steric clash between the C20 ethyl group and the C16 proton is

energetically unfavourable enough to promote formation of the antiperiplanar lactone, even if this led to the formation of the thermodynamically less favourable *cis*-decalin ring system.



130b **131**

Scheme 1.31 – i) DIBAL, DCM, −78 °C; ii) 20% $Pd(OH)_2/C$, H_2, TFE

With the ability to generate the desired lactone **130b** from both C16 cyano alcohol epimers, efforts were then concentrated on completing the final synthetic steps. Reduction of the lactone using DIBAL gave the lactol with complete selectivity, as was seen during the synthesis of de-ethyl raumacline, and this was followed by catalytic hydrogenolysis of the benzyl group to give the target natural product **131** (Scheme 1.31).

Chapter 2

The stereoselective Pictet-Spengler reaction

2.1 Tetrahydro-β-carbolines

The tetrahydro-β-carboline moiety is a common structural feature of a large number of indole alkaloid natural products. The tricyclic motif has plenty of scope for elaboration on both the aromatic and aliphatic ring systems and this potential structural diversification is highlighted by the large number of tetrahydro-β-carboline natural products isolated to date.

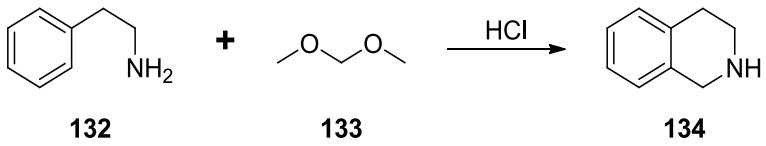
Tetrahydro-β-carboline derivatives are ubiquitous amongst plant and animal biological systems and it has been shown that simple tetrahydro-β-carboline compounds can affect the biochemistry of monoamine oxidases by binding to benzodiazepine receptors.[59]

With such important documented biological responses (see section 1.1) and the potential for further therapeutic medicinal applications, the construction of the tetrahydro-β-carboline core has proven to be an important area for synthetic research. By far the most prevalent methods for their formation are Pictet-Spengler and Bischler-Napieralski cyclisations of indole derivatives.

2.2 The Pictet-Spengler reaction

Ever since it was first demonstrated by Pictet and Spengler in 1911,[60] the Pictet-Spengler reaction has remained a hugely important and useful means of accessing a wide range of alkaloid natural products. In the first example of this reaction, Pictet and Spengler condensed together phenylethylamine with

dimethoxymethane in the presence of hydrochloric acid to give tetrahydroisoquinoline **134** (Scheme 2.1).

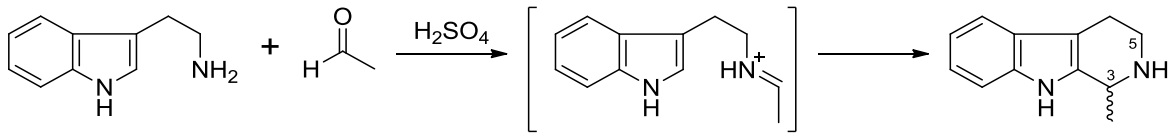


132 **133** **134**

Scheme 2.1 – First documented Pictet-Spengler reaction

The Pictet-Spengler cyclisation is in essence a two-step process, the first being condensation of a β-arylethylamine with a carbonyl compound, and the second a ring-closing reaction by means of an electrophilic aromatic substitution onto the pre-formed iminium ion.

The Pictet-Spengler reaction was used exclusively for the formation of tetrahydroisoquinolines until 1928 when Tatsui condensed tryptamine **135** with acetaldehyde in the presence of sulfuric acid to form the 1-methyl tetrahydro-β-carboline **138** (Scheme 2.2).[61]



135 **136** **137** **138**

Scheme 2.2 – Pictet-Spengler reaction between tryptamine and acetaldehyde

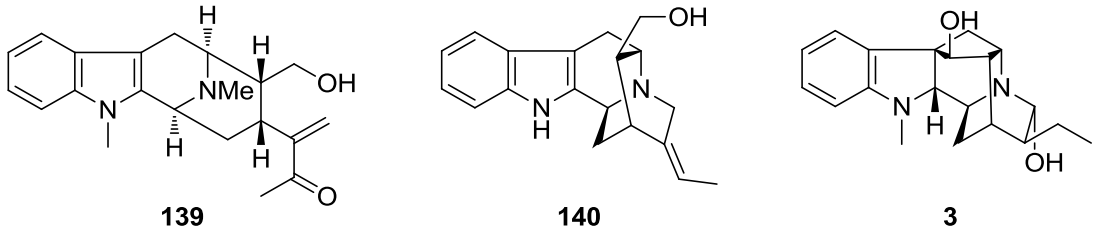
As can be seen from the reaction in scheme 2.2, the use of any carbonyl compound longer than one carbon unit during Pictet-Spengler cyclisation leads to the generation of a new stereocentre at the 3-position (indole alkaloid numbering).[1] In particular, the apparently simple 6-*endo*-trig ring-closing reaction which is an allowed, favourable process according to Baldwin's rules,[62] is laden with steric and electronic nuances which are determined by a number of factors including:

- the type of nucleophilic aromatic species
- the substitution at the aryl β-position
- whether the amine is primary or secondary
- the nature of the amino substituent
- the nature of the carbonyl compound
- the specific reaction conditions
- whether the indole nitrogen is derivatised

These factors can act cooperatively or competitively to determine the stereochemistry at the newly-formed C3 chiral centre.

2.3 Medicinally-important tetrahydro-β-carbolines

Extensive research into how to control the stereochemistry at C3 has subsequently led to numerous asymmetric syntheses of indole based alkaloids. The tetrahydro-β-carboline skeleton is a key feature of some of the medicinally-important indole based natural products, especially those derived from the macroline, sarpagine and ajmaline parent compounds. The Pictet-Spengler reaction has proven to be an efficient and reliable method of forming common key intermediates in order to access these compounds synthetically.



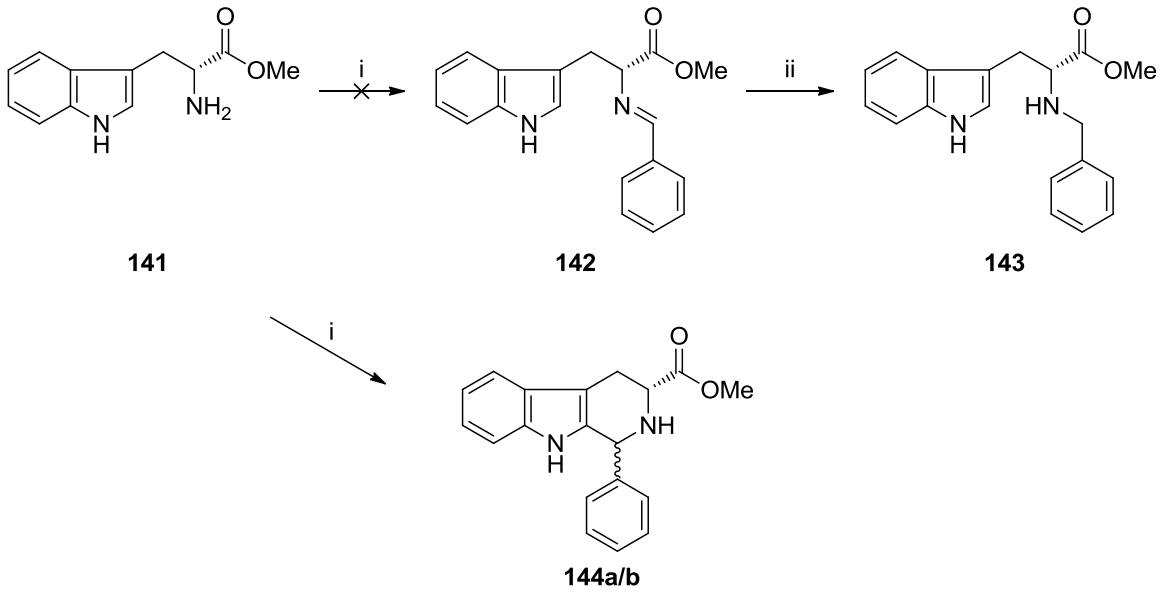
139 **140** **3**

Figure 2.1 – macroline **139**, sarpagine **140** and ajmaline **3**

A key feature of the macroline, sarpagine and ajmaline family of indole alkaloids is that, in a retrosynthetic sense, they can be seen to be derived from the proteinogenic amino acid L-tryptophan, although the inherent chirality is not necessarily biosynthetically acquired from L-tryptophan.[24] As a chiral substrate for Pictet-Spengler condensation, L-tryptophan adds further complexity to controlling the stereoselectivity of the reaction since there is the potential for diastereoisomers to be formed. It is upon this subject, the diastereoselectivity of the Pictet-Spengler cyclisation, which this work focuses.

2.4 The *trans*-selective Pictet-Spengler reaction

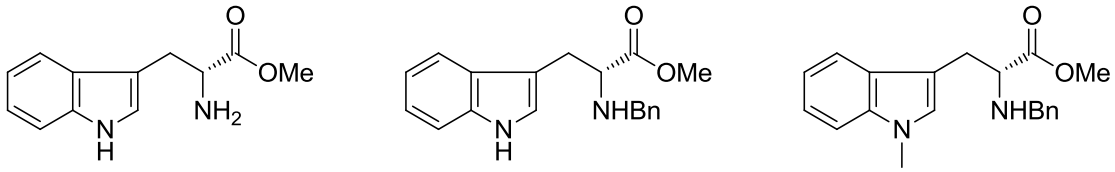
Classically, the Pictet-Spengler reaction had been carried out in protic solvent with the aid of acid catalysis, since this gave the greatest yields in relatively short reaction times.[63,64] During the course of preparing N_b-benzyl tryptophan methyl ester **143** from D-tryptophan methyl ester **141** and benzaldehyde,[35] Cook's group employed conditions of refluxing benzene with a Dean-Stark trap to expedite formation of the intermediate imine **142**, which would then be treated with sodium borohydride to yield the N_b-benzyl tryptophan methyl ester, according to Yoneda's work.[65]



Scheme 2.3 – i) PhCHO, PhH, DS-trap; ii) $NaBH_4$

Under extended reaction times, they noticed the formation of c*is* and *trans* diastereoisomers of 3,4,5,6-tetrahydro-β-carboline compounds (Scheme 2.3). This was surprising since the imine had undergone Pictet-Spengler cyclisation without the aid of acid catalysis, and Jackson had previously noted that treating benzaldehyde and tryptamine under similar conditions yielded only the imine.[66] So began a series of investigative experiments by Cook's group to develop their conditions of non-acidic, aprotic conditions to yield Pictet-Spengler products.

They soon noted that the yields of tetrahydro-β-carboline compounds were improved over acidic, protic conditions and that their non-acidic, aprotic conditions also led to drastic improvements in yield when acid labile aldehydes were employed. Cook's group obtained good yields of the subsequent tetrahydro-β-carboline compounds with tryptophan methyl ester **141**, N_b-benzyl tryptophan methyl ester **143** and N_a-methyl N_b-benzyl tryptophan methyl ester **27**.



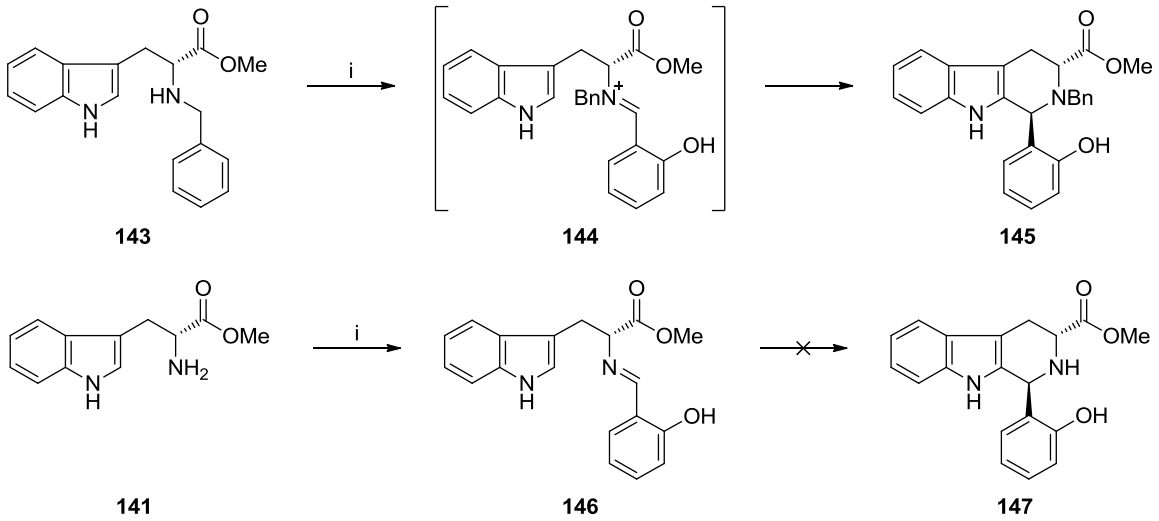
141 **143** **27**

Figure 2.2 – Cook's Pictet-Spengler substrates

The reactivity of the electrophile is a key factor in enabling electrophilic aromatic substitution reactions such as the Pictet-Spengler cyclisation to occur.[35] During Pictet-Spengler cyclisation, the electrophilicity of the imine carbon induces the interruption of the indole aromaticity and hence the formation of the new carbon-carbon bond. The formation of an iminium ion, by virtue of employing a secondary amine during the Pictet-Spengler reaction, removes the need for an acid catalyst. Similarly, Cook found that the best conversion to Pictet-Spengler products was realised when N_b-benzyl tryptophan alkyl esters were employed as the starting substrates.

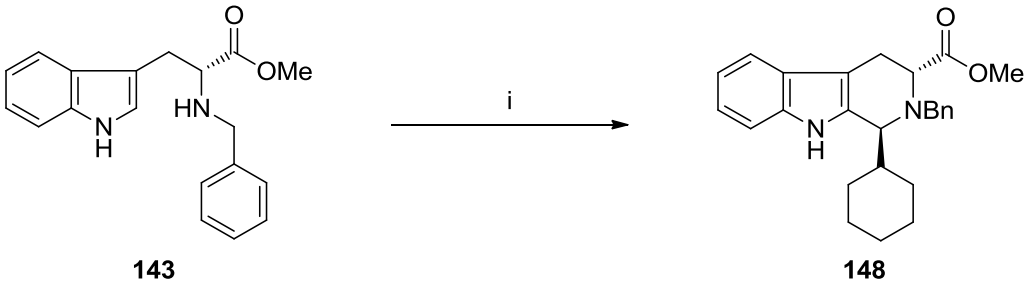
It was noted by Ungemach *et al.* that the Pictet-Spengler reaction between N_b-benzyl tryptophan methyl ester **143** and salicylaldehyde (2-hydroxybenzaldehyde) led to the formation of a single Pictet-Spengler product **145** in 97% yield (Scheme 2.4).[67] Subsequent catalytic hydrogenolysis of the benzyl group and comparison with independently formed *cis* and *trans* Pictet-Spengler products confirmed that the *trans* diastereoisomer had been formed in a stereospecific manner. Interestingly, this was in contrast to the results noted by Hamaguchi; under similar conditions the reaction between salicylaldehyde and tryptophan methyl ester **141** yielded only the corresponding imine **146**.[68] It was thought that the electron

releasing effect of the *ortho*-hydroxyl group was enough to attenuate the electrophilicity of the imine carbon centre in compound **146**, but not enough to overly affect the iminium carbon centre in compound **144** (Scheme 2.4).



Scheme 2.4 – i) 2-hydroxybenzaldehyde, PhH, reflux

To ascertain whether the *ortho*-hydroxyl group was affecting the selectivity of the reaction through some form of hydrogen bonding interaction, a further example employing cyclohexanecarboxaldehyde was carried out. Again, only one Pictet-Spengler product was formed, the *trans* tetrahydro-β-carboline **148** (Scheme 2.5). Empirical evidence suggested that the N_b-benzyl moiety was able to direct the specific formation of the *trans* diastereoisomer in compounds where the indole nitrogen was not derivatised.



143 **148**

Scheme 2.5 – i) cyclohexanecarboxaldehyde, PhH, reflux

Cook also described the effect that the size of the aldehyde used has on the stereochemical outcome of the reaction; bulkier aldehydes lead to greater *trans*-selectivity than smaller aldehydes. For example, the Pictet-Spengler reaction between N_b-benzyl tryptophan methyl ester **143** and cyclohexanecarboxaldehyde led to complete formation of the *trans* isomer, whereas *trans/cis* ratios of 77:23 and 74:26 were observed with butyraldehyde and acetaldehyde respectively (Table 2.1).[69]

Entry	**Aldehyde**	**% *trans* diastereoisomer**	**% *cis* diastereoisomer**
1	cyclohexanecarboxaldehyde	100	0
2	butyraldehyde	77	23
3	acetaldehyde	74	26

Table 2.1 – Variation in selectivity with the use of different aldehydes in the Pictet-Spengler reactions of N_b-benzyl tryptophan methyl ester **143**

Ungemach *et al.* hypothesised that an increased steric interaction between the ester at C5 and the aldehyde substituent at position C3 would also lead to a greater preclusion of the *cis* diastereoisomer during Pictet-Spengler reaction.[70] To test this, the isopropyl ester was prepared in an analogous manner to the methyl ester and an increase in the *trans*-selectivity to 87:13 *trans/cis* was noted in the condensation with butyraldehyde (compare with the reaction of N_b-benzyl tryptophan methyl ester – 77:23 *trans/cis* Table 2.1). Experiments where the N_b-benzyl group was replaced with a diphenylmethyl group also served to increase the preference for the *trans* diastereoisomer in instances where it was known that a mix of the *cis* and *trans* isomers were formed.[71]

Work by Ottenheijm during his synthesis of the eudistomin alkaloids had shown that employing N_b-benzyloxy tryptophan ethyl ester as the starting substrate for Pictet-Spengler reaction had resulted in decreased stereoselectivity.[72] To determine whether this reduction in selectivity was the result of a steric or an electronic effect, Cook prepared the N_b-methyl and N_b-phenethyl tryptophan methyl esters.[73] A comparison could then be made with the oxygenated analogues N_b-hydroxyl and N_b-benzyloxy tryptophan ethyl esters respectively, as employed by Ottenheijm.

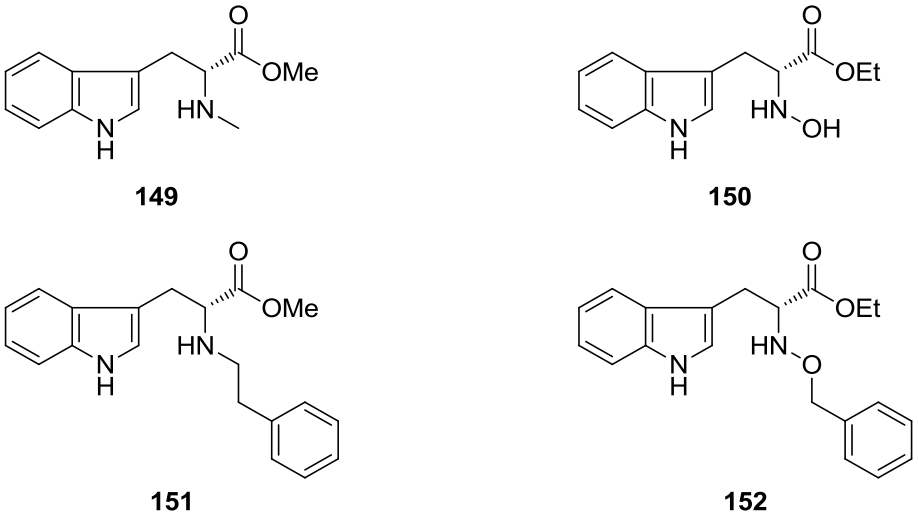


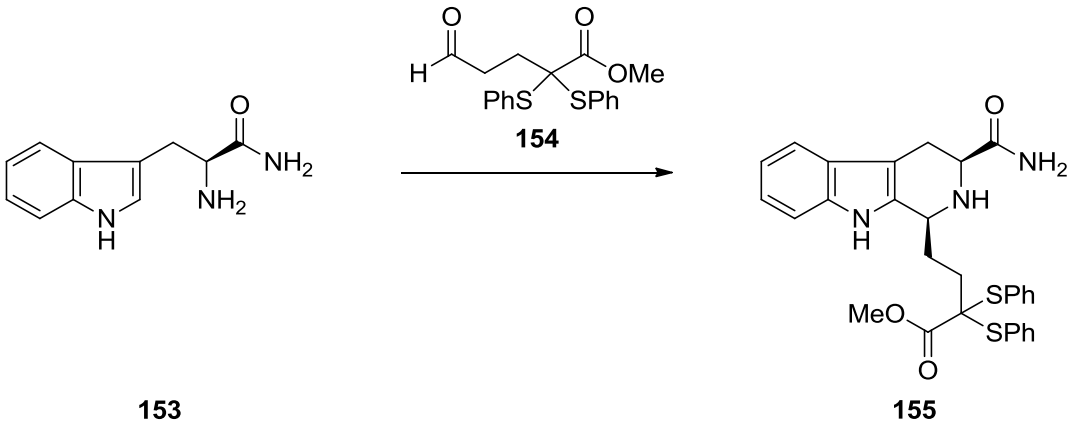
Figure 2.3 – Comparison of hydroxyamine tryptophan esters with analogous alkyl-substituted compounds

The results showed that the oxygenated analogues led to the formation of substantial amounts of the *cis* products and in general, lower *trans*-stereoselectivity in the formation of tetrahydro-β-carbolines as compared with the N_b-alkyl derivatives. Comparison of the N_b-alkoxy derivatives with the N_b-alkyl derivatives also showed that as the steric bulk of the substituents around the imine centre was increased so was the preference for the *trans* diastereoisomer, in line with the findings already made by Cook. During this study Cook employed catalytic trifluoroacetic acid in dichloromethane, the same reaction conditions as Ottenheijm. Cook makes no comment on the potential impact the reaction conditions have on the selectivity as an independent factor to the potential electronic effect due to the oxygen. This is slightly surprising since work by Bailey *et al*. had already shown that employing conditions of kinetic control during Pictet-Spengler reaction, as was used in this study, leads to preferential formation of the *cis* isomer.[74]

Placing these individual works conducted by Cook's group in context with each other leads to some general trends. Increasing the steric size of the C5 substituent, the C3 substituent (steric bulk of the aldehyde) and the size of the N_b substituent, regardless of the electronic factors mentioned above, all serve to increase the *trans*-selectivity of the Pictet-Spengler reaction as a result of the increased steric interactions, as will be discussed further in section 2.6.

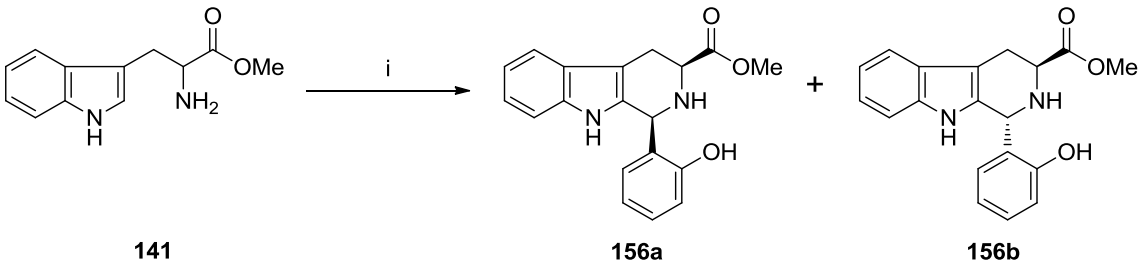
2.5 The c*is*-selective Pictet-Spengler reaction

A few select Pictet-Spengler reactions have shown a preference for the formation of the *cis*-3,5-disubstituted tetrahydro-β-carboline product. Massiot was able to prepare the *cis* diastereoisomer **155** exclusively during the reaction of L-tryptophanamide **153** and the aldehyde, methyl 4-formyl-2,2-bis(phenylthio)butyrate **154** (Scheme 2.6).[75]



Scheme 2.6 – Massiot's *cis*-selective Pictet-Spengler reaction

Selectivity of 9:1 in favour of the *cis* isomer was shown when the Pictet-Spengler reaction of tryptophan methyl ester **141** and 2-hydroxybenzaldehyde was carried out under aqueous conditions.[76]



141 **156a** **156b**

Scheme 2.7 – i) PhCHO, TFA/H_2O (1:9)

Clearly the substrates for these individual reactions had varied, but importantly, the key cyclisation steps were carried out at room temperature. As described in section 2.4, the key to directing the stereoselective formation of *trans* diastereoisomers of 3,5-disubstituted tetrahydro-β-carboline compounds is by increasing the steric bulk of the groups located on the newly-formed formed six-membered ring.

Bailey was the first to propose a correlation between the Pictet-Spengler reaction conditions and the distribution of the *cis* and *trans* diastereoisomers, more specifically, a relationship between the reaction temperature and the diastereoselectivity of the reaction was suggested.[74] Bailey postulated that at low temperature, under conditions of kinetic control, the formation of the piperidine ring in which the substituents would adopt the preferred equatorial positions would be favoured, leading to *cis*-3,5-disubstituted products. Subsequently, it was found that

if the Pictet-Spengler reactions between L-tryptophan methyl ester and a range of aldehydes were carried out at low temperatures, the *cis* isomer could be formed preferentially in a typical ratio of 4:1 (Table 2.2).[74]

Entry	Aldehyde	Kinetic control (DCM, 0 °C)	Thermodynamic control (benzene, reflux)
		cis/trans ratio	*cis/trans* ratio
1	Benzaldehyde	82:18	37:63
2	Cyclohexane-carboxaldehyde	71:29	59:41
3	Butyraldehyde	80:20	47:53
4	Hydrocinnamaldehyde	83:17	51:49
5	Isobutyraldehyde	83:17	43:57

Table 2.2 – Pictet-Spengler reactions of L-tryptophan methyl ester under conditions of kinetic control and thermodynamic control

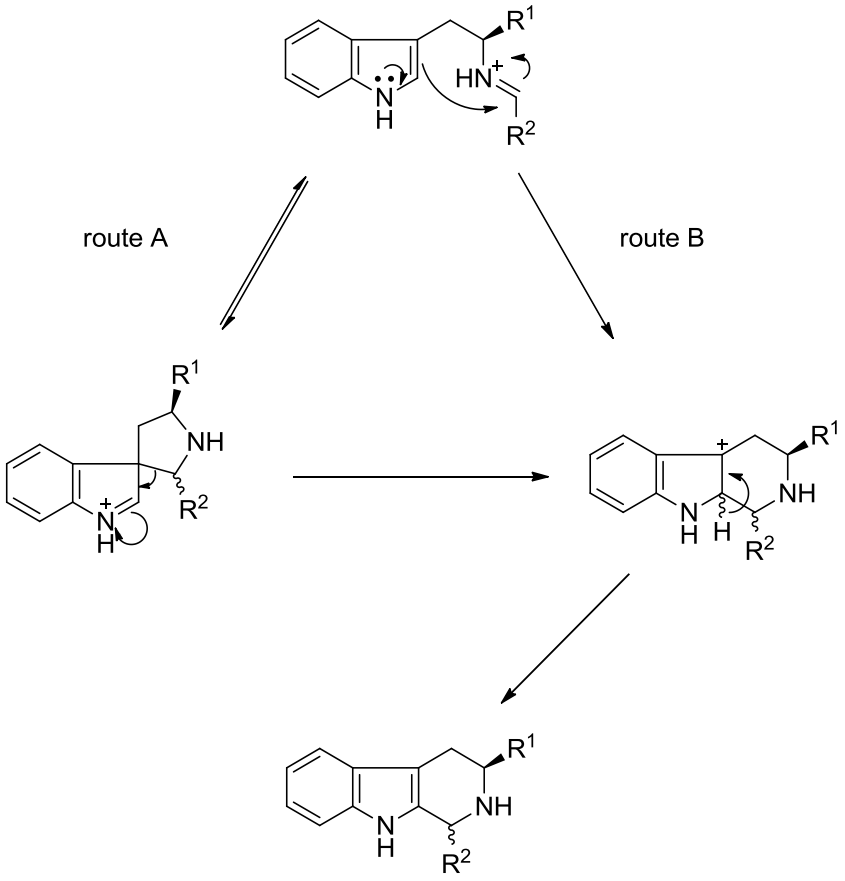
2.6 Pictet-Spengler mechanism in the formation of *cis*- and *trans*-3,5-disubstituted tetrahydro-β-carbolines

A consideration of the possible mechanism(s) for the Pictet-Spengler reaction is required to explain why *trans*-3,5-disubstituted tetrahydro-β-carboline compounds are the favoured reaction products when the cyclisation is carried out under conditions of thermodynamic control (non-acidic, aprotic conditions), compared with *cis*-3,5-disubstituted products under conditions of kinetic control (low temperature and acid catalysis).

The Pictet-Spengler reaction begins by condensation of a tryptophan derivative with an aldehyde to generate the corresponding iminium ion; the *E*-iminium ion is formed predominantly, which arranges the bulkiest substituents in a *trans* relationship.

A strong case for the formation of a spiroindolenine intermediate *via* attack from C3 of the indole ring onto the iminium bond has been presented,[77] but more importantly, through the use of isotopic labelling, it has been shown that the formation of the *spiro*-intermediate is fast and reversible.[78] This mechanism is represented by route A in scheme 2.8.

Casnati showed that when cyclisation is taking place onto very reactive iminium species, the addition can occur *via* C2 of the indole ring to form the carbenium ion directly.[79] Cook noted that imines of the corresponding N_b-benzyl substituted tryptophan alkyl esters can be considered as very reactive imine species, so a consideration of both reaction pathways must take place to rationalise the mechanism of formation in the reactions of these derivatives, represented by routes A and B in scheme 2.8.



Scheme 2.8 – Two proposed reaction pathways for Pictet-Spengler cyclisation. Route B is only accessible to very reactive imine species. Route A is available to all compounds of this type

In either case, the formation of a six-membered ring carbenium ion intermediate is thought to be rate determining and as such, the relative energies of the associated *cis* and *trans* transition states determine the stereochemical outcome of the cyclisation step, in line with the idea of a late transition state (Hammond postulate).[80]

Under Cook's conditions of thermodynamic control, the product which orientates the bulky C3, C5 and N_b-alkyl groups to minimise the steric interactions will be favoured. A consideration of the available piperidine ring conformations reveals

that the most favourable steric arrangement places the C5 substituent (ester group) equatorially and the C3 substituent (aldehyde group) axially. This particular arrangement minimises both the unfavourable $A^{(1,2)}$ steric interactions between the indole nitrogen substituent and the C3 substituent, and the C3, C5 diaxial interactions.

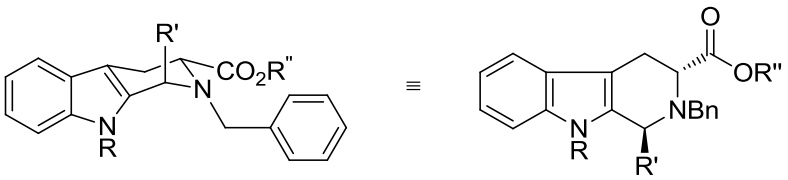


Figure 2.4 – Cook's thermodynamic *trans*-3,5-disubstituted tetrahydro-β-carboline

Bailey's N_b-H Pictet-Spengler reaction precursors can be considered to be relatively less reactive and as such, it is likely that the formation of the spiroindolenine *via* nucleophilic attack from the indole 3-position occurs first. It is known that the formation of the spiroindolenine intermediate is fast and reversible and so formation of the six-membered ring carbenium ion, either directly or *via* the *spiro*-intermediate, is thought to be rate determining. At low temperature, the kinetically-favoured carbenium ion is the diequatorial piperidine ring, a fast deprotonation of which regenerates the aromaticity of the indole ring giving the *cis* product.

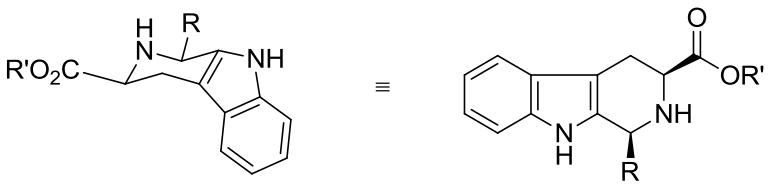
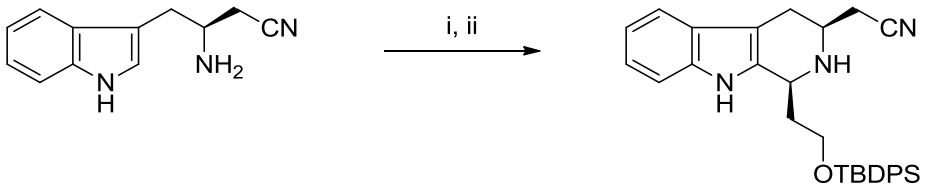


Figure 2.5 – Bailey's kinetic *cis*-3,5-disubstituted tetrahydro-β-carboline

The Bailey group have exploited their conditions of kinetic control in order to generate a number of late-stage intermediates with a high level of stereocontrol during the synthesis of a number of indole alkaloids.[47,57,81] During investigations towards suaveoline, the Pictet-Spengler reaction of the amino nitrile **108** and the TBDPS-protected aldehyde **109** led to the formation of the *cis* isomer exclusively with no evidence of the formation of the *trans* isomer.[49]



108 **110** *cis* only

Scheme 2.9 – i) **109**, 3 Å MS, DCM, 0 °C to rt; ii) 2 eq. TFA, DCM, −78 °C to rt

Following further investigations into this exceptional *cis*-stereoselectivity, Bailey reported that Pictet-Spengler reactions of tryptophan allyl ester with aromatic aldehydes gave the *cis* isomer with an exceptional level of stereocontrol.[82] To explain the enhanced stereoselectivity of the Pictet-Spengler reactions of the homologated tryptophan nitrile and tryptophan allyl ester, it was proposed that favourable π-stacking interactions between the allyl/nitrile group at C5 and the

aromatic protecting group at C3 during formation of the reaction transition state are the reason for this enhanced stereoselectivity. To support this statement, it was found that replacement of the allyl ester for the propyl ester gave typical *cis/trans*-selectivity of 4:1, in line with previous findings reported by Bailey.[54] In addition, replacement of the TBDPS protecting group for the TBDMS group in the aldehyde **109** also resulted in a reduction in selectivity to 3.6:1 *cis/trans*.[54]

It was suggested that the extra π-stacking interaction, in addition to the resultant reduction in $A^{(1,2)}$ strain, was enough to overcome the unfavourable 3,5-diaxial interactions leading to a *syn*-arrangement of groups in the *spiro* and carbenium ion intermediates, ultimately leading to predominantly *cis*-arranged Pictet-Spengler products.[82] Work is currently being carried out by the Bailey group to gain a better understanding of the factors controlling the *cis*-selective Pictet-Spengler cyclisation.

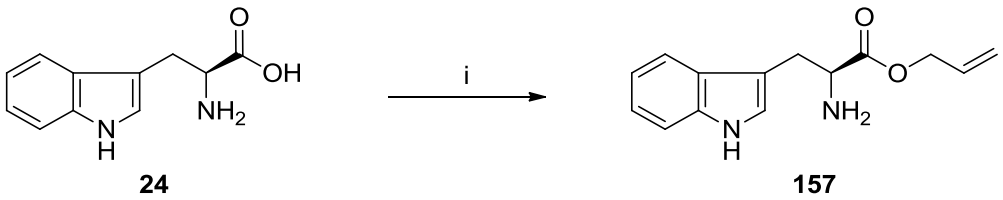
2.7 Investigation into the Pictet-Spengler cyclisations of L-tryptophan allyl ester

As mentioned previously, the kinetically-controlled Pictet-Spengler reaction of tryptophan derivatives can provide access to *cis*-3,5-disubstituted tetrahydro-β-carbolines with exceptional stereocontrol (see Sections 2.5 and 2.6).[49,75] However, these results are quite specific and limiting in their synthetic potential, and as such, the initial aim of this project was to try and expand the range of substrates suited to the *cis*-selective Pictet-Spengler reaction, whilst trying to uncover further experimental and mechanistic evidence for the enhanced selectivity.

Based on a previously reported communication,[82] the selectivity during Pictet-Spengler reactions of L-tryptophan allyl ester and a number of phenyl aldehydes was first investigated.

2.7.1 The Pictet-Spengler reactions of L-tryptophan allyl ester

L-tryptophan allyl ester is not readily available commercially so first had to be prepared by stirring L-tryptophan in allyl alcohol and ethyl chloroformate. The resulting solution was stirred at reflux and the ester product purified by chromatography (Scheme 2.10).

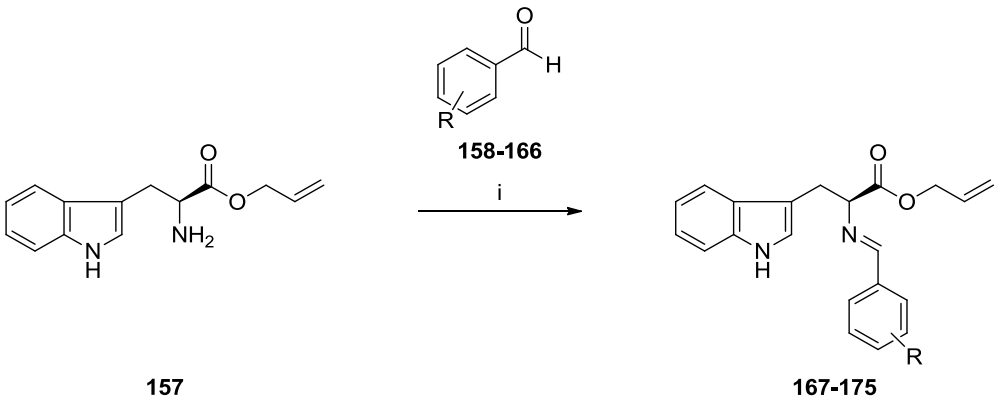


24 **157**

Scheme 2.10 – i) Ethyl chloroformate, allyl alcohol, 97 °C, 5 hrs, 56%

In order to establish a general rule for the *cis/trans*-selectivity with L-tryptophan allyl ester as the starting substrate, a range of aldehydes was chosen as the condensation partners for the reaction. This range of aldehydes was chosen to include both electron withdrawing and donating groups in both *meta*- and *para*-aromatic positions. The equivalent *ortho*-substituted aldehydes were omitted due to the potential for the *ortho*-substituents of those compounds to influence the selectivity of the reaction through steric effects.

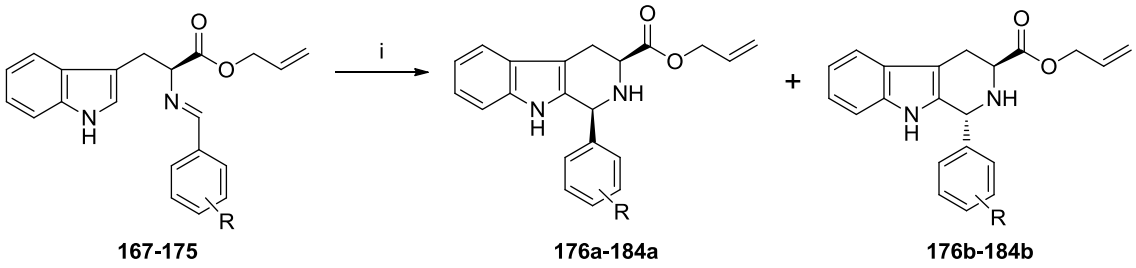
The Pictet-Spengler reactions were then carried out following the standard conditions as previously reported.[82] An imine intermediate was first formed *via* condensation of L-tryptophan allyl ester **157** with the appropriate aldehyde in dichloromethane over 3 Å molecular sieves (Scheme 2.11). Anhydrous conditions were important to ensure that hydrolysis of the imine was prevented, non-quantitative formation of which would lead to lower yields during the cyclisation step.



Scheme 2.11 – i) **158-166**, 3 Å MS, DCM, 0 °C to rt, 16 hrs

The dropwise addition of two equivalents of trifluoroacetic acid at 0 °C then triggered cyclisation (Scheme 2.12). Only once the imine nitrogen was protonated was the double bond electrophilic enough to break the aromaticity of the indole ring and allow generation of the new six-membered ring. An excess of trifluoroacetic acid was necessary to protonate the resulting amine and prevent a retro-Pictet-Spengler reaction from occurring. Cook has shown that under appropriate acidic conditions, 3,4,5-trisubstituted tetrahydro-β-carboline rings can

be opened and reformed *via* a carbocation intermediate to give the thermodynamically favourable *trans*-3,5-diastereoisomer.[83]



Scheme 2.12 – i) 2 eq. TFA, 0 °C, 8 hrs

Entry	Aldehyde (R)	Yield of tetrahydro-β-carbolines	*cis*/*trans* ratio	Recovered starting material
1	H (**158**)	66%	4:1 **(176a:176b)**	27%
2	3-CH_3 **(159)**	64%	9:1 **(177a:177b)**	19%
3	4-CH_3 **(160)**	45%	5:1 **(178a:178b)**	45%
4	3-Cl **(161)**	68%	9:1 **(179a:179b)**	29%
5	4-Cl **(162)**	69%	7:1 **(180a:180b)**	24%
6	3-OCH_3 **(163)**	71%	6:1 **(181a:181b)**	24%
7	4-OCH_3 **(164)**	39%	7:1 **(182a:182b)**	58%
8	3-NO_2 **(165)**	75%	7:1 **(183a:183b)**	8%
9	4-NO_2 **(166)**	90%	5:1 **(184a:184b)**	6%

Table 2.3 – Summary of results from the Pictet-Spengler cyclisations of L-tryptophan allyl ester and a range of phenyl aldehydes

The results summarised in table 2.3 show that for most of the aldehydes used, *cis/trans* Pictet-Spengler selectivity was in the range of 6:1-9:1. This represents reduced stereoselectivity compared with the findings previously reported under the same reaction conditions,[82] but still indicates improved selectivity as compared with the typical selectivity found with kinetically-controlled Pictet-Spengler reactions (4:1 *cis/trans*).[74]

2.7.2 The *cis/trans* tetrahydro-β-carboline diastereoisomeric ratio

A key objective of this study was to establish a consistent and reliable method for the elucidation of the *cis/trans* ratio of the diastereoisomeric reaction products. This ratio however proved difficult to obtain. Initially, efforts were concentrated on obtaining the two isomers as separate entities *via* column chromatography, which seemed to provide consistent results. However, concerns were raised that the isolated masses were not a true reflection of the reaction selectivity when the *cis/trans* ratio was generally found to be lower than expected. ^{1}H NMR analysis of crude mixtures of the reaction products failed to provide a clear ratio due to the terminal allylic protons effectively masking the chemical shift and the splitting of the hydrogen at the newly-formed stereocentre at C3.

It was thought that if the allylic protons could be removed chemically, this would enable a clearer analysis of the ^{1}H NMR spectrum to take place in the region of δ 5-6 ppm and would thus enable the diastereoisomeric ratio to be positively established. However, attempts to do this *via* catalytic hydrogenation proved to be inconclusive due to the formation of a number of unidentified reaction products.

As is the case historically (Cook[67,84] and Bailey[52] have both reported the use of ^{13}C NMR spectroscopy to identify their *cis* and *trans* diastereoisomers), the use of semi-quantitative ^{13}C NMR proved to be the most reliable and consistent means of establishing the *cis/trans* ratios with these 3,5-disubstituted compounds. The relative integrations of the C3 and C5 peaks in the crude product spectra revealed consistent ratios that were in line with those ratios obtained by measurement of the masses of the two diastereoisomers obtained following purification.

As a result of the reduced Pictet-Spengler selectivity, the *trans* Pictet-Spengler products could be fully characterised.

Entry	**Aldehyde**	**C3 proton shifts (ppm)**	
		cis isomer **(176a-184a)**	*trans* isomer **(176b-184b)**
1	H **(158)**	5.16	5.30
2	3-CH_3 **(159)**	5.07	5.30
3	4-CH_3 **(160)**	5.05	5.37
4	3-Cl **(161)**	5.04	5.36
5	4-Cl **(162)**	5.04	5.30
6	3-OCH_3 **(163)**	5.08	5.28
7	4-OCH_3 **(164)**	5.04	5.39
8	3-NO_2 **(165)**	5.14 – 5.22[a]	5.46
9	4-NO_2 **(166)**	5.12 – 5.22[a]	5.42

Table 2.4 – Comparison of *cis* and *trans* isomer proton chemical shifts at C3; [a]desired singlet within a multiplet region

In general, the chemical shift of the C3 protons from the *trans* isomers were downfield compared with the C3 protons from the *cis* isomers (Table 2.4).

In agreement with Cook's observations, the chemical shifts of the *trans* C3 and C5 carbons in the ^{13}C NMR spectra were upfield compared with those of the *cis* isomers.[67] One further interesting spectroscopic observation was that the allyl ester carbonyl stretch in the infrared spectra of the *cis* isomers was on average 2.7 cm^{-1} higher than that of the *trans* isomers (Table 2.5).

Entry	**Aldehyde**	**Carbonyl IR stretch (cm^{-1})**	
		cis isomer **(176a-184a)**	*trans* isomer **(176b-184b)**
1	H **(158)**	1735.7	1732.6
2	3-CH_3 **(159)**	1736.0	1731.7
3	4-CH_3 **(160)**	1736.0	1735.2
4	3-Cl **(161)**	1734.2	1731.7
5	4-Cl **(162)**	1735.2	1732.0
6	3-OCH_3 **(163)**	1735.5	1732.2
7	4-OCH_3 **(164)**	1735.7	1733.7
8	3-NO_2 **(165)**	1734.3	1731.8
9	4-NO_2 **(166)**	1734.9	1732.1

Table 2.5 – Comparison of *cis* and *trans* isomer ester carbonyl stretches

2.7.3 Efforts towards improving the *cis*-stereoselectivity

Once all intended products had been synthesised and characterised, efforts were then concentrated on altering the reaction conditions in order to improve the selectivity of the Pictet-Spengler cyclisation in favour of the *cis* isomer.

Since reversal of selectivity from *trans*-favoured products to *cis*-favoured products occurred when the reaction temperature was lowered from that of refluxing benzene to 0 °C,[74] the first obvious tactic to try and improve the *cis*-selectivity was to lower the temperature further. Carrying out the cyclisation step at a reduced temperature of −8 °C revealed no improvement in selectivity, but on lowering the temperature further to −40 °C an enhancement in selectivity was observed. In the condensation using 4-chlorobenzaldehyde **162** a selectivity of 11:1 was obtained, an improvement on the 7:1 ratio obtained when the experiment was run at 0 °C. It was found that the overall yield of the reaction was not significantly reduced by the lower reaction temperature. The reaction between benzaldehyde **158** and tryptophan allyl ester **157** at −40 °C also provided evidence for the increased selectivity, as at 0 °C the selectivity for this reaction was 4:1 *cis/trans*, whereas at −40 °C it had increased to 11:1.

Encouraged by this improvement in *cis*-selectivity, it was decided to employ slightly modified conditions, as used during the kinetically-controlled Pictet-Spengler reaction between nitrile amine **108** and the TBDPS-protected propionaldehyde **109**. Addition of trifluoroacetic acid at −78 °C followed by a

gradual warming to room temperature over the course of sixteen hours led to moderate and in some cases significant improvements in *cis*-selectivity.

These results showing the improvement in selectivity under the altered reaction conditions are shown in table 2.6.

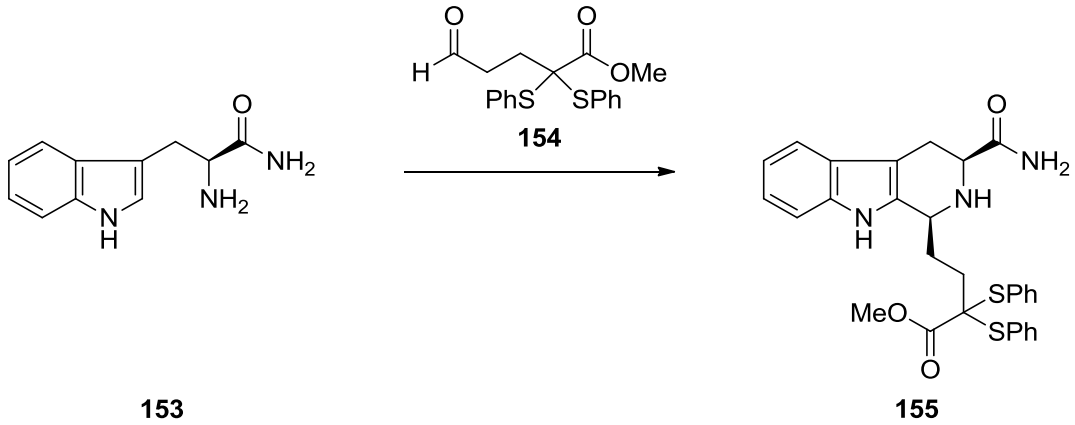
Entry	**Aldehyde**	**PS conditions** (0 °C, 8 hours) *cis/trans*-selectivity	**PS conditions** (−78 °C to rt, 16 hours) *cis/trans*-selectivity
1	H **(158)**	4:1	15:1
2	3-CH_3 **(159)**	9:1	9:1
3	4-CH_3 **(160)**	5:1	8:1
4	3-Cl **(161)**	7:1	12:1
5	4-Cl **(162)**	7:1	12:1
6	3-OCH_3 **(163)**	6:1	11:1
7	4-OCH_3 **(164)**	7:1	7:1
8	3-NO_2 **(165)**	7:1	20:1
9	4-NO_2 **(166)**	5:1	16:1

Table 2.6 – *cis/trans*-selectivity optimisation

These results show that, with the exception of the 3-methyl and the 4-methoxy aldehydes (entries 2 and 7, Table 2.6), improvements in the *cis*-selectivity were found with the modified Pictet-Spengler reaction conditions. From these findings it is impossible to say at what temperature cyclisation is taking place, but it is clear that keeping the temperature lower for extended periods of time is important in increasing the *cis*-selectivity for the N_a-H N_b-H L-tryptophan allyl ester series of compounds.

2.8 Pictet-Spengler cyclisations of L-tryptophanamide derivatives

One example of exceptional *cis*-selectivity was demonstrated by Massiot and Mulamba, where the Pictet-Spengler reaction of L-tryptophanamide **153** with the aldehyde methyl 4-formyl-2,2-bis(phenylthio)butyrate **154** gave the *cis* diastereoisomer exclusively **155** (Scheme 2.13).[75] With regard to the original research question, the tryptophanamide derived compounds represent an extra avenue of investigation into the range of compounds which could possibly yield enhanced *cis*-selectivity. It was decided to initially investigate the selectivity with the simplest derivative, L-tryptophanamide itself, the first challenge being its synthesis.

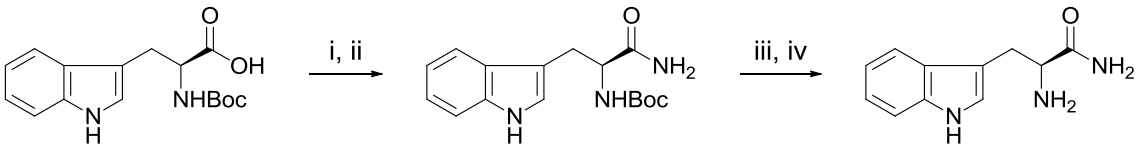


Scheme 2.13 – Massiot's *cis*-specific Pictet-Spengler cyclisation

2.8.1 Preparation of L-tryptophanamide

Efforts to amidate L-tryptophan using ethyl chloroformate to form the mixed anhydride, followed by aminolysis with aqueous ammonia, gave tryptophanamide

directly but in a yield of only 27%. It was thought that tryptophanamide could be obtained more efficiently *via* an amino-protected tryptophan derivative, however, an attempt to install the carbobenzyloxy (Cbz) protecting group to L-tryptophan *via* the benzyl chloroformate proved to be equally unsuccessful. At this point it was decided to try the amidation on commercially available *tert*-butyloxycarbonyl- (Boc) protected tryptophan **185**. This process was found to be very efficient and the Boc-protected tryptophanamide **186** was obtained in excellent yield. Boc deprotection with aqueous trifluoroacetic acid gave the tryptophanamide salt and a subsequent base wash gave the free amine, also in excellent yield (Scheme 2.14).



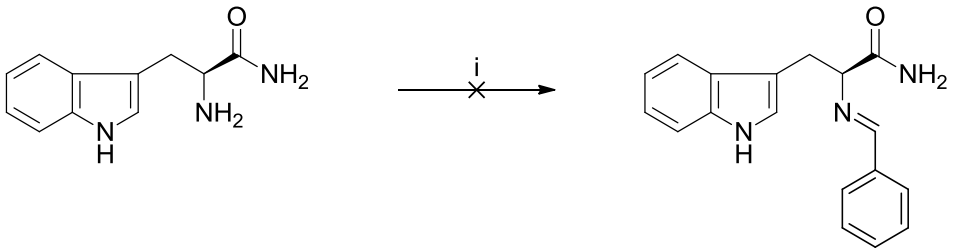
185 **186** **153**

Scheme 2.14 – i) Ethyl chloroformate, NEt_3, DCM/MeCN; ii) aq. NH_3, 94% (over two steps); iii) 1:1 TFA/H_2O; iv) sat. aq. $NaHCO_3$, 88% (over two steps)

2.8.2 Pictet-Spengler reaction of L-tryptophanamide

The first attempt at a Pictet-Spengler cyclisation of L-tryptophanamide with benzaldehyde failed under the conditions used previously. Analysis of the imine formation step through the use of ^{1}H NMR showed that the imine intermediate **187** had not formed cleanly, possibly because of the poor solubility of tryptophanamide in dichloromethane, the reaction solvent. Altering the solvent system to a 1:1 mixture of dichloromethane and acetonitrile enhanced the polarity enough to dissolve the starting material, but again the imine formation step was not efficient

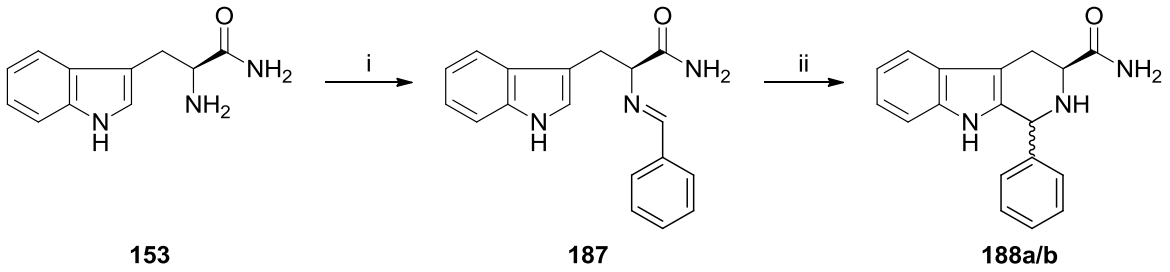
enough to enable the cyclisation step to occur successfully. A number of unidentifiable products were formed in low yield (Scheme 2.15).



153 **187**

Scheme 2.15 – i) PhCHO, 3 Å MS, DCM/MeCN, 0 °C to rt

Clean formation of the imine **187** could be carried out by stirring the starting materials in refluxing toluene in the presence of a Dean-Stark trap, rather than using molecular sieves as a desiccant. A solvent swap from toluene to dichloromethane was then necessary, followed by the addition of trifluoroacetic acid to trigger cyclisation. Stirring at room temperature for six hours, the conditions used by Massiot,[75] yielded a diastereoisomeric mixture of the *cis* and *trans* compounds **188a** and **188b** in a ratio of 3:1 (Scheme 2.16). The two diastereoisomers ran at similar R_f values and their separation by column chromatography proved to be extremely difficult. Fortunately, since there were no allylic protons to mask the chemical shift of the proton at the newly-formed stereocentre, the diastereoisomeric ratio could be easily obtained from the ^{1}H NMR spectrum of the crude material.



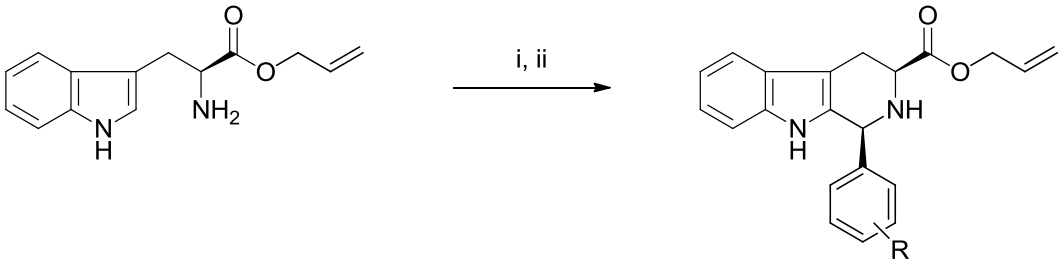
153 **187** **188a/b**

Scheme 2.16 – i) PhCHO, toluene, reflux, 30 min; ii) 2 eq. TFA, DCM, rt, 6 hrs, 44% (over two steps)

Due to the poor selectivity achieved during this initial test reaction, the Pictet-Spengler reactions of L-tryptophanamide were not pursued any further. However, it would be interesting to investigate whether this initial *cis/trans*-selectivity could be improved by optimisation of the reaction conditions in a similar fashion to the study undertaken for the allyl ester series of compounds.

2.9 Summary of results from the Pictet-Spengler selectivity investigation

Despite not being as stereoselective as originally reported, the kinetically-controlled Pictet-Spengler reactions of L-tryptophan ester **157** still gave high levels of stereocontrol (Scheme 2.17). Indeed, following optimisation of the reaction conditions, the *cis* diastereoisomer could be formed with selectivity as high as 20:1 (entry 8, Table 2.6).



157

176a/b-184a/b
9 examples d.r. 7:1-20:1

Scheme 2.17 – i) **158-166**, 3 Å MS, DCM, 0 °C to rt, 16 hrs; ii) 2 eq. TFA, −78 °C to rt, 16 hrs

The Pictet-Spengler reaction of L-tryptophanamide with benzaldehyde proved not to be as selective as in Massiot's original reaction.[75] This result provides evidence that the specific nature of the aldehyde has a key role to play in determining the selectivity of the Pictet-Spengler reaction under conditions of kinetic control.

Chapter 3

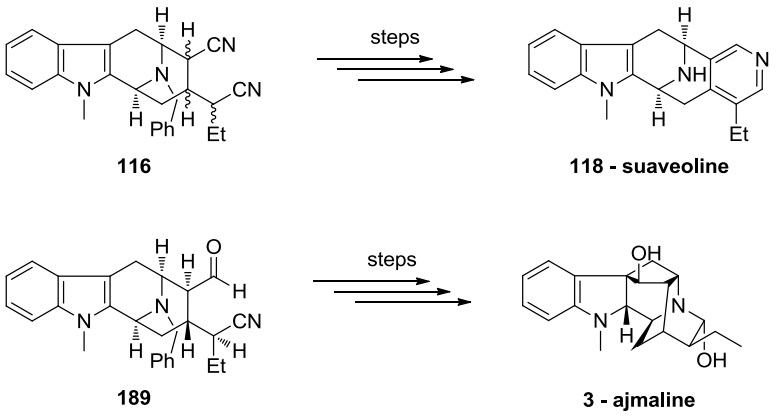
Studies towards the total synthesis of (+)-ajmaline

3.1 The Bailey group's previous investigations towards (+)-ajmaline

3.1.1 Attempted synthesis of nitrile aldehyde 189[56]

Through the use of a kinetically-controlled Pictet-Spengler reaction, Bailey *et al.* have stereoselectively-accessed late-stage intermediates towards the synthesis of a number of indole alkaloids (see section 1.4). Having already completed a formal synthesis of (+)-ajmaline,[48] Bailey planned to apply a similar methodological approach towards a previously-prepared late-stage intermediate, and then establish a new route featuring enhanced stereoselectivity and brevity to complete the challenging final synthetic steps of a total synthesis of ajmaline.

During the synthesis of suaveoline, the dinitrile **116** was used as an advanced intermediate (see section 1.4.3), but it was felt the inherent difficulty of having to desymmetrise the two nitrile groups would prohibit its use as an intermediate towards ajmaline. It was expected that the two nitriles could be differentiated at an earlier stage in the synthesis and as such, the aldehyde **189** was initially targeted.

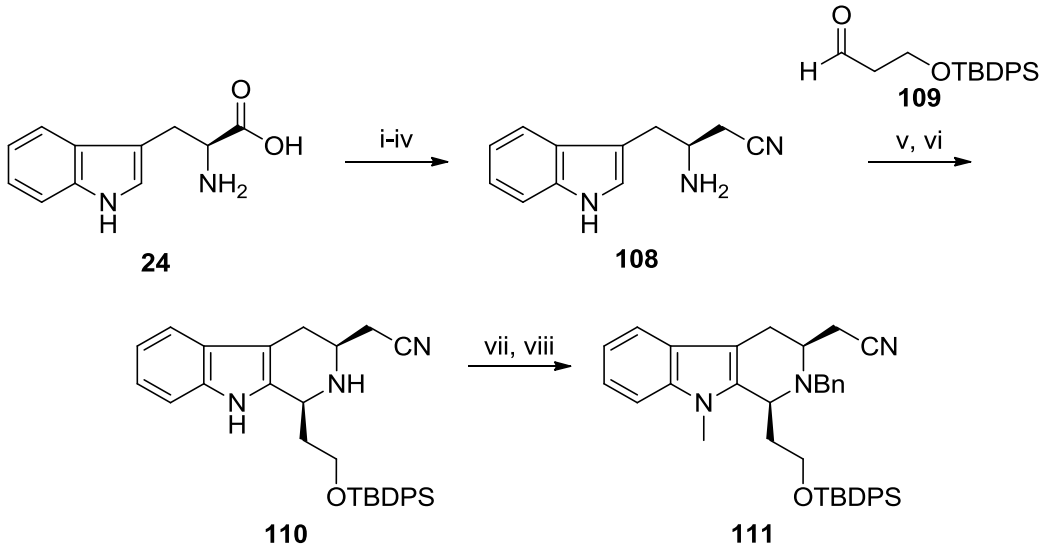


116 **118 - suaveoline**

189 **3 - ajmaline**

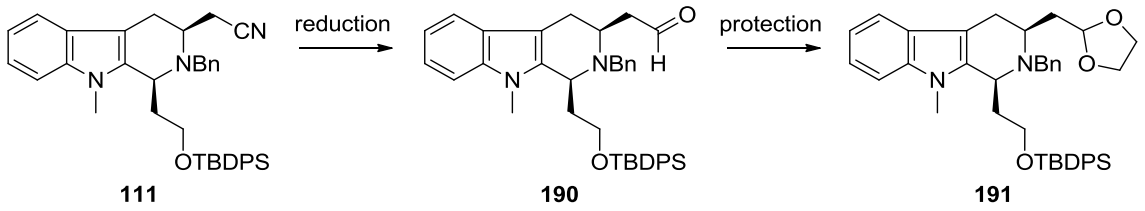
Scheme 3.1 – Bailey's intended route to ajmaline

cis-3,5-Disubstituted tetrahydro-β-carbolines can be formed with exceptional stereocontrol, and as a result, the corresponding nitrile **108** was used by Bailey's group as a common intermediate during the synthesis of a number of indole alkaloids.



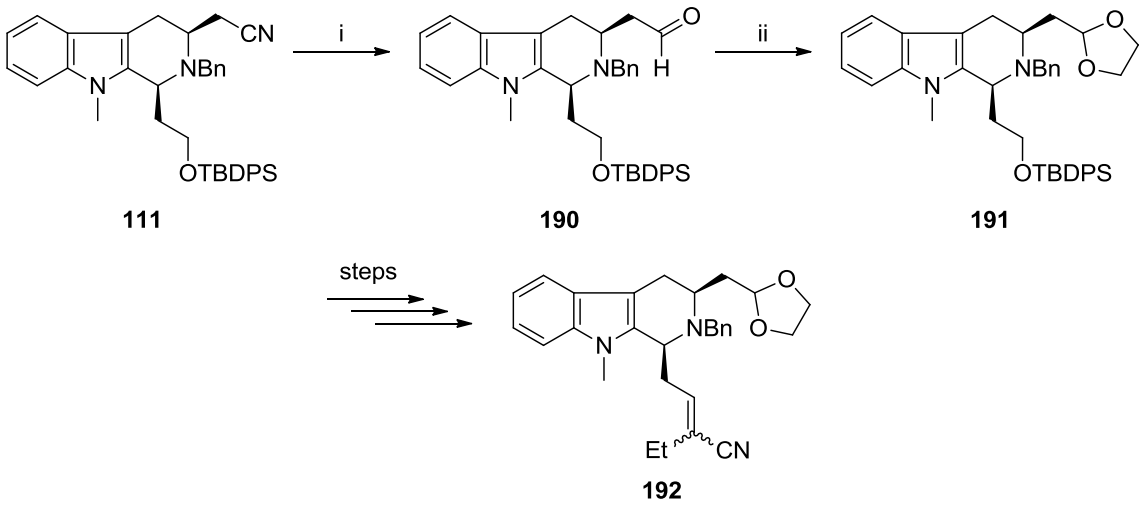
Scheme 3.2 – i) $LiAlH_4$, THF, reflux; ii) TsCl, py.; iii) KCN, MeOH, reflux; iv) Na/NH_3, THF, −78 °C, v) **109**, 3 Å MS, DCM, 0 °C; vi) 2 eq. TFA, DCM, −78 °C to rt; vii) BnBr, $NaHCO_3$, 70 °C; viii) MeI, NaH, DMF

Synthetic attempts began with reduction of L-tryptophan followed by simultaneous tosylation of the amine and alcohol groups. Cyanide S_N2 displacement of the activated alcohol, and amino detosylation then proceeded as previously shown, to give the homologated nitrile tryptophan derivative **108**.[53] The *cis*-selective Pictet-Spengler reaction then took place, followed by benzyl protection of the N_b nitrogen and indole methylation (Scheme 3.2).



Scheme 3.3 – Reduction and protection of nitrile **111**

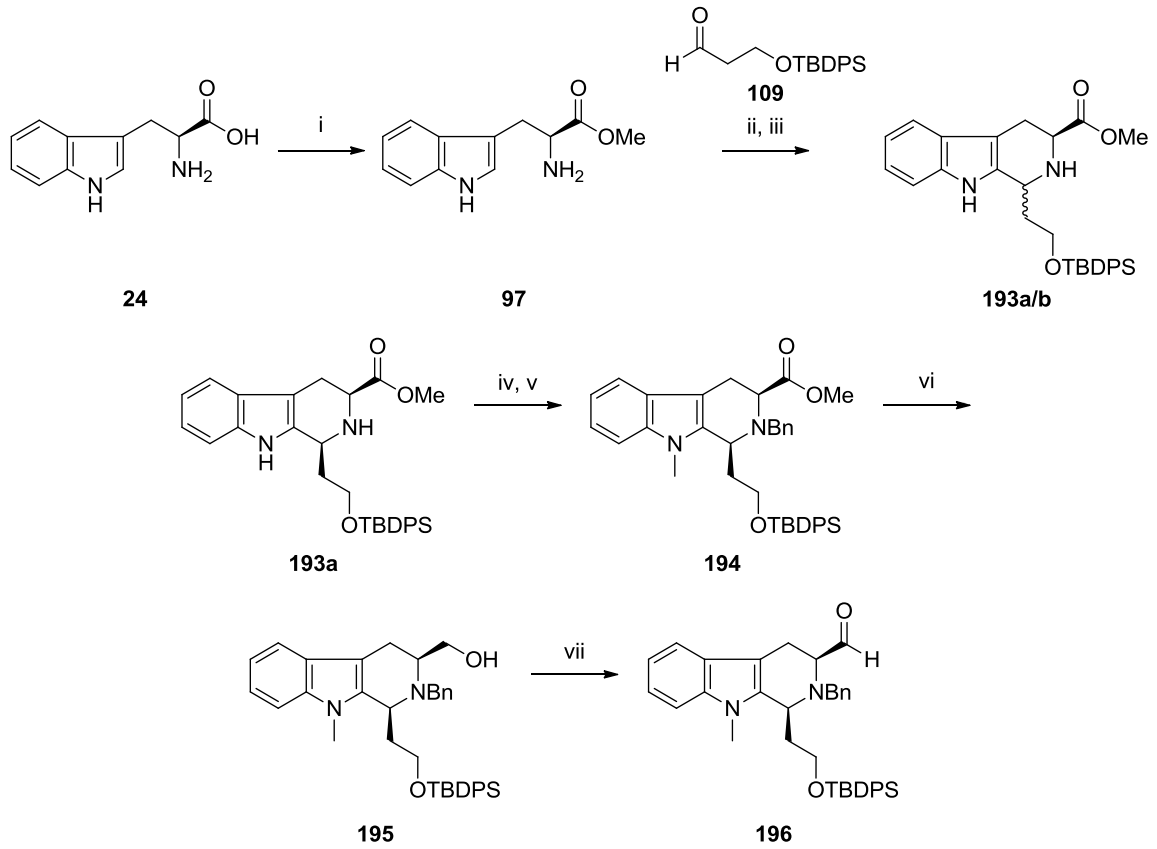
At this point, reduction of the nitrile **111** to aldehyde **190** was planned, which would then be protected to allow elaboration of the TBDPS-protected alcohol.



Scheme 3.4 – i) DIBAL, DCM, −78 °C to rt; ii) ethylene glycol, *p*-TsOH, benzene, reflux

Unfortunately, attempted DIBAL reduction of the nitrile to the aldehyde led to decomposition of starting materials in the majority of cases. Some aldehyde **190** was isolated, which was then protected as the acetal, but due to the unreliability of the nitrile reduction this approach was abandoned (Scheme 3.4).

Having failed to generate the desired aldehyde functionality in the attempted reduction of nitrile **111**, an alternative analogous approach *via* reduction of a methyl ester was planned.

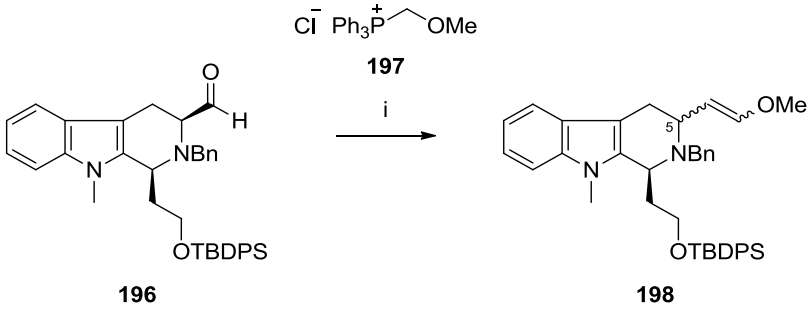


Scheme 3.5 – i) CH_3COCl, MeOH, reflux, then aq. $NH_3/CHCl_3$; ii) **109**, 3 Å MS, DCM; iii) 2 eq. TFA, DCM, −78 °C to rt; iv) BnBr, K_2CO_3, MeCN; v) MeI, NaH, DMF; vi) $LiAlH_4$, THF; vii) $(COCl)_2$, DMSO, NEt_3, DCM, −60 °C

Again starting from L-tryptophan **24**, formation of the methyl ester took place *via* the mixed anhydride using acetyl chloride in refluxing methanol. The kinetically-controlled Pictet-Spengler cyclisation with aldehyde **109** gave a mixture of the *cis* and *trans* diastereoisomers **193a** and **193b** in a ratio of 3.2:1, evidence that the nitrile group has a large part to play in the high *cis*-selectivity observed when nitrile

amine **108** is employed in the kinetically-controlled Pictet-Spengler reaction. Benzylation of the secondary amine was carried out using potassium carbonate in acetonitrile at room temperature. The use of sodium bicarbonate in neat benzyl bromide at 70 °C, as used previously, was found to cause epimerisation of the stereocentre adjacent to the ester group. Standard indole methylation was then carried out using methyl iodide and sodium hydride, which was followed by reduction of the methyl ester in good yield using lithium aluminium hydride (Scheme 3.5). In contrast to the previous route attempted, as shown in scheme 3.4, homologation of alcohol **195** was required in order to provide the necessary carbon framework for ajmaline.

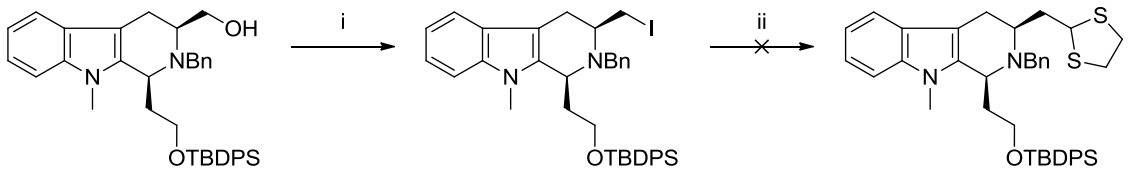
Swern oxidation of alcohol **195** provided the appropriate aldehyde and homologation was attempted using Wittig chemistry to generate the enol ether **198**, which could then be further elaborated. However, under a range of reaction conditions, Wittig reaction of aldehyde **196** resulted in significant epimerisation of the C5 stereocentre (Scheme 3.6).



Scheme 3.6 – i) **197**, NaHMDS, THF, −78 °C then **196**

As an alternative, homologation efforts were then focused on conversion of the alcohol **195** to an effective leaving group, followed by alkylation with a lithiated dithiane as demonstrated by Corey.[85]

Alcohol **195** was treated with iodine, imidazole and triphenylphosphine to generate the iodide compound **199** in moderate yield. Unfortunately, treatment of the iodo compound failed to produce any of the desired dithiane **200** and as such, this approach to ajmaline was also abandoned (Scheme 3.7).

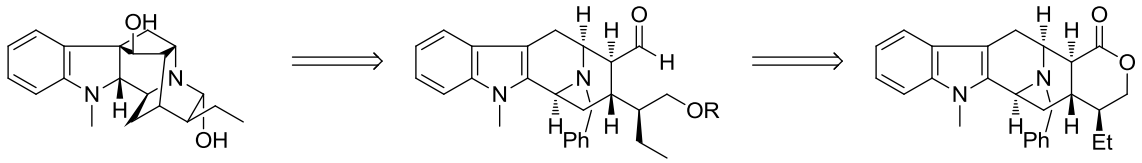


195 **199** **200**

Scheme 3.7 – i) I_2, imidazole, PPh_3, Et_2O/MeCN, 0 °C; ii) ^{n}BuLi, 1,3-dithiane, THF, −40 °C then −78 °C, **199**

3.1.2 Ajmaline synthesis *via* raumacline lactone 130b and the significance of the N_b protecting group

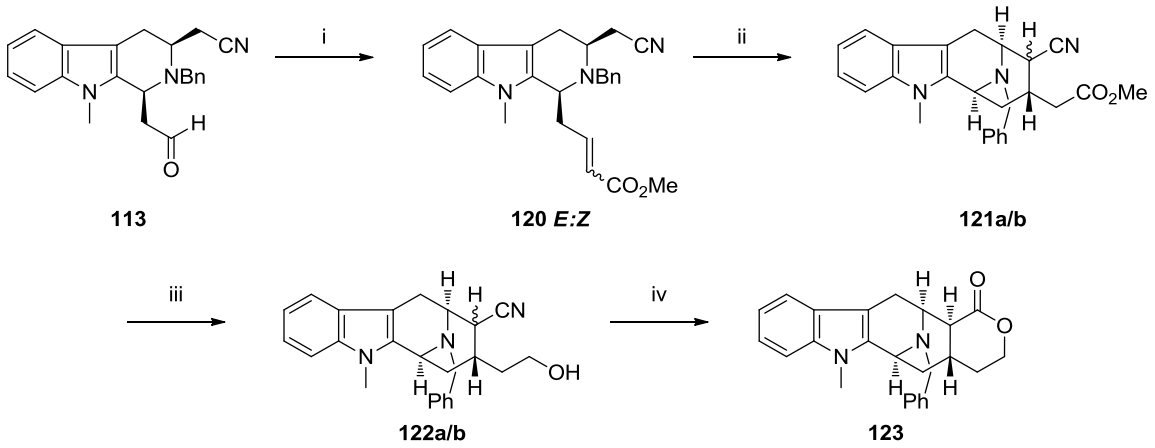
Based on the success of the total synthesis of (−)-raumacline (see section 1.4.4), Bailey's group planned to use lactone **130b** as a key intermediate towards ajmaline (Scheme 3.8).



3 **130b**

Scheme 3.8 – Retrosynthetic analysis of ajmaline to lactone **130b**

The synthesis of aldehyde **113** took place as shown previously (see section 1.4.2, Scheme 1.26).



113 **120 *E:Z*** **121a/b**

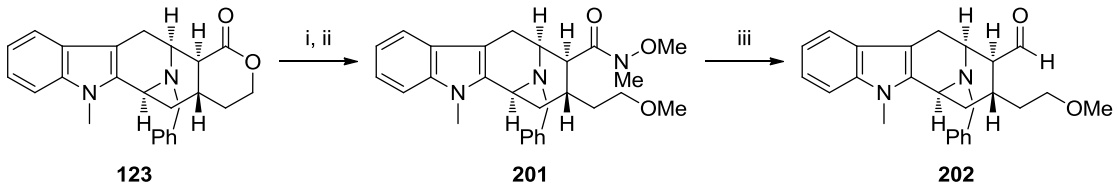
122a/b **123**

Scheme 3.9 – i) Ph_3PCHCO_2Me, DCM, 0 °C; ii) $LiNEt_2$, THF, −78 °C; iii) $LiBH_4$, THF, reflux; iv) *p*-TsOH.H_2O, THF, reflux

Bearing in mind the lack of selectivity during formation of the lactone with the ethyl substituent incorporated (see section 1.4.4), it was decided at this point to concentrate synthetic efforts towards a de-ethyl derivative of ajmaline. The C20 ethyl group would then be installed at the most appropriate point between formation of lactone **123** and the end of the synthesis. As a result, a Wittig procedure was used to homologate aldehyde **113** using the commercially available

phosphorus ylid methyl (triphenylphosphoranylidene)acetate to prepare the α,β-unsaturated methyl ester **120** as a mixture of the *E* and *Z* geometric isomers in a ratio of 4:1. An intramolecular Michael cyclisation initiated by deprotonation of the nitrile α-position was then carried out with lithium diethylamide at −78 °C to generate a mixture of two diastereoisomers at C16. Lithium borohydride reduction of both esters gave the corresponding alcohols, which was then followed by lactonisation to generate the desired de-ethyl lactone **123** as a single diastereoisomer (Scheme 3.9).

Having prepared lactone **123** in a stereoselective manner, the key cyclisation onto the indole 3-position was planned *via* aldehyde **202**.



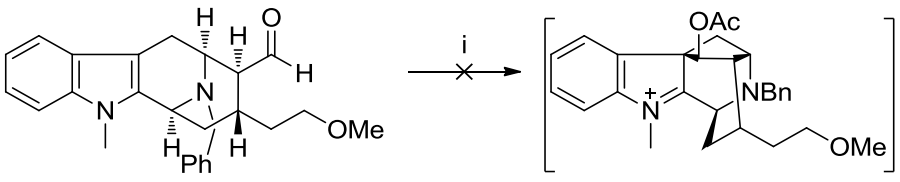
123 **201** **202**

Scheme 3.10 – i) HNMeOMe.HCl, $AlMe_3$, DCM; ii) MeI, NaH, DMF; iii) $LiAlH_4$, THF, 0 °C

Ring-opening of the lactone was carried out by adding the Lewis acid trimethyl aluminium, followed by the addition of *N*,*O*-dimethylhydroxylamine hydrochloride, resulting in generation of the Weinreb amide. Protection of the resulting alcohol was then required and the robust methyl ether protecting group was chosen. Literature shows that the deprotection of aromatic methyl ethers can be carried out using boron tribromide; preliminary studies within the Bailey group demonstrated that the use of boron tribromide could be transferred to the deprotection of

aliphatic primary methyl ethers. Reduction of the Weinreb amide **201** using lithium aluminium hydride then took place to give the C16 aldehyde **202** as a single diastereoisomer (Scheme 3.10). Other groups have reported difficulties in maintaining the optical integrity of the C16 stereocentre (Masamune, see section 1.2.1; Van Tamelen, see section 1.2.3; Kluge, see section 1.2.4), since the thermodynamically-favoured epimer at this point gives the wrong C16 stereochemistry for the natural product. Stereoselective production of aldehyde **202** therefore represented a significant achievement.

Using the conditions originally utilised by Bartlett,[27] cyclisation of the E-ring was attempted by stirring aldehyde **202** in acetic acid, concentrated hydrochloric acid and hydrogen chloride gas. Acetic anhydride was also used in order to trap the resulting alcohol as the acetate ester and prevent the reverse ring-opening reaction from occurring. Under these conditions, a number of products were formed, none of which suggested that the ring-closing reaction had taken place successfully (Scheme 3.11).



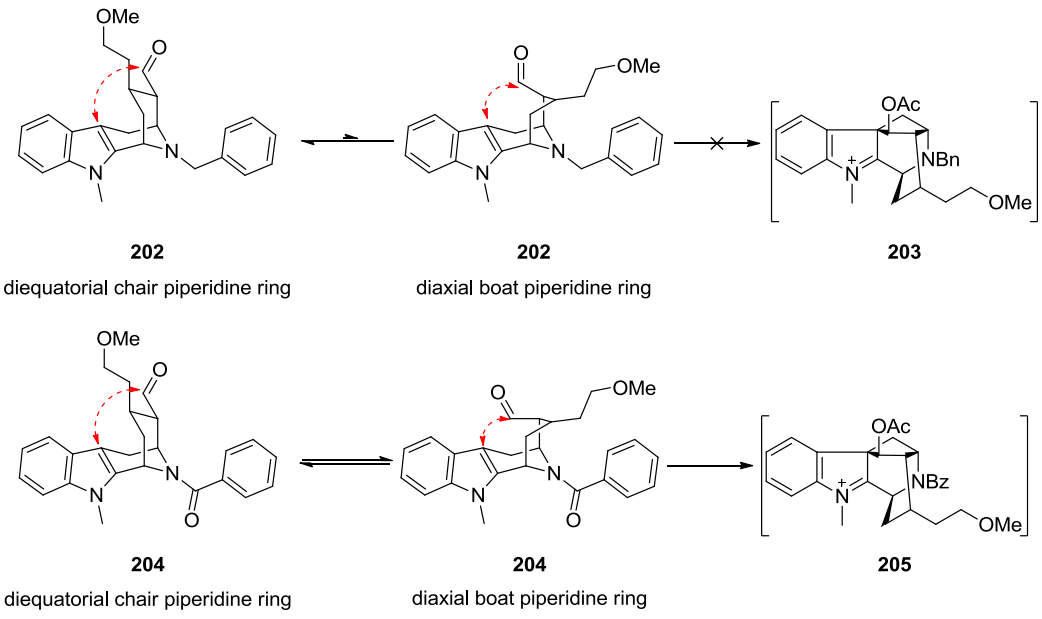
202 **203**

Scheme 3.11 – i) AcOH, Ac_2O, $HCl_{(l)}$, $HCl_{(g)}$

During Cook's total synthesis of ajmaline, modelling work carried out had suggested that a similar substrate would not cyclise due to conformational effects

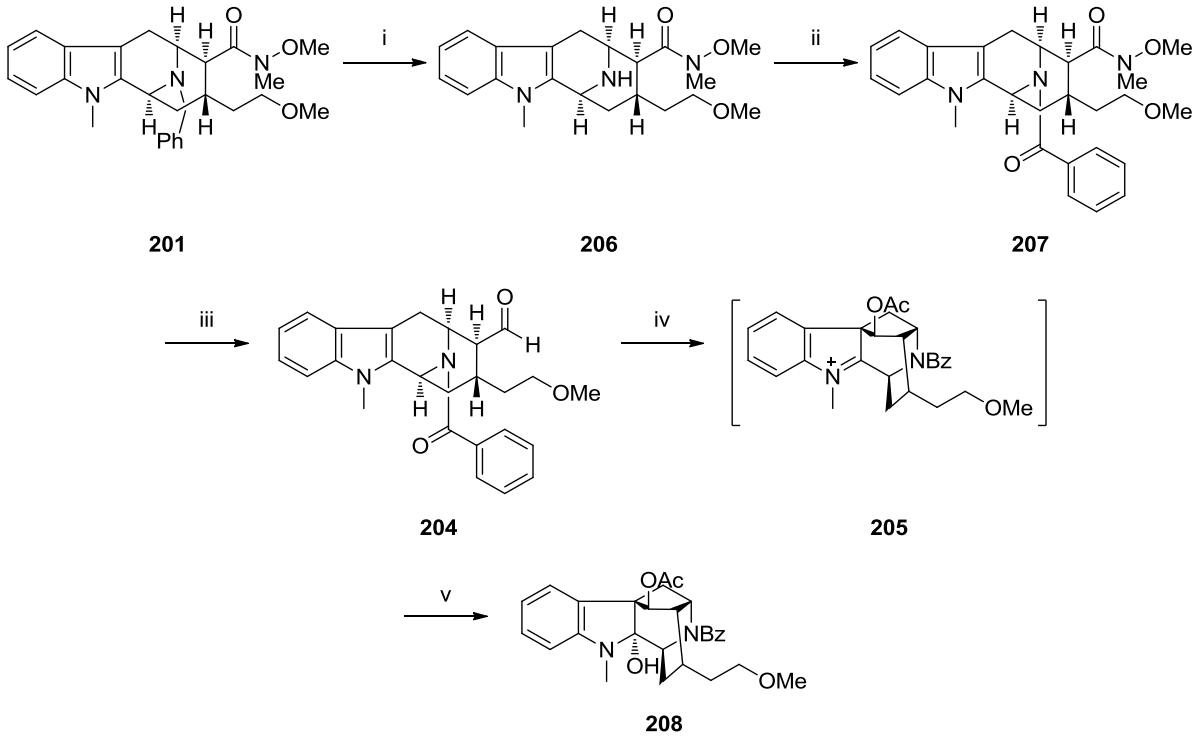
intrinsic to the molecule.[34] The favoured chair conformation of the piperidine ring places the aldehyde in an equatorial position, and at a significantly unfavourable distance away from the indole ring for reaction to occur. Cook suggested that too great an energy barrier would have to be overcome in order for successful cyclisation to take place.

However, during his synthesis of ajmaline, Masamune had successfully managed to cyclise the N_b-benzoyl-protected compound.[16] As a result, Bailey postulated that a change in the hybridisation of the N_b nitrogen from sp^3 to sp^2, alkyl to acyl protecting group, would enable cyclisation to take place.[86] This was justified by suggesting that the piperidine ring containing an sp^2 centre would result in an increase in the equilibrium population of the boat form of the six-membered ring, with the boat conformation placing the aldehyde much closer to the indole π-system. Also, an sp^2-containing six-membered ring results in a slight flattening of the ring such that the aldehyde is located closer to the indole ring (Scheme 3.12).



Scheme 3.12 – Conformational constraints to E-ring cyclisation

With these findings in mind, a protecting group switch from benzyl to benzoyl at the Weinreb amide stage followed by reduction and cyclisation conditions did lead to successful cyclisation, to obtain firstly the intermediate indolenine iminium ion **205**, and the subsequent C2-hydroxy compound **208** (Scheme 3.13).



201 **206** **207**

204 **205**

208

Scheme 3.13 – i) Pd/C, H_2, TFE; ii) BzCl, NEt_3, DCM; iii) $LiAlH_4$, THF, −78 °C to −40 °C; iv) AcOH, Ac_2O, $HCl_{(l)}$, $HCl_{(g)}$, 0 °C to rt; v) $NaHCO_3$

Having successfully managed to obtain the cyclised carbinolamine **208**, attention was focused on how to control the stereoselectivity during the reduction of the iminium ion **205**. During his synthesis of ajmaline, Cook first closes the D-ring in order to facilitate E-ring closure. Pre-forming the D-ring conformationally locks the piperidine ring in its boat form which, as already stated, enables the reacting aldehyde to approach much closer to the indole ring. However, having first closed

the D-ring, Cook was then unable to achieve any favourable selectivity during the indole ring reduction step, and the best selectivity achieved at C2 was 2:3 ajmaline:*epi*-ajmaline. Bailey *et al.* proposed that the selectivity for reduction occurring on the necessary β-face of the iminium ion could be improved if there was some way to block access of reducing agents to the α-face of the indole ring. The presence of an N_b protecting group provides an ideally located blocking group (Figure 3.1).

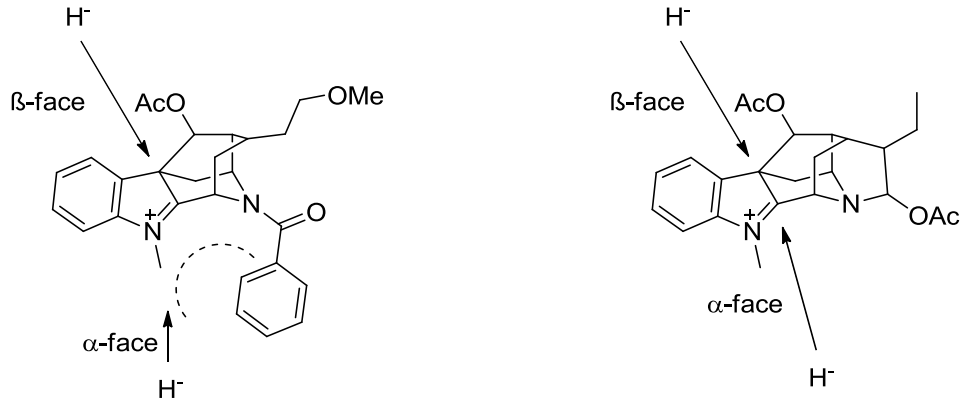
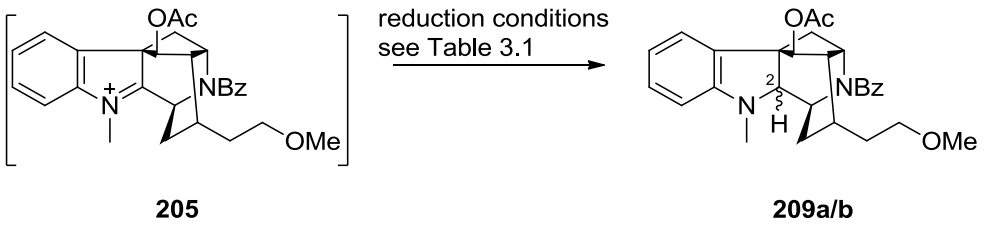


Figure 3.1 – Comparison of steric blocking effects when D-ring is not closed and when the D-ring is closed

Having managed to obtain E-ring-cyclised iminium ion **205** from the benzoyl-protected aldehyde **204**, a range of reducing conditions were then investigated (Table 3.1).



205 **209a/b**

Scheme 3.14 – Iminium ion reduction

Entry	Reducing Agent	C2 Stereochemistry (%)	
		ajmaline	*epi*-ajmaline
1	$NaBH_4$	0	100
2	H_2, Pd/C	0	100
3	BH_3.THF	0	100
4	*N*-selectride®	0	100
5	H_2, PtO_2, 6 M HCl	25[a]	75

Table 3.1 – Indolenine iminium reduction conditions; [a]product was benzoyl ring reduced cyclohexyl derivative

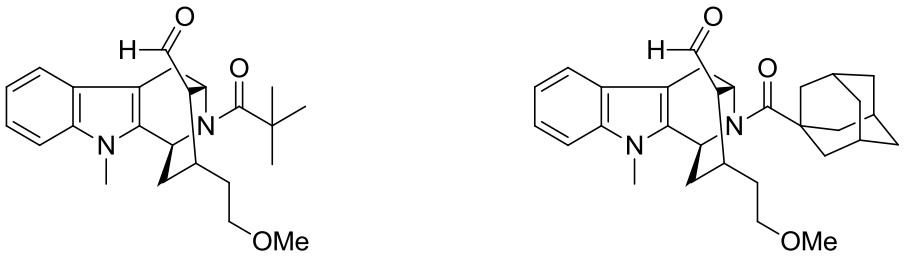
Most conditions attempted failed to give anything other than the C2 *epi*-ajmaline reduced derivative (entries 1-4, Table 3.1). However, when catalytic hydrogenation over Adam's catalyst in hydrochloric acid was attempted (entry 5, Table 3.1), some product was isolated which had the correct C2 stereochemistry for the ajmaline series of compounds. Closer inspection of the crude ^{1}H NMR spectrum showed that the benzoyl ring in this product had been reduced to the corresponding cyclohexyl derivative. It was suggested that the extra steric bulk of the cyclohexyl

ring, as compared with the benzoyl ring, had increased steric hindrance to reduction of the α-face of the indole ring (see Figure 3.1) and thus had increased the relative amount of reduction *via* the β-face of the indole ring.

Based on this finding, Bailey *et al.* suggested that the selectivity of the indole reduction step could be improved by:

- increasing the steric bulk of the N_b protecting group
- increasing the size of the reducing agent
- a combination of the two above effects

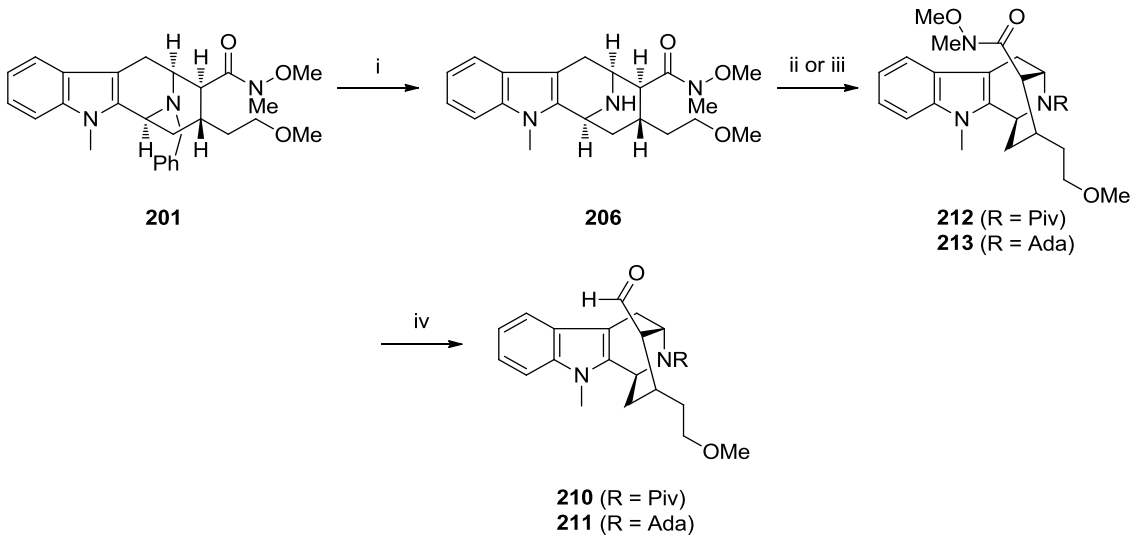
To explore this idea, two new protecting groups were proposed – a pivaloyl amide and an adamantoyl amide.



210 **211**

Figure 3.2 – Pivaloyl- and adamantoyl-protected aldehydes

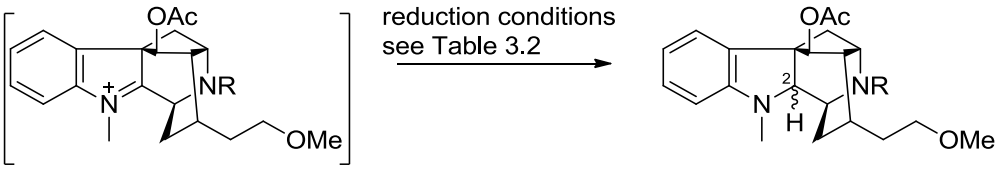
The intended aldehyde targets **210** and **211** were prepared in analogous fashion to the benzoyl-protected aldehyde.



Scheme 3.15 – i) Pd/C, H_2, TFE; ii) PivCl, NEt_3, DCM, iii) AdaCl, NEt_3, DCM; iv) $LiAlH_4$, THF, −78 °C to −40 °C

Catalytic debenzylation of Weinreb amide **201** was carried out over a palladium catalyst followed by acylation using the appropriate acid chloride in triethylamine and dichloromethane. A controlled lithium aluminium hydride reduction of the Weinreb amide to the aldehyde was then carried out such that reduction of the amide protecting group carbonyls was prevented (Scheme 3.15).

Having prepared the pivaloyl- and adamantoyl-protected aldehydes, E-ring cyclisation was carried out as before and reduction conditions were explored.



214 (R = Piv)
215 (R = Ada)

216a/b (R = Piv)
217a/b (R = Ada)

Scheme 3.16 – Iminium ion reduction

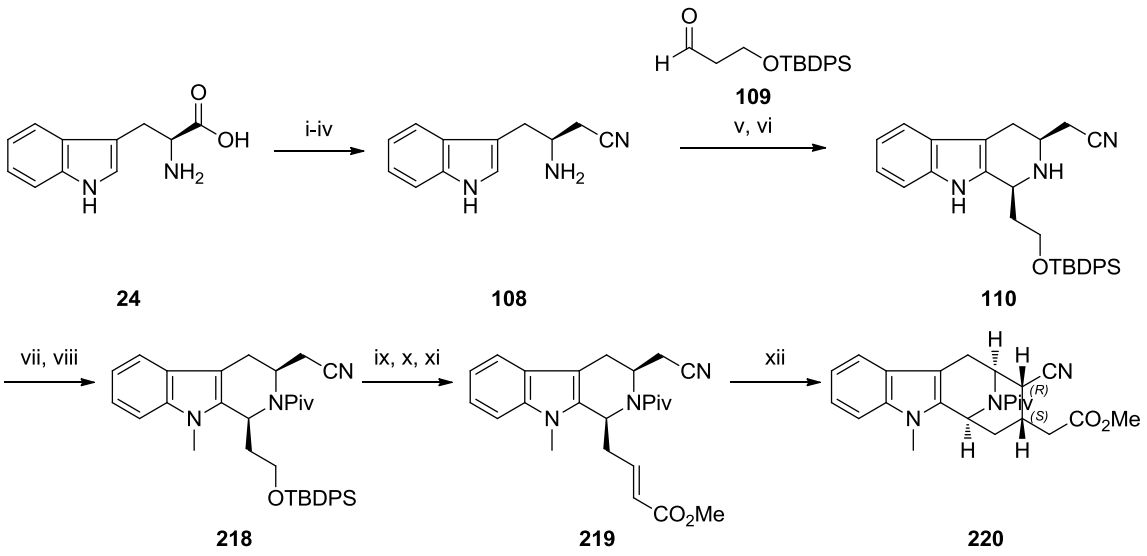
Entry	R	Reducing Agent	Yield (%)	C2 Stereochemistry (%)	
				ajmaline	*epi*-ajmaline
1	pivaloyl	$NaBH_4$	32	0	100
2	pivaloyl	H_2, Pd/C	47	45	55
3	pivaloyl	$LiAl(O^tBu)_3H$	37	58	42
4	adamantoyl	$NaBH_4$	100	0	100
5	adamantoyl	H_2, Pd/C	69	42	58
6	adamantoyl	$LiAl(O^tBu)_3H$	48	72	28

Table 3.2 – Indolenine iminium reduction conditions

The results in table 3.2 show that as the size of the N_b protecting group was increased, the amount of the desired C2 epimer formed also increased. In addition, when combined with bulkier hydride delivering agents the selectivity increased further. The combination of adamantoyl protecting group and the bulky lithium tri(*tert*-butoxy) aluminium hydride reducing agent (entry 6, Table 3.2) gave the greatest selectivity for the ajmaline C2 stereochemistry reported to date.

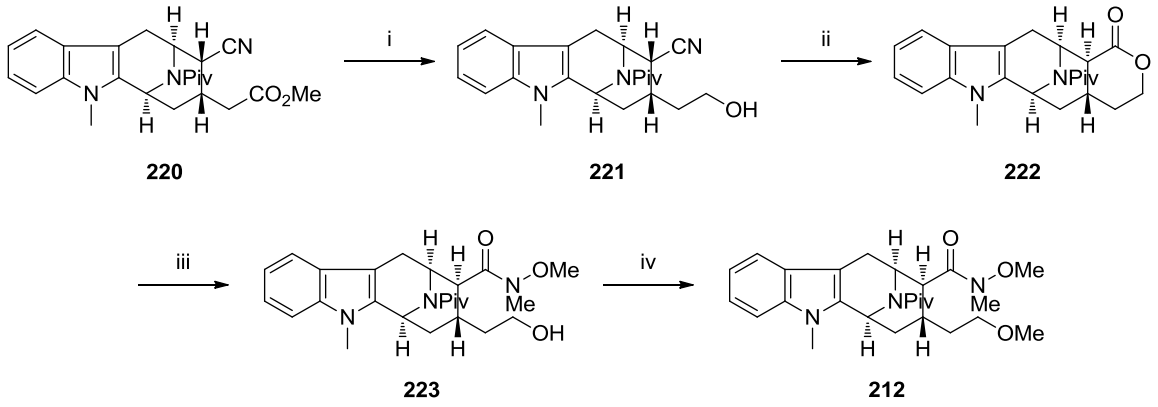
Having demonstrated the viability of a bulky N_b protecting group in combination with a bulky reducing agent to improve the selectivity during indole ring reduction, it was decided to attempt the total synthesis of ajmaline with a bulky amide protecting group in place throughout. It was anticipated that the switch from an sp^3- to an sp^2-based protecting group would alter the known reactivities and stereoselectivities of a number of the synthetic steps. Considerable work would therefore be needed to fully elucidate the subtleties of this new protecting group strategy, and coupled with the fact that amides of this type give complex NMR spectra due to the presence of rotational isomers, the less selective but structurally-simpler pivaloyl amide was chosen as the initial protecting group of choice.

3.1.3 N_b-pivaloyl-protected ajmaline total synthesis[87]



Scheme 3.17 – i) $LiAlH_4$, THF; ii) TsCl, py.; iii) KCN, MeOH, reflux; iv) Na/NH_3, THF, −78 °C; v) **109**, 3 Å MS, DCM, 0 °C to rt; vi) 2 eq. TFA, DCM, −78 °C to rt; vii) PivCl, NEt_3, DCM; viii) MeI, NaH, DMF; ix) TBAF, THF; x) $(COCl)_2$, DMSO, NEt_3, DCM, −60 °C; xi) Ph_3PCHCO_2Me, DCM; xii) LiHMDS, THF, −78 °C

Nitrile amine **108** was prepared as shown previously in four steps from L-tryptophan. Kinetically-controlled Pictet-Spengler cyclisation was then carried out to give the *cis* tetrahydro-β-carboline in 60% yield and the *trans* isomer in 1% yield. At this point, protection of the N_b nitrogen with pivaloyl chloride in the presence of triethylamine led to the pivaloyl-protected carboline. An excess of reagents and extended reaction times were required in order to obtain reasonable yields of the product. Indole methylation was then carried out followed by TBAF-mediated deprotection of the silyl protecting group. The cyano alcohol was then oxidised under Swern conditions and Wittig alkylation of the aldehyde gave the *E* unsaturated ester **219** exclusively in good yield. The selectivity for the Wittig reaction was unexpected since the equivalent reaction carried out previously with N_b-benzyl-protected aldehyde had given the *E* and *Z* esters in a ratio of 4:1, typical for a Wittig alkylation.[57] An intramolecular Michael reaction was then carried out to give the tetracycle **220** as a single diastereoisomer. Lithium diethylamide, the base used for this reaction on the benzyl derivative, gave the desired product in low yield, and as such, a switch to a commercially available solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran resulted in a higher yielding Michael reaction. Examination of the product from this reaction revealed that the stereocentre generated at C15 was (*S*) configured, as was required for ajmaline, with the methyl ester located equatorially on the new ring. The nitrile substituent at C16 was shown to be in an axial position exclusively, which was epimeric to that required for the ajmaline series of compounds (Scheme 3.17). This centre in the equivalent benzyl-protected compound undergoes epimerisation during the subsequent lactonisation step and it was anticipated that the same would be true for the pivaloyl-protected compound to give the desired stereochemistry at C16.



Scheme 3.18 – i) $LiBH_4$, THF, 0 °C; ii) *p*-TsOH, 1,4-dioxane, reflux; iii) HNMeOMe.HCl, $AlMe_3$, DCM; iv) MeI, NaH, THF

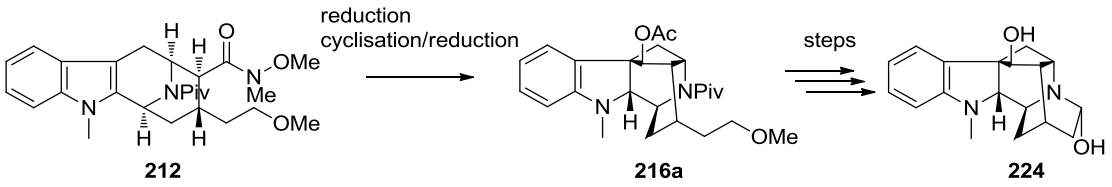
Reduction of methyl ester **220** took place using lithium borohydride in tetrahydrofuran at room temperature to give the cyano alcohol **221**. In contrast to the N_b-benzyl-protected compounds employed previously, the lactonisation and concurrent epimerisation process proved to be problematic. Using the known conditions gave disappointing yields of the desired product, along with the formation of a number of undesired impurities. This process was improved by changing solvent from tetrahydrofuran to 1,4-dioxane, allowing the reaction to be run at a higher temperature. In this manner, the lactone **222** was formed as a single diastereoisomer as anticipated but in a modest 41% yield. Opening of the lactone to the Weinreb amide **223** was carried out using trimethyl aluminium and *N*,*O*-dimethylhydroxylamine hydrochloride, which was then followed by protection of the resulting alcohol as the methyl ether (Scheme 3.18).

3.2 Investigations towards the synthesis of de-ethylajmaline

3.2.1 Introduction

Beard successfully developed a synthetic route which included the sp^2-based pivaloyl N_b protecting group, in place of that previously established, which featured the sp^3-based benzyl protecting group. However, in order for a total synthesis of ajmaline to be completed, the route to Weinreb amide **212** would require significant improvements in yield. Furthermore, the challenging one-pot indole cyclisation and iminium ion reduction required thorough investigation and optimisation, a strategy for the cyclisation of the D-ring needed establishing, and a method of stereoselectively introducing the C20 ethyl group still had to be determined. So, whilst great progress had been made, a significant amount of chemistry still needed to be established and, in some cases, improved.

The initial aim therefore was to prepare synthetic de-ethylajmaline based on the work of Beard.[87] Provided Weinreb amide intermediate **212** could be prepared in sufficient quantity, it was envisioned that reduction of the Weinreb amide to the aldehyde would first take place, followed by the indole cyclisation procedure. Further investigation into the stereoselectivity of the indolenine iminium ion reduction would then take place. Having prepared N_b-pivaloyl-protected acetate **216a**, a strategy for the final deprotection steps and the subsequent D-ring cyclisation would then be established (scheme 3.19).



Scheme 3.19 – Planned route to de-ethyl ajmaline

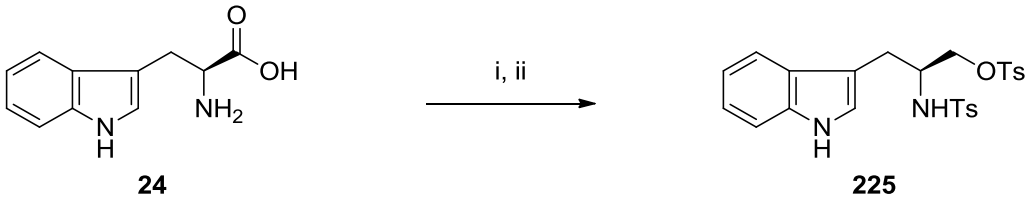
3.2.2 Synthesis of the *cis*-3,5-disubstituted tetrahydro-β-carboline core

The initial objective for the synthesis was homologation of L-tryptophan *via* installation of the nitrile functionality. As previously reported, the nitrile is essential for the enhanced *cis*-selectivity during Pictet-Spengler cyclisation.[54]

Synthetic steps proceeded with the reduction of L-tryptophan **24** to tryptophanol, a reaction that is well known in the literature and was most effectively carried out using lithium aluminium hydride. The reducing agent was introduced *via* cannula under anhydrous conditions and left to stir overnight. An aqueous work-up enabled the aluminium and lithium salts to be removed through filtration and provided the alcohol, usually in quantitative yield, without the need for further purification (Scheme 3.20).

The alcohol was then activated as a tosylate ester in order to provide a good leaving group. Selective tosylation of the alcohol over the amine using *para*-toluenesulfonyl chloride was known to be difficult and, as a result, tosylation of both the alcohol and amine groups was carried out. This was accomplished by the careful addition of tosyl chloride to a solution of the starting material in anhydrous

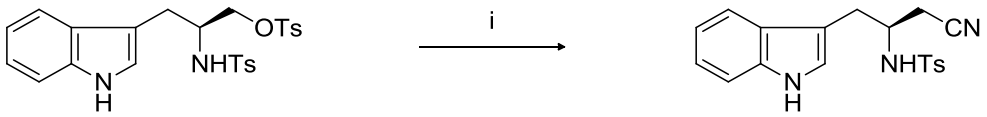
pyridine at 0 °C. Filtration of the crude product through a plug of silica provided analytically pure ditosylate **225**, maximum yields of which were obtained when the reaction was carried out immediately following formation of tryptophanol (Scheme 3.20).



24 **225**

Scheme 3.20 – i) $LiAlH_4$, THF, rt, 16 hrs; ii) TsCl, py., 0 °C, 16 hrs, 92% (over two steps)

An S_N2 displacement of the *O*-tosyl group then took place using potassium cyanide in refluxing methanol for two hours (Scheme 3.21). Displacement of the *O*-tosyl group occured most favourably, leading to the formation of a single product in excellent yield. Recrystallisation of the crude product from methanol gave the pure amino-protected nitrile **226** as a pale brown solid.

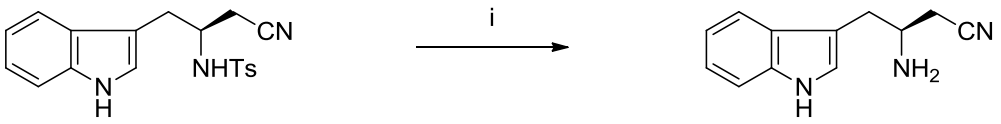


225 **226**

Scheme 3.21 – i) KCN, MeOH, reflux, 2 hrs, 81%

Removal of the amino tosyl group was then required, a process that had proven to be particularly unpredictable. A single-electron reduction of the sulfonamide, using sodium metal in liquid ammonia and anhydrous tetrahydrofuran, yielded the free

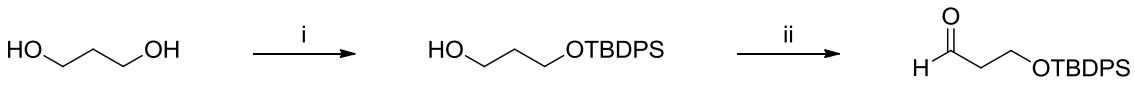
amine most consistently. This method, after an acid/base work-up, gave the nitrile amine **108** as an orange solid in a best yield of 91% (Scheme 3.22).



226 **108**

Scheme 3.22 – i) Na, $NH_{3(l)}$, THF, 30 min, 91%

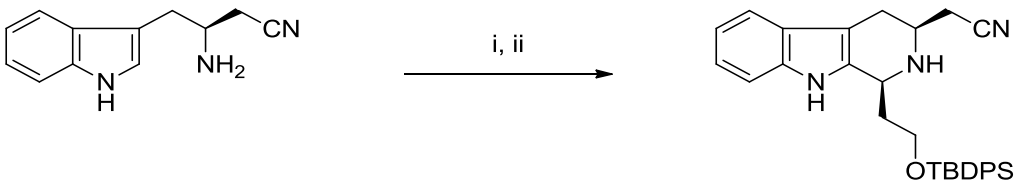
Having prepared amine **108** ready for Pictet-Spengler cyclisation, the necessary aromatic aldehyde **109** had to be synthesised. *tert*-Butyldiphenylsilyl (TBDPS) protection of propane-1,3-diol was achieved to give the monoprotected alcohol **228**, which was sufficiently pure to make chromatography unnecessary (Scheme 3.23). Use of the silyl chloride as the rate limiting reagent helped to minimise formation of the *bis*-protected diol. Swern oxidation of alcohol **228** then yielded TBDPS-protected propionaldehyde in excellent yield (Scheme 3.23). This compound tended to decompose relatively quickly, so was always used as soon as possible following its preparation.



227 **228** **109**

Scheme 3.23 – i) TBDPSCl, NaH, THF, 95%; ii) $(COCl)_2$, DMSO, NEt_3, DCM, −60 °C, quant.

Pictet-Spengler cyclisation of the nitrile amine **108** and the TBDPS-protected aldehyde **109** then took place to install the second stereocentre of ajmaline. Employing kinetic control during this reaction, by carrying out the cyclisation at −78 °C, induced preferential formation of the *cis* diastereoisomer in a selectivity of greater than 25:1, as determined by the detection limits of the available NMR facilities. Full conversion to the imine intermediate occurred usually within twenty-four hours and was confirmed by ^{1}H NMR analysis. Cyclisation was then triggered by the addition of two equivalents of trifluoroacetic acid at −78 °C. TLC analysis of the reaction products suggested that traces of the *trans* isomer were present, but this was undetectable in the crude ^{1}H NMR spectrum (Scheme 3.24).



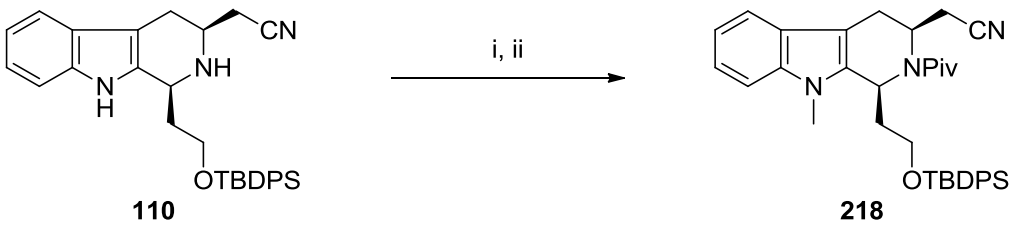
108 **110**

Scheme 3.24 – i) **109**, 3 Å MS, DCM, 0 °C to rt; ii) 2 eq. TFA, DCM, −78 °C to rt, 53% (over two steps)

3.2.3 Amine protection steps

Having prepared *cis*-3,5-disubstituted tetrahydro-β-carboline **110** in a highly stereoselective manner on a multigram scale, installation of the crucial pivaloyl amide protecting group was then planned. Acylation of the N_b position proved to be kinetically unfavourable due to its hindered nature. Given extended reaction times, and a large excess of pivaloyl chloride, a best yield of 80% of the protected

amine could be obtained (Scheme 3.25). Since the natural product is methylated on the indole nitrogen, it was decided at this point to protect this position with a methyl group. Initial indole methylation conditions of two equivalents of sodium hydride and two equivalents of methyl iodide resulted in only a 50% conversion to product. Extended reaction times in the presence of the strong base sodium hydride resulted in the formation of an undesired side product in appreciable yields. Presumably the lability of the proton at the α-position to the nitrile was the source of the undesired by-products. In order to try and prevent the formation of this by-product, a reduced number of mole equivalents of sodium hydride were employed (1.1) and a further 2 equivalents of methyl iodide were added once TLC analysis suggested that the reaction had come to a halt, after approximately thirty minutes. Under these conditions the methylated product **218** could be obtained in a yield of 83%, a significant improvement on the 50% yield previously obtained (Scheme 3.25). The fully protected tetrahydro-β-carboline product proved to be particularly stable and could be stored for extended periods of time.



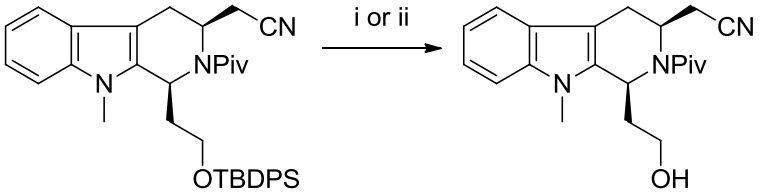
110 **218**

Scheme 3.25 – i) PivCl, NEt_3, DCM, 48 hrs, 80%; ii) MeI, NaH, DMF, 2.5 hrs, 83%

3.2.4 Intramolecular Michael cyclisation

The following experimental steps were planned with a view to the formation of the next ring, to be carried out using an intramolecular Michael addition onto an α,β-unsaturated ester.

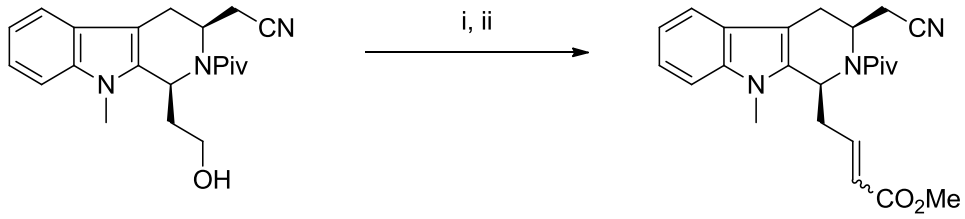
The first step towards this goal was deprotection of the TBDPS-protected alcohol. The well-known literature conditions of tetra-*N*-butylammonium fluoride (TBAF) in anhydrous tetrahydrofuran yielded the free alcohol **229**, but careful control of the reaction conditions were required in order to obtain good yields of the desired product (Scheme 3.26). Extended reaction times and/or the presence of moisture, led to the formation of undesired side products, again hinting at the base sensitivity of the molecule. TBAF induced deprotection of the silyl group provided the alcohol in a best yield of 96%. Alternatively, it was found that the TBDPS group could be removed using acid-mediated deprotection conditions; a solution of acetyl chloride in methanol cleaved the TBDPS group to give the desired alcohol **229** in a best yield of 92% (Scheme 3.26).



218 **229**

Scheme 3.26 – i) TBAF, THF, 0 °C, 2 hrs, 96%; ii) AcCl, MeOH, 16 hrs, 92%

Another Swern oxidation provided the aldehyde in quantitative yield which was then set-up for homologation. Wittig alkylation of the aldehyde with methyl (triphenylphosphoranylidene)acetate yielded the *E* and *Z* α,β-unsaturated methyl esters in a best yield of 87% (Scheme 3.27). Formation of the *E* alkene was favoured as expected, since the use of a stabilised phosphorane results in the reversible formation of the intermediate oxaphosphetane. This thermodynamic control leads to the preferential formation of the *anti*-oxaphosphetane which in turn eliminates stereospecifically to the *E* alkene. The product ratio for this reaction was found to be typically 9:1 (*E*:*Z*) though, since this relative stereochemistry was to be subsequently lost, both geometric isomers could be used in the following ring-closing step.

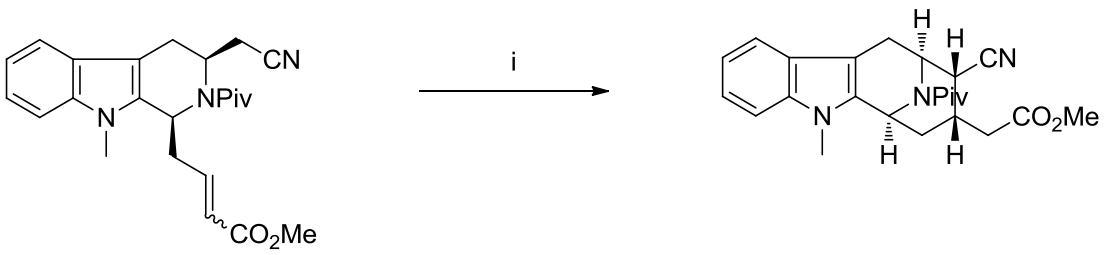


229 **219 *E:Z***

Scheme 3.27 – i) $(COCl)_2$, DMSO, NEt_3, DCM, −60 °C, quant.; ii) Ph_3PCHCO_2Me, DCM, 4 hrs, 87%

The next planned transformation was preparation of the tetracyclic nitrile **220** *via* an intramolecular Michael addition, and was crucial to the overall synthesis since it was used to install two new stereocentres simultaneously. Use of the base lithium diethylamide to deprotonate the nitrile α-position led to 1,4-addition onto the α,β-unsaturated ester generally with yields of less than 50%. Bearing in mind the molecule's sensitivity to basic conditions as shown in previous steps, the use of

the more hindered, milder base lithium bis(trimethylsilyl)amide was attempted. This improved the yield of the desired tetracycle significantly and gave the product as a single diastereoisomer (Scheme 3.28). The preference for the methyl ester substituent to occupy an equatorial position in the ring-forming transition state led to an (*S*) configured stereocentre at C15 exclusively. The nitrile adopted an axial position in the new ring making the new chiral centre at C16 (*R*) configured, which is epimeric to the C16 stereochemistry found in ajmaline. The formation of a single diastereoisomer during this procedure was significant since the equivalent reaction carried out on the N_b-benzyl-protected compound provided the tetracyclic product as a mixture of C16 epimers (2:1 ratio, (*S:R*)). Clearly, the presence of the pivaloyl amide protecting group in place of the benzyl moiety was having a significant effect on the stereoselectivity of the Michael addition.



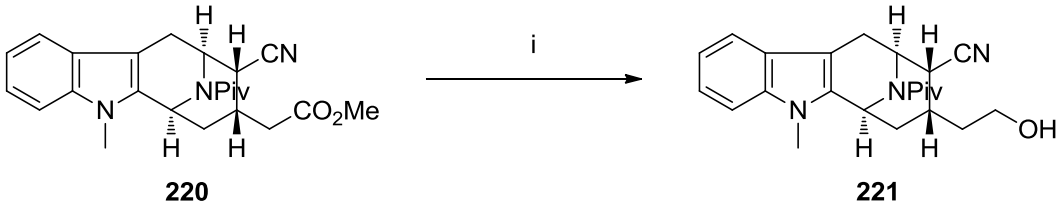
219 *E:Z* **220**

Scheme 3.28 – i) LiHMDS, THF, −78 °C, 2 hrs, 90%

3.2.5 Lactone formation and C16 epimerisation

For the analogous N_b-benzyl-protected compounds, the stereocentre at C16 could be epimerised *via* the formation of a pentacyclic lactone[56] and this convergence of stereochemistry had also been demonstrated for the N_b-pivaloyl-protected

compound **221** (see section 3.1.3). Prior to epimerisation though, the methyl ester was selectively reduced in the presence of the amide and nitrile functionalities using lithium borohydride in refluxing tetrahydrofuran to give alcohol **221** in quantitative yield (Scheme 3.29).



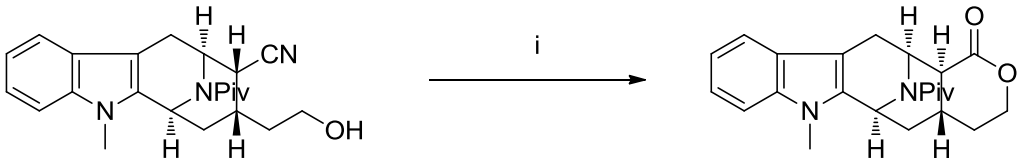
220 **221**

Scheme 3.29 – i) $LiBH_4$, THF, reflux, 16 hrs, quant.

Ring closure of the alcohol onto the nitrile was then carried out using an excess of *para*-toluenesulfonic acid, which resulted in the formation of the desired lactone **222**. This step had two key functions. The first was that the formation of the decalin ring junction in the presence of acid resulted in epimerisation of the stereocentre at C16 to that present in the target molecule, de-ethyl ajmaline. The thermodynamic preference for the *trans*-decalin ring system was thought to be the driving force for this epimerisation. The second key feature of this reaction was that it installed the carbonyl functionality, which would be essential for the intended cyclisation step onto the indole ring.

It transpired that the temperature at which this reaction was carried out had an important role in the determination of the purity and amount of the lactone formed. The use of refluxing tetrahydrofuran proved too low a temperature to drive the reaction to completion, whereas the use of refluxing toluene resulted in significant

decomposition of the reaction components. Through variation of the precise reaction conditions, it was found that carrying out the reaction in 1,4-dioxane at 90 °C resulted in the highest yields of lactone **222** (Scheme 3.30).



221 **222**

Scheme 3.30 – i) *p*-TsOH.H_2O, 1,4-dioxane, 90 °C, 16 hrs, 74%

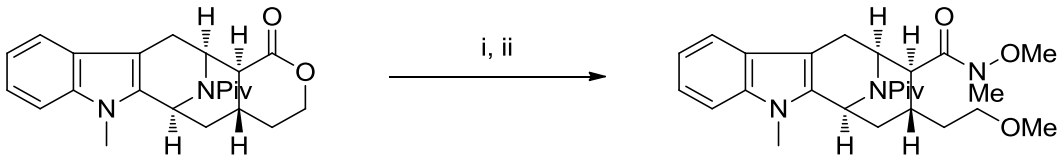
3.2.6 E-ring cyclisation

Up to this point in the synthesis, three new stereocentres had been created, all with exceptional stereocontrol.

The next major step towards construction of the ajmaline framework was the formation of the *spiro* centre at the indole 3-position. Two steps were first required to set up the ring-closing reaction, the first being opening of the lactone using *N*,*O*-dimethylhydroxylamine hydrochloride. The use of the Lewis acid trimethyl aluminium in combination with the hydroxylamine gave the ring opened Weinreb amide in a best yield of 79% (Scheme 3.31).

The resulting alcohol group then required protecting. The use of methyl iodide and sodium hydride provided the methyl ether, which proved to be robust enough to survive the harsh acidic conditions used during the next cyclisation step (Scheme

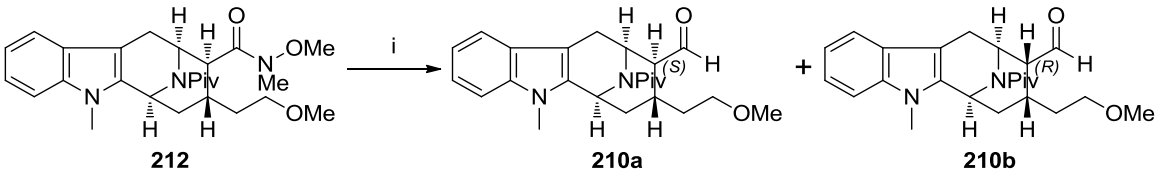
3.33). The relatively small size of the methyl group also meant that it did not interfere in a steric sense during the subsequent cyclisation. Methylation of this alcohol was generally low yielding, though the starting material could be recovered following chromatography and was subsequently recycled to give a good overall level of conversion to the desired product.



222 **212**

Scheme 3.31 – i) HNMeOMe.HCl, $AlMe_3$, DCM, 16 hrs, 79%; ii) MeI, NaH, THF, 16 hrs, 83%

Reduction of the Weinreb amide **212** to the aldehyde using lithium aluminium hydride was then carried out. Careful control of the reaction temperature was necessary to prevent reduction of the pivaloyl amide also taking place, and consequently, the reduction was carried out at −78 °C with a sodium hydroxide quench following warming to −40 °C (Scheme 3.32).

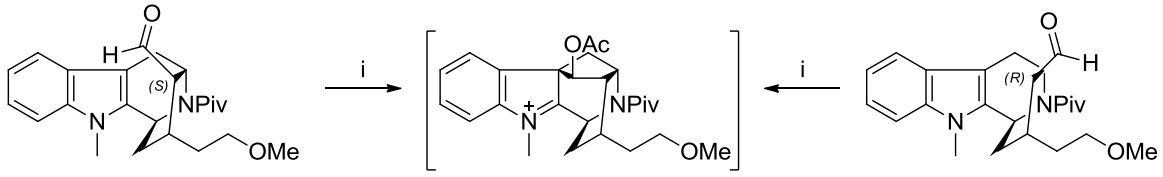


212 **210a** **210b**

Scheme 3.32 – i) $LiAlH_4$, THF, −78 °C to −40 °C, NaOH quench, 77%

Examination of the crude ^{1}H NMR from this reaction usually revealed the presence of two distinct aldehyde peaks in ratios varying from 3:1 to 7:1. The major product had a doublet aldehyde proton peak at 9.67 ppm with a *J* value of 2.3 Hz. The minor product aldehyde proton peak was downfield at 9.77 ppm and appeared as a broad singlet. The two aldehyde compounds were separable by column chromatography and preliminary examination of the ^{1}H NMR spectra suggested that the two products were epimeric at C16. Further NMR and mass spectrometry analysis confirmed this initial characterisation to be correct, the major product being the desired (*S*)-aldehyde **210a** and the minor product being the (*R*)-aldehyde **210b**.

It was found that by carrying out the subsequent cyclisation on both epimers separately that they both cyclised on to the indole 3-position, the (*S*) C16 epimer ring closed directly whilst the (*R*) compound epimerised under the reaction conditions prior to ring closure (Scheme 3.33).

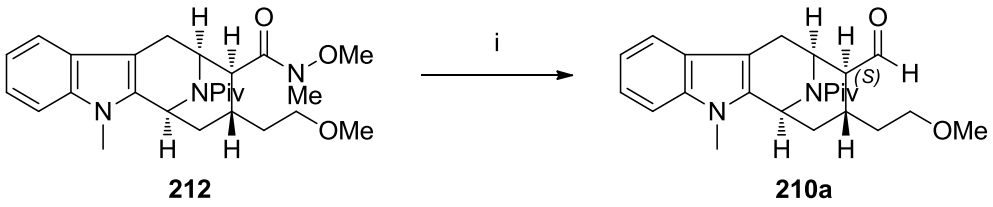


210a **214** **210b**

Scheme 3.33 – i) AcOH, Ac_2O, $HCl_{(l)}$, $HCl_{(g)}$, 0 °C to rt, 24 hrs

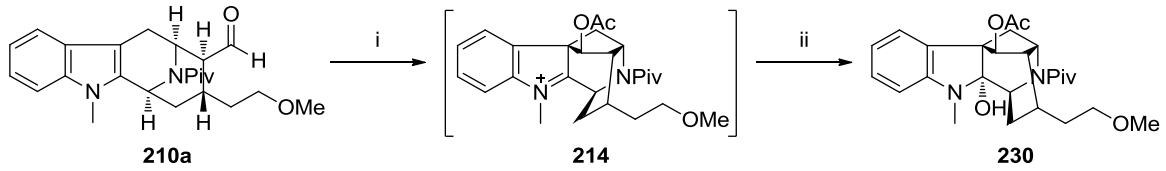
By carefully monitoring the progress of the Weinreb amide reduction by TLC analysis, it was found that epimerisation of the aldehyde was taking place upon the addition of sodium hydroxide during the work-up. Modification of the work-up

procedure to an ethyl acetate quench, followed by the addition of a few drops of saturated sodium sulfate to chelate the aluminium and lithium salts, successfully resulted in reduction of the Weinreb amide without compromising the chirality at C16 (Scheme 3.34).



Scheme 3.34 – i) $LiAlH_4$, THF, −78 °C to −40 °C, EtOAc quench, 82%

With the ability to generate diastereomerically pure aldehyde **210a**, ring closure onto the indole 3-position was then planned. Literature precedent had shown that if the D-ring had already been formed, the aldehyde carbonyl was conformationally restricted within reacting distance of the aromatic ring.[34] It was therefore anticipated that the latent flexibility of aldehyde **210a** would mean the cyclisation step would be more difficult to achieve in good yield. The cyclisation was carried out by stirring the aldehyde in acetic acid, acetic anhydride and concentrated hydrochloric acid and then bubbling hydrogen chloride gas through the reaction mixture (Scheme 3.35). TLC analysis of the crude mixture showed that the reaction had generated one major product.

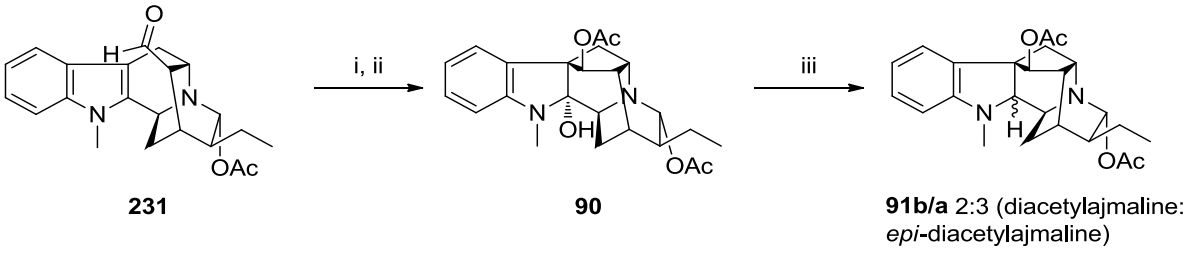


210a **214** **230**

Scheme 3.35 – i) AcOH, Ac_2O, $HCl_{(l)}$, $HCl_{(g)}$, 0 °C to rt, 24 hrs; ii) $NaHCO_3$, DCM

An aqueous work-up with saturated sodium bicarbonate yielded a single product (Scheme 3.35). It was assumed that a small nucleophile such as the hydroxyl anion would add to the iminium ion from the least-hindered α-face of the indole ring to give the C2-hydroxy *epi*-ajmaline compound **230** (Figure 3.1).

By first isolating carbinolamine **90**, Cook was able to reduce the C2 position to the diacetyl ajmaline compound but only in a ratio of 2:3 diacetylajmaline **91b**:*epi*-diacetylajmaline **91a** (Scheme 3.36).[34]

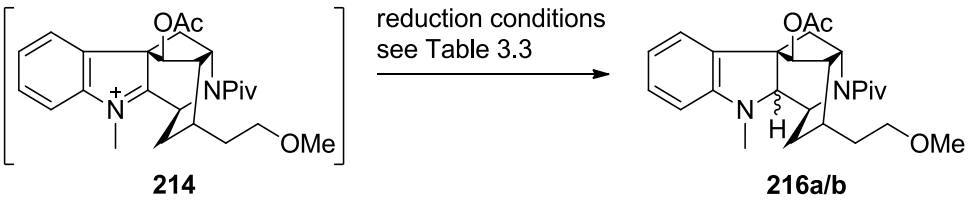


231 **90** **91b/a** 2:3 (diacetylajmaline: *epi*-diacetylajmaline)

Scheme 3.36 – i) AcOH, Ac_2O, $HCl_{(l)}$, $HCl_{(g)}$, rt, 48 hrs; ii) $NaHCO_3$, 85% (over two steps); iii) $BF_3.OEt_2$, PtO_2, H_2, 14 hrs, 89%

3.2.7 Indolenine iminium ion reduction

By carrying out the ring-closing step and the subsequent iminium ion reduction in a one-pot sequence, with the presence of a bulky amine protecting group proximal to the least-hindered face of the indole ring, it was hoped that a much greater preference for the desired C2 epimer could be created. The cyclisation was carried out to form the iminium ion and a range of reductions were attempted.



214 **216a/b**

Scheme 3.37 – Iminium ion reduction

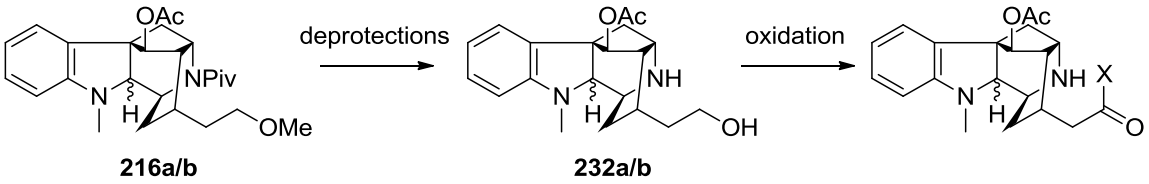
Entry	Reducing Agent	C2 ratio *epi*-ajmaline:ajmaline	Yield (%)
1	$NaBH_4$	100:0	32
2	H_2, Pd/C (10%)	58:42	36
3	*N*-Selectride®	70:30	49 (deacetylated at C17)
4	$LiAl(O^tBu)_3H$	37:63	34

Table 3.3 – Summary of reduction reactions

The results summarised in table 3.3 show that the sodium borohydride reduction yielded the undesired epimer **216b** exclusively whilst better selectivity was achieved with an alternative hydride reducing agent, *N*-Selectride®. Hydrogenation over a palladium catalyst yielded a roughly 1:1 mixture of epimers. The bulky lithium tri(*tert*-butoxy) aluminium hydride proved the most promising, yielding the desired C2 epimer **216a** with moderate selectivity.

3.2.8 Deprotection reactions

Having achieved enhanced selectivity during the iminium ion reduction, efforts were then focused on achieving the final ring closure. It was anticipated that removal of the amine protecting group followed by removal of the methyl ether and an oxidation of the resulting alcohol would set up the ring closure.

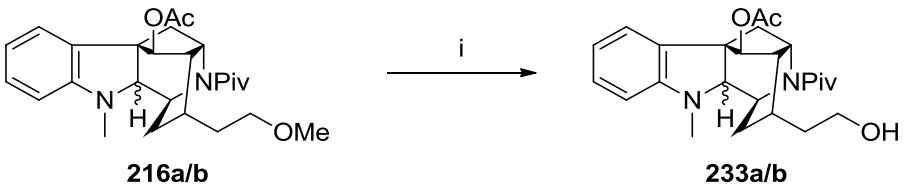


216a/b **232a/b**

Scheme 3.38 – Planned steps to D-ring closure

Boron tribromide cleavage of the methyl ether was attempted prior to amine deprotection so that routes towards α-alkylation of an aldehyde equivalent could be explored, with a view to introducing the C20 ethyl group. Under these conditions, TLC analysis showed that the methyl group was cleaved cleanly, but

due to the small scale of the reaction, the purified alcohols **233a** and **233b** were isolated in only 25% yield (Scheme 3.39).

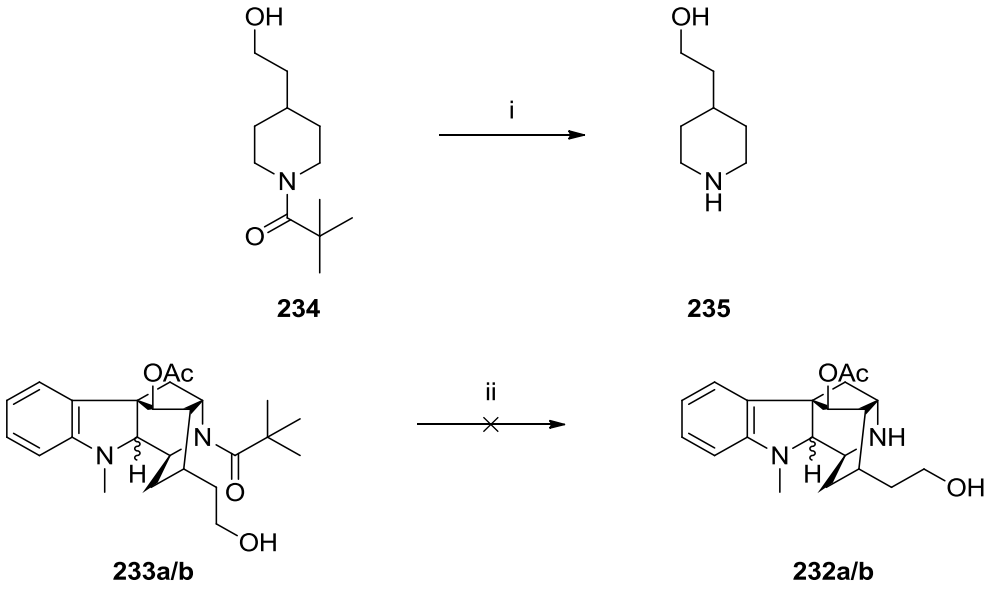


216a/b **233a/b**

Scheme 3.39 – i) BBr_3, DCM, −78 °C to rt, 24 hrs, 25%

Deprotection of the pivaloyl amide was then required. An amide based protecting group is necessary in order for successful E-ring cyclisation to take place and the pivaloyl amide gives the desired products from indolenine iminium reduction favourably. The deprotection of the pivaloyl amide was anticipated to be difficult to achieve, but it was thought that conditions to remove the protecting group effectively could be developed.

During investigations to find suitable deprotection conditions, it was found that refluxing concentrated hydrochloric acid did hydrolyse the pivaloyl amide from a piperidine model system, but similar conditions on an advanced synthetic intermediate caused extensive decomposition of the starting material (Scheme 3.40).



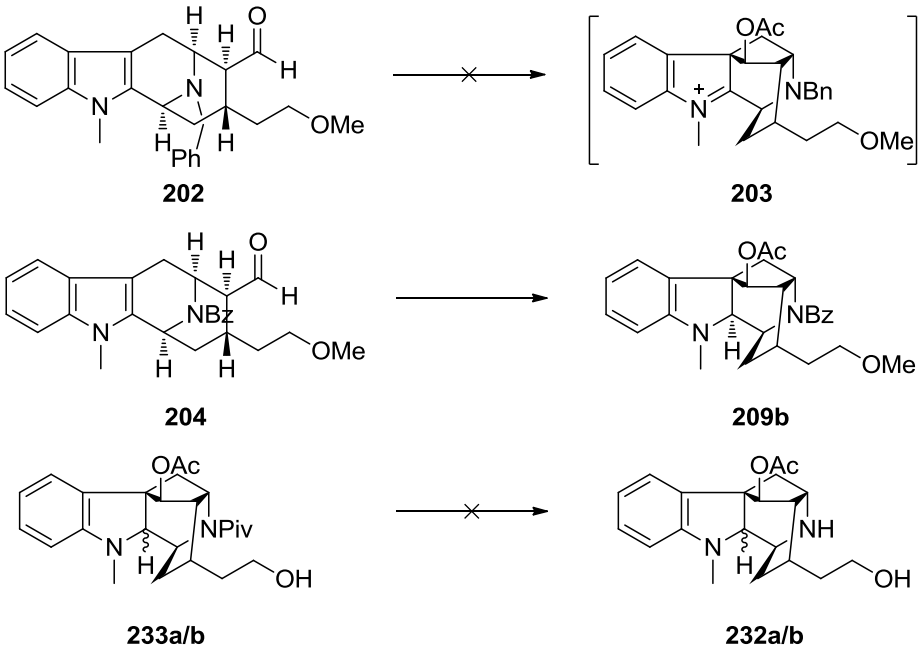
Scheme 3.40 – i) $HCl_{(l)}$, 1,4-dioxane, 100 °C, 5 days; ii) 6 M HCl, 1,4-dioxane, 50 °C, 24 hrs

Attempts with thiolate nucleophiles[88] and reductive elimination efforts using lithium hydride reducing agents,[89] DIBAL[90] and lithium metal[91] also failed to provide any of the free amine. Thus, an inability to remove the pivaloyl amide brought to an end its use as the N_b protecting group and with it this particular route to ajmaline.

3.2.9 2,2-Dimethyl-2-(*ortho*-nitrophenyl)acetyl (DMNA) protecting group

There had been significant drawbacks to all the amine protecting groups used up to this point. The benzyl-protected aldehyde **202** fails to cyclise onto the indole 3-position, due to highly unfavourable conformational constraints. The benzoyl-protected aldehyde **204** cyclises, but reduction of the resulting iminium ion gives the undesired C2 epimer **209b** only. Pivaloyl-protected aldehyde **210a** also cyclised successfully, and reduction of the iminium ion gave the desired C2 epimer

with moderate stereocontrol, but was then resistant to all attempts at amide deprotection (Scheme 3.41).



Scheme 3.41 – Protecting group problems

Clearly, the pivaloyl amide protecting group displayed the most synthetically useful attributes of those used up to this point, so a literature search for a modified pivaloyl protecting group was undertaken. The 2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl (DMNA) group was found to be a promising candidate as it is structurally-similar to the pivaloyl group, but modified to include a nitrophenyl ring, and crucially, the presence of the *ortho*-nitro group would enable a more effective intramolecular deprotection to take place. Compared to the pivaloyl amide, the DMNA group is much bulkier and it was also hoped that this extra steric influence would result in a more favourable reduction of the indolenine iminium ion to give the desired C2 epimer with greater selectivity.

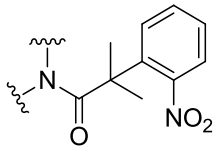
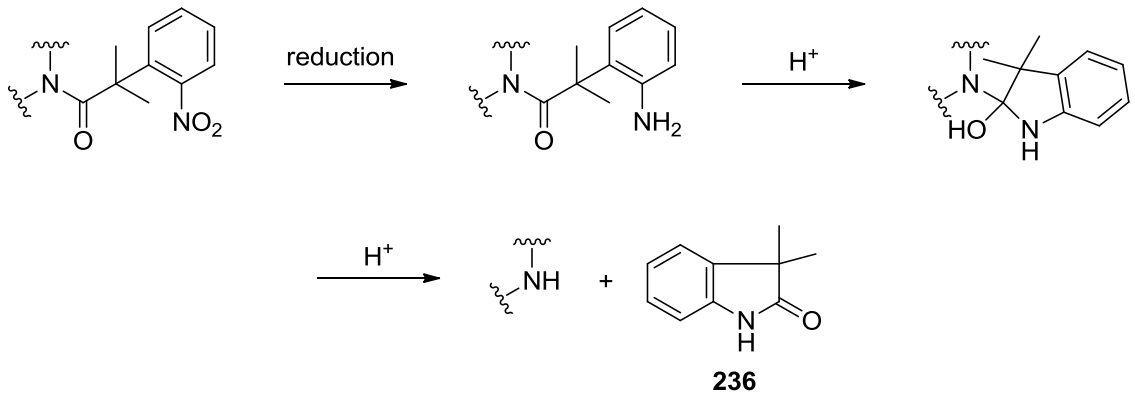


Figure 3.3 – 2,2-Dimethyl-2-(*ortho*-nitrophenyl)acetyl (DMNA) amide

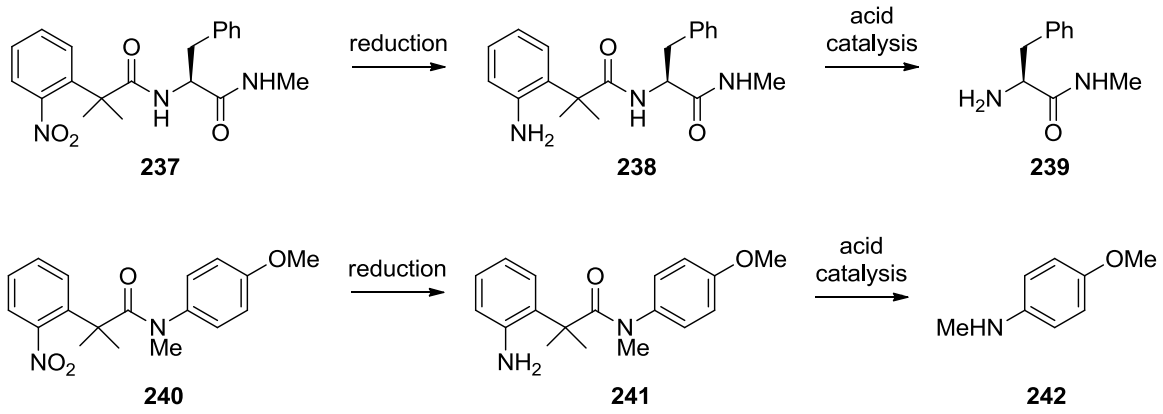
Aromatic nitro derived amides had been identified as useful peptide chemistry protecting groups in 1952 – in that particular example, a nitrophenoxyacetyl protecting group was applied.[92] In 1979 Entwistle reported the use of 2-nitrophenylpropionic acid as a general protecting group for amino and hydroxyl functionalities.[93] A study was later carried out which investigated the relationships between the structures and cyclisation kinetics of 2-nitrophenyl amides and their potential use as bioreductive prodrugs.[94] The DMNA protecting group was first reported as a general assisted-cleavage amine protecting group in 2002.[95]

All the reports outlined above have some crucial parallels. The key to removal of nitrophenyl amide protecting groups, and as such the DMNA group, is reduction of the aromatic nitro group to the corresponding amine or hydroxylamine group using transition metal catalysis. The reduced compound, under acidic catalysis, then undergoes intramolecular ring closure onto the amide carbonyl to give the free amine and the thermodynamically favourable lactam **236** (Scheme 3.42).



Scheme 3.42 – DMNA deprotection mechanism

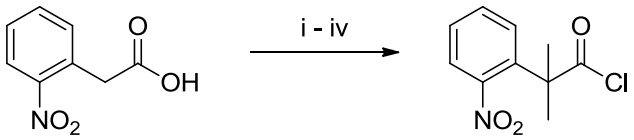
As can be seen from the examples in scheme 3.43, deprotection of the DMNA-protected tertiary amide **240** goes as well as deprotection of the secondary DMNA amide **237**.



Scheme 3.43 – Deprotection of a secondary amide[95] and a tertiary amide[94]

3.2.10 Synthesis of DMNA-Cl

The DMNA group is typically introduced using the acid chloride and it was felt this would be the most efficient method of protecting a suitable late-stage ajmaline intermediate. DMNA-Cl could be prepared in four steps from commercially available *ortho*-nitrophenylacetic acid (Scheme 3.44).



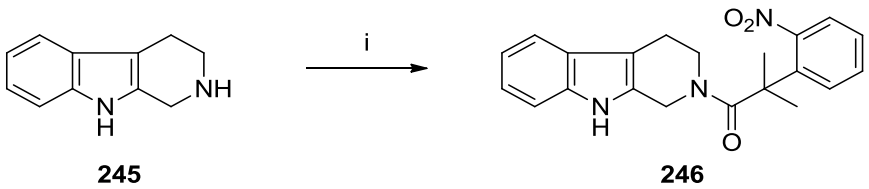
243 **244**

Scheme 3.44 – i) $SOCl_2$, MeOH, reflux, 2 hrs, 88%; ii) MeI, NaH, 18-crown-6, DMF, 2 hrs, quant.; iii) MeOH, 15% aq. NaOH, 100 °C, 6 hrs, 89%; iv) $SOCl_2$, 50 °C, 2 hrs, quant.

Conversion of acid **243** to the methyl ester took place using thionyl chloride in refluxing methanol, which was followed by di-alkylation at the benzylic position using methyl iodide, sodium hydride and a crown ether. Kinetic studies have shown that the gem-dimethyl groups cause the lactam deprotection product to form more readily due to the Thorpe-Ingold effect,[94] steric repulsion between the geminal dimethyls leading to a decompression of the bond angle such that the aromatic amine can approach closer to the carbonyl group.[96] Hydrolysis of the methyl ester in 15% sodium hydroxide gave the crude acid, recrystallisation of which gave an orange solid in excellent yield. When ready to be used, acid chloride **244** was formed by stirring the acid in thionyl chloride at 50 °C for two hours.

3.2.11 DMNA model system protection and deprotection procedures

With acid chloride **244** readily available, it was decided to first investigate the protection and deprotection protocols of the DMNA group on a simple tetrahydro-β-carboline derivative (Scheme 3.45).



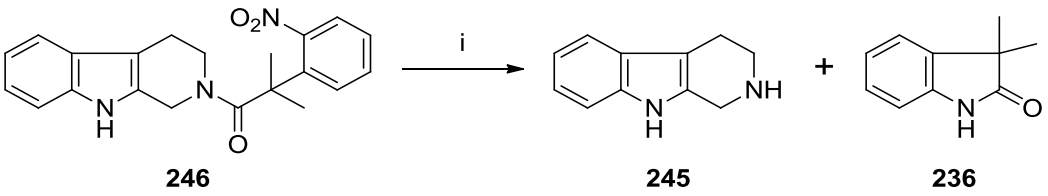
245 **246**

Scheme 3.45 – i) DMNA-Cl, NEt_3, DCM, rt, 1 hr, quant.

Stirring carboline **245** with a slight excess of DMNA acid chloride **244** and a base gave the DMNA-protected amine **246** in excellent yield. The presence of amide rotamers in a ratio of 4:1 was noted in the NMR spectra of the product, which is in line with similar amide-protected systems and is unsurprising given the bulky nature of the DMNA group. This simple model experiment showed that amines could be protected as DMNA amides with great success and relative ease.

Using the same model system, the deprotection conditions were then attempted. Rather than carry out the reduction of the nitro group followed by acid-catalysed cleavage as two distinct steps, it was decided to try and carry out the deprotection procedure in a one-pot reaction as was demonstrated by Hu.[95] As such, the DMNA-protected carboline **246** was stirred in 10% acetic acid in methanol over a palladium catalyst under an atmosphere of hydrogen for thirty minutes. Acid/base

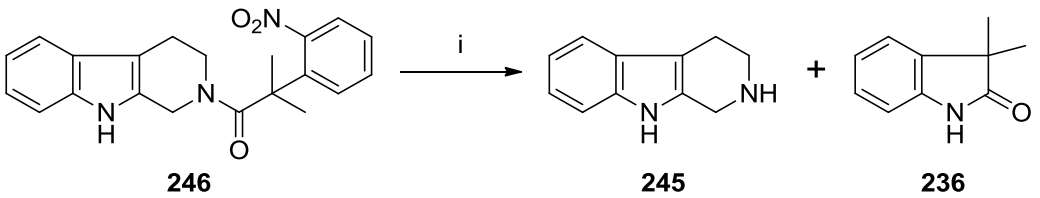
work-up of the crude product yielded two products; the amine-deprotected tetrahydro-β-carboline **245** and the lactam by-product **236** (Scheme 3.46).



Scheme 3.46 – i) Pd/C (10%), H_2, 10% AcOH in MeOH, rt, 30 min, quant.

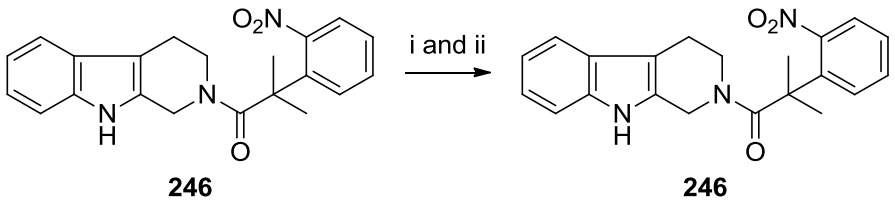
The lactam by-product was distinctive by TLC analysis and its presence was indicative of the progress of the reaction. For this particular reaction, the excellent yield was based on isolation of the lactam since recovery of the deprotected amine proved to be more difficult.

As a potential alternative, the one-step deprotection was also carried out using Adams' catalyst. In this instance dichloromethane was used as the reaction solvent, and again, a quantitative amount of the lactam was obtained. The lack of an acid catalyst or even a protic solvent hinted at how facile the cleavage of the DMNA group was for this particular amine (Scheme 3.47).



Scheme 3.47 – i) PtO_2, H_2, DCM, 16 hrs, quant.

At this point, DMNA-protected carboline **246** was also stirred in the presence of the reducing agents lithium aluminium hydride and sodium borohydride in order to check whether the integrity of the aromatic nitro group would be retained during subsequent synthetic transformations. Reduction of the Weinreb amide **247** and the indolenine iminium ion **249** was to be carried out using lithium aluminium hydride and sodium borohydride respectively. It was found that both sets of conditions returned the aromatic nitro group unaffected (Scheme 3.48).

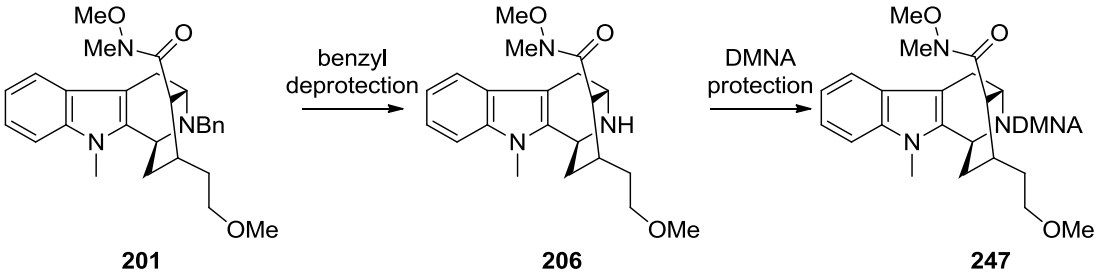


Scheme 3.48 – i) $LiAlH_4$, THF, −78 °C to −20 °C; ii) $NaBH_4$, THF, rt, 48 hrs

3.2.12 Preparation of DMNA-protected Weinreb amide 247

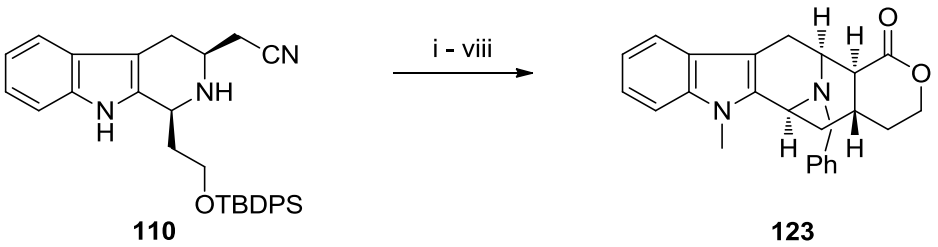
Having shown that the DMNA group could be introduced and removed from suitable model systems, and that it would be stable to the various synthetic transformations of the intended route, the point of its introduction needed to be decided. Given the significant time and work needed to incorporate the pivaloyl group by protecting the Pictet-Spengler product **110** near the beginning of the synthetic route, it was thought that introduction of the DMNA group to a more advanced intermediate would be more appropriate. Provided the DMNA group could be successfully incorporated into the synthetic route, DMNA protection of carboline **110** would then be considered.

The Weinreb amide intermediate **206** was deemed the most suitable point at which to introduce the new protecting group, giving DMNA-protected Weinreb amide **247**. It was therefore necessary to prepare benzyl-protected Weinreb amide **201**, the benzyl deprotection of which was known to take place with relative ease (see Scheme 3.13).



Scheme 3.49 – Planned introduction of the DMNA protecting group

The synthesis of benzyl-protected Weinreb amide **201** began from TBDPS-protected tetrahydro-β-carboline **110**, the synthesis of which was carried out as described previously (see section 3.2.2). The subsequent route to lactone **123** was carried out following the method of Clingan (see sections 1.4.2 and 1.4.4), with some slight modifications to improve the efficiency of the route (Scheme 3.50).[56]



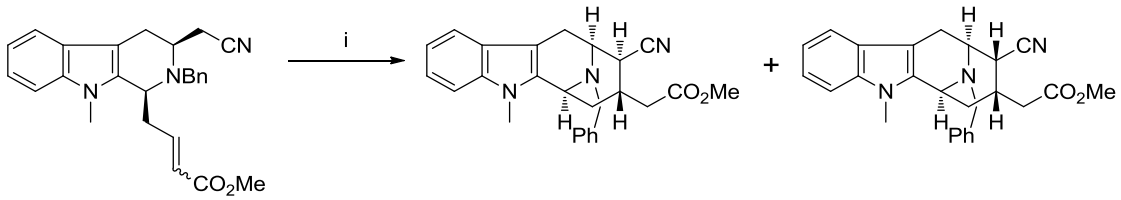
110 **123**

Scheme 3.50 – i) BnBr, DIPEA, MeCN, 80 °C, 95%; ii) MeI, NaH, DMF, 96%; iii) TBAF, THF, 90%; iv) $(COCl)_2$, DMSO, NEt_3, DCM, −60 °C, 97%; v) $Ph_3PCH_2CO_2Me$, DCM, 81%; vi) LiHMDS, THF, −78 °C, 66%; vii) $LiBH_4$, THF, 66 °C, 82%; viii) *p*-TsOH.H_2O, THF, 66 °C, 63%

As with the pivaloyl-protected compounds, protection of the basic secondary amine took place first. The use of sodium bicarbonate in refluxing benzyl bromide gave disappointing yields and obtaining the pure benzylated compound proved to be extremely difficult. By following an adapted method of Soloshonok,[97] the benzyl-protected compound could be formed in a much greater yield by stirring the amine in an excess of benzyl bromide and diisopropylethylamine in hot acetonitrile for two days. Indole methylation, TBDPS deprotection and Swern oxidation were carried out in analogous fashion to the pivaloyl-protected compounds, as reported above (see sections 3.2.3 and 3.2.4), and Wittig alkylation of the aldehyde gave the *E* and *Z* unsaturated esters in a ratio of 11:1.

Deprotonation of the α-position using lithium bis(trimethylsilyl)amide initiated intramolecular Michael cyclisation as seen previously, though TLC analysis of the crude reaction mixture revealed the presence of two diastereoisomeric products. Separation of the two isomers by chromatography and further NMR analysis revealed the products to be the two C16 epimers **121a** and **121b** in a ratio of 1:1 (Scheme 3.51). This was in contrast to the selectivity reported by Clingan (2:1,

(*S:R*) see section 1.4.4) and may have been as a consequence of using lithium bis(trimethylsilyl)amide as the base instead of lithium diethylamide.

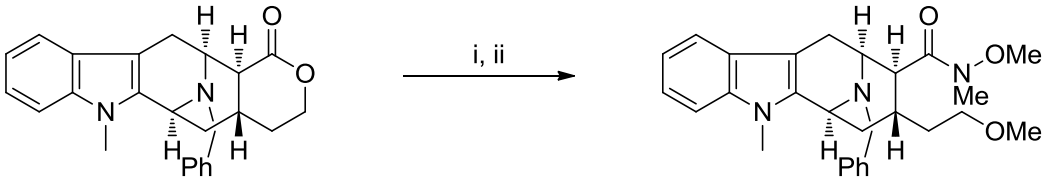


120 *E:Z* **121a** **121b**

Scheme 3.51 – i) LiHMDS, THF, −78 °C, 2 hrs, 66%

As was found with the pivaloyl-protected series of compounds, the ester group was located equatorially in the new ring at C15, whilst the nitrile at C16 was seen as a 1:1 mixture of axial and equatorial isomers. Reduction of the methyl esters and lactonisation was carried out on the two epimers independently, which confirmed that both C16 stereoisomers cyclised selectively to the *trans*-decalin lactone. As a result, subsequent attempts were carried out on the diastereoisomeric mixture of esters and then the following alcohols.

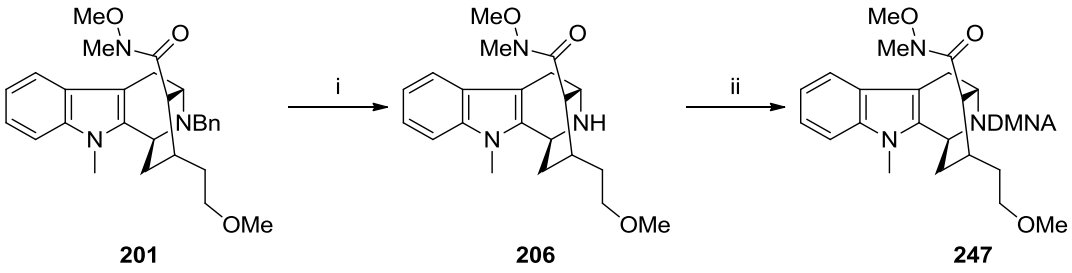
Having converged both epimers to diastereomerically pure lactone **123**, its opening to the Weinreb amide with *N,O*-dimethylhydroxylamine hydrochloride and trimethyl aluminium took place. This was again followed by protection of the alcohol as the methyl ether (Scheme 3.52).



123 **201**

Scheme 3.52 – i) HNMeOMe.HCl, $AlMe_3$, DCM, 16 hrs, 86%; ii) MeI, NaH, THF, 16 hrs, 92%

The protecting group switch was then planned on benzyl-protected Weinreb amide **201**. Catalytic hydrogenolysis of the benzyl group over a palladium catalyst gave the free amine and acylation was carried out using 1.5 equivalents of DMNA acid chloride and 1.5 equivalents of triethylamine, to give DMNA carboxamide **247** in excellent yield (Scheme 3.53).

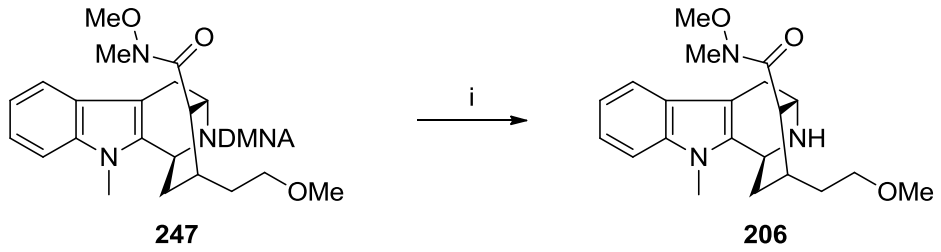


201 **206** **247**

Scheme 3.53 – i) Pd/C (10%), H_2, TFE, 24 hrs, 89%; DMNA-Cl, NEt_3, DCM, 16 hrs, 92%

TLC analysis of the crude amide product revealed the presence of one reaction product, whilst ^{1}H NMR analysis showed two amide products in a ratio of 3.5:1. These two products were shown to be amide rotamers through the use of ^{13}C NMR and elevated temperature ^{1}H NMR, as running the proton NMR experiment at 90 °C in *d*-DMSO resulted in convergence of the rotameric peaks.

Having shown that the DMNA group could be introduced in excellent yield to the more hindered Weinreb amide type system, the deprotection protocol was again tested.



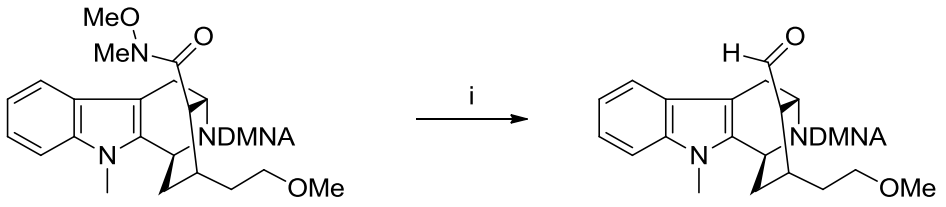
247 **206**

Scheme 3.54 – i) Pd/C (10%), H_2, 10% AcOH in MeOH, 1 hr, quant.

As with the carboline model compound, DMNA deprotection of Weinreb amide **247** went in good yield to give free amine **206** (Scheme 3.54). Encouraged by this result, the next steps of the total synthesis were attempted.

3.2.13 E-ring cyclisation and indole ring reduction

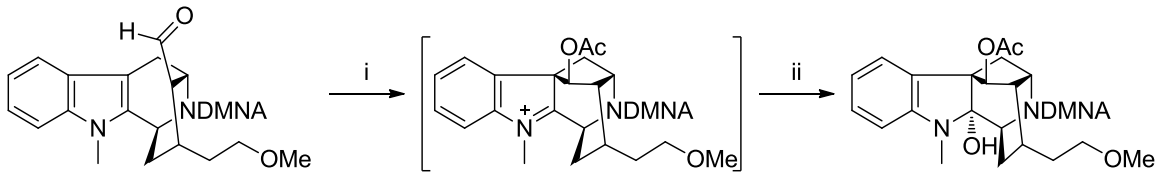
Controlled reduction of the Weinreb amide using lithium aluminium hydride gave aldehyde **248** as expected. Quenching the reaction at −30 °C gave maximum conversion of the Weinreb amide to the aldehyde whilst ensuring that reductions of the amide carbonyl and the aromatic nitro group were prevented. The aldehyde product was isolated as a mixture of rotamers in a ratio of 1:1 (Scheme 3.55).



247 **248**

Scheme 3.55 – i) $LiAlH_4$, THF, −78 °C to −30 °C, 4 hrs, 90%

DMNA-protected aldehyde **248** was then stirred under the standard acidic conditions used previously for twenty-four hours at room temperature and the solvents removed to give the cyclised salt **249** as a brown, amorphous solid (Scheme 3.56).



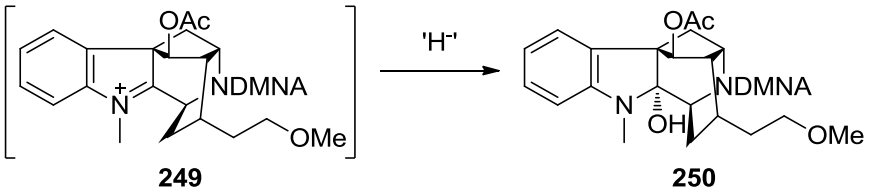
248 **249** **250**

Scheme 3.56 – i) AcOH, Ac_2O, $HCl_{(l)}$, $HCl_{(g)}$, 0 °C to rt, 24 hrs; ii) $NaHCO_3$, DCM

A sodium bicarbonate work-up of a small portion of this material was then carried out with ^1H NMR analysis of the resulting product revealing a number of distinctive changes from the precursor aldehyde. An upfield shift of the indole aromatic protons from ~7.2-7.5 ppm to ~6.6-6.8 ppm was noted, which indicated reduction of the indole ring, as was an upfield shift of the aromatic *N*-methyl singlet, again indicative of reduction of the indole ring. The presence of a distinctive *O*-acetyl singlet at ~2.1 ppm also provided further evidence that cyclisation had gone

successfully as the resulting C17 alcohol had been trapped as the acetate ester (Scheme 3.56). Full characterisation of this product by NMR analysis proved to be difficult due to the presence of a set of complimentary amide rotamer peaks.

Having confirmed that cyclisation and hydration of the iminium ion had taken place through the isolation of C2-hydroxy carbinolamine **250**, investigations were then carried out into the stereoselectivity of the reduction of indolenine iminium ion **249**.



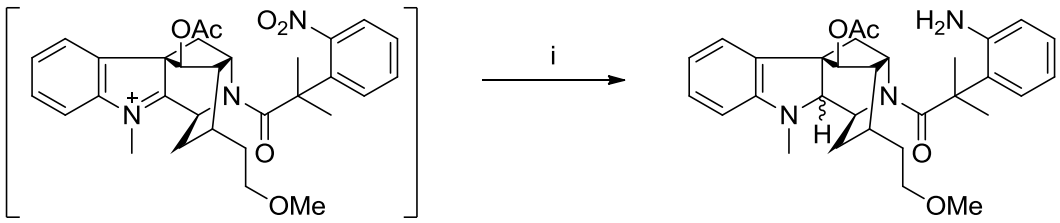
249 **250**

Scheme 3.57 – Indolenine iminium ion reduction

Unfortunately, despite numerous attempts under a variety of conditions, reductions carried out using the hydride reducing agents sodium borohydride, lithium tri(*tert*-butoxy) aluminium hydride and tetramethylammonium triacetoxy borohydride,[98] with which it was hoped an increase in the selectivity for the desired C2 epimer would be observed, seemingly gave C2-hydroxy compound **250** as the major product (Scheme 3.57). The reasons for the failure of hydride based reagents to reduce the DMNA-protected indolenine iminium ion are unclear. If the DMNA group was sufficiently bulky to completely prevent reduction from the undesired α-face of the iminium ion, as was intended, then it might be expected that only the desired C2 reduced product would be formed. However, it is possible that under the reaction conditions attempted, reduction of the indolenine iminium ion *via* the

desired β-face was unfavourable enough such that no hydride reduced products were formed at all and that the C2-hydroxy product was generated during the aqueous work-up.

Reduction of the iminium ion did go successfully by carrying out the reaction under conditions of catalytic hydrogenation, this however only gave slight selectivity for the desired C2 epimer (~1.5:1). Carrying out the reduction *via* catalytic hydrogenation also went with an extra complication – reduction of the DMNA aromatic nitro group. This result had not been completely unexpected and it had been hoped that under these reaction conditions the DMNA group would concomitantly deprotect. It had already been shown that under similar conditions carried out on the model systems the DMNA group had spontaneously deprotected (Schemes 3.46 and 3.54).



249 **251a/b**

Scheme 3.58 – Pd/C (10%), H_2, DCM, 16 hrs

An upfield shift of the DMNA aromatic protons confirmed reduction of the nitro group to the amine, with this shift resulting from the exchange of a relatively electron-deficient aromatic ring for an electron-rich system. The asymmetric (1550-1475 cm^{-1}) and symmetric (1360-1290 cm^{-1}) stretching frequencies of the nitro

group nitrogen-oxygen bonds were no longer seen in the infrared spectrum and mass spectrometry confirmed the presence of a molecular ion corresponding to the mass of the aromatic amino compound.

3.2.14 DMNA deprotection

Since the DMNA group had failed to deprotect under conditions of catalytic hydrogenation during reduction of the indolenine iminium ion, attempts were then made to remove the protecting group through a distinct second step. Hu *et al*. had shown that reductive cleavage of the DMNA group was achieved by carrying out the reaction in acidic conditions and it was thought that the lack of an acidic medium was the reason that amide **251** had not deprotected upon reduction to the aniline type system.[95]

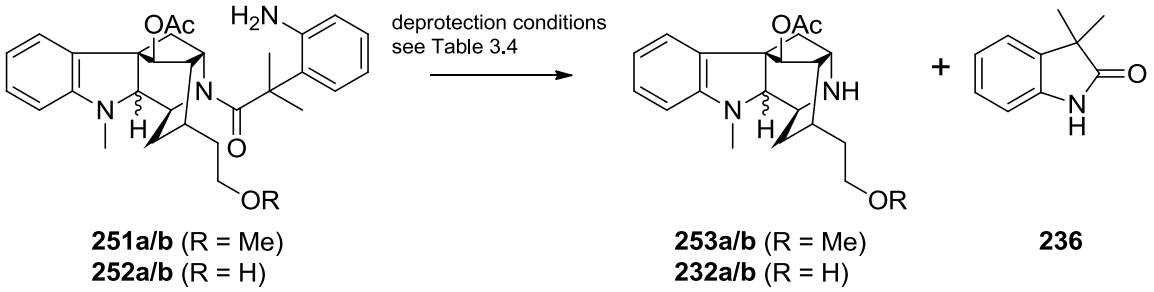
As a result, deprotection of aromatic amines **251a/b** was attempted under a range of conditions whilst varying:

- reaction temperature – in order to overcome any unfavourable steric effects
- acid concentration – in order to investigate whether catalytic or excessive amounts of catalyst was more favourable
- the use of aqueous or anhydrous acidic conditions – to see whether water was attacking the amide carbonyl in favour of the intended amine

The major results from these deprotection attempts are summarised in table 3.4 and show that most attempts were entirely unsuccessful.

Entry	R	Deprotection Conditions	Temperature (°C)	Product
1	Me	10% AcOH/MeOH	rt[a]	None seen
2	Me	10% AcOH/MeOH	40	None seen
3	Me	0.05 eq. *p*-TsOH, dioxane	rt	None seen
4	Me	1.5 eq. *p*-TsOH, dioxane	rt	None seen
5	Me	3 eq. *p*-TsOH, dioxane	40	None seen
6	Me	3 eq. *p*-TsOH, dioxane	100	None seen
7	Me	2 M HCl/dioxane	100	None seen
8	Me	4 M HCl/dioxane	rt	Lactam[b]
9	Me	0.05 eq. *p*-TsOH, dioxane, 3 Å MS	100	Lactam[b]
10	H	10% AcOH/MeOH	rt	None seen
11	H	10% AcOH/MeOH	40	None seen
12	H	0.05 eq. *p*-TsOH, dioxane	rt	None seen
13	H	0.05 eq. *p*-TsOH, dioxane	50	None seen
14	H	0.05 eq. *p*-TsOH, dioxane	100	None seen
15	H	1.5 eq. *p*-TsOH, dioxane	100	None seen
16	H	2.5 eq. *p*-TsOH, dioxane	100	None seen
17	H	2.5 eq. *p*-TsOH, dioxane, 3 Å MS	100	None seen

Table 3.4 – Summary of acid-catalysed DMNA deprotection conditions; [a]rt in the range of 15-19 °C; [b]less than 5% of lactam **236** isolated



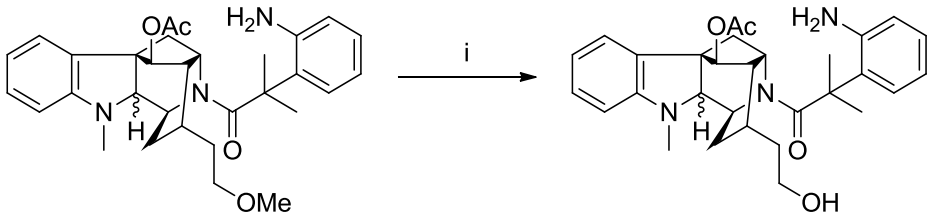
251a/b (R = Me)
252a/b (R = H)

253a/b (R = Me)
232a/b (R = H)

236

Scheme 3.59 – DMNA deprotection attempts

In light of the failed deprotection attempts, and to circumvent the possibility that a nucleophilic aromatic amino group hadn't been formed during reduction of the nitro group, the deprotection of the methyl ether was planned. It was thought that the presence of the alcohol may facilitate removal of the protecting group *via* an intramolecular acyl transfer, and whilst DMNA transfer would have to occur through the formation of an unfavourable eight-membered ring, conformational analysis suggested that the amide carbonyl would be within reacting distance of the alcohol. As such, the methyl ether group was deprotected using boron tribromide which, in contrast to the amine deprotection, went cleanly to give the free alcohol **252** (Scheme 3.60).



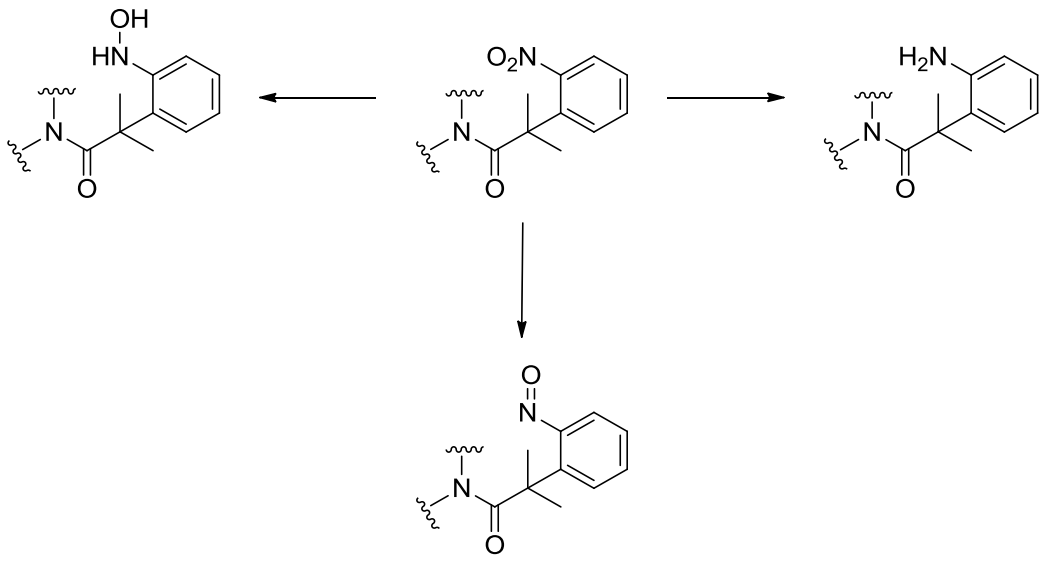
251a/b

252a/b

Scheme 3.60 – i) BBr_3, DCM, −78 °C to rt, 24 hrs, 66%

Having obtained alcohols **252a** and **252b** in good yield, a range of deprotection conditions were again attempted, but with even less success than had already been seen (Table 3.4).

Given the ease with which the DMNA group had deprotected from the model reaction systems and the systems seen in the literature, it was completely baffling that deprotection had not occurred. To explain possible reasons for this it was considered that the aromatic group had not reduced to the amine. However, examination of the relevant NMR and IR spectra provided no evidence to suggest that the nitro or nitroso groups were the prevalent products following catalytic reduction. Even if reduction had ceased at the hydroxylamine, it is known that these types of species are even more nucleophilic than the corresponding amines due to the α-effect.[99]



Scheme 3.61 – Nitro group reduction possibilities

The next factor to consider was whether a steric effect was hindering approach of the aromatic amine to the amide carbonyl, which is thought to be the rate determining step during deprotection of the DMNA group.[94]

Examination of both amide rotamer conformations suggested no reason why approach of the amino group should be blocked or disfavoured, but, the fact that a fraction of the DMNA group could be removed at high temperature (entry 9, Table 3.4) suggested that there was a significant energy barrier to overcome for successful reaction to take place. Unfortunately, extended reaction times under those conditions led to significant decomposition of the reaction components.

In contrast, the result demonstrating a small amount of deprotection at room temperature (entry 8, Table 3.4) suggested that the significant reaction variable was not temperature, but the necessity for anhydrous acidic conditions. The inefficiency of the two sets of deprotection conditions from which the lactam by-product was isolated, and the failure to isolate any of the corresponding amine, meant that those particular deprotection conditions were rendered unpractical.

Despite achieving selectivity for the desired C2 epimer during reduction of the indolenine iminium ion, an inability to remove the amine protecting group resulted in this particular route towards de-ethyl ajmaline being abandoned.

3.2.15 2,4,6-Trimethylbenzoyl protecting group

Masamune employed a benzoyl group to protect the N_b nitrogen during his synthesis of ajmaline (see section 1.2.1), and the deprotection of benzoyl amides can be achieved by reduction of the carbonyl, followed by catalytic hydrogenolysis of the resulting benzyl group. However, reduction of the benzoyl amide requires the use of the strong reducing agent lithium aluminium hydride, and by virtue of having to employ a second hydrogenolysis step, this is overall a less desirable deprotection method. Bearing in mind that an inability to remove both the pivaloyl and DMNA amide protecting groups had cut short the previous synthetic attempts towards ajmaline, it was felt that the use of a benzoyl derived protecting group would prove to be more successful. The decision to employ a modified benzoyl group with extra steric bulk was therefore made, in order to try and improve the selectivity during reduction of the iminium ion. As such, the trimethylbenzoyl (TMB) group was thought to be a viable alternative.

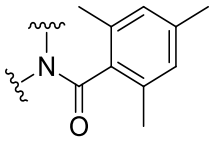
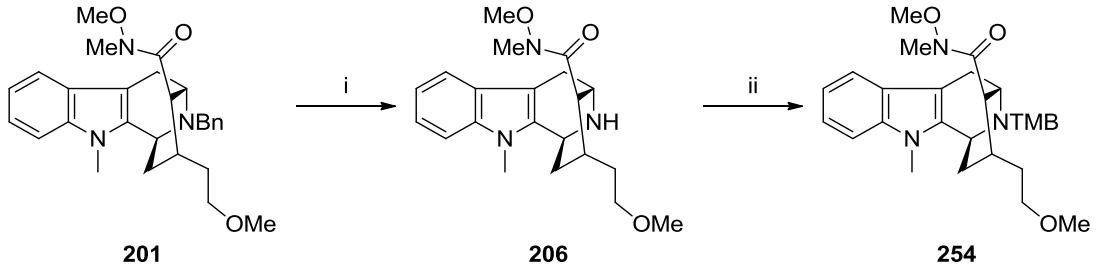


Figure 3.4 – 2,4,6-Trimethylbenzoyl amide protecting group

The trimethylbenzoyl group was introduced in a similar manner to the DMNA group; deprotection of benzyl-protected Weinreb amide **201** followed by acylation using commercially available TMB-Cl (Scheme 3.62).



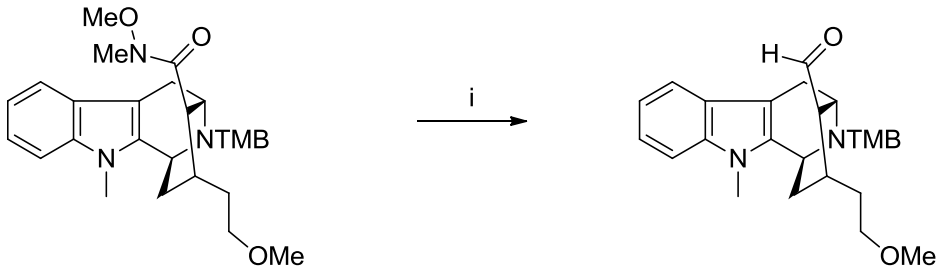
201 **206** **254**

Scheme 3.62 – i) Pd/C (10%), H_2, TFE, 24 hrs, 89%; ii) TMB-Cl, NEt_3, DCM, rt, 22 hrs, 85%

Stirring amine **206** with a slight excess of the acid chloride and triethylamine in dichloromethane gave trimethylbenzoyl carboxamide **254** in good yield. TLC analysis of the crude product revealed the presence of two new compounds and further analysis using ^{1}H NMR confirmed these two compounds to be amide products in a ratio of approximately 4:1 (Scheme 3.62). The two amides were separable by column chromatography, but surprisingly, both compounds re-equilibrated during collection of the fractions to give 4:1 mixtures of the two compounds, both with similar distributions to the crude products. Based on examination of the crude NMR spectra, it was assumed that the two compounds were amide rotational isomers, in line with other amide based protecting groups and as was noted with the DMNA group. It was thought that the 2,6-substituted aromatic methyl groups provided enough hindrance to rotation of the amide group such that the conformers were separable at room temperature, but at the elevated temperatures employed during removal of the solvents, enough energy was provided for equilibration to take place.

Reduction of the Weinreb amide to the aldehyde was carried out on a mixture of the two conformers; a lithium aluminium hydride reduction at −78 °C with a quench

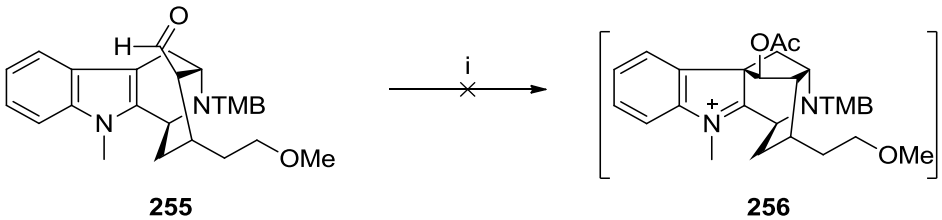
at −30 °C, gave two reaction products by TLC and ^{1}H NMR analysis. Again, the presence of amide rotamers was noted but in a ratio of 1:1 in this instance. The two compounds were again separable by chromatography but re-equilibrated during collection of the fractions to give 1:1 mixtures of the aldehydes (Scheme 3.63).



254 **255**

Scheme 3.63 – i) $LiAlH_4$, THF, −78 °C to −30 °C, 4 hrs, 89%

Having prepared aldehyde **255**, cyclisation onto the indole 3-position was planned. Unfortunately, employing the standard acidic cyclisation conditions failed to yield any of the corresponding indolenine iminium ion **256** despite repeated attempts (Scheme 3.64).



255 **256**

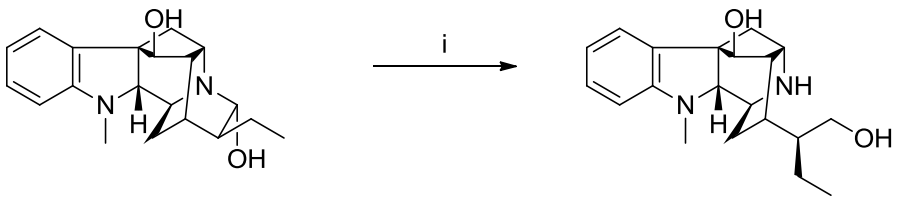
Scheme 3.64 – i) AcOH, Ac_2O, $HCl_{(l)}$, $HCl_{(g)}$, 0 °C to rt, 24 hrs

Based on previous findings it was known that because of the resulting conformational effects, amide based N_b protecting groups were necessary for successful cyclisation onto the indole ring to take place.[86] TMB-protected aldehyde **255** failed to cyclise despite fulfilling this requirement. The exact reasons for the cyclisation reaction to fail are not known but spectroscopic analysis of the reaction products suggested that, under the conditions of the reaction, the aldehyde was degrading before successful cyclisation was able to take place.

The failure of aldehyde **255** to cyclise, led to use of the TMB protecting group being abandoned, and given the unresolved protecting group issues, efforts towards the total synthesis of de-ethyl ajmaline were also abandoned.

3.2.16 D-ring closure investigation

Whilst the forward synthetic steps were being investigated, and given the commercial availability of ajmaline, it was decided to attempt the intended final steps of the synthetic route in order to formulate a strategy for completion of the total synthesis. Using the method of Stöckigt, ajmaline was converted to 4,21-secoajmaline **52** (Scheme 3.65).[100]



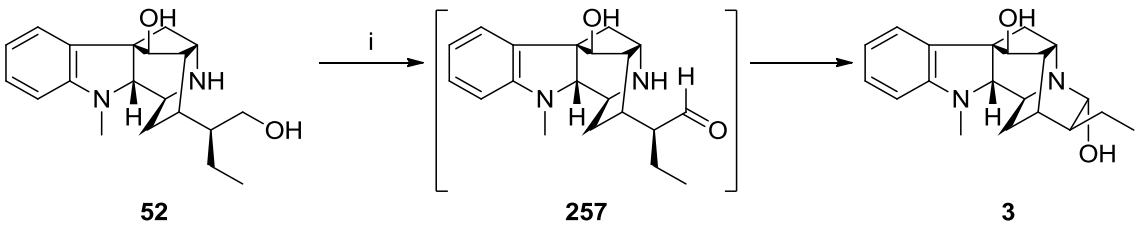
3 **52**

Scheme 3.65 – i) 0.1 M citrate/NaOH buffer, $NaBH_4$, MeOH, 0 °C, 16 hrs, 89%

The portion-wise addition of sodium borohydride to ajmaline dissolved in a citrate/sodium hydroxide buffer at pH 6 cleanly reduced the carbinolamine bond to give amino alcohol **52**.

The oxidation of amino alcohols is known to be problematic and protection of the amine with a non-basic group is usually required. It has been shown that the use of *ortho*-iodoxybenzoic acid (IBX), as a source of hypervalent iodine, is effective for the selective oxidation of amino alcohols to amino carbonyls.[101] The use of an equimolar amount of trifluoroacetic acid to temporarily protonate the amino group is crucial in obtaining the desired carbonyl product in good yield. It was hoped that this methodology could be applied to ajmaline derivative **52** to give the corresponding aldehyde **257,** from which cyclisation of the D-ring could be carried out.

The presence of the secondary alcohol on C17 added a further complication to the process but it was thought that by using just 1.1 equivalents of the oxidising agent, the kinetic preference for oxidation of primary over secondary alcohols would give the desired C21 aldehyde as the major product.



52 **257** **3**

Scheme 3.66 – i) IBX, TFA, DMSO, 20 hrs, 53%

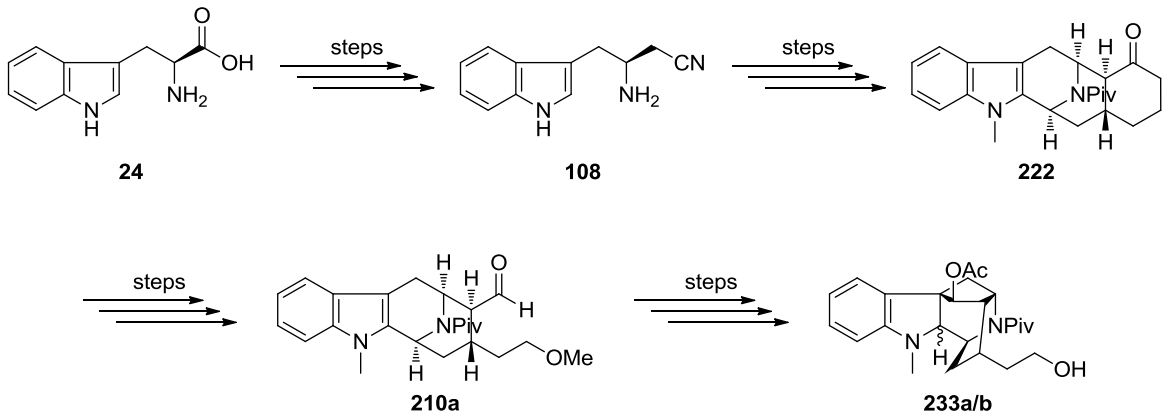
TLC analysis of the crude product following work-up showed the presence of a new compound with a lower R_f. Following chromatography, the new component was found to be ajmaline and not aldehyde **257**, which was confirmed by TLC and NMR comparison of the reaction product with a commercial sample of ajmaline. This result had not been completely unexpected since the amine was suitably placed to trap any aldehyde once formed. Further analysis of the reaction product also confirmed that the ring closure had taken place stereoselectively to generate the necessary stereochemistry at C21 (Scheme 3.66).

Based on literature precedent, the selectivity for D-ring closure was expected and could be explained by the anomeric effect, whereby heteroatomic ring substituents that are α to heteroatoms within a ring system tend to adopt sterically less-favourable axial positions in order to reduce unfavourable dipole-dipole interactions. However, during Kluge's studies towards the synthesis of ajmaline (see section 1.2.4), D-ring closure of a de-ethyl intermediate had given a mixture of C21 epimers in an unspecified ratio, suggesting that the steric requirements of the adjacent ethyl group have an important role to play in determining the stereoselectivity of the D-ring-closing reaction. Based on Kluge's work it can be suggested that the analogous ring-closing reaction during a synthesis of de-ethyl ajmaline may not go with the same level of stereocontrol as demonstrated by this oxidation/ring-closing protocol.

This result was significant in that it not only showed that selective oxidation of the primary alcohol could take place cleanly in the presence of both amino and secondary alcohol groups, but also that ring closure could take place

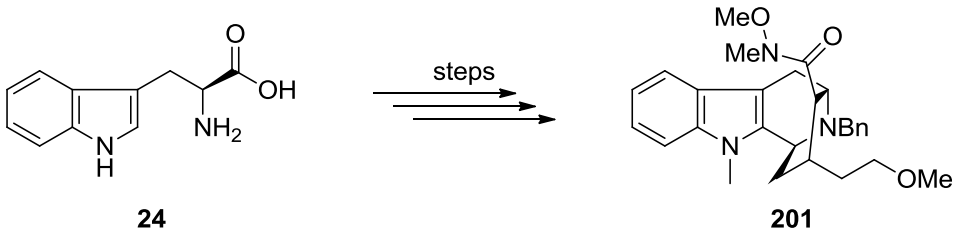
stereoselectively. Due to its process and atom efficiency, this method for D-ring cyclisation could prove to be useful during subsequent syntheses of ajmaline or related derivatives.

3.2.17 Summary of attempts towards (+)-ajmaline



Scheme 3.67 – Synthesis of advanced pivaloyl-protected intermediate **232a/b**

The preparation of nitrile amine **108** is well known[53] and the synthesis of pivaloyl-protected lactone **222** was first established by Beard.[87] Generation of these two key intermediates was significantly optimised such that sufficient quantities of advanced intermediate aldehyde **210a** could be produced and investigations towards the completion of the total synthesis could be carried out. Advanced ajmaline derivative **233a/b** was formed with exceptional stereocontrol of six stereocentres, whilst the stereocentre at C2 could be formed with moderate control in a ratio of 63:37 for the desired diastereoisomer. Unfortunately, an inability to deprotect the pivaloyl amide prevented the final steps of the synthesis from being carried out.

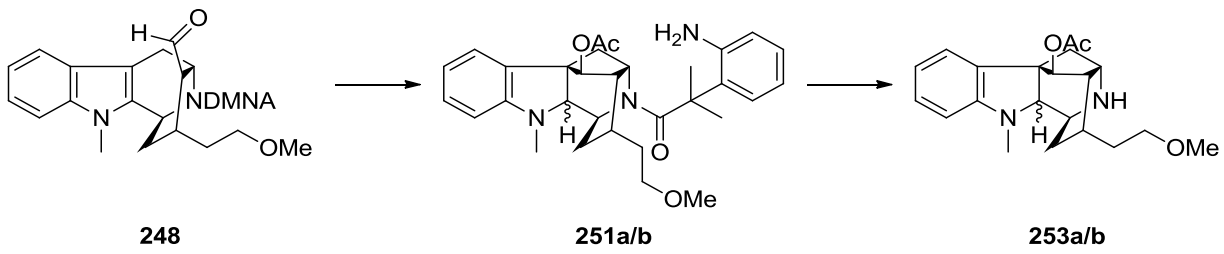


24 **201**

Scheme 3.68 – Advanced benzyl-protected intermediate

Benzyl-protected Weinreb amide **201** was prepared with exceptional control of all new stereocentres and in improved overall yield than previously shown. Catalytic hydrogenolysis of the benzyl group meant that alternative protecting group strategies could be explored with a view to using remote steric induction to control the formation of the stereocentre at C2.

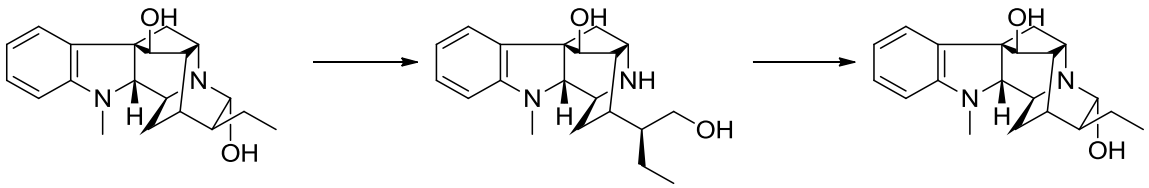
Use of the DMNA-protected aldehyde **248** during the one-pot indole cyclisation/iminium ion reduction protocol gave slight selectivity for the desired C2 epimer (~1.5:1). Following catalytic hydrogenation and acid-mediated deprotection conditions, cleavage of the DMNA group was thought to have occurred due to isolation of small amounts of the DMNA lactam, though synthetically useful amounts of the corresponding deprotected amine **253a/b** could not be isolated.



248 **251a/b** **253a/b**

Scheme 3.69 – E-ring cyclisation, iminium ion reduction and DMNA deprotection

Despite not being able to isolate any of the corresponding de-ethyl amino alcohol **232a**, a protocol for the closure of the D-ring was investigated by preparing 4,21-secoajmaline **52** from commercially available ajmaline. Oxidation of the primary alcohol took place selectively in the presence of a secondary alcohol and an amine, and the resulting aldehyde spontaneously ring closed to give ajmaline with exceptional stereocontrol.



3 **52** **3**

Scheme 3.70 – D-ring closure protocol

Chapter 4

Experimental details

4.1 General methods

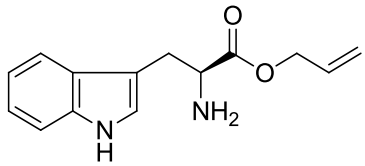
Melting points were determined on a Stuart Scientific SMP1 machine and are uncorrected. NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C). Chemical shifts (δ) were measured in ppm (to the nearest 0.01 ppm) from a tetramethylsilane internal standard. Coupling constants (*J*) are recorded in Hz to the nearest 0.1 Hz. Splitting patterns are reported as follows: chemical shift, integration, multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or as any combination of these) and atom. Infrared spectra were recorded on a Thermo Nicolet Nexus FT-IR spectrophotometer. Mass spectra were obtained by nano-electrospray on a Thermofisher LTQ Orbitrap XL spectrometer. Optical rotations were measured using a Rudolph Research Analytical Autopol I automatic polarimeter with sodium D light (λ = 589 nm); $[\alpha]_D^T$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Analytical TLC was carried out on Macherey-Nagel aluminium sheet silica gel 60 UV_{254} plates; retention factors (R_f) are quoted to the nearest 0.01. Spots were visualised with a UV lamp or with phosphomolybdic acid in ethanol. Flash column chromatography was carried out on silica gel 60 (40-63 μm mesh). All reactions were carried out in dry glassware under an atmosphere of dry nitrogen unless otherwise stated. All chemicals were used as bought from suppliers (Sigma-Aldrich, Acros Organics or Lancaster) without further purification unless otherwise stated. Commercial grade solvents were used; tetrahydrofuran was distilled over sodium and benzophenone, and dichloromethane was distilled over calcium hydride prior to use.

Many of the indole based compounds were found to be oils. Under vigorous drying conditions and if sufficient material was available, some compounds were transformed into solid foams. Attempted melting point analysis of these foams failed to produce distinct, reproducible phase transitions and as such are not reported.

The carbon framework for all compounds noted in chapters 2 and 3 is numbered by the convention for ajmaline type compounds as stated in the section 'Ajmaline framework numbering and ring lettering' (page iv). However, all compounds in the experimental section are numbered by formal IUPAC convention and as a result may differ slightly from the main text.

4.2 Chapter 2 experimental details

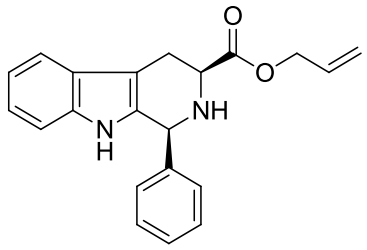
Preparation of **allyl L-tryptophanate 157**



Acetyl chloride (12.9 mL, 180 mmol) was added slowly to a suspension of L-tryptophan **24** (15 g, 73.40 mmol) in allyl alcohol (150 mL). This mixture was stirred at reflux for five hours and then allowed to cool to room temperature. A 10% aqueous solution of ammonia (300 mL) was then added. The aqueous layer was extracted with dichloromethane (3 x 200 mL), the organic portions combined and washed with saturated sodium chloride (300 mL), dried ($MgSO_4$) and then

concentrated under reduced pressure. Purification by flash column chromatography (dichloromethane/methanol 19:1) gave the ester **157** (10.06 g, 56%) as a yellow solid: mp 72-74 °C (from DCM); R_f = 0.09 (diethyl ether/dichloromethane 1:1); $[\alpha]_D^{25.3}$ −6.22 (*c* 0.96 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3365.0, 3176.2, 2925.8, 1732.3, 1456.9, 1187.8 and 742.9; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.59 (2 H, br s, N*H*$_2$), 2.95 (1 H, dd, *J* 14.3 and 7.7, ArC*H*$_2$), 3.20 (1 H, dd, *J* 14.3 and 4.7, ArC*H*$_2$), 3.76 (1 H, dd, *J* 7.7 and 4.8, ArCH$_2$C*H*), 4.50 (2 H, d, *J* 5.8, OC*H*$_2$CHCH$_2$), 5.13 (1 H, dd, *J* 10.4 and 0.8, OCH$_2$CHC*H*$_2$), 5.19 (1 H, dd, *J* 17.2 and 1.3, OCH$_2$CHC*H*$_2$), 5.70-5.86 (1 H, m, OCH$_2$C*H*CH$_2$), 6.82 (1 H, d, *J* 1.9, Ar*H*), 7.00 (1 H, t, *J* 7.2, Ar*H*), 7.07 (1 H, t, *J* 7.3, Ar*H*), 7.17 (1 H, d, *J* 7.9, Ar*H*), 7.51 (1 H, d, *J* 7.7, Ar*H*) and 8.70 (1 H, br s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 30.8, 55.1, 65.7, 110.6, 111.0, 111.4, 118.7, 119.4, 122.0, 123.3, 127.5, 131.9, 136.4 and 175.1; *m/z* (ESI) 245.1288 $[M+H]^+$ $C_{14}H_{17}N_2O_2$ requires 245.1285.

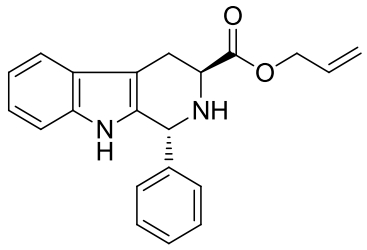
Preparation of **allyl (1*S*,3*S*)-1-phenyl-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate[82] 176a**



L-Tryptophan allyl ester **157** (152.0 mg, 0.62 mmol) was dissolved in dichloromethane (5 mL) in the presence of 3 Å molecular sieves (9.2 mg) and the mixture cooled to 0 °C. Benzaldehyde (102 μL, 1.00 mmol) was added and after

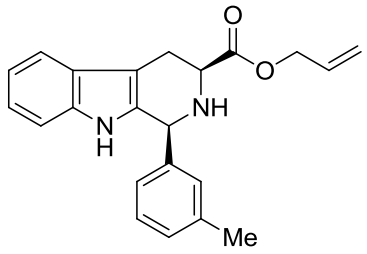
thirty minutes the solution allowed to warm to room temperature and stirred overnight. A small aliquot was then taken, the solvents removed and the crude solid analysed by ^{1}H NMR to confirm complete formation of the imine. The solution was then cooled to 0 °C, trifluoroacetic acid (94 µL, 1.23 mmol) added and the mixture stirred at this temperature for eight hours. The reaction was quenched with saturated sodium bicarbonate (12 mL) and the solution warmed to room temperature. The phases were separated and the aqueous portion washed with dichloromethane (3 x 15 mL). The organic portions were combined, washed with saturated sodium chloride (15 mL), dried ($MgSO_4$) and the solvents removed under reduced pressure. Flash column chromatography (petrol/diethyl ether 9:1, 3:1, 1:1, dichloromethane/methanol 4:1) gave the *trans* product **176b** (25.9 mg, 13%) as a yellow, amorphous solid and the *cis* product **176a** (106.2 mg, 52%) as a white, amorphous solid: R_f = 0.19 (dichloromethane/diethyl ether = 49:1); $[\alpha]_D^{23.6}$ −20.75 (*c* 1.06 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3391.2, 3057.4, 1735.7, 1454.6, 1205.1 and 741.6; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.40 (1 H, br s, N*H*), 2.95 (1 H, ddd, *J* 15.0, 11.1 and 2.5, ArCH_2), 3.17 (1 H, ddd, *J* 15.1, 4.2 and 1.7, ArCH_2), 3.92 (1 H, dd, *J* 11.1 and 4.3, ArCH$_2$C*H*), 4.56-4.71 (2 H, m, OCH_2CHCH$_2$), 5.16 (1 H, s, ArC*H*), 5.22 (1 H, dd, *J* 10.4 and 0.9, OCH$_2$CHCH_2), 5.31 (1 H, dd, *J* 17.2 and 1.2, OCH$_2$CHCH_2), 5.81-5.98 (1 H, m, OCH$_2$C*H*CH$_2$), 7.00-7.16 (3 H, m, Ar*H*), 7.30 (5 H, s, Ar*H*), 7.37 (1 H, s, ArN*H*) and 7.43-7.51 (1 H, m, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 24.7, 55.9, 57.7, 64.8, 107.9, 109.9, 117.2, 117.9, 118.6, 120.9, 126.1, 127.6, 127.6, 127.9, 130.8, 133.7, 135.1, 139.7 and 171.4; *m/z* (ESI) 333.1603 $[M+H]^+$ $C_{21}H_{21}N_2O_2$ requires 333.1598.

allyl (1*R*,3*S*)-1-phenyl-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 176b



R_f = 0.21 (diethyl ether/petrol = 1:1); $[\alpha]_D^{24.2}$ −34.78 (*c* 0.23 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3390.8, 3058.9, 2926.1, 2852.7, 1732.6, 1455.2 and 740.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.46 (1 H, br s, N*H*), 3.06 (1 H, ddd, *J* 15.4, 6.8 and 1.1, ArCH_2), 3.21 (1 H, ddd, *J* 15.2, 5.4 and 1.0, ArCH_2), 3.90 (1 H, t, *J* 6.1, ArCH_2C*H*), 4.45-4.60 (2 H, m, OCH_2CHCH_2), 5.14 (1 H, dd, *J* 10.4 and 1.1, OCH_2CHCH_2), 5.20 (1 H, dd, *J* 17.2 and 1.4, OCH_2CHCH_2), 5.30 (1 H, s, ArC*H*), 5.74-5.90 (1 H, m, OCH_2C*H*CH_2) and 7.00-7.72 (10 H, m, ArN*H* and Ar*H*), δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.6, 51.6, 53.9, 64.6, 107.4, 109.9, 117.2, 117.5, 118.5, 120.9, 125.9, 127.1, 127.4, 127.7, 130.8, 132.1, 135.1, 140.9 and 172.3; *m/z* (ESI) 333.1601 $[M+H]^+$ $C_{21}H_{21}N_2O_2$ requires 333.1598.

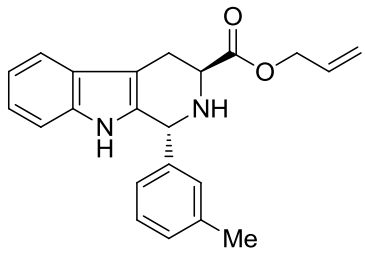
Preparation of **allyl (1*S*,3*S*)-1-(3-methylphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 177a**



L-Tryptophan allyl ester **157** (154.0 mg, 0.63 mmol) was dissolved in dichloromethane (5 mL) in the presence of 3 Å molecular sieves (9.2 mg) and the mixture cooled to 0 °C. 3-Tolualdehyde (118 µL, 1.00 mmol) was added and after thirty minutes the solution allowed to warm to room temperature and stirred overnight. A small aliquot was then taken, the solvents removed and the crude solid analysed by ^{1}H NMR to confirm complete formation of the imine. The solution was then cooled to 0 °C, trifluoroacetic acid (94 µL, 1.23 mmol) added and the mixture stirred at this temperature for eight hours. The reaction was quenched with saturated sodium bicarbonate (12 mL) and the solution warmed to room temperature. The phases were separated and the aqueous portion washed with dichloromethane (3 x 15 mL). The organic portions were combined, washed with saturated sodium chloride (15 mL), dried ($MgSO_4$) and the solvents removed under reduced pressure. Flash column chromatography (petrol/diethyl ether 19:1, 2.33:1) gave the *trans* product **177b** (13.7 mg, 6%) as a yellow, amorphous solid and the *cis* product **177a** (122.6 mg, 58%) as a white, amorphous solid: R_f = 0.26 (dichloromethane/diethyl ether 49:1); $[\alpha]_D^{31.2}$ −18.27 (*c* 0.60 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3392.5, 3056.6, 2926.4, 2849.1, 1736.0, 1452.6, 1320.9, 1203.9,

1175.3 and 738.2; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.23 (4 H, br s, ArCH_3 and N*H*), 2.93 (1 H, ddd, *J* 15.0, 11.1 and 2.3, ArCH_2), 3.15 (1 H, ddd, *J* 15.1, 4.1 and 1.5, ArCH_2), 3.88 (1 H, dd, *J* 11.1 and 4.2, $ArCH_2CH$), 4.52-4.70 (2 H, m, OCH_2CHCH_2), 5.07 (1 H, s, ArC*H*), 5.20 (1 H, d, *J* 10.3, OCH_2CHCH_2), 5.29 (1 H, dd, *J* 17.2 and 0.9, OCH_2CHCH_2), 5.78-5.98 (1 H, m, OCH_2CHCH_2), 6.98-7.12 (6 H, m, Ar*H*), 7.13-7.22 (1 H, m, Ar*H*) and 7.38-7.50 (2 H, m, ArN*H* and Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.4, 25.8, 57.0, 58.7, 65.8, 108.8, 111.0, 118.2, 118.9, 119.6, 121.9, 125.7, 127.2, 128.8, 129.2, 129.4, 131.9, 134.9, 136.2, 138.8, 140.7 and 172.5; *m/z* (ESI) 347.1758 $[M+H]^+$ $C_{22}H_{23}N_2O_2$ requires 347.1754.

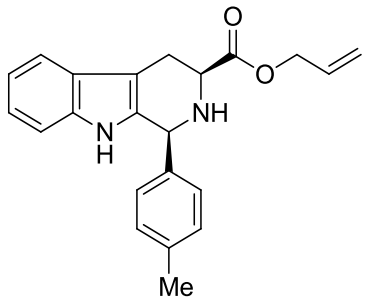
allyl (1*R*,3*S*)-1-(3-methylphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 177b



R_f = 0.40 (dichloromethane/diethyl ether 4:1); $[\alpha]_D^{30.2}$ −29.61 (*c* 0.30 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3392.2, 3055.6, 2923.9, 2853.4, 1731.7, 1454.1 and 738.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.24 (3 H, s, ArCH_3), 2.39 (1 H, br s, N*H*), 3.08 (1 H, ddd, *J* 15.4, 6.5 and 1.0, ArCH_2), 3.22 (1 H, dd, *J* 15.3 and 5.3, ArCH_2), 3.94 (1 H, t, *J* 5.9, $ArCH_2CH$), 4.47-4.62 (2 H, m, OCH_2CHCH_2), 5.15 (1 H, dd, *J* 10.4 and 0.9, OCH_2CHCH_2), 5.21 (1 H, dd, *J* 7.1 and 1.2, OCH_2CHCH_2), 5.30 (1 H, s, ArC*H*), 5.75-5.92 (1 H, m, OCH_2CHCH_2), 6.96-7.20 (7 H, m, Ar*H*) and 7.45-7.56 (2 H, m,

ArN*H* and Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.4, 24.6, 52.8, 54.9, 65.6, 108.3, 110.9, 118.3, 118.6, 119.5, 121.9, 125.6, 127.0, 128.6, 129.0, 129.0, 131.8, 133.3, 136.2, 138.6, 141.8 and 173.4; *m/z* (ESI) 347.1756 $[M+H]^+$ $C_{22}H_{23}N_2O_2$ requires 347.1754.

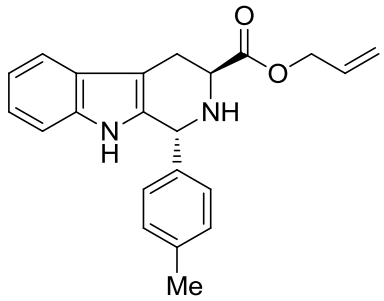
Preparation of **allyl (1*S*,3*S*)-1-(4-methylphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 178a**



L-Tryptophan allyl ester **157** (150.0 mg, 0.61 mmol) was dissolved in dichloromethane (5 mL) in the presence of 3 Å molecular sieves (9.2 mg) and the mixture cooled to 0 °C. 4-Tolualdehyde (118 µL, 1 mmol) was added and after thirty minutes the solution allowed to warm to room temperature and stirred overnight. A small aliquot was then taken, the solvents removed and the crude solid analysed by ^{1}H NMR to confirm complete formation of the imine. The solution was then cooled to 0 °C, trifluoroacetic acid (94 µL, 1.23 mmol) added and the mixture stirred at this temperature for eight hours. The reaction was quenched with saturated sodium bicarbonate (12 mL) and the solution warmed to room temperature. The phases were separated and the aqueous portion washed with dichloromethane (3 x 15 mL). The organic portions were combined, washed with saturated sodium chloride (15 mL), dried ($MgSO_4$) and the solvents removed

under reduced pressure. Flash column chromatography (petrol/diethyl ether 19:1, 3:1, dichloromethane/methanol 4:1) gave the *trans* product **178b** (16.5 mg, 8%) as a yellow, amorphous solid and the *cis* product **178a** (77.7 mg, 37%) as a white, amorphous solid: R_f = 0.24 (dichloromethane/diethyl ether = 49:1); $[\alpha]_D^{26.1}$ −15.21 (*c* 0.72 in $CHCl_3$); v_{max}(film)/cm^{-1} 3392.2, 3054.3, 2924.0, 2849.1, 1736.0, 1451.7, 1306.5, 1205.1, 1176.5, and 741.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.26 (4 H, br s, ArC*H*$_3$ and N*H*), 2.92 (1 H, ddd, *J* 15.1, 11.2 and 2.5, ArC*H*$_2$), 3.14 (1 H, ddd, *J* 15.1, 4.2 and 1.7, ArC*H*$_2$), 3.86 (1 H, dd, *J* 11.1 and 4.2, ArCH$_2$C*H*), 4.52-4.68 (2 H, m, OC*H*$_2$CHCH$_2$), 5.05 (1 H, s, ArC*H*), 5.19 (1 H, dd, *J* 10.4 and 0.9, OCH$_2$CHC*H*$_2$), 5.28 (1 H, dd, *J* 17.2 and 1.3, OCH$_2$CHC*H*$_2$), 5.79-5.96 (1 H, m, OCH$_2$C*H*CH$_2$), 6.97-7.11 (5 H, m, Ar*H*), 7.12-7.19 (2 H, m, Ar*H*) and 7.38-7.48 (2 H, m, ArN*H* and Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 20.1, 24.7, 55.9, 57.3, 64.7, 107.6, 109.9, 117.2, 117.8, 118.5, 120.8, 126.1, 127.5, 128.5, 130.8, 133.9, 135.1, 136.7, 137.3 and 171.4; *m/z* (ESI) 347.1756 $[M+H]^+$ $C_{22}H_{23}N_2O_2$ requires 347.1754.

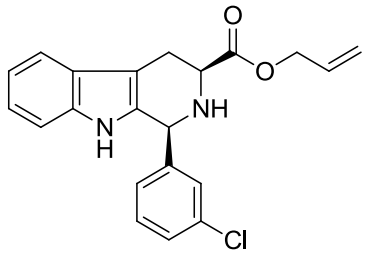
allyl (1*R*,3*S*)-1-(4-methylphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 178b



R_f = 0.15 (petrol/ethyl acetate 3:1); $[\alpha]_D^{27.2}$ −40.74 (*c* 0.27 in $CHCl_3$); v_{max}(film)/cm^{-1} 3291.5, 2922.3, 2852.1, 1735.2, 1173.5 and 743.8; δ_H(300 MHz; $CDCl_3$; Me_4Si)

2.12 (1 H, br s, N*H*), 2.35 (3 H, s, ArCH_3), 3.14 (1 H, dd, *J* 15.1 and 6.7, ArCH_2), 3.29 (1 H, dd, *J* 15.3 and 5.1, ArCH_2), 3.93-4.04 (1 H, m, ArCH_2C*H*), 4.54-4.70 (2 H, m, OCH_2CHCH_2), 5.23 (1 H, d, *J* 10.6, OCH_2CHCH_2), 5.30 (1 H, dd, *J* 17.3 and 1.3, OCH_2CHCH_2), 5.37 (1 H, s, ArC*H*), 5.83-5.99 (1 H, m, OCH_2C*H*CH_2), 7.08-7.26 (7 H, m, Ar*H*), 7.53-7.60 (1 H, m, Ar*H*) and 7.68 (1 H, br s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 20.1, 23.7, 51.4, 53.6, 64.6, 107.3, 109.9, 117.2, 117.5, 118.4, 120.8, 125.9, 127.3, 128.3, 130.8, 132.4, 135.1, 136.8, 137.9 and 172.3; *m/z* (ESI) 347.1759 $[M+H]^+$ $C_{22}H_{23}N_2O_2$ requires 347.1754.

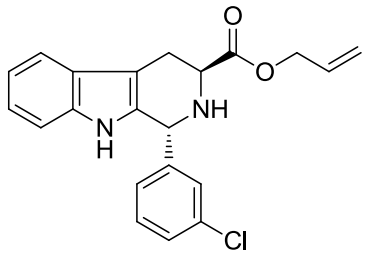
Preparation of **allyl (1*S*,3*S*)-1-(3-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 179a**



L-Tryptophan allyl ester **157** (157.0 mg, 0.64 mmol) was dissolved in dichloromethane (5 mL) in the presence of 3 Å molecular sieves (9.2 mg) and the mixture cooled to 0 °C. 3-Chlorobenzaldehyde (113 µL, 1.00 mmol) was added and after thirty minutes the solution allowed to warm to room temperature and stirred overnight. A small aliquot was then taken, the solvents removed and the crude solid analysed by ^{1}H NMR to confirm complete formation of the imine. The solution was then cooled to 0 °C, trifluoroacetic acid (94 µL, 1.23 mmol) added and the mixture stirred at this temperature for eight hours. The reaction was quenched

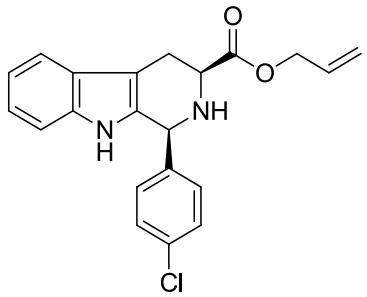
with saturated sodium bicarbonate (12 mL) and the solution warmed to room temperature. The phases were separated and the aqueous portion washed with dichloromethane (3 x 15 mL). The organic portions were combined, washed with saturated sodium chloride (15 mL), dried ($MgSO_4$) and the solvents removed under reduced pressure. Flash column chromatography (petrol/diethyl ether 19:1, 3:1, dichloromethane/methanol = 4:1) gave the *trans* product **179b** (15.7 mg, 7%) as a yellow, amorphous solid and the *cis* product **179a** (142.9 mg, 51%) as a white, amorphous solid: R_f = 0.31 (dichloromethane/diethyl ether 49:1); $[\alpha]_D^{23.7}$ −13.46 (*c* 1.04 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3390.4, 3058.3, 2929.1, 2849.9, 1734.2, 1467.5, 1205.4 and 740.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.35 (1 H, br s, N*H*), 2.91 (1 H, ddd, *J* 15.1, 11.2 and 2.4, ArCH_2), 3.14 (1 H, ddd, *J* 15.1, 4.1 and 1.5, ArCH_2), 3.83 (1 H, dd, *J* 11.1 and 4.1, ArCH_2C*H*), 4.50-4.68 (2 H, m, OCH_2CHCH_2), 5.04 (1 H, s, ArC*H*), 5.19 (1 H, dd, *J* 10.4 and 0.9, OCH_2CHCH_2), 5.28 (1 H, dd, *J* 17.2 and 1.3, OCH_2CHCH_2), 5.78-5.96 (1 H, m, OCH_2C*H*CH_2), 6.97-7.09 (3 H, m, Ar*H*), 7.10-7.23 (3 H, m, Ar*H*), 7.25 (1 H, s, Ar*H*) and 7.40-7.51 (2 H, m, ArN*H* and Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 25.7, 56.8, 58.2, 65.9, 109.1, 111.1, 118.3, 119.0, 119.8, 122.2, 126.9, 127.0, 128.8, 128.8, 130.3, 131.8, 133.9, 134.8, 136.3, 143.0 and 172.4; *m/z* (ESI) 367.1205 $[M+H]^+$ $C_{21}H_{20}N_2O_2Cl$ requires 367.1208.

allyl (1*R*,3*S*)-1-(3-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 179b



R_f = 0.15 (petrol/ethyl acetate 3:1); $[\alpha]_D^{28.2}$ −42.86 (*c* 0.42 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3392.8, 2927.1, 2852.4, 1731.7 and 740.5; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.32 (1 H, br s, N*H*), 3.14 (1 H, ddd, *J* 15.5, 6.8 and 1.1, ArCH_2), 3.30 (1 H, ddd, *J* 15.4, 5.3 and 1.1, ArCH_2), 3.94-4.01 (1 H, m, ArCH$_2$C*H*), 4.56-4.70 (2 H, m, OCH_2CHCH$_2$), 5.21-5.34 (2 H, m, OCH$_2$CHCH_2), 5.36 (1 H, s, ArC*H*), 5.84-6.00 (1 H, m, OCH$_2$C*H*CH$_2$), 7.11-7.35 (7 H, m, Ar*H*), 7.57 (1 H, d, *J* 6.9, Ar*H*) and 7.76 (1 H, s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 24.7, 52.6, 54.5, 65.7, 108.6, 111.0, 118.4, 118.7, 119.6, 122.2, 126.6, 126.9, 128.3, 128.5, 130.0, 131.8, 132.5, 134.7, 136.2, 144.2 and 173.4; *m/z* (ESI) 367.1212 $[M+H]^+$ $C_{21}H_{20}N_2O_2Cl$ requires 367.1208.

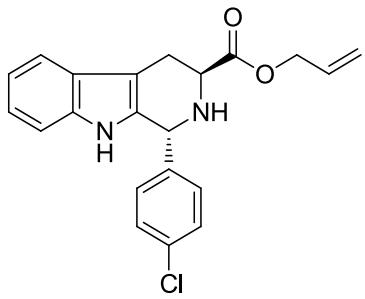
Preparation of **allyl (1*S*,3*S*)-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 180a**



L-Tryptophan allyl ester **157** (152.0 mg, 0.62 mmol) was dissolved in dichloromethane (5 mL) in the presence of 3 Å molecular sieves (9.2 mg) and the mixture cooled to 0 °C. 4-Chlorobenzaldehyde (141.0 mg, 1.00 mmol) was added and after thirty minutes the solution allowed to warm to room temperature and stirred overnight. A small aliquot was then taken, the solvents removed and the crude solid analysed by ^{1}H NMR to confirm complete formation of the imine. The solution was then cooled to 0 °C, trifluoroacetic acid (94 µL, 1.23 mmol) added and the mixture stirred at this temperature for eight hours. The reaction was quenched with saturated sodium bicarbonate (12 mL) and the solution warmed to room temperature. The phases were separated and the aqueous portion washed with dichloromethane (3 x 15 mL). The organic portions were combined, washed with saturated sodium chloride (15 mL), dried ($MgSO_4$) and the solvents removed under reduced pressure. Flash column chromatography (petrol/diethyl ether 19:1, 3:1, dichloromethane/methanol = 4:1) gave the *trans* product **180b** (20.8 mg, 9%) as a yellow, amorphous solid and the *cis* product **180a** (136.0 mg, 60%) as a white, amorphous solid: R_f = 0.25 (dichloromethane/diethyl ether 49:1); $[\alpha]_D^{25.0}$ −9.09 (*c* 1.21 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3388.9, 3058.4, 2933.8, 2848.8, 1735.2, 1489.4,

1206.7 and 739.3; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.30 (1 H, br s, N*H*), 2.90 (1 H, ddd, *J* 15.0, 11.2 and 2.2, ArCH_2), 3.13 (1 H, ddd, *J* 15.1, 4.0 and 1.4, ArCH_2), 3.83 (1 H, dd, *J* 11.1 and 4.1, $ArCH_2CH$), 4.48-4.67 (2 H, m, OCH_2CHCH_2), 5.04 (1 H, s, ArC*H*), 5.19 (1 H, dd, *J* 10.4 and 0.7, OCH_2CHCH_2), 5.27 (1 H, dd, *J* 17.2 and 1.1, OCH_2CHCH_2), 5.77-5.95 (1 H, m, OCH_2CHCH_2), 6.96-7.10 (3 H, m, Ar*H*), 7.13-7.24 (4 H, m, Ar*H*), 7.39-7.47 (1 H, m, Ar*H*) and 7.53 (1 H, s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 25.7, 56.9, 58.0, 65.9, 109.0, 111.0, 118.3, 119.0, 119.7, 122.1, 127.0, 129.1, 130.1, 131.8, 134.2, 134.4, 136.2, 139.4 and 172.4; *m/z* (ESI) 367.1209 $[M+H]^+$ $C_{21}H_{20}N_2O_2Cl$ requires 367.1208.

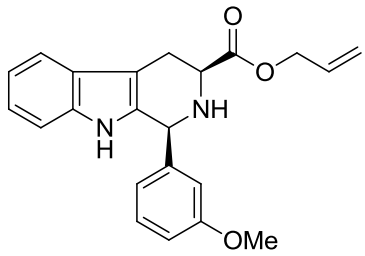
allyl (1*R*,3*S*)-1-(4-chlorophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 180b



R_f = 0.13 (dichloromethane/diethyl ether 49:1); $[\alpha]_D^{27.2}$ −182.61 (*c* 0.23 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3392.2, 3058.7, 2931.8, 2851.5, 1732.0, 1488.1 and 745.9; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.23 (1 H, br s, N*H*), 3.06 (1 H, ddd, *J* 15.3, 6.7 and 0.9, ArCH_2), 3.20 (1 H, dd, *J* 15.3 and 5.4, ArCH_2), 3.87 (1 H, t, *J* 6.0, $ArCH_2CH$), 4.46-4.60 (2 H, m, OCH_2CHCH_2), 5.15 (1 H, dd, *J* 10.6 and 0.9, OCH_2CHCH_2), 5.20 (1 H, dd, *J* 15.3 and 1.2, OCH_2CHCH_2), 5.30 (1 H, s, ArC*H*), 5.74-5.90 (1 H, m, OCH_2CHCH_2), 7.00-7.30 (7 H, m, Ar*H*), 7.48 (1 H, d, *J* 6.8, Ar*H*) and 7.55 (1 H, s,

ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.6, 51.6, 53.2, 64.6, 107.5, 109.9, 117.3, 117.6, 118.6, 121.1, 125.9, 127.9, 128.8, 130.7, 131.7, 132.9, 135.1, 139.4 and 172.3; *m/z* (ESI) 367.1212 $[M+H]^+$ $C_{21}H_{20}N_2O_2Cl$ requires 367.1208.

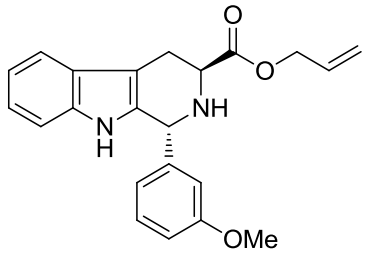
Preparation of **allyl (1*S*,3*S*)-1-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 181a**



L-Tryptophan allyl ester **157** (154.0 mg, 0.63 mmol) was dissolved in dichloromethane (5 mL) in the presence of 3 Å molecular sieves (9.2 mg) and the mixture cooled to 0 °C. 3-Anisaldehyde (122µL, 1.00 mmol) was added and after thirty minutes the solution allowed to warm to room temperature and stirred overnight. A small aliquot was then taken, the solvents removed and the crude solid analysed by ^{1}H NMR to confirm complete formation of the imine. The solution was then cooled to 0 °C, trifluoroacetic acid (94 µL, 1.23 mmol) added and the mixture stirred at this temperature for eight hours. The reaction was quenched with saturated sodium bicarbonate (12 mL) and the solution warmed to room temperature. The phases were separated and the aqueous portion washed with dichloromethane (3 x 15 mL). The organic portions were combined, washed with saturated sodium chloride (15 mL), dried ($MgSO_4$) and the solvents removed under reduced pressure. Flash column chromatography (petrol/diethyl ether 5.67:1,

1.5:1, dichloromethane/methanol = 4:1) gave the *trans* product **181b** (23.3 mg, 10%) as a yellow, amorphous solid and the *cis* product **181a** (138.6 mg, 61%) as a white, amorphous solid: R_f = 0.24 (dichloromethane/diethyl ether 49:1); $[\alpha]_D^{25.9}$ −19.81 (*c* 1.06 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3389.8, 3056.0, 2933.6, 2837.1, 1735.5, 1599.2, 1454.3, 1266.3 and 740.1; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.28 (1 H, br s, N*H*), 2.92 (1 H, ddd, *J* 15.1, 11.2 and 2.5, ArCH_2), 3.15 (1 H, ddd, *J* 15.1, 4.2 and 1.7, ArCH_2), 3.64 (3 H, s, ArOCH_3), 3.87 (1 H, dd, *J* 11.1 and 4.2, ArCH_2C*H*), 4.54-4.70 (2 H, m, OCH_2CHCH_2), 5.08 (1 H, s, ArC*H*), 5.20 (1 H, dd, *J* 10.4 and 1.0, OCH_2CHCH_2), 5.29 (1 H, dd, *J* 17.2 and 1.3, OCH_2CHCH_2), 5.81-5.98 (1 H, m, OCH_2C*H*CH_2), 6.75-6.92 (3 H, m, Ar*H*), 6.97-7.11 (3 H, m, Ar*H*), 7.18 (1 H, t, *J* 8.1, Ar*H*), 7.41-7.48 (1 H, m, Ar*H*) and 7.51 (1 H, s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 25.7, 55.3, 57.0, 58.7, 65.9, 108.7, 111.0, 113.9, 114.3, 118.2, 118.9, 119.6, 120.8, 121.9, 127.1, 130.0, 131.8, 134.6, 136.2, 142.3, 160.1 and 172.5; *m/z* (ESI) 363.1700 $[M+H]^+$ $C_{22}H_{23}N_2O_3$ requires 363.1703.

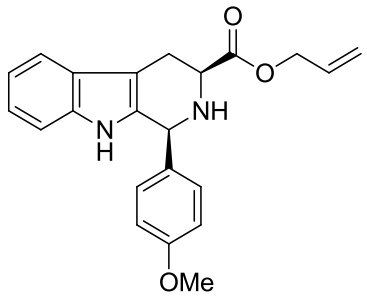
allyl (1*R*,3*S*)-1-(3-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 181b



R_f = 0.13 (diethyl ether/petrol 1:1); $[\alpha]_D^{26.6}$ −31.82 (*c* 0.22 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3387.9, 3055.4, 2934.4, 2836.7, 1732.2, 1598.4, 1454.0, 1266.3 and 742.0;

δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.30 (1 H, br s, N*H*), 3.06 (1 H, ddd, *J* 15.3, 6.8 and 1.1, ArCH_2), 3.21 (1 H, dd, *J* 15.4 and 5.3, ArCH_2), 3.66 (3 H, s, ArOCH_3), 3.93 (1 H, t, *J* 6.1, $ArCH_2CH$), 4.46-4.60 (2 H, m, OCH_2CHCH_2), 5.14 (1 H, dd, *J* 10.4 and 1.1, OCH_2CHCH_2), 5.21 (1 H, dd, *J* 17.3 and 1.4, OCH_2CHCH_2), 5.28 (1 H, s, ArC*H*), 5.74-5.90 (1 H, m, OCH_2CHCH_2), 6.72-6.80 (3 H, m, Ar*H*), 7.00-7.22 (4 H, m, Ar*H*), 7.43-7.50 (1 H, m, Ar*H*) and 7.62 (1 H, s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.6, 51.7, 53.9, 54.2, 64.6, 107.2, 109.9, 112.4, 113.0, 117.2, 117.5, 118.4, 119.6, 120.9, 125.9, 128.7, 130.8, 132.1, 135.1, 142.5, 158.9 and 172.4; *m/z* (ESI) 363.1704 $[M+H]^+$ $C_{22}H_{23}N_2O_3$ requires 363.1703.

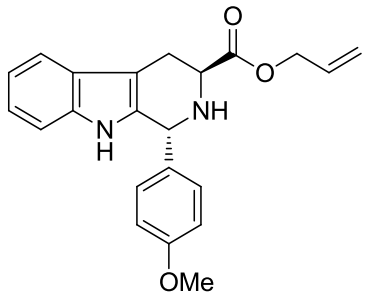
Preparation of **allyl (1*S*,3*S*)-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 182a**



L-Tryptophan allyl ester **157** (156.0 mg, 0.64 mmol) was dissolved in dichloromethane (5 mL) in the presence of 3 Å molecular sieves (9.2 mg) and the mixture cooled to 0 °C. 4-Anisaldehyde (122μL, 1.00 mmol) was added and after thirty minutes the solution allowed to warm to room temperature and stirred overnight. A small aliquot was then taken, the solvents removed and the crude solid analysed by ^{1}H NMR to confirm complete formation of the imine. The solution was then cooled to 0 °C, trifluoroacetic acid (94 μL, 1.23 mmol) added and the

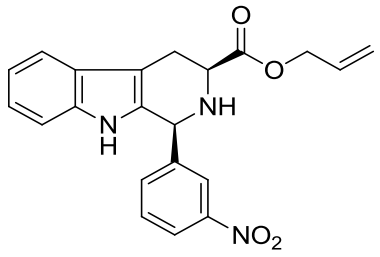
mixture stirred at this temperature for eight hours. The reaction was quenched with saturated sodium bicarbonate (12 mL) and the solution warmed to room temperature. The phases were separated and the aqueous portion washed with dichloromethane (3 x 15 mL). The organic portions were combined, washed with saturated sodium chloride (15 mL), dried ($MgSO_4$) and the solvents removed under reduced pressure. Flash column chromatography (petrol/diethyl ether 9:1, 1.9:1, dichloromethane/methanol 4:1) gave the *trans* product **182b** (11.5 mg, 5%) as a yellow, amorphous solid and the *cis* product **182a** (78.3 mg, 34%) as a white, amorphous solid: R_f = 0.08 (dichloromethane/diethyl ether 49:1); $[\alpha]_D^{26.2}$ −15.00 (*c* 0.80 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3386.7, 3057.6, 2933.5, 2837.3, 1735.7, 1511.8, 1247.2, 1174.4 and 738.8; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.23 (1 H, br s, N*H*), 2.91 (1 H, ddd, *J* 15.1, 11.2 and 2.3, ArCH_2), 3.14 (1 H, ddd, *J* 15.1, 4.1 and 1.6, ArCH_2), 3.69 (3 H, s, ArOCH_3), 3.86 (1 H, dd, *J* 11.2 and 4.2, ArCH_2C*H*), 4.52-4.68 (2 H, m, OCH_2CHCH_2), 5.04 (1 H, s, ArC*H*), 5.19 (1 H, dd, *J* 9.7 and 0.9, OCH_2CHCH_2), 5.28 (1 H, dd, *J* 17.2 and 1.3, OCH_2CHCH_2), 5.79-5.96 (1 H, m, OCH_2C*H*CH_2), 6.77 (2 H, d, *J* 8.6, Ar*H*), 6.98-7.10 (3 H, m, Ar*H*), 7.17 (2 H, d, *J* 8.6, Ar*H*), 7.40-7.47 (1 H, m, Ar*H*) and 7.53 (1 H, s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 24.7, 54.3, 55.9, 56.9, 64.7, 107.6, 109.9, 113.2, 117.1, 117.8, 118.5, 120.8, 126.1, 128.8, 130.8, 131.7, 134.0, 135.1, 158.7 and 171.4; *m/z* (ESI) 363.1706 $[M+H]^+$ $C_{22}H_{23}N_2O_3$ requires 363.1703.

allyl (1*R*,3*S*)-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 182b



R_f = 0.07 (diethyl ether/petrol 1:1); $[\alpha]_D^{24.6}$ −25.00 (*c* 0.16 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3387.1, 3058.0, 2930.0, 2837.5, 1733.7, 1510.0, 1247.6, 1175.1 and 742.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.00 (1 H, br s, N*H*), 3.15 (1 H, ddd, *J* 15.4, 6.7 and 1.2, ArCH_2), 3.29 (1 H, dd, *J* 15.4 and 5.4, ArCH_2), 3.79 (3 H, s, ArOCH_3), 4.00 (1 H, t, *J* 6.0, ArCH_2C*H*), 4.54-4.71 (2 H, m, OCH_2CHCH_2), 5.22 (1 H, d, *J* 10.6, OCH_2CHCH_2), 5.29 (1 H, dd, *J* 17.2 and 1.1, OCH_2CHCH_2), 5.39 (1 H, s, ArC*H*), 5.83-5.98 (1 H, m, OCH_2C*H*CH_2), 6.85 (2 H, d, *J* 8.7, Ar*H*), 7.08-7.27 (5 H, m, Ar*H*), 7.53-7.58 (1 H, m, Ar*H*) and 7.61 (1 H, br s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.6, 51.6, 53.3, 54.3, 64.6, 107.2, 109.8, 113.0, 117.2, 117.5, 118.5, 120.9, 126.0, 128.6, 130.8, 132.5, 133.0, 135.1, 158.4 and 172.3; *m/z* (ESI) 363.1706 $[M+H]^+$ $C_{22}H_{23}N_2O_3$ requires 363.1703.

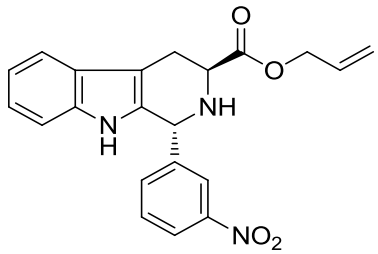
Preparation of **allyl (1*S*,3*S*)-1-(3-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 183a**



L-Tryptophan allyl ester **157** (156.0 mg, 0.64 mmol) was dissolved in dichloromethane (5 mL) in the presence of 3 Å molecular sieves (9.2 mg) and the mixture cooled to 0 °C. 3-Nitrobenzaldehyde (151.0 mg, 1.00 mmol) was added and after thirty minutes the solution allowed to warm to room temperature and stirred overnight. A small aliquot was then taken, the solvents removed and the crude solid analysed by ^{1}H NMR to confirm complete formation of the imine. The solution was then cooled to 0 °C, a 10% solution of trifluoroacetic acid in dichloromethane (94 µL, 1.23 mmol) added and the mixture stirred at this temperature for eight hours. The reaction was quenched with saturated sodium bicarbonate (12 mL) and the solution warmed to room temperature. The phases were separated and the aqueous portion washed with dichloromethane (3 x 15 mL). The organic portions were combined, washed with saturated sodium chloride (15 mL), dried ($MgSO_4$) and the solvents removed under reduced pressure. Flash column chromatography (petrol/diethyl ether 9:1, 3:1, 1:1, 1:3, dichloromethane/methanol 4:1) gave the *trans* product **183b** (18.5 mg, 8%) as a yellow, amorphous solid and the *cis* product **183a** (139.0 mg, 58%) as a yellow solid: mp 175-176 °C (from $CHCl_3$); R_f = 0.19 (dichloromethane/diethyl ether 49:1);

$[\alpha]_D^{24.5}$ +21.90 (*c* 1.05 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3397.3, 3059.8, 2934.6, 2848.2, 1734.3, 1528.0, 1350.7, 1208.3 and 736.6; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.42 (1 H, br s, N*H*), 2.85-2.98 (1 H, m, ArCH_2), 3.13 (1 H, dd, *J* 15.0 and 2.5, ArCH_2), 3.82 (1 H, dd, *J* 11.1 and 4.0, $ArCH_2CH$), 4.52-4.66 (2 H, m, OCH_2CHCH_2), 5.14-5.22 (2 H, m, OCH_2CHCH_2 and ArC*H*), 5.27 (1 H, d, *J* 17.3, OCH_2CHCH_2), 5.78-5.94 (1 H, m, OCH_2CHCH_2), 6.94-7.04 (3 H, m, Ar*H*), 7.30 (1 H, t, *J* 7.9, Ar*H*), 7.40-7.47 (1 H, m, Ar*H*), 7.56 (1 H, d, *J* 7.6, Ar*H*), 7.72 (1 H, s, Ar*H*), 7.95 (1 H, d, *J* 8.1, Ar*H*) and 8.08 (1 H, s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 24.4, 55.6, 56.9, 64.9, 108.2, 110.0, 117.3, 118.0, 118.7, 121.2, 122.4, 122.5, 125.8, 128.8, 130.6, 132.1, 134.0, 135.3, 142.2, 147.1 and 171.2; *m/z* (ESI) 378.1448 $[M+H]^+$ $C_{21}H_{20}N_3O_4$ requires 378.1448.

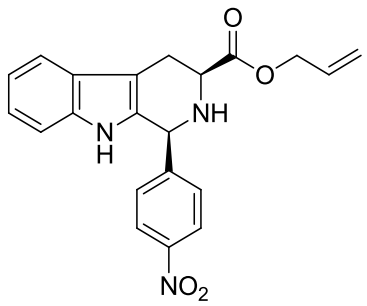
allyl (1*R*,3*S*)-1-(3-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 183b



R_f = 0.11 (diethyl ether/petrol 1:1); $[\alpha]_D^{20.6}$ −38.10 (*c* 0.21 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3396.0, 3062.2, 2933.2, 1731.8, 1529.0, 1349.4 and 734.2; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.37 (1 H, br s, N*H*), 3.10 (1 H, ddd, *J* 15.6, 6.3 and 0.9, ArCH_2), 3.24 (1 H, dd, *J* 15.3 and 5.4, ArCH_2), 3.89 (1 H, t, *J* 5.9, $ArCH_2CH$), 4.47-4.62 (2 H, m, OCH_2CHCH_2), 5.11-5.25 (2 H, m, OCH_2CHCH_2), 5.46 (1 H, s, ArC*H*), 5.74-5.89 (1

H, m, OCH_2CHCH_2), 7.03-7.22 (3 H, m, Ar*H*), 7.38-7.64 (4 H, m, Ar*H*), 8.07 (1 H, d, *J* 8.1, Ar*H*) and 8.13 (1 H, s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.5, 51.8, 53.2, 64.7, 107.8, 110.0, 117.4, 117.7, 118.8, 121.4, 122.2, 122.3, 125.8, 128.6, 130.6, 130.7, 133.5, 135.3, 143.3, 147.4 and 172.2; *m/z* (ESI) 378.1451 $[M+H]^+$ $C_{21}H_{20}N_3O_4$ requires 378.1448.

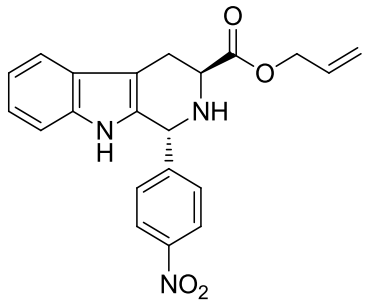
Preparation of **allyl (1*S*,3*S*)-1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 184a**



L-Tryptophan allyl ester **157** (151.0 mg, 0.62 mmol) was dissolved in dichloromethane (5 mL) in the presence of 3 Å molecular sieves (9.2 mg) and the mixture cooled to 0 °C. 4-Nitrobenzaldehyde (151.0 mg, 1.00 mmol) was added and after thirty minutes the solution allowed to warm to room temperature and stirred overnight. A small aliquot was then taken, the solvents removed and the crude solid analysed by ^1H NMR to confirm complete formation of the imine. The solution was then cooled to 0 °C, a 10% solution of trifluoroacetic acid in dichloromethane (94 µL, 1.23 mmol) added and the mixture stirred at this temperature for eight hours. The reaction was quenched with saturated sodium bicarbonate (12 mL) and the solution warmed to room temperature. The phases were separated and the aqueous portion washed with dichloromethane (3 x 15

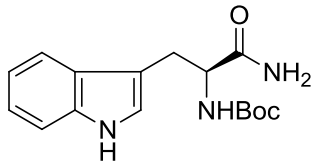
mL). The organic portions were combined, washed with saturated sodium chloride (15 mL), dried ($MgSO_4$) and the solvents removed under reduced pressure. Flash column chromatography (petrol/diethyl ether 6:1, 3:1, 1:3, dichloromethane/methanol 4:1) gave the *trans* product **184b** (41.8 mg, 18%) as a yellow, amorphous solid and the *cis* product **184a** (181.6 mg, 78%) as a yellow, amorphous solid: R_f = 0.36 (dichloromethane/diethyl ether 49:1); $[\alpha]_D^{23.5}$ −26.04 (*c* 0.96 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3393.8, 3076.8, 2932.3, 2850.1, 1734.9, 1519.8, 1348.6, 1208.4 and 738.9; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.38 (1 H, br s, N*H*), 2.83-2.97 (1 H, m, ArCH_2), 3.13 (1 H, dd, *J* 15.1 and 2.5, ArCH_2), 3.82 (1 H, dd, *J* 11.0 and 3.9, $ArCH_2CH$), 4.51-4.67 (2 H, m, OCH_2CHCH_2), 5.12-5.22 (2 H, m, OCH_2CHCH_2 and ArC*H*), 5.26 (1 H, dd, *J* 17.1 and 1.1, OCH_2CHCH_2), 5.77-5.94 (1 H, m, OCH_2CHCH_2), 6.96-7.04 (2 H, m, Ar*H*), 7.04-7.10 (1 H, m, Ar*H*), 7.35 (2 H, d, *J* 8.5, Ar*H*), 7.39-7.47 (1 H, m, Ar*H*), 7.76 (1 H, s, ArN*H*) and 7.91 (2 H, d, *J* 8.6, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 24.5, 55.6, 57.0, 64.9, 108.4, 110.1, 117.4, 118.0, 118.8, 121.3, 122.5, 125.8, 128.9, 130.6, 132.1, 133.9, 135.4, 142.3, 147.4 and 171.2; *m/z* (ESI) 378.1444 $[M+H]^+$ $C_{21}H_{20}N_3O_4$ requires 378.1448.

allyl (1*R*,3*S*)-1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxylate 184b



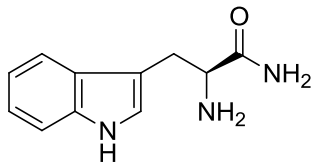
R_f = 0.10 (dichloromethane/diethyl ether 49:1); $[\alpha]_D^{24.4}$ −52.63 (*c* 0.38 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3396.9, 3075.6, 2927.7, 2852.6, 1732.1, 1519.6, 1347.5 and 741.9; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.42 (1 H, br s, N*H*), 3.07 (1 H, ddd, *J* 15.5, 6.6 and 0.7, ArCH_2), 3.21 (1 H, dd, *J* 15.6 and 5.2, ArCH_2), 3.84 (1 H, t, *J* 6.0, $ArCH_2CH$), 4.46-4.60 (2 H, m, OCH_2CHCH_2), 5.11-5.24 (2 H, m, OCH_2CHCH_2), 5.42 (1 H, s, ArC*H*), 5.73-5.88 (1 H, m, OCH_2CHCH_2), 7.02-7.14 (2 H, m, Ar*H*), 7.17 (1 H, s, Ar*H*), 7.37 (2 H, d, *J* 8.5, Ar*H*), 7.48 (1 H, d, *J* 7.2, Ar*H*), 7.66 (1 H, s, ArN*H*) and 8.04 (2 H, d, *J* 8.6, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 24.7, 52.7, 54.2, 65.8, 108.8, 111.1, 118.5, 118.7, 119.9, 122.5, 123.9, 126.8, 129.3, 131.7, 131.7, 136.3, 147.6, 149.4 and 173.3; *m/z* (ESI) 378.1451 $[M+H]^+$ $C_{21}H_{20}N_3O_4$ requires 378.1448.

Preparation of ***N*α-(*tert*-butoxycarbonyl)-L-tryptophanamide 186**



Commercially sourced Boc-protected L-tryptophan **185** (500.0 mg, 1.64 mmol) and triethylamine (190 µL, 1.97 mmol) were dissolved in a 1.2:1 mixture of acetonitrile (9.8 mL) and dichloromethane (8.2 mL). Ethyl chloroformate (190 µL, 1.97 mmol) was added at −8 °C and the reaction mixture stirred for thirty minutes. 28% aqueous ammonia (0.5 mL) was then added and this mixture stirred at room temperature for three hours. This solution was poured into dichloromethane (20 mL) and washed with 0.5 M hydrochloric acid (3 x 7 mL). The organic layer was separated, washed with water (40 mL), dried ($MgSO_4$), filtered and the solvents removed under reduced pressure to yield the Boc-protected amide **186** (532.0 mg, 94%) as a white, amorphous solid which required no further purification: R_f = 0.47 (dichloromethane/methanol 9:1); $[\alpha]_D^{21.5}$ +3.85 (*c* 0.78 in EtOH)[102]; ν_{max}(film)/cm^{-1} 3330.5, 2978.0, 2930.9, 2463.1, 1670.3, 1409.5 and 742.1 δ_H(300 MHz; DMSO; Me_4Si) 1.32 (9 H, s, C(C*H*$_3$)$_3$), 2.90 (1 H, dd, *J* 14.5 and 9.2, ArC*H*$_2$), 3.08 (1 H, dd, *J* 14.4 and 4.5, ArC*H*$_2$), 4.10-4.20 (1 H, m, ArCH$_2$C*H*), 6.70 (1 H, d, *J* 8.3, Ar*H*), 6.94-7.18 (4 H, m, Ar*H* and CON*H*$_2$), 7.33 (1 H, d, *J* 7.90, Ar*H*), 7.41 (1 H, s, N*H*Boc), 7.62 (1 H, d, *J* 7.5, Ar*H*) and 10.82 (1 H, br s, ArN*H*).

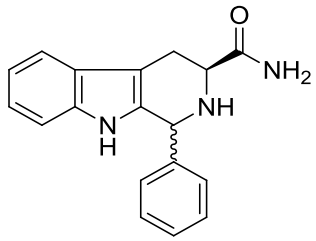
Preparation of **L-tryptophanamide**[103] **153**



Boc-tryptophanamide **186** (96.2 mg, 0.33 mmol) was dissolved in a 1:1 solution of trifluoroacetic acid (0.5 mL) and water (0.5 mL) and stirred at room temperature overnight. The solvents were removed under reduced pressure. The oily residue was dissolved in ethyl acetate (20 mL) and then washed with saturated sodium bicarbonate (10 mL). The aqueous portion was then washed with ethyl acetate (5 x 20 mL) and the combined organic fractions dried ($MgSO_4$), filtered and solvents removed under reduced pressure to yield the free amine **153** (53.7 mg, 88%) which was used directly in the next step without further purification.

Preparation of **(1*S*,3*S*)-1-phenyl-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxamide 188a** and

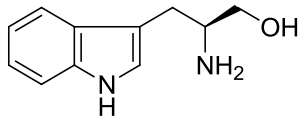
(1*R*,3*S*)-1-phenyl-2,3,4,9-tetrahydro-1*H*-β-carboline-3-carboxamide[104] 188b



L-Tryptophanamide **153** (77.4 mg, 0.38 mmol) and benzaldehyde **158** (48 µL, 0.48 mmol) were heated at reflux in toluene (5 mL) under Dean-Stark conditions for thirty minutes. A small aliquot was taken to confirm complete conversion to the imine and then the toluene was removed under reduced pressure. The imine was dissolved in dichloromethane (5 mL) under nitrogen at room temperature and then trifluoroacetic acid (58 µL, 0.76 mmol) added dropwise. The mixture was left to stir at room temperature for six hours. The solution was then neutralised with saturated sodium bicarbonate (10 mL) and ethyl acetate (20 mL) added. The organic portion was washed with saturated sodium bicarbonate (10 mL) and the aqueous portion washed with ethyl acetate (3 x 20 mL). The combined organics were washed with saturated sodium chloride (20 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure. Purification by column chromatography (ethyl acetate) yielded an inseparable mixture of the two C3 epimers **188a/b** (48.7 mg, 44%) in a ratio of 2.4:1 *cis/trans*.

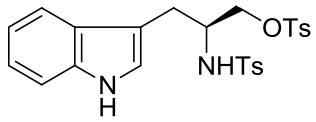
4.3 Chapter 3 experimental details

Preparation of **(2*S*)-2-amino-3-(1*H*-indol-3-yl)propan-1-ol[53] 258**



Lithium aluminium hydride (122 mL, 2.4 M solution in tetrahydrofuran) was added dropwise *via* cannula to a suspension of L-tryptophan **24** (20.00 g, 97.90 mmol) in tetrahydrofuran under nitrogen and stirred overnight. The mixture was then cooled in ice before the addition of water (11 mL), 15% sodium hydroxide (11 mL, w/v) and then water again (33 mL). The mixture was then stirred for two hours and the solids removed by filtration through Celite®, washing with ethyl acetate. The filtrate was then removed under reduced pressure to give an orange oil, trituration of which with petroleum ether gave the product **258** as a waxy, orange solid: R_f = 0.13 (dichloromethane/methanol 4:1); $[\alpha]_D^{24.8}$ −20.30 (*c* 1.38 in EtOH); ν_{max}(film)/cm^{-1} 3283.3, 2923.5, 1657.1 and 744.3; δ_H(300 MHz; CD_3OD; Me_4Si) 2.67 (1 H, dd, *J* 14.3 and 7.9, ArC*H*$_2$), 2.89 (1 H, dd, *J* 14.3 and 6.0, ArC*H*$_2$), 3.07-3.17 (1 H, m, ArCH$_2$C*H*), 3.38 (1 H, dd, *J* 10.9 and 7.2, C*H*$_2$OH), 3.56 (1 H, dd, *J* 10.5 and 4.5, C*H*$_2$OH), 6.94-7.01 (1 H, m, Ar*H*), 7.03-7.10 (2 H, m, Ar*H*), 7.31 (1 H, dt, *J* 7.9 and 0.8 Ar*H*), 7.51-7.56 (1 H, m, Ar*H*); δ_C(75 MHz; CD_3OD; Me_4Si) 30.2, 54.4, 67.2, 112.3, 112.4, 119.4, 119.7, 122.4, 124.3, 128.9 and 138.3; *m/z* (ESI) 191.1179 $[M+H]^+$ $C_{11}H_{15}N_2O$ requires 191.1179.

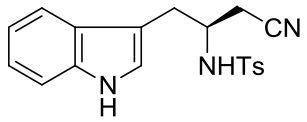
Preparation of **(2*S*)-3-(1*H*-indol-3-yl)-2-{[(4-methylphenyl)sulfonyl]amino}propyl 4-methylbenzene sulfonate[53] 225**



para-Toluenesulfonyl chloride (56.22 g, 294.89 mmol) was added in small portions to a solution of the starting alcohol **258** (18.70 g, 98.30 mmol) in anhydrous pyridine (60 mL) at 0 °C and the mixture was stirred overnight with warming to room temperature. The mixture was then poured into saturated sodium chloride (200 mL) and filtered through Celite®, washing with dichloromethane. The phases were separated and the aqueous fraction washed with dichloromethane (3 x 200 mL). The organic portions were combined and then washed with 2 M HCl (3 x 200 mL), saturated sodium chloride (2 x 200 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure. The resulting crude solid was taken up in dichloromethane and passed through a short plug of silica eluting with diethyl ether/dichloromethane (1:9). Solvents were removed under reduced pressure to give the ditosylate **225** as an orange, amorphous solid (35.64 g, 73% over two steps): R_f = 0.46 (dichloromethane/methanol 9:1); $[\alpha]_D^{26.4}$ −67.09 (*c* 0.79 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3410.9, 2923.2, 1175.6 and 1159.7; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.34 (3 H, s, ArC*H*$_3$), 2.47 (3 H, s, ArC*H*$_3$), 2.81 (1 H, dd, *J* 14.7 and 7.2, ArC*H*$_2$), 3.02 (1 H, dd, *J* 14.7 and 6.8, ArC*H*$_2$), 3.54-3.65 (1 H, m, ArCH$_2$C*H*), 3.92 (1 H, dd, *J* 10.2 and 5.7, C*H*$_2$OTs), 4.14 (1 H, dd, *J* 9.8 and 3.4, C*H*$_2$OTs), 4.93 (1 H, d, *J* 7.2, N*H*Ts), 6.89 (1 H, d, *J* 2.3, Ar*H*), 6.96-7.06 (3 H, m, Ar*H*), 7.13-7.22 (2 H, m, Ar*H*), 7.28-7.38 (3 H, m, Ar*H*) 7.43-7.49 (2 H, m, Ar*H*), 7.76-7.81 (2 H, m, Ar*H*) and

8.20 (1 H, br s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.6, 21.7, 27.3, 52.2, 70.7, 109.3, 111.4, 118.2, 119.6, 122.1, 123.5, 126.7, 128.0, 129.5, 130.1, 132.2, 136.1, 136.3, 143.4 and 145.3; *m/z* (ESI) 516.1619 $[M+NH_4]^+$ $C_{25}H_{30}N_3O_5S_2$ requires 516.1621.

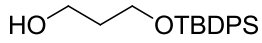
Preparation of ***N*-[(2*S*)-1-cyano-3-(1*H*-indol-3-yl)propan-2-yl]-4-methylbenzenesulfonamide[53] 226**



Potassium cyanide (10.07 g, 154.64 mmol) was added to a solution of the ditosylate **225** (38.64 g, 77.50 mmol) in anhydrous methanol (390 mL) and then heated at reflux for two hours. The mixture was then cooled to room temperature and methanol removed under reduced pressure. The resulting residue was partitioned between ethyl acetate (300 mL) and saturated sodium chloride (200 mL). The aqueous portion was washed with ethyl acetate (2 x 200 mL) and the organic portions combined and washed with saturated sodium chloride (2 x 200 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure. Recrystallisation from methanol gave the desired amino-protected nitrile **226** as a pale brown, crystalline solid (15.96 g, 58%): mp 189-190 °C (from MeOH); R_f = 0.50 (dichloromethane/ethyl acetate 9:1); $[\alpha]_D^{26.3}$ −24.21 (*c* 0.95 in C_5H_5N); ν_{max}(film)/cm^{-1} 3344.9, 3254.2, 2270.2, 1328.0 and 1151.3; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.28 (3 H, s, ArCH_3), 2.60 (2 H, dd, *J* 5.3 and 1.5, CH_2CN), 2.88 (1 H, dd, *J* 15.1 and 7.9, ArCH_2), 3.00 (1 H, dd, *J* 14.7 and 6.4, ArCH_2), 3.58-3.67 (1 H, m,

ArCH$_2$C*H*), 4.60 (1 H, d, *J* 6.0, N*H*), 6.91-6.98 (2 H, m, Ar*H*), 7.00 (2 H, d, *J* 7.9, Ar*H*), 7.14 (2 H, d, *J* 7.5, Ar*H*), 7.25-7.30 (1 H, m, Ar*H*), 7.37-7.42 (2 H, m, Ar*H*) and 8.01 (1 H, br s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.5, 25.0, 30.4, 51.6, 110.2, 112.4, 118.3, 118.8, 119.7, 122.2, 124.8, 127.5, 127.9, 130.2, 137.7, 138.3 and 143.8; *m/z* (ESI) 371.1539 $[M+NH_4]^+$ $C_{19}H_{23}N_4O_2S$ requires 371.1536.

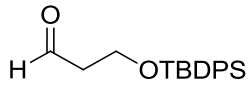
Preparation of **3-{[*tert*-butyl(diphenyl)silyl]oxy}propan-1-ol[105] 228**



Propan-1,3-diol **227** (2.53 mL, 35.01 mmol) was added to a suspension of sodium hydride (1.40 g, 35.01 mmol, 60% dispersion in mineral oil) in tetrahydrofuran (75 mL) and stirred for one hour. A solution of TBDPS-Cl (8.58 mL, 33.00 mmol) in tetrahydrofuran (15 mL) was then added dropwise. The reaction mixture was stirred for a further hour and then poured into diethyl ether (300 mL). This solution was then washed with 10% aqueous potassium carbonate (200 mL, w/v), saturated sodium chloride (200 mL) and dried ($MgSO_4$). The solvents were then removed under reduced pressure to give a colourless oil. Purification by column chromatography (dichloromethane) yielded the monoprotected alcohol **228** as a colourless oil which crystallised to a white solid (4.20 g, 40%) on standing: mp 36-39 °C (from DCM); R_f = 0.17 (dichloromethane); ν_{max}(film)/cm^{-1} 3354.6, 2930.4, 2857.4, 1472.1, 1427.6, 1111.9 and 702.2; δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.97 (9 H, s, SiC(C*H*$_3$)$_3$), 1.72 (2 H, quint, *J* 5.6, HOCH$_2$C*H*$_2$CH$_2$), 2.44 (1 H, br s, O*H*), 3.76 (4 H, t, *J* 5.6, HOC*H*$_2$CH$_2$C*H*$_2$), 7.26-7.40 (6 H, m, Ar*H*) and 7.56-7.64 (4 H, m,

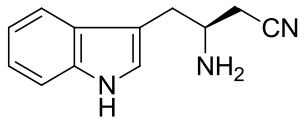
Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.1, 26.9, 34.3, 62.0, 63.3, 127.8, 129.8, 133.2 and 135.6; *m/z* (ESI) 315.1733 $[M+H]^+$ $C_{19}H_{27}O_2Si$ requires 315.1775.

Preparation of **3-{[*tert*-butyl(diphenyl)silyl]oxy}propanal[105] 109**



Oxalyl chloride (4.75 mL, 2 M in dichloromethane) was added to dichloromethane (44 mL) and cooled to −60 °C. Dimethyl sulfoxide (1.35 mL, 19.10 mmol) was then added dropwise and the reaction mixture left to stir for two minutes at −60 °C. A solution of the TBDPS-protected diol **228** (2.51 g, 7.95 mmol) in dichloromethane (25 mL) was then added *via* cannula over a period of fifteen minutes. The solution was stirred for a further fifteen minutes at −60 °C before the dropwise addition of triethylamine (5.53 mL, 39.70 mmol). The reaction mixture was then allowed to warm to room temperature and quenched by the addition of saturated sodium chloride (40 mL). The organic portion was washed with saturated sodium bicarbonate (3 x 50 mL), washed with saturated sodium chloride (50 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure to give a yellow oil **109** which crystallised on standing to an off-white/yellow solid (2.38 g, 95%): R_f = 0.56 (dichloromethane); ν_{max}(film)/cm^{-1} 3436.0, 3071.0, 2931.4, 2857.7, 2736.9, 2600.9, 2495.7, 1727.9 and 1112.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.95 (9 H, s, SiC(C*H*$_3$)$_3$), 2.50 (2 H, td, *J* 6.0 and 2.2, SiOCH$_2$C*H*$_2$), 3.92 (2 H, t, *J* 6.0, SiOC*H*$_2$), 7.21-7.38 (6 H, m, Ar*H*), 7.54-7.61 (4 H, m, Ar*H*) and 9.71 (1 H, t, *J* 2.2, C=O*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.2, 26.8, 46.4, 58.3, 127.8, 129.9, 133.3, 135.6 and 201.9.

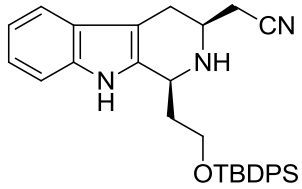
Preparation of **(3*S*)-3-amino-4-(1*H*-indol-3-yl)butanenitrile[53] 108**



Ammonia gas (125 mL) was condensed into a solution of the sulfonamide **226** (5.18 g, 14.70 mmol) in tetrahydrofuran (50 mL) at −78 °C under a nitrogen atmosphere. Sodium metal (1.00 g, 43.50 mmol) was added in small portions until a deep blue colour persisted, the reaction mixture was then stirred for a further thirty minutes at −78 °C. The reaction was then quenched with methanol (25 mL) and ammonium chloride (2.50 g). The ammonia was allowed to evaporate at room temperature and the tetrahydrofuran removed under reduced pressure. The residue was then partitioned between ethyl acetate (100 mL) and 2 M hydrochloric acid (100 mL). The aqueous phase was basified with 2 M ammonium hydroxide and then extracted with ethyl acetate (3 x 125 mL). The organic portion was then washed with saturated sodium chloride (100 mL), dried ($MgSO_4$) and solvents removed under reduced pressure to give an orange oil **108** (1.30 g, 45%) which was used directly in the next step: R_f = 0.19 (dichloromethane/methanol 19:1); $[\alpha]_D^{23.9}$ +19.35 (*c* 2.79 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3404.7, 2921.9 and 2247.2; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.44 (2 H, br s, N*H*$_2$), 2.14 (1 H, dd, *J* 16.7 and 6.4, C*H*$_2$CN), 2.26 (1 H, dd, *J* 16.6 and 5.0, C*H*$_2$CN), 2.70 (1 H, dd, *J* 14.3 and 7.3, ArC*H*$_2$), 2.79 (1 H, dd, *J* 14.3 and 6.1, ArC*H*$_2$), 3.21-3.32 (1 H, m, ArCH$_2$C*H*), 6.84 (1 H, d, *J* 2.2, Ar*H*), 6.95-7.11 (2 H, m, Ar*H*), 7.21 (1 H, d, *J* 8.0, Ar*H*), 7.43 (1 H, d, *J* 7.7, Ar*H*) and 8.65 (1 H, br s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 25.9, 32.9, 48.8, 111.1,

111.6, 118.6, 118.7, 119.7, 122.3, 123.3, 127.3 and 136.5; *m/z* (ESI) 200.1182 $[M+H]^+$ $C_{12}H_{14}N_3$ requires 200.1182.

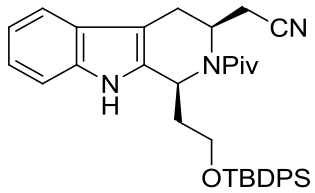
Preparation of **[(1*S*,3*S*)-1-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2,3,4,9-tetrahydro-1*H*-β-carbolin-3-yl]acetonitrile[55] 110**



Amine **108** (1.30 g, 6.52 mmol) was dissolved in dichloromethane (10 mL) and stirred with 3 Å molecular sieves (0.24 g). Aldehyde **109** (2.32 g, 7.43 mmol) was then added as a solution in dichloromethane (15 mL) at 0 °C and the reaction mixture left to warm to room temperature and stirred for forty-eight hours. The mixture was then cooled to −78 °C and trifluoroacetic acid (1.00 mL, 13.04 mmol) added dropwise. The reaction mixture was stirred at −78 °C for two hours, 0 °C for one hour and then room temperature for three hours. The mixture was then filtered and the molecular sieves washed with dichloromethane. The filtrate was then washed with saturated sodium bicarbonate (25 mL), saturated sodium chloride (25 mL), dried ($MgSO_4$) and solvents removed under reduced pressure. Purification by column chromatography (dichloromethane/diethyl ether 9:1) gave the *cis*-cyclised compound **110** as a white, amorphous solid (1.72 g, 54%): R_f = 0.15 (dichloromethane/diethyl ether 9:1); $[\alpha]_D^{24.3}$ −48.39 (*c* 0.31 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3358.0, 2930.1, 2857.3, 2250.0 and 1111.9; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.07 (9 H, s, SiC(CH_3)$_3$), 1.56 (1 H, br s, N*H*), 1.74-1.85 (1 H, m, OCH_2CH_2), 2.03-2.19 (1 H,

m, OCH_2CH_2), 2.43-2.51 (1 H, m, $ArCH_2$), 2.54 (2 H, d, *J* 6.5, CH_2CN), 2.87 (1 H, ddd, *J* 15.1, 3.9 and 1.9, $ArCH_2$), 3.15-3.28 (1 H, m, $ArCH_2CH$), 3.88 (2 H, dd, *J* 7.3 and 3.4, OCH_2), 4.19-4.29 (1 H, m, ArC*H*), 6.97-7.06 (3 H, m, Ar*H*), 7.26-7.42 (7 H, m, Ar*H*), 7.56-7.65 (4 H, m, Ar*H*) and 8.89 (1 H, br s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.3, 25.0, 27.1, 28.5, 37.7, 51.3, 53.7, 63.0, 107.3, 111.1, 118.0, 119.4, 121.6, 127.0, 128.0, 128.1, 130.1, 132.7, 132.8, 135.6 and 135.7; *m/z* (ESI) 494.2612 $[M+H]^+$ $C_{31}H_{36}N_3OSi$ requires 494.2622.

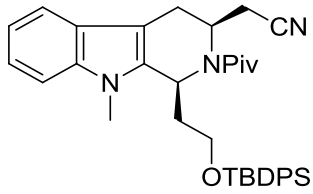
Preparation of **[(1*S*,3*S*)-1-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-(2,2-dimethylpropanoyl)-2,3,4,9-tetrahydro-1*H*-β-carbolin-3-yl]acetonitrile[87] 259**



Pivaloyl chloride (1.51 mL, 12.23 mmol) and diisopropylethylamine (2.13 mL, 12.23 mmol) were added to a solution of the tricyclic amine **110** (1.51 g, 3.06 mmol) in dichloromethane (25 mL) at room temperature under nitrogen. This mixture was left to stir for thirty-six hours and solvents were then removed under reduced pressure. The resulting residue was purified by column chromatography (petrol/ethyl acetate 19:1, 4:1) to give the pivaloyl-protected tricycle **259** as a white, amorphous solid (1.42 g, 81%): R_f = 0.34 (petrol/ethyl acetate 2.33:1); $[\alpha]_D^{25.9}$ +55.06 (*c* 0.89 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3377.0, 2961.2, 2931.5, 2858.2, 2247.3, 1621.0 and 734.4; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.26 (9 H, s, $SiC(CH_3)_3$), 1.43 (9 H, s, $C(CH_3)_3$), 1.90-2.01 (1 H, m, OCH_2CH_2), 2.13-2.19 (1 H, m, OCH_2CH_2), 2.62 (1

H, dd, *J* 16.8 and 6.6, C*H*$_2$CN), 2.74 (1H, dd, *J* 16.8 and 8.0, C*H*$_2$CN), 3.02 (1 H, d, *J* 15.8, ArC*H*$_2$), 3.18 (1 H, ddd, *J* 15.8, 5.0 and 1.8, ArC*H*$_2$), 4.05 (1 H, dt, *J* 10.4 and 3.1, OC*H*$_2$), 4.38 (1 H, td, *J* 10.6 and 2.0, OC*H*$_2$), 5.10-5.22 (1 H, m, ArCH$_2$C*H*), 5.56 (1 H, d, *J* 7.6, ArC*H*), 6.81-6.88 (1 H, m, Ar*H*), 7.07-7.16 (2 H, m, Ar*H*), 7.40-7.56 (7 H, m, Ar*H*), 7.70-7.80 (4 H, m, Ar*H*) and 9.74 (1 H, br s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 18.4, 21.9, 24.4, 26.3, 27.6, 38.5, 39.4, 48.1, 20.7, 64.3, 100.8, 110.1, 116.5, 116.8, 118.4, 120.7, 125.7, 127.1, 129.2, 131.3, 131.7, 132.1, 134.5, 134.9 and 176.0; *m/z* (ESI) 578.3196 $[M+H]^+$ $C_{36}H_{44}N_3O_2Si$ requires 578.3197.

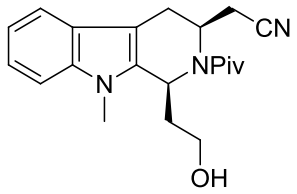
Preparation of **[(1*S*,3*S*)-1-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-(2,2-dimethylpropanoyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-3-yl]acetonitrile[87] 218**



The pivaloyl-protected nitrile **259** (1.32 g, 2.29 mmol) was dissolved in dimethylformamide (25 mL) and then methyl iodide (0.29 mL, 4.62 mmol) and sodium hydride (101.6 mg, 2.54 mmol, 60% dispersion in mineral oil) were added at 0 °C under a nitrogen atmosphere. This reaction mixture was stirred for thirty minutes and then allowed to warm to room temperature. After a further thirty minutes a further two equivalents of methyl iodide (0.29 mL, 4.62 mmol) were added. After a further thirty minutes excess methyl iodide and dimethylformamide

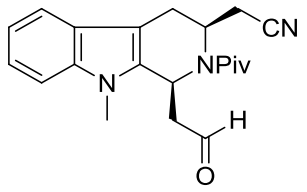
were removed under reduced pressure and the resulting orange residue was partitioned between ethyl acetate (150 mL) and water (150 mL). The aqueous phase was separated and then washed with ethyl acetate (3 x 150 mL) and the combined organic fractions washed with saturated sodium chloride (150 mL), dried ($MgSO_4$) and solvents removed under reduced pressure. The resulting oil was purified by flash column chromatography (petrol/ethyl acetate 9:1) to give the indole-methylated product **218** as a white, amorphous solid (1.13 g, 83%): R_f = 0.34 (petrol/ethyl acetate 4:1); $[\alpha]_D^{25.7}$ −2.47 (*c* 0.81 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3377.0, 2961.2, 2931.5, 2858.2, 2247.3, 1621.0 and 734.4; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.11 (9 H, s, SiC(C*H*$_3$)$_3$), 1.32 (9 H, s, C(C*H*$_3$)$_3$), 1.76-1.96 (1 H, m, OCH$_2$C*H*$_2$), 2.11-2.34 (2 H, m, OCH$_2$C*H*$_2$ and ArC*H*$_2$), 2.72-2.86 (1 H, m, ArC*H*$_2$), 3.01 (1 H, dd, *J* 15.6 and 2.8, C*H*$_2$CN), 3.08-3.20 (1 H, m, C*H*$_2$CN), 3.51-3.63 (1 H, m, OC*H*$_2$), 3.67 (3 H, s, ArNC*H*$_3$), 4.01-4.11 (1 H, m, OC*H*$_2$), 4.81-4.92 (1 H, m, ArCH$_2$C*H*), 5.97 (1 H, dd, *J* 9.7 and 4.9, ArC*H*), 7.12-7.19 (1 H, m, Ar*H*), 7.22-7.34 (2 H, m, Ar*H*), 7.38-7.53 (7 H, m, Ar*H*) and 7.66-7.74 (4 H, m, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.2, 23.4, 25.1, 27.0, 28.7, 30.5, 39.4, 39.6, 46.1, 49.2, 61.3, 109.2, 117.9, 118.0, 119.7, 122.0, 126.1, 127.9, 130.0, 130.1, 133.3, 133.6, 135.7, 137.7 and 177.2; *m/z* (ESI) 592.3353 $[M+H]^+$ $C_{37}H_{46}N_3O_2Si$ requires 592.3354.

Preparation of **[(1*S*,3*S*)-2-(2,2-dimethylpropanoyl)-1-(2-hydroxyethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-3-yl]acetonitrile[87] 229**



Tetrabutylammonium fluoride (2.26 mL, 1 M solution in tetrahydrofuran) was added dropwise to a solution of the TBDPS-protected starting material **218** (1.11 g, 1.88 mmol) in tetrahydrofuran (21 mL) under nitrogen at 0 °C. The resulting red solution was stirred at 0 °C for two hours. The reaction mixture was then concentrated under reduced pressure and purified by flash column chromatography (petrol/ethyl acetate 3:1) to give the alcohol **229** as a white, amorphous solid (470.7 mg, 71%): R_f = 0.30 (petrol/ethyl acetate 1:1); $[\alpha]_D^{25.2}$ +56.76 (*c* 1.11 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3440.1, 2926.2, 2854.3, 2246.6, 1613.2 and 736.2; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s, C(C*H*$_3$)$_3$), 1.65-1.78 (1 H, m, OCH$_2$C*H*$_2$), 2.29-2.43 (1 H, m, OCH$_2$C*H*$_2$), 2.80 (1 H, dd, *J* 16.7 and 7.2, C*H*$_2$CN), 2.87 (1 H, dd, *J* 16.8 and 8.1, C*H*$_2$CN), 2.99 (1 H, d, *J* 15.8, ArC*H*$_2$), 3.18 (1 H, ddd, *J* 15.8, 6.1 and 1.2, ArC*H*$_2$), 3.57-3.69 (1 H, m, OC*H*$_2$), 3.72-3.82 (4 H, m, OC*H*$_2$ and ArNC*H*$_3$), 4.22 (1 H, br s, O*H*), 5.16-5.26 (1 H, m, ArCH$_2$C*H*), 5.93-6.01 (1 H, m, ArC*H*), 7.12-7.18 (1 H, m, Ar*H*), 7.23-7.29 (1 H, m, Ar*H*), 7.34 (1 H, d *J* 8.1, Ar*H*) and 7.47 (1 H, d *J* 7.8, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.6, 25.7, 29.0, 30.9, 38.3, 40.1, 46.1, 48.9, 58.3, 102.3, 109.3, 117.4, 117.9, 119.7, 122.2, 126.2, 133.2, 138.1 and 179.4; *m/z* (ESI) 354.2177 $[M+H]^+$ $C_{21}H_{28}N_3O_2$ requires 354.2176.

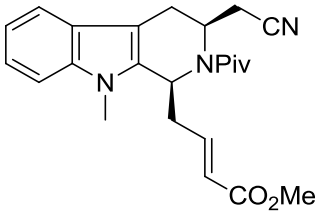
Preparation of **[(1*S*,3*S*)-2-(2,2-dimethylpropanoyl)-9-methyl-1-(2-oxoethyl)-2,3,4,9-tetrahydro-1*H*-β-carbolin-3-yl]acetonitrile[87] 260**

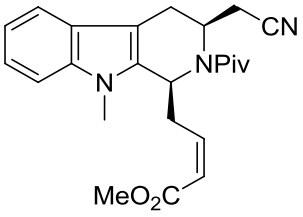


Oxalyl chloride (2 M in dichloromethane, 1.75 mL) was added to dichloromethane (15 mL) and cooled to −60 °C. Dimethyl sulfoxide (0.50 mL, 6.99 mmol) was then added and the resulting solution stirred for two minutes ensuring the temperature stayed at −60 °C. A solution of the starting alcohol **229** (1.03 g, 2.91 mmol) in dichloromethane (10 mL) was then added and the mixture stirred for a further fifteen minutes. Triethylamine (2.03 mL, 14.56 mmol) was then added dropwise and the mixture allowed to warm to room temperature. The reaction was then quenched with saturated sodium chloride (125 mL). The phases were separated and the organic portion was washed with saturated sodium bicarbonate (125 mL). The aqueous portions were combined and extracted with dichloromethane (125 mL). The combined organic portions were then washed with saturated sodium chloride (125 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure to give the crude aldehyde **260** (1.00 g, 98%) as a yellow, amorphous solid, a portion of which was subject to column chromatography (petrol/ethyl acetate 3:1) for characterisation: R_f = 0.19 (petrol/ethyl acetate 1:1); $[\alpha]_D^{23.5}$ +94.70 (*c* 0.26 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3422.5, 2975.4, 2927.2, 2248.0, 1718.2, 1634.7 and 752.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.30 (9 H, s, C(C*H*$_3$)$_3$), 2.47-2.59 (1 H, m, C*H*$_2$C=O), 2.80-2.86 (2 H, m, C*H*$_2$CN), 3.03-3.12 (3 H, m, ArC*H*$_2$ and C*H*$_2$C=O),

3.66 (3 H, s, ArNCH_3), 5.01-5.10 (1 H, m, ArCH$_2$CH), 5.95 (1 H, dd, *J* 9.4 and 4.9, ArCH), 7.06-7.13 (1 H, m, ArH), 7.17-7.29 (2 H, m, ArH), 7.44 (1 H, d *J* 7.9, ArH) and 9.81 (1 H, dd, *J* 4.1 and 1.5, C=OH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.6, 24.9, 28.4, 30.9, 39.6, 45.2, 49.1, 50.2, 103.4, 109.3, 117.6, 118.4, 119.9, 122.6, 126.1, 131.9, 138.1, 177.8 and 198.1.

Preparation of **methyl (2*E*)-4-[(1*S*,3*S*)-3-(cyanomethyl)-2-(2,2-dimethylpropanoyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl]but-2-enoate[87] 219*E*** and **methyl (2*Z*)-4-[(1*S*,3*S*)-3-(cyanomethyl)-2-(2,2-dimethylpropanoyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl]but-2-enoate 219*Z***



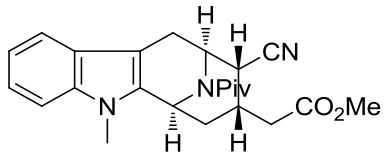


The Wittig reagent methyl (triphenylphosphoranylidene)acetate (1.19 g, 3.56 mmol) was added to a solution of the starting aldehyde **260** (1.00 g, 2.85 mmol) in dichloromethane (36 mL) at 0 °C. The resulting solution was stirred at 0 °C for one hour, warmed to room temperature and stirred for a further four hours. The mixture was then concentrated under reduced pressure and purified by column chromatography (petrol/ethyl acetate 4:1) to give the *E* and *Z* unsaturated esters **219** (800.1 mg, 69%) in a ratio of 8:1 respectively.

***E* ester 219*E*:** R_f = 0.17 (petrol/ethyl acetate 3:1); $[\alpha]_D^{23.4}$ +51.79 (*c* 0.25 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2951.6, 2249.6, 1721.1, 1635.9, 1190.9 and 736.5; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.30 (9 H, s, C(C*H*$_3$)$_3$), 2.48-2.67 (2 H, m, C*H*$_2$CN and ArCHC*H*$_2$), 2.80-2.95 (2 H, m, C*H*$_2$CN and ArCHC*H*$_2$), 3.01-3.06 (2 H, m, ArC*H*$_2$), 3.61 (3 H, s, ArNC*H*$_3$), 3.67 (3 H, s, CO_2C*H*$_3$), 4.96-5.06 (1 H, m, $ArCH_2C$*H*), 5.80 (1 H, dt, *J* 15.5 and 1.5, C*H*CO_2CH_3), 5.96 (1 H, dd, *J* 8.7 and 5.3, ArC*H*), 6.96-7.11 (2 H, m, C*H*$CHCO_2CH_3$ and Ar*H*), 7.15-7.21 (1 H, m, Ar*H*), 7.24 (1 H, d, *J* 8.3, Ar*H*) and 7.42 (1 H, d, *J* 7.9, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 22.5, 24.2, 27.6, 30.3, 38.7, 38.9, 46.6, 47.9, 50.7, 102.1, 108.3, 116.5, 117.2, 118.8, 121.3, 122.5, 125.1, 131.9, 137.0, 143.7, 165.2 and 176.3; *m/z* (ESI) 425.2547 $[M+NH_4]^+$ $C_{24}H_{33}N_4O_3$ requires 425.2547.

***Z* ester 219*Z*:** R_f = 0.27 (petrol/ethyl acetate 3:1); $[\alpha]_D^{23.4}$ +100.00 (*c* 0.79 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2974.5, 2247.6, 1717.3, 1636.2 and 748.3; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.31 (9 H, s, C(C*H*$_3$)$_3$), 2.76 (1 H, dd, *J* 16.6 and 4.9, ArC*H*$_2$), 2.86 (1 H, dd, *J* 16.6 and 9.8, ArC*H*$_2$), 3.02 (2 H, d, *J* 3.0, C*H*$_2$CN), 3.08-3.22 (1 H, m, ArCHC*H*$_2$), 3.26-3.37 (1 H, m, ArCHC*H*$_2$), 3.61 (3 H, s, CO_2C*H*$_3$), 3.64 (3 H, s, ArNC*H*$_3$), 4.99-5.08 (1 H, m, $ArCH_2C$*H*), 5.83 (1 H, dt, *J* 11.7 and 1.9, C*H*CO_2CH_3), 6.01 (1 H, dd, *J* 10.2 and 4.5, ArC*H*), 6.44-6.55 (1 H, m, C*H*$CHCO_2CH_3$), 7.03-7.10 (1 H, m, Ar*H*), 7.14-7.21 (1 H, m, Ar*H*), 7.24 (1 H, d, *J* 7.9, Ar*H*) and 7.41 (1 H, d, *J* 7.5, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 22.2, 24.3, 27.7, 29.7, 34.7, 38.7, 46.7, 47.9, 50.3, 101.6, 108.2, 116.8, 117.1, 118.6, 119.6, 121.1, 125.2, 132.1, 136.9, 145.3, 165.7 and 176.6; *m/z* (ESI) 425.2547 $[M+NH_4]^+$ $C_{24}H_{33}N_4O_3$ requires 425.2547.

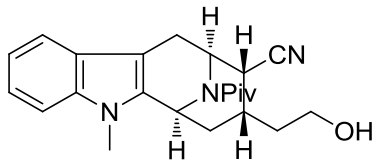
Preparation of **methyl [(6*S*,8*S*,9*R*,10*S*)-9-cyano-12-(2,2-dimethylpropanoyl)-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indol-8-yl]acetate[87] 220**



A solution of the *E* and *Z* unsaturated esters **219*E:Z*** (100.0 mg, 245 μmol) in tetrahydrofuran (4 mL) was cooled to −78 °C and then lithium bis(trimethylsilyl)amide (307 μL, 1 M in tetrahydrofuran) was added dropwise. The resulting solution was stirred at −78 °C for a further two hours. The reaction was quenched with saturated sodium chloride (5 mL) and allowed to warm to room temperature. The mixture was then diluted with saturated sodium chloride (10 mL) and ethyl acetate (10 mL). The aqueous phase was separated and then washed with ethyl acetate (3 x 10 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure. Column chromatography (petrol/ethyl acetate 9:1) gave the tetracyclic ester **220** (71.9 mg, 72%): R_f = 0.43 (petrol/ethyl acetate 1:1); $[\alpha]_D^{22.9}$ −9.09 (*c* 0.33 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2953.8, 2926.6, 2852.8, 2242.3, 1735.5, 1633.1 and 736.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.26 (9 H, s, C(C*H*$_3$)$_3$), 1.62 (1 H, d, *J* 13.6, ArCHC*H*$_2$), 1.94 (1 H, td, *J* 13.2 and 3.8, ArCHC*H*$_2$), 2.24 (1 H, dd, *J* 15.1 and 3.4, C*H*$_2$COCH$_3$), 2.32-2.51 (2 H, m, C*H*CH$_2$CO$_2$CH$_3$ and C*H*$_2$CO$_2$CH$_3$), 2.66 (1 H, d, *J* 16.6, ArC*H*$_2$), 3.24 (1 H, br s, C*H*CN), 3.38 (1 H, dd, *J* 17.0 and 7.9, ArC*H*$_2$), 3.53 (3 H, s, ArNC*H*$_3$), 3.62 (3 H, s, CO$_2$C*H*$_3$), 5.23-5.33 (1 H, m, ArCH$_2$C*H*), 5.82 (1 H, br s, ArC*H*), 7.02-7.09 (1 H, m, Ar*H*), 7.12-7.19 (1 H, m, Ar*H*), 7.23 (1 H, d, *J* 8.1, Ar*H*) and 7.38 (1 H, d, *J* 7.7, Ar*H*); δ_C(75 MHz; $CDCl_3$;

Me_4Si) 25.8, 26.6, 28.8, 29.3, 32.1, 37.0, 39.0, 39.6, 46.0, 48.2, 51.9, 107.1, 109.3, 118.3, 118.3, 119.5, 121.9, 125.9, 133.8, 137.1, 171.5 and 176.8; *m/z* (ESI) 408.2284 $[M+H]^+$ $C_{24}H_{30}N_3O_3$ requires 408.2282.

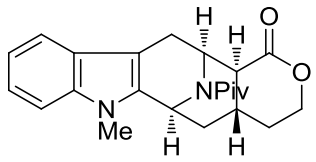
Preparation of **(6*S*,8*S*,9*R*,10*S*)-12-(2,2-dimethylpropanoyl)-8-(2-hydroxyethyl)-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carbonitrile[87] 221**



Lithium borohydride (7.48 mg, 344 μmol) was added in one portion to a solution of the starting ester **220** (70.0 mg, 172 μmol) in tetrahydrofuran (4 mL) at 0 °C and stirred for fifteen minutes. The reaction mixture was then heated at reflux overnight. The reaction was quenched with methanol (3 mL) and water (5 mL). The aqueous phase was separated and extracted with ethyl acetate (4 x 10 mL). The combined organic portions were washed with saturated sodium chloride (10 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure. Column chromatography (petrol/ethyl acetate 1:1) gave the alcohol **221** (33.2 mg, 51%) as a white, amorphous solid: R_f = 0.59 (ethyl acetate); $[\alpha]_D^{24.3}$ −10.70 (*c* 0.37 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3396.1, 2928.0, 2237.8, 1668.7 and 1630.5; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.26 (9 H, s, C(C*H*$_3$)$_3$), 1.44-1.69 (3 H, m, ArCHC*H*$_2$, C*H*$_2$CH$_2$OH), 1.85-2.00 (1 H, m, ArCHC*H*$_2$), 2.02-2.16 (1 H, m, ArCHCH$_2$C*H*), 2.60 (1 H, d, *J* 16.8, ArC*H*$_2$), 3.03 (1 H, br s, C*H*CN), 3.36 (1 H, dd, *J* 16.4 and 7.9. ArC*H*$_2$), 3.44-3.58 (2 H, m, C*H*$_2$OH), 3.61 (3 H, s, ArNC*H*$_3$), 5.26 (1 H, br s, ArCH$_2$C*H*), 5.78 (1 H, br s,

ArC*H*), 7.01-7.08 (1 H, m, Ar*H*), 7.12-7.19 (1 H, m, Ar*H*), 7.23 (1 H, d, *J* 7.9, Ar*H*) and 7.37 (1 H, d, *J* 7.7, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 24.8, 25.8, 27.8, 28.2, 31.6, 34.8, 38.3, 38.5, 46.1, 48.3, 58.6, 105.9, 108.2, 117.1, 117.7, 118.4, 120.7, 124.8, 133.2, 135.9 and 175.8; *m/z* (ESI) 380.2327 $[M+H]^+$ $C_{23}H_{30}N_3O_2$ requires 380.2333.

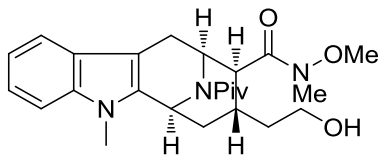
Preparation of **(4a*S*,6*S*,13*S*,13a*S*)-14-(2,2-dimethylpropanoyl)-7-methyl-4,4a,5,6,7,12,13,13a-octahydro-6,13-epiminopyrano[3',4':5,6]cycloocta[1,2-*b*]indol-1(3*H*)-one[87] 222**



The starting alcohol **221** (68.2 mg, 180 μmol) was dissolved in 1,4-dioxane (3 mL) then *para*-toluenesulfonic acid monohydrate (342.4 mg, 1.80 mmol) was added. The reaction mixture was then stirred at reflux overnight. The resulting solution was quenched with saturated sodium bicarbonate (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic portions were then washed with saturated sodium chloride (20 mL), dried ($MgSO_4$), filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (petrol/ethyl acetate 1:1) to give the lactone product **222** as a white, amorphous solid (34.6 mg, 51%): R_f = 0.46 (ethyl acetate); $[\alpha]_D^{24.5}$ −56.25 (*c* 0.32 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3054, 2926, 2852, 1726, 1628 and 749; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.24 (9 H, s, C(C*H*$_3$)$_3$), 1.50-1.69 (3 H, m, ArCHC*H*$_2$, C*H*$_2$CH$_2$OC=O), 1.73 (1 H, ddd, *J* 13.2, 3.6 and 2.8, ArCHC*H*$_2$), 1.91-2.11 (1 H, m,

ArCHCH$_2$C*H*), 2.35 (1 H, dd, *J* 12.8 and 4.0, C*H*C=O), 2.75 (1 H, d, *J* 17.0, ArC*H*$_2$), 3.23 (1 H, dd, *J* 17.3 and 7.2, ArC*H*$_2$), 3.58 (3 H, s, ArNC*H*$_3$), 3.98-4.10 (1 H, m, C*H*$_2$O), 4.22-4.31 (1 H, m, C*H*$_2$O). 5.27-5.35 (1 H, m, ArCH$_2$C*H*), 5.94 (1 H, br s, ArC*H*), 6.97-7.05 (1 H, m, Ar*H*), 7.07-7.13 (1 H, m, Ar*H*), 7.19 (1 H, d, *J* 8.1, Ar*H*) and 7.37 (1 H, d, *J* 7.7, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 23.5, 27.8, 28.4, 29.2, 29.3, 36.2, 39.4, 44.3, 48.5, 51.0, 69.2, 107.3, 109.2, 118.3, 119.4, 121.7, 126.0, 134.4, 137.0, 169.8 and 175.9; *m/z* (ESI) 381.2166 $[M+H]^+$ $C_{23}H_{29}N_2O_3$ requires 381.2173.

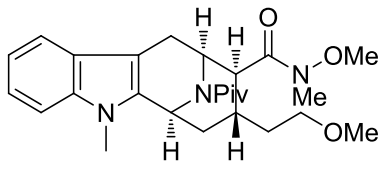
Preparation of **(6*S*,8*S*,9*S*,10*S*)-12-(2,2-dimethylpropanoyl)-8-(2-hydroxyethyl)-*N*-methoxy-*N*,5-dimethyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carboxamide[87] 223**



N,*O*-Dimethylhydroxylamine hydrochloride (225.3 mg, 2.31 mmol) was suspended in dichloromethane (10 mL) under a nitrogen atmosphere and trimethylaluminium solution (1.16 mL, 2 M in toluene) added dropwise. The resulting solution was stirred at room temperature for forty-five minutes. A solution of the lactone **222** (87.9 mg, 231 μmol) in dichloromethane (10 mL) was then added dropwise and the reaction left to stir overnight. The reaction mixture was cooled in ice and NH_4OH/NH_4Cl solution at pH 8 added slowly. The resulting solution was filtered through Celite®, washing with dichloromethane. The phases were then separated and the organics dried ($MgSO_4$), filtered and the solvents removed under reduced

pressure. The resulting crude oil was purified by flash column chromatography (ethyl acetate) to give the Weinreb amide **223** as a white, amorphous solid (58.0 mg, 57%): R_f = 0.16 (ethyl acetate); $[\alpha]_D^{25.7}$ +15.79 (*c* 0.57 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3445.2, 3051.8, 2971.0, 2935.7, 2850.1, 1722.6 and 1626.9; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.33 (9 H, s, C(C*H*$_3$)$_3$), 1.36-1.46 (2 H, m, C*H*$_2$CH$_2$OH), 1.68 (1 H, td, *J* 12.8 and 4.5, ArCHC*H*$_2$), 1.89-1.98 (1 H, m, ArCHC*H*$_2$), 2.17-2.33 (1 H, m, ArCHCH$_2$C*H*), 2.88-2.97 (1 H, m, C*H*C=O), 2.94 (1 H, d, *J* 16.6, ArC*H*$_2$), 3.01 (1 H, dd, *J* 16.6 and 6.4, ArC*H*$_2$), 3.28 (3 H, s, NC*H*$_3$OCH$_3$), 3.42 (2 H, t, *J* 6.2, C*H*$_2$OH), 3.67 (3 H, s, ArNC*H*$_3$), 3.74 (3 H, s, NCH$_3$OC*H*$_3$), 5.12 (1 H, br s, ArCH$_2$C*H*), 5.93 (1 H, br s, ArC*H*), 7.04-7.11 (1 H, m, Ar*H*), 7.15-7.22 (1 H, m, Ar*H*), 7.27 (1 H, d, *J* 8.7, Ar*H*) and 7.44 (1 H, d, *J* 7.5, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 22.5, 26.2, 28.3, 29.2, 32.4, 38.5, 39.2, 44.7, 49.0, 50.0, 59.8, 60.4, 61.7, 107.2, 109.0, 118.4, 119.1, 121.2, 126.2, 134.4, 137.1, 173.0 and 175.8; *m/z* (ESI) 442.2702 $[M+H]^+$ $C_{25}H_{36}N_3O_4$ requires 442.2700.

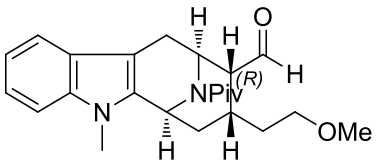
Preparation of **(6*S*,8*S*,9*S*,10*S*)-12-(2,2-dimethylpropanoyl)-*N*-methoxy-8-(2-methoxyethyl)-*N*,5-dimethyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carboxamide[87] 212**

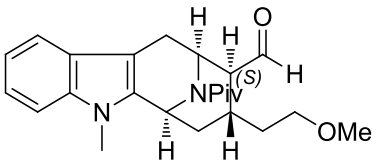


Methyl iodide (78 µL, 1.25 mmol) was added dropwise to a solution of the alcohol **223** (109.9 mg, 249 µmol) and sodium hydride (19.9 mg, 498 µmol, 60% dispersion in mineral oil) in tetrahydrofuran at 0 °C. The reaction mixture was

allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated sodium chloride (25 mL) and diluted with ethyl acetate (25 mL). The phases were separated and the aqueous extracted with ethyl acetate (3 x 25 mL). The combined organics were washed with saturated sodium chloride (25 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure. The crude product was purified by column chromatography (dichloromethane/diethyl ether 19:1) to give a yellow oil **212** (49.0 mg, 44%): R_f = 0.50 (ethyl acetate); $[\alpha]_D^{21.5}$ +31.86 (*c* 0.97 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3051.4, 2972.2, 2934.7, 1655.4, 1627.9, 1469.8, 1195.9 and 737.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.27-1.41 (1 H, m, C*H*$_2$CH$_2$OCH$_3$), 1.35 (9 H, s, C(C*H*$_3$)$_3$), 1.54-1.66 (1 H, m, C*H*$_2$CH$_2$OCH$_3$), 1.73 (1 H, td, *J* 12.8 and 4.0, ArCHC*H*$_2$), 1.95 (1 H, ddd, *J* 13.4, 4.5 and 2.4, ArCHC*H*$_2$), 2.13-2.30 (1 H, m, ArCHCH$_2$C*H*), 2.94-3.07 (3 H, m, ArC*H*$_2$ and C*H*CO), 3.22 (3 H, s, OC*H*$_3$), 3.25-3.30 (5 H, m, NC*H*$_3$OCH$_3$ and C*H*$_2$OCH$_3$), 3.69 (3 H, s, ArNC*H*$_3$), 3.75, (3 H, s, NCH$_3$OC*H*$_3$), 5.12 (1 H, br s, ArCH$_2$C*H*), 5.96 (1 H, br s, ArC*H*), 7.09 (1 H, td, *J* 7.9 and 1.1, Ar*H*), 7.20 (1 H, td, *J* 7.5 and 1.1, Ar*H*), 7.30 (1 H, d, *J* 7.9, Ar*H*) and 7.47 (1 H, d, *J* 7.7, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 22.4, 27.5, 28.4, 29.2, 32.2, 34.3, 35.0, 39.2, 44.7, 48.7, 50.0, 58.4, 61.6, 70.7, 107.3, 108.9, 118.5, 119.0, 122.2, 126.3, 134.4, 137.1, 172.3 and 175.7; *m/z* (ESI) 456.2852 $[M+H]^+$ $C_{26}H_{38}N_3O_4$ requires 456.2857.

Preparation of **(6*S*,8*S*,9*R*,10*S*)-12-(2,2-dimethylpropanoyl)-8-(2-methoxyethyl)-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carbaldehyde 210b** and **(6*S*,8*S*,9*S*,10*S*)-12-(2,2-dimethylpropanoyl)-8-(2-methoxyethyl)-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carbaldehyde 210a**





The methylated Weinreb amide **212** (78.0 mg, 171 μmol) was dissolved in anhydrous tetrahydrofuran (8 mL) and cooled to −78 °C. Lithium aluminium hydride (356 μL, 2.4 M solution in tetrahydrofuran) was added dropwise and the reaction mixture stirred for two hours. The mixture was then allowed to warm to −40 °C and was quenched with water (one drop), 15% NaOH (one drop) and water (three drops). The resulting emulsion was stirred vigorously for one hour at which point it was filtered through Celite® washing with diethyl ether. The organic phase was dried ($MgSO_4$) and solvents removed under reduced pressure to give two aldehydes, epimeric at carbon 9, which were purified by column chromatography (petrol/ethyl acetate 5.67:1) giving the (*R*)-aldehyde **210b** (9.8 mg, 14%), (*S*)-aldehyde **210a** (19.0 mg, 28%) and a mixture of the two epimers (23.4 mg, 34%) as opaque oils.

The above method was modified as follows to prevent epimerisation of the stereochemistry at C9, giving the C9 (*S*)-aldehyde **210a** exclusively.

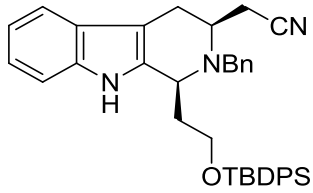
Once the reaction mixture had warmed to −40 °C, it was quenched with ethyl acetate (10 mL), then a few drops of saturated sodium sulfate were added and the solution was left to stir for thirty minutes. The resulting mixture was filtered through Celite® washing with ethyl acetate. The organic phase was dried ($MgSO_4$) and solvents removed to give analytically pure aldehyde **210a** (best yield of 82%).

C9 (*R*)-aldehyde 210b: R_f = 0.41 (petrol/ethyl acetate 1:1); $[\alpha]_D^{25.2}$ −19.23 (*c* 0.10 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3053.0, 2927.3, 1719.9, 1613.9, 1470.4 and 744.1; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.27 (9 H, s, C(C*H*$_3$)$_3$), 1.53-1.85 (3 H, m, C*H*$_2$CH$_2$OCH$_3$ and ArCHC*H*$_2$), 2.02-2.13 (1 H, m, ArCHCH$_2$C*H*), 2.27 (1 H, td, *J* 12.6 and 4.3, ArCHC*H*$_2$), 2.67 (1 H, br s, C*H*C=O), 2.72 (1 H, d, *J* 16.6, ArC*H*$_2$), 3.19 (3 H, s, OC*H*$_3$), 3.29 (2 H, t, *J* 6.1, C*H*$_2$OCH$_3$), 3.48 (1 H, dd, *J* 16.6 and 8.3, ArC*H*$_2$), 3.71, (3 H, s, ArNC*H*$_3$), 5.51 (1 H, br s, ArCH$_2$C*H*), 5.74 (1 H, br s, ArC*H*), 7.10-7.17 (1 H, m, Ar*H*), 7.20-7.28 (1 H, m, Ar*H*), 7.32 (1 H, d, *J* 8.3, Ar*H*), 7.50 (1 H, d, *J* 7.9, Ar*H*) and 9.86 (1 H, br s, C=O*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 25.8, 27.3, 28.5, 29.1, 31.8, 33.0, 39.2, 56.1, 58.6, 70.5, 109.1, 118.3, 119.3, 121.6, 126.2, 134.1, 137.1, 176.4 and 188.1; *m/z* (EI) 397.2488 $[M+H]^+$ $C_{24}H_{33}N_2O_3$ requires 397.2486.

C**9 (*S*)-aldehyde 210a**: R_f = 0.38 (petrol/ethyl acetate 1:1); $[\alpha]_D^{23.9}$ +45.75 (*c* 0.15 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3051.0, 2974.0, 2927.4, 1717.8, 1629.5, 1408.1 and 738.7; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.34 (9 H, s, C(C*H*$_3$)$_3$), 1.40-1.57 (1 H, m, C*H*$_2$CH$_2$OCH$_3$), 1.63-1.77 (2 H, m, ArCHC*H*$_2$ and C*H*$_2$CH$_2$OCH$_3$), 1.88-1.98 (1 H, m, ArCHC*H*$_2$), 2.13-2.30 (1 H, m, ArCHCH$_2$C*H*), 2.48-2.58 (1 H, m, C*H*C=O), 2.73 (1 H, d, *J* 16.6, ArC*H*$_2$), 3.15-3.25 (1 H, m, ArC*H*$_2$), 3.21 (3 H, s, OC*H*$_3$), 3.26-3.35

(2 H, m, CH_2OCH$_3$), 3.70, (3 H, s, ArNCH_3), 5.22 (1 H, br s, ArCH$_2$C*H*), 5.93 (1 H, br s, ArC*H*), 7.10-7.16 (1 H, m, Ar*H*), 7.20-7.27 (1 H, m, Ar*H*), 7.32 (1 H, d, *J* 7.9, Ar*H*), 7.45 (1 H, d, *J* 7.5, Ar*H*) and 9.76 (1 H, d, *J* 2.3, C=O*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 25.0, 26.5, 28.4, 29.3, 33.9, 34.9, 39.3, 58.2, 58.5, 69.8, 104.9, 109.2, 118.1, 119.3, 121.5, 126.0, 133.9, 137.1, 175.6 and 203.2; *m/z* (ESI) 397.2490 $[M+H]^+$ $C_{24}H_{33}N_2O_3$ requires 397.2486.

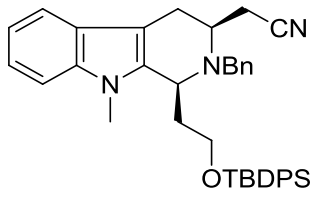
Preparation of **[(1*S*,3*S*)-2-benzyl-1-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2,3,4,9-tetrahydro-1*H*-β-carbolin-3-yl]acetonitrile[55] 261**



Diisopropylethylamine (33.81 mL, 194.08 mmol) and benzyl bromide (4.61 mL, 38.82 mmol) were added to a solution of the Pictet-Spengler product **110** (6.39 g, 12.94 mmol) in anhydrous acetonitrile (65 mL) at 0 °C under a nitrogen atmosphere. This mixture was heated at 80 °C overnight. A further 3 equivalents of benzyl bromide (4.61 mL) were added and the reaction stirred at 80 °C for two days. Volatile liquids were removed under reduced pressure and the resulting residue was dissolved in dichloromethane (200 mL). This was then washed with water (100 mL), the aqueous phase separated and extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvents removed under reduced pressure. The crude product was purified by column chromatography (petrol/ethyl acetate 19:1) to give the benzylated product

261 as a white, amorphous solid (7.18 g, 95%): R_f = 0.25 (petrol/ethyl acetate 9:1); $[\alpha]_D^{27.6}$ −15.97 (*c* 0.50 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2930.4, 2856.6 and 1112.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.06 (9 H, s, SiC(C*H*$_3$)$_3$), 1.85-2.01 (1 H, m, OCH$_2$C*H*$_2$), 2.03-2.15 (1 H, m, OCH$_2$C*H*$_2$), 2.38 (1 H, dd, *J* 16.6 and 6.8, C*H*$_2$CN), 2.51 (1 H, dd, *J* 16.6 and 8.3, C*H*$_2$CN), 2.66 (1 H, dd, *J* 16.2 and 1.9, ArC*H*$_2$), 3.10 (1 H, dd, *J* 16.2 and 1.9, ArC*H*$_2$), 3.58-3.69 (2 H, m, ArCH$_2$C*H* and OC*H*$_2$), 3.79-3.94 (3 H, m, NC*H*$_2$Bn and OC*H*$_2$), 4.05-4.11 (1 H, m, ArC*H*), 6.97-7.64 (19 H, m, Ar*H*) and 8.87 (1 H, br s, ArN*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.3, 22.1, 23.4, 27.2, 39.2, 54.2, 54.8, 58.9, 63.7, 103.8, 111.0, 118.0, 119.2, 119.4, 121.7, 127.3, 127.4, 128.1, 128.6, 130.1, 132.7, 133.1, 133.9, 135.5, 136.0 and 139.4; *m/z* (ESI) 584.3099 $[M+H]^+$ $C_{38}H_{42}N_3OSi$ requires 584.3092.

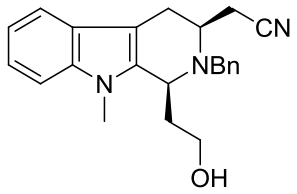
Preparation of **[(1*S*,3*S*)-2-benzyl-1-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-3-yl]acetonitrile[55] 111**



The benzylated product **261** (8.15 g, 13.97 mmol) was dissolved in dimethylformamide (170 mL) and then methyl iodide (1.74 mL, 27.93 mmol) and sodium hydride (614.4 mg, 15.36 mmol, 60% dispersion in mineral oil) were added at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for thirty minutes then allowed to warm to room temperature. After another thirty minutes a further two equivalents of methyl iodide (1.74 mL, 27.93 mmol) were added and

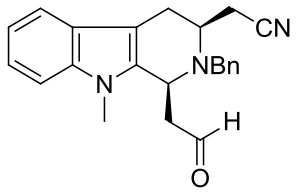
the reaction left for another thirty minutes. Volatile liquids were removed under reduced pressure and the resulting residue partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 100 mL). The combined organic portions were washed with saturated sodium chloride (100 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure to give the methylated product **111** (8.03 g, 96%) which was pure enough for subsequent reactions. A portion of the crude material was purified by column chromatography (petrol/ethyl acetate 19:1) to give the product as a white, amorphous solid R_f = 0.29 (petrol/ethyl acetate 9:1); $[\alpha]_D^{27.7}$ −42.25 (*c* 0.21 in $CHCl_3$); v_{max}(film)/cm^{-1} 3068.9, 2930.1, 2247.8, 1470.9 and 1111.1; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.16 (9 H, s, SiC(C*H*$_3$)$_3$), 1.81-1.97 (1 H, m, OCH$_2$C*H*$_2$), 2.03-2.17 (1 H, m, OCH$_2$C*H*$_2$), 2.45-2.64 (2 H, m, C*H*$_2$CN), 2.70 (1 H, d, *J* 16.2, ArC*H*$_2$), 3.22 (1 H, dd, *J* 16.2 and 6.4, ArC*H*$_2$), 3.52-3.63 (1 H, m, ArCH$_2$C*H*), 3.72 (3 H, s, ArNC*H*$_3$), 3.88 (1 H, d, *J* 13.6, NC*H*$_2$Bn), 3.95 (1 H, d, *J* 13.6, NC*H*$_2$Bn), 4.00-4.11 (1 H, m, OC*H*$_2$), 4.18-4.28 (1 H, m, OC*H*$_2$), 4.32 (1 H, d, *J* 10.2, ArC*H*) and 7.19-7.86 (19 H, m, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.3, 20.6, 24.7, 27.1, 30.5, 38.8, 51.5, 52.5, 61.3, 61.7, 103.5, 109.0, 118.1, 118.9, 119.4, 121.7, 126.9, 127.6, 127.9, 128.7, 129.0, 130.0, 133.6, 134.9, 135.7, 137.9 and 139.1; *m/z* (ESI) 598.3246 $[M+H]^+$ $C_{39}H_{44}N_3OSi$ requires 598.3248.

Preparation of **[(1*S*,3*S*)-2-benzyl-1-(2-hydroxyethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-3-yl]acetonitrile[55] 112**



Tetrabutylammonium fluoride (35.50 mL, 1 M solution in tetrahydrofuran) was added dropwise to a solution of the TBDPS-protected starting material **111** (10.62 g, 17.76 mmol) in tetrahydrofuran (185 mL) under nitrogen at room temperature and was stirred for two hours. The reaction mixture was then concentrated under reduced pressure and purified by flash column chromatography (petrol/ethyl acetate 1:1) to give the alcohol **112** as a white, amorphous solid (5.78 g, 90%): R_f = 0.37 (petrol/ethyl acetate 1:1); $[\alpha]_D^{29.1}$ −41.44 (*c* 0.92 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3397.9, 2929.8, 2248.4, 1470.4 and 743.6; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.76-2.01 (2 H, m, OCH_2CH_2), 2.70 (1 H, dd, *J* 16.4 and 8.9, CH_2CN), 2.85 (1 H, d, *J* 16.6, $ArCH_2$), 2.95 (1 H, dd, *J* 16.6 and 6.8, CH_2CN), 3.27 (1 H, dd, *J* 16.0 and 5.8, $ArCH_2$), 3.68 (3 H, s, $ArNCH_3$), 3.71-3.98 (5 H, m, OCH_2, NCH_2Bn, $ArCH_2CH$), 4.08-4.16 (1 H, m, ArC*H*), 7.17-7.50 (8 H, m, Ar*H*) and 7.60 (1 H, d, *J* 7.6, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 20.9, 24.9, 30.6, 36.9, 52.8, 53.8, 60.9, 61.3, 103.4, 109.1, 118.2, 118.9, 119.5, 122.0, 126.8, 128.1, 128.9, 129.5, 133.5, 137.9 and 138.5; *m/z* (ESI) 360.2074 $[M+H]^+$ $C_{23}H_{26}N_3O$ requires 360.2070.

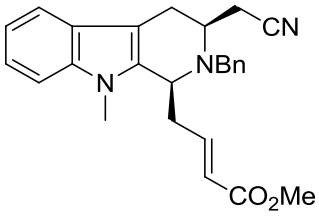
Preparation of **[(1*S*,3*S*)-2-benzyl-9-methyl-1-(2-oxoethyl)-2,3,4,9-tetrahydro-1*H*-β-carbolin-3-yl]acetonitrile[55] 113**

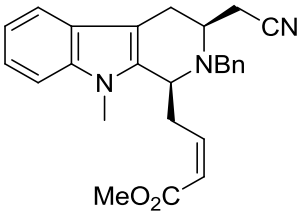


Oxalyl chloride (4.97 mL, 2 M in dichloromethane) was added to dichloromethane (30 mL) and cooled to −60 °C. Dimethyl sulfoxide (1.41 mL, 19.90 mmol) was then added and the resulting solution stirred for two minutes ensuring the temperature stayed at −60 °C. A solution of the starting alcohol **112** (2.98 g, 8.29 mmol) in dichloromethane (40 mL) was then added and the mixture stirred for a further fifteen minutes. Triethylamine (5.78 mL, 41.45 mmol) was then added dropwise and the mixture allowed to warm to room temperature. The reaction was then quenched with saturated sodium chloride (200 mL). The phases were separated and the organic portion was washed with saturated sodium bicarbonate (200 mL). The aqueous portions were combined and extracted with dichloromethane (200 mL). The combined organic portions were then washed with saturated sodium chloride (200 mL), dried ($MgSO_4$), filtered and solvents removed under reduced pressure to give the crude aldehyde **113** (2.91 g, 98%) as a brown, amorphous solid: R_f = 0.54 (petrol/ethyl acetate 1:1); $[\alpha]_D^{24.3}$ −14.49 (*c* 0.14 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3056.7, 2924.0, 2844.1, 2248.3, 1721.0, 1470.5 and 743.3; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.61 (1 H, dd, *J* 16.6 and 8.7, C*H*$_2$CN), 2.71-2.85 (3 H, m, C*H*$_2$CN, ArC*H*$_2$, C*H*$_2$C=O), 2.95 (1 H, ddd, *J* 17.0, 10.5 and 3.4, C*H*$_2$C=O), 3.22 (1 H, ddd, *J* 16.2, 6.0 and 1.5, ArC*H*$_2$), 3.62-3.67 (1 H, m, ArCH$_2$C*H*), 3.64 (3 H, s,

ArNCH_3), 3.92 (2 H, s, NCH_2Bn), 4.66 (1 H, ddd, *J* 9.8, 4.1 and 1.5, ArC*H*), 7.16-7.22 (1 H, m, Ar*H*), 7.26-7.44 (7 H, m, Ar*H*), 7.56 (1 H, d, *J* 7.9, Ar*H*) and 9.75 (1 H, dd, *J* 3.0 and 0.8, C=O*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.1, 24.2, 30.5, 49.5, 50.1, 52.5, 61.0, 104.4, 109.1, 118.3, 118.7, 119.6, 122.2, 126.6, 127.9, 128.7, 129.0, 132.6, 137.8, 138.3 and 200.5.

Preparation of **methyl (2*E*)-4-[(1*S*,3*S*)-2-benzyl-3-(cyanomethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl]but-2-enoate[56] 120*E*** and **methyl (2*Z*)-4-[(1*S*,3*S*)-2-benzyl-3-(cyanomethyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl]but-2-enoate[56] 120*Z***





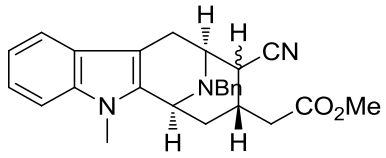
The Wittig reagent methyl (triphenylphosphoranylidene)acetate **119** (6.38 g, 19.08 mmol) was added to a solution of the starting aldehyde **113** (5.46 g, 15.27 mmol) in dichloromethane (175 mL) at 0 °C. The resulting solution was stirred at 0 °C for one hour, warmed to room temperature and stirred for a further four hours. The mixture was then concentrated under reduced pressure and purified by column chromatography (petrol/ethyl acetate 17:3) to give the *E* and *Z* unsaturated esters **120*E*** and **120*Z*** (5.01 g, 79%) in a ratio of 10:1 respectively.

***E* ester 120*E*:** R_f = 0.36 (petrol/ethyl acetate 3:1); $[\alpha]_D^{27.6}$ −12.23 (*c* 0.65 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3022.7, 2948.1, 2844.8, 2247.7 and 1720.6; δ_H(300 MHz; $CDCl_3$;

Me_4Si) 2.58-2.88 (5 H, m, ArC*H*$_2$, C*H*$_2$CN and ArCHC*H*$_2$), 3.25 (1 H, dd, *J* 16.2 and 6.4, ArC*H*$_2$), 3.61-3.71 (1 H, m, ArCH$_2$C*H*), 3.65 (3 H, s, ArNC*H*$_3$), 3.76-3.85 (1 H, m, NC*H*$_2$Bn), 3.81 (3 H, s, CO_2C*H*_3), 3.95 (1 H, d, *J* 13.6, NC*H*$_2$Bn), 3.98-4.06 (1 H, m, ArC*H*), 5.91 (1 H, d, *J* 15.8, C*H*CO_2CH_3), 7.03 (1 H, m, C*H*$CHCO_2CH_3$), 7.17-7.24 (1 H, m, Ar*H*), 7.27-7.46 (7 H, m, Ar*H*) and 7.59 (1 H, d, *J* 7.9, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.7, 24.6, 30.7, 39.1, 51.6, 53.8, 54.8, 61.2, 104.4, 109.2, 118.3, 118.8, 119.6, 122.1, 122.9, 126.6, 127.7, 128.7, 129.1, 133.6, 137.9, 138.4, 146.4 and 166.6; *m/z* (ESI) 414.2172 $[M+H]^+$ $C_{26}H_{28}N_3O_2$ requires 414.2176.

***Z* ester 120*Z*:** R_f = 0.58 (petrol/ethyl acetate 3:1); $[\alpha]_D^{27.2}$ −22.16 (*c* 0.36 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3055.2, 2948.0, 2847.2, 2248.4 and 1715.9; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.65 (1 H, dd, *J* 16.8 and 7.7, C*H*$_2$CN), 2.75-2.92 (3 H, m,C*H*$_2$CN, ArC*H*$_2$, ArCHC*H*$_2$), 3.27 (1 H, dd, *J* 16.2 and 6.2, ArC*H*$_2$), 3.42-3.55 (1 H, m, ArCHC*H*$_2$), 3.63-3.74 (1 H, m, ArCH$_2$C*H*), 3.77 (3 H, s, CO_2C*H*_3), 3.79-3.86 (1 H, m, NC*H*$_2$Bn), 3.83 (3 H, s, ArNC*H*$_3$), 3.95 (1 H, d, *J* 13.8, NC*H*$_2$Bn), 4.13-4.22 (1 H, m, ArC*H*), 5.93 (1 H, dd, *J* 11.6 and 1.0, C*H*CO_2CH_3), 6.70 (1 H, dt, *J* 11.3 and 7.1, C*H*$CHCO_2CH_3$), 7.25 (1 H, t, *J* 7.3, Ar*H*), 7.31-7.51 (7 H, m, Ar*H*), 7.63 (1 H, d, *J* 7.7, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.5, 24.6, 30.7, 34.8, 51.2, 53.3, 55.5, 61.5, 104.0, 109.2, 118.3, 119.1, 119.4, 120.3, 122.0, 126.7, 127.7, 128.6, 129.3, 134.0, 138.0, 138.9, 148.1 and 166.8; *m/z* (ESI) 414.2176 $[M+H]^+$ $C_{26}H_{28}N_3O_2$ requires 414.2176.

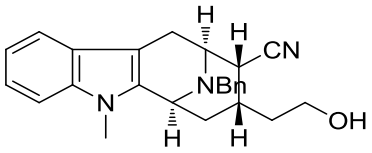
Preparation of **methyl [(6*S*,8*S*,9*R*,10*S*)-12-benzyl-9-cyano-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indol-8-yl]acetate[56] 121a** and **methyl [(6*S*,8*S*,9*S*,10*S*)-12-benzyl-9-cyano-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indol-8-yl]acetate[56] 121b**

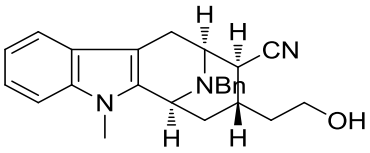


Lithium bis(trimethylsilyl)amide (35 mL, 1 M in tetrahydrofuran) was added to anhydrous tetrahydrofuran (100 mL) at −78 °C and the unsaturated esters **120*E:Z*** (4.88 g, 11.80 mmol) added dropwise as a solution in tetrahydrofuran (110 mL). The resulting mixture was stirred at −78 °C for two hours. The reaction was then quenched with saturated sodium chloride (375 mL) and warmed to room temperature. The mixture was then diluted with saturated sodium chloride (350 mL) and ethyl acetate (350 mL). The phases were separated and the aqueous fraction was extracted with ethyl acetate (3 x 200 mL). The organic portions were combined and washed with saturated sodium chloride (400 mL), dried ($MgSO_4$), filtered and the solvents removed under reduced pressure to give the crude product which was purified by column chromatography to give the *cis* tetracycle **121a** (1.27 g, 26%) and an inseparable mixture of the *cis* and *trans* tetracycles (2.38 g, 49%): R_f = 0.55 (petrol/ethyl acetate 7:3); $[\alpha]_D^{27.3}$ −46.70 (*c* 0.36 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3054.4, 3026.6, 2917.5, 2842.3, 2237.2 and 1735.1; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.69 (1 H, d, *J* 12.2, ArCHC*H*$_2$), 2.17 (1 H, td, *J* 12.8 and 4.0, ArCHC*H*$_2$), 2.27-2.45 (2 H, m, C*H*$_2$CO$_2$Me, C*H*CH$_2$CO$_2$Me), 2.55-2.69 (2 H, m, C*H*$_2$CO$_2$Me, ArC*H*$_2$), 3.24-3.29 (1 H, m, C*H*CN), 3.35 (1 H, dd, *J* 17.0 and 7.6,

ArCH_2), 3.63 (3 H, s, ArNCH_3), 3.67 (3 H, s, CO_2CH_3), 3.69-3.74 (3 H, m, NCH_2Bn, ArCH_2CH), 4.10-4.14 (1 H, m, ArCH), 7.19-7.26 (1 H, m, ArH), 7.29-7.52 (7 H, m, ArH) and 7.61 (1 H, d, J 7.7, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.6, 26.2, 29.1, 33.4, 37.5, 40.1, 50.2, 51.8, 53.3, 57.6, 106.2, 109.2, 118.3, 119.3, 120.0, 121.4, 126.3, 127.4, 128.6, 128.7, 133.5, 137.1, 138.5 and 171.9; *m/z* (ESI) 414.2174 $[M+H]^+$ $C_{26}H_{28}N_3O_2$ requires 414.2176.

Preparation of **(6*S*,8*S*,9*R*,10*S*)-12-benzyl-8-(2-hydroxyethyl)-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carbonitrile[56] 122a** and **(6*S*,8*S*,9*S*,10*S*)-12-benzyl-8-(2-hydroxyethyl)-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carbonitrile[56] 122b**





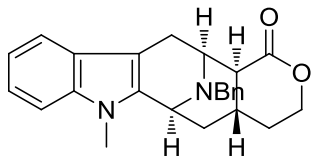
The *cis*- and *trans*-tetracyclic esters **121a/b** (3.23 g, 7.81 mmol) were dissolved in tetrahydrofuran (110 mL) under an atmosphere of nitrogen and lithium borohydride was added (340.2 mg, 15.62 mmol) at 0 °C. The resulting mixture was stirred at this temperature for fifteen minutes then heated at reflux overnight. The mixture was cooled to room temperature and then quenched with methanol (50 mL) and water (100 mL). The aqueous phase was separated and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with saturated sodium chloride (50 mL), dried ($MgSO_4$), filtered and the solvents removed under reduced pressure to give the crude product which was purified by column

chromatography (dichloromethane/diethyl ether 19:1 to 4:1) to yield the *cis* **122a** (1.48 g, 49%) and *trans* **122b** (0.89 g, 30%) alcohols as white, amorphous solids.

***cis* alcohol 122a**: R_f = 0.31 (petrol/ethyl acetate 1:1); $[\alpha]_D^{24.7}$ −48.35 (*c* 0.39 in $CHCl_3$); v_{max}(film)/cm^{-1} 3430.7, 3054.0, 2922.1, 2842.8, 2237.8 and 1468.9; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.52-1.77 (3 H, m, ArCHC*H*$_2$, C*H*$_2$CH$_2$OH), 1.87-2.16 (2 H, m, ArCHC*H*$_2$, C*H*CH$_2$CH$_2$OH), 2.54 (1 H, d, *J* 17.1, ArC*H*$_2$), 2.91-2.98 (1 H, m, C*H*CN), 3.30 (1 H, dd, *J* 17.0 and 7.5, ArC*H*$_2$), 3.49-3.58 (2 H, m, C*H*$_2$OH), 3.60 (3 H, s, ArNC*H*$_3$), 3.62-3.74 (3 H, m, NC*H*$_2$Bn, ArCH$_2$C*H*), 4.05-4.11 (1 H, m, ArC*H*), 7.18-7.25 (1 H, m, Ar*H*), 7.27-7.52 (7 H, m, Ar*H*) and 7.59 (1 H, d, *J* 7.7, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 21.6, 26.1, 29.1, 33.9, 36.4, 40.5, 50.3, 53.3, 57.6, 59.7, 106.0, 109.2, 118.2, 119.2, 120.5, 121.3, 126.2, 127.4, 128.5, 128.7, 134.1, 137.0 and 138.7; *m/z* (ESI) 386.2231 $[M+H]^+$ $C_{25}H_{28}N_3O$ requires 386.2227.

***trans* alcohol 122b**: R_f = 0.20 (petrol/ethyl acetate 1:1); $[\alpha]_D^{25.5}$ −86.56 (*c* 0.88 in $CHCl_3$); v_{max}(film)/cm^{-1} 3403.5, 3056.7, 2919.7, 2844.9, 2241.6 and 1468.9; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.46-1.61 (1 H, m, C*H*$_2$CH$_2$OH), 1.73-1.97 (4 H, m, C*H*$_2$CH$_2$OH, C*H*CH$_2$CH$_2$OH, ArCHC*H*$_2$), 2.98 (1 H, dd, *J* 11.0 and 4.2, C*H*CN), 3.06 (1 H, d, *J* 17.1, ArC*H*$_2$), 3.27 (1 H, dd, *J* 17.3 and 7.2, ArC*H*$_2$), 3.56-3.75, (5 H, m, NC*H*$_2$Bn, ArCH$_2$C*H*, C*H*$_2$OH), 3.58 (3 H, s, ArNC*H*$_3$), 3.99-4.03 (1 H, m, ArC*H*), 7.17-7.24 (1 H, m, Ar*H*), 7.26-7.43 (7 H, m, Ar*H*) and 7.62 (1 H, d, *J* 7.5, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 18.9, 28.3, 29.1, 35.3, 37.1, 41.2, 49.8, 53.0, 57.5, 59.7, 106.1, 109.1, 118.4, 119.3, 121.0, 121.4, 126.3, 127.5, 128.6, 128.8, 133.6, 137.1 and 138.4; *m/z* (ESI) 386.2227 $[M+H]^+$ $C_{25}H_{28}N_3O$ requires 386.2227.

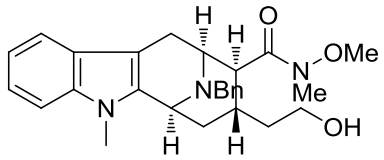
Preparation of **(4a*S*,6*S*,13*S*,13a*S*)-14-benzyl-7-methyl-4,4a,5,6,7,12,13,13a-octahydro-6,13-epiminopyrano[3',4':5,6]cycloocta[1,2-*b*]indol-1(3*H*)-one[56] 123**



para-Toluenesulfonic acid (12.93 g, 67.97 mmol) was added to a solution of the *cis*- and *trans*-tetracyclic alcohols **122a/b** (2.62 g, 6.80 mmol) in tetrahydrofuran (110 mL) and the resulting solution was stirred at reflux overnight. The reaction mixture was cooled to room temperature and quenched with saturated sodium bicarbonate solution (50 mL). The aqueous fraction was separated and then extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with saturated sodium chloride (100 mL), dried ($MgSO_4$), filtered and the solvents removed under reduced pressure to yield the crude lactone which was purified by column chromatography to give the product **123** as a white, amorphous solid (1.04 g, 40%) and the starting alcohol (0.95 g, 37%) which could be recycled: R_f = 0.34 (dichloromethane/diethyl ether 19:1); $[\alpha]_D^{23.4}$ −169.91 (*c* 1.18 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3053.9, 2925.7, 2843.4 and 1731.1; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.72-2.04 (5 H, m, ArCHCH_2, ArCHCH_2CH, CH_2CH_2OH), 2.73 (1 H, d, *J* 17.5, ArCH_2), 2.80 (1 H, dd, *J* 11.9 and 4.0, CHC=O), 3.30 (1 H, dd, *J* 17.5 and 7.2, ArCH_2), 3.62 (3 H, s, ArNCH_3), 3.68 (1 H, d, *J* 13.4, NCH_2Bn), 3.81 (1 H, d, *J* 13.4, NCH_2Bn), 3.98 (1 H, dd, *J* 7.0 and 4.0, ArCH_2CH), 4.03-4.08 (1 H, m, ArCH), 4.14-4.25 (1 H, m, CH_2OC=O), 4.42 (1 H, dt, *J* 11.2 and 4.1, CH_2OC=O), 7.19-7.26 (1 H, m, ArH), 7.27-7.44 (7 H, m, ArH) and 7.59-7.65 (1 H, m, ArH); δ_C(75 MHz; $CDCl_3$; Me_4Si) 19.3, 27.3, 29.2, 29.3, 37.3, 49.9, 51.6, 51.7, 57.8, 69.1, 107.2, 109.0,

118.4, 119.2, 121.2, 126.4, 127.3, 128.5, 128.9, 134.2, 137.0, 139.1 and 171.4; *m/z* (ESI) 387.2065 $[M+H]^+$ $C_{25}H_{27}N_2O_2$ requires 386.2067.

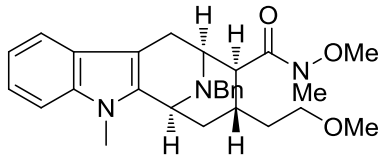
Preparation of **(6*S*,8*S*,9*S*,10*S*)-12-benzyl-8-(2-hydroxyethyl)-*N*-methoxy-*N*,5-dimethyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carboxamide 262**



N,*O*-Dimethylhydroxylamine hydrochloride (1.05 g, 10.74 mmol) was suspended in dichloromethane (40 mL) under a nitrogen atmosphere and trimethylaluminium (5.37 mL, 2 M in heptane) added dropwise. The resulting solution was left to stir for forty-five minutes at which point the lactone **123** (413.5 mg, 1.07 mmol) was added dropwise *via* cannula as a solution in dichloromethane (40 mL). The reaction mixture was left to stir overnight at room temperature. The mixture was then cooled to 0 °C, quenched by the careful addition of NH_4OH/NH_4Cl solution (40 mL) adjusted to pH 8 and filtered through Celite® washing thoroughly with dichloromethane. The phases were separated and the organic fraction dried ($MgSO_4$), filtered and solvents removed under reduced pressure to yield the crude product. Purification by column chromatography gave the Weinreb amide **262** as a white, amorphous solid (332 mg, 69%): R_f = 0.28 (ethyl acetate); $[\alpha]_D^{27.3}$ −43.10 (*c* 0.41 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3423.2, 3052.5, 2931.6, 2843.0 and 1648.8; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.41-1.51 (2 H, m, C*H*$_2$CH$_2$OH), 1.82-1.91 (2 H, m, ArCHC*H*$_2$), 2.00-2.16 (1 H, m, C*H*CH$_2$CH$_2$OH), 2.35 (1H, br s, O*H*), 2.82 (1 H, d, *J* 17.0,

ArCH_2), 2.96 (1 H, dd, *J* 17.0 and 6.8, ArCH_2), 3.15-3.22 (1 H, m, C*H*C=O), 3.23 (3 H, s, NCH_3OCH$_3$), 3.46 (2 H, td, *J* 6.4 and 1.8, CH_2OH), 3.51-3.56 (1 H, m, ArCH$_2$C*H*), 3.59 (3 H, s, ArNCH_3), 3.63-3.75 (2 H, m, NCH_2Bn), 3.66 (3 H, s, NCH$_3$OCH_3), 3.97-4.02 (1 H, m, ArC*H*), 7.10-7.18 (1 H, m, Ar*H*), 7.20-7.40 (7 H, m, Ar*H*) and 7.55 (1 H, d, *J* 7.7, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 17.5, 25.4, 29.0, 32.3, 37.2, 38.7, 50.5, 50.5, 52.1, 57.3, 60.1, 61.8, 106.7, 108.8, 118.4, 118.8, 120.8, 126.6, 127.1, 128.3, 128.8, 134.3, 137.0, 139.3 and 174.9; *m/z* (ESI) 448.2585 $[M+H]^+$ $C_{27}H_{34}N_3O_3$ requires 448.2595.

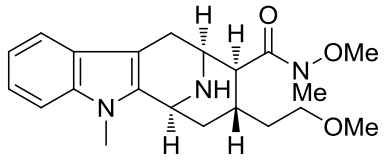
Preparation of **(6*S*,8*S*,9*S*,10*S*)-12-benzyl-*N*-methoxy-8-(2-methoxyethyl)-*N*,5-dimethyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carboxamide 201**



Methyl iodide (231 µL, 3.71 mmol) was added dropwise to a solution of the alcohol **262** (332 mg, 742 µmol) and sodium hydride (60.0 mg, 1.48 mmol, 60% dispersion in mineral oil) in tetrahydrofuran at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated sodium chloride (40 mL) and diluted with ethyl acetate (50 mL). The phases were separated and the aqueous extracted with ethyl acetate (3 x 50 mL). The combined organics were dried ($MgSO_4$), filtered and solvents removed under reduced pressure. The crude product was purified by column chromatography (dichloromethane/diethyl ether 19:1) to give a white, amorphous solid **201** (200 mg,

58%): R_f = 0.26 (petrol/ethyl acetate 1:1); $[\alpha]_D^{24.1}$ −23.61 (*c* 0.46 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3053.5, 3026.4, 2929.6, 1652.0, 1468.3 and 730.1; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.33-1.52 (1 H, m, C*H*$_2$CH$_2$OCH$_3$), 1.61-1.74 (1 H, m, C*H*$_2$CH$_2$OCH$_3$), 1.80-2.10 (3 H, m, ArCHC*H*$_2$, ArCHCH$_2$C*H*), 2.86-3.03 (2 H, m, ArC*H*$_2$), 3.24 (3 H, s, NC*H*$_3$OCH$_3$), 3.27 (3 H, s, CH$_2$OC*H*$_3$), 3.22-3.39 (3 H, m, C*H*$_2$OCH$_3$, C*H*C=O), 3.51-3.58 (1 H, m, ArCH$_2$C*H*), 3.61 (3 H, s, ArNC*H*$_3$), 3.64-3.78 (2 H, m, NC*H*$_2$Bn), 3.69 (3 H, s, NCH$_3$OC*H*$_3$), 3.99-4.04 (1 H, m, ArC*H*), 7.12-7.43 (8 H, m, Ar*H*) and 7.59 (1 H, d, *J* 7.5, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 17.4, 26.7, 29.0, 32.2, 34.4, 36.4, 50.5, 50.6, 52.2, 57.4, 58.5, 61.7, 71.0, 107.0, 108.8, 118.6, 118.8, 120.7, 126.7, 127.1, 128.3, 128.8, 134.5, 137.0, 139.4 and 174.1; *m/z* (ESI) 462.2740 $[M+H]^+$ $C_{28}H_{36}N_3O_3$ requires 462.2751.

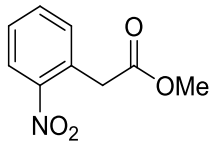
Preparation of **(6*S*,8*S*,9*S*,10*S*)-*N*-methoxy-8-(2-methoxyethyl)-*N*,5-dimethyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carboxamide 206**



Pd/C (200 mg, 10% by weight) was added to a solution of the benzyl-protected tetracycle **201** (200 mg, 433 μmol) in trifluoroethanol (20 mL). The reaction flask was evacuated and placed under an atmosphere of hydrogen gas (1 atm.). The reaction mixture was left to stir for twenty-four hours. The reaction was then diluted with ethyl acetate (50 mL) and filtered through Celite® washing thoroughly with ethyl acetate. The solvents were removed under reduced pressure to give a crude

product which was purified by column chromatography (dichloromethane/methanol 19:1) to give the amine **206** as a white amorphous solid (143 mg, 89%): R_f = 0.23 (dichloromethane/methanol 19:1); $[\alpha]_D^{25.2}$ +32.67 (*c* 0.70 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3438.5, 3291.0, 3051.2, 2929.0, 1653.4, 1469.5, 1117.8 and 741.6; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.28-1.42 (1 H, m, C*H*$_2$CH$_2$OCH$_3$), 1.52-1.65 (1 H, m, C*H*$_2$CH$_2$OCH$_3$), 1.75-2.07 (3 H, m, ArCHC*H*$_2$, ArCHCH$_2$C*H*), 2.87 (1 H, dd, *J* 16.4 and 7.0, ArC*H*$_2$), 2.97 (1 H, d, *J* 17.0, ArC*H*$_2$), 3.05-3.32 (3 H, m, C*H*$_2$OCH$_3$, C*H*C=O), 3.20 (3 H, s, CH$_2$OC*H*$_3$), 3.23 (3 H, s, NC*H*$_3$OCH$_3$), 3.48 (3 H, s, ArNC*H*$_3$), 3.75 (3 H, s, NCH$_3$OC*H*$_3$), 3.81-3.88 (1 H, m, ArCH$_2$C*H*), 4.19-4.24 (1 H, m, ArC*H*), 7.05-7.12 (1 H, m, Ar*H*), 7.15-7.22 (1 H, m, Ar*H*), 7.24 (1 H, d, *J* 7.5, Ar*H*) and 7.47 (1 H, d, *J* 7.7, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 22.5, 26.9, 28.9, 32.1, 34.5, 35.8, 45.7, 47.6, 49.8, 61.7, 70.7, 107.3, 108.7, 118.4, 118.8, 120.9, 126.7, 136.5, 136.7 and 173.5; *m/z* (ESI) 372.2281 $[M+H]^+$ $C_{21}H_{30}N_3O_3$ requires 372.2282.

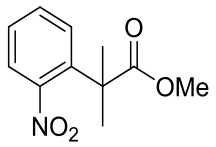
Preparation of **methyl (2-nitrophenyl)acetate[106] 263**



Commercially available 2-nitrophenyl acetic acid **243** (5.00 g, 276 mmol) was dissolved in methanol (100 mL) and thionyl chloride (50 mL, 690 mmol) was added cautiously under nitrogen. This mixture was heated at reflux for two hours. The resulting solution was allowed to cool to room temperature and solvents were removed under reduced pressure. The resulting residue was dissolved in ethyl

acetate (200 mL) which was then washed firstly with saturated sodium bicarbonate (200 mL) and then saturated sodium chloride (200 mL). The organic layer was then dried ($MgSO_4$), filtered and solvents removed under reduced pressure to give the methyl ester **263** as a brown oil (4.75 g, 88%): R_f = 0.50 (petrol/ethyl acetate 3:1); v_{max}(film)/cm^{-1} 2953.8, 1733.2, 1522.0 and 1343.7; δ_H(300 MHz; $CDCl_3$; Me_4Si) 3.64 (3 H, s, OC*H*$_3$), 3.97 (2 H, s, ArC*H*$_2$), 7.32 (1 H, d *J* 7.5, Ar*H*), 7.41 (1 H, t, *J* 7.9, Ar*H*), 7.55 (1 H, t, *J* 7.2, Ar*H*) and 8.03 (1 H, d, *J* 8.3, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 39.5, 52.2, 125.2, 128.7, 129.7, 133.4, 133.7, 148.6 and 170.5; *m/z* (ESI) 196.0600 $[M+H]^+$ $C_9H_{10}NO_4$ requires 196.0604.

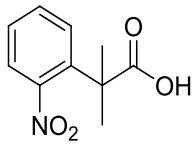
Preparation of **methyl 2-methyl-2-(2-nitrophenyl)propanoate[106] 264**



The methyl ester **263** (4.75 g, 24.40 mmol), methyl iodide (3.48 mL, 56 mmol) and 18-crown-6 ether (1.61 g, 6.08 mmol) were dissolved in dimethylformamide and then sodium hydride (2.24 g, 56 mmol, 60% dispersion in mineral oil) was added at 0 °C. The mixture was then allowed to warm to room temperature and stirred for two hours at which point it was quenched with water (100 mL). The aqueous portion was separated and extracted with diethyl ether (3 x 100 mL). The combined organics were washed with water (100 mL), saturated sodium chloride (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude gem-dimethyl ester **264** as a yellow oil (6.08 g, 100%). A portion of the crude compound was purified by column chromatography to give an analytically

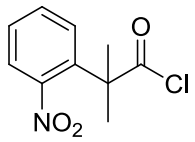
pure sample for characterisation: R_f = 0.59 (petrol/ethyl acetate 3:1); v_{max}(film)/cm^{-1} 2984.7, 2950.6, 1737.4, 1523.3 and 1386.6; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.65 (6 H, s, ArC(C*H*$_3$)$_2$), 3.61 (3 H, s, OC*H*$_3$), 7.36-7.43 (1 H, m, Ar*H*), 7.58-7.62 (2 H, m, Ar*H*), 7.85-7.90 (1 H, m, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 27.4, 46.3, 52.0, 125.5, 128.1, 133.3, 139.2, 146.7 and 175.8; *m/z* (ESI) 224.0915 $[M+H]^+$ $C_{11}H_{14}NO_4$ requires 224.0917.

Preparation of **2-methyl-2-(2-nitrophenyl)propanoic acid[106] 265**



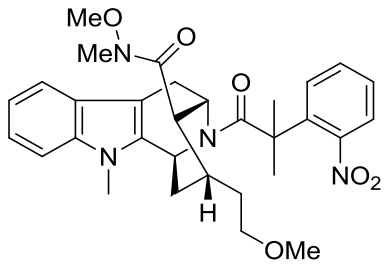
The gem-dimethyl ester **264** (5.23 g, 23.40 mmol) was dissolved in methanol (50 mL) and a 15% aqueous solution of sodium hydroxide (50 mL, w/v) was added. This solution was stirred at reflux for six hours and then the methanol removed under reduced pressure. The reaction mixture was then acidified to pH 2 with 1 M hydrochloric acid (approx. 200 mL) after which it was extracted with ethyl acetate (3 x 100 mL). The combined organics were washed with saturated sodium chloride (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the product acid **265** as an orange solid (4.35 g, 89%): mp 144-148 °C (from methanol); R_f = 0.64 (ethyl acetate); v_{max}(film)/cm^{-1} 2979.3, 2662.6, 1694.0, 1522.9 and 1341.1; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.71 (6 H, s, ArC(C*H*$_3$)$_2$), 7.39-7.49 (1 H, m, Ar*H*), 7.61-7.66 (2 H, m, Ar*H*), 7.99 (1 H, d, *J* 7.9, Ar*H*) 9.72 (1 H, br s, CO_2*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) 27.2, 46.4, 125.8, 128.0, 128.2, 133.5, 138.8, 148.3 and 181.8; *m/z* (ESI) 210.0761 $[M+H]^+$ $C_{10}H_{12}NO_4$ requires 210.0761.

Preparation of **2-methyl-2-(2-nitrophenyl)propanoyl chloride 244**



Thionyl chloride (836 µL, 11.50 mmol) was added dropwise to acid **265** (802 mg, 3.83 mmol) and heated at 50 °C for two hours. Excess thionyl chloride was then removed under reduced pressure to give the acid chloride as a brown oil (873 mg, 100%) which was always used directly in the following acylation reaction: R_f = 0.65 (ethyl acetate); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.68 (6 H, s, ArC(CH_3)$_2$), 7.43-7.50 (1 H, m, Ar*H*), 7.54-7.68 (2 H, m, Ar*H*), 7.97-8.03 (1 H, m, Ar*H*).

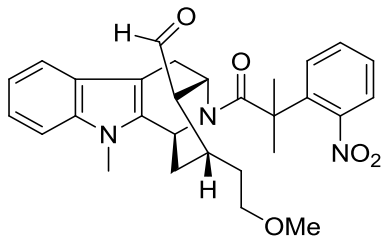
Preparation of **(6*S*,8*S*,9*S*,10*S*)-*N*-methoxy-8-(2-methoxyethyl)-*N*,5-dimethyl-12-[2-methyl-2-(2-nitrophenyl)propanoyl]-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carboxamide 247**



Amine **206** (143 mg, 385 µmol) was dissolved in anhydrous dichloromethane (5 mL) under a nitrogen atmosphere and triethylamine was added (83 µL, 597 µmol). DMNA-chloride **244** (136 mg, 597 µmol) was then added as a solution in dichloromethane (10 mL) and the reaction mixture left to stir for sixteen hours. The

resulting solution was concentrated under reduced pressure and subject to column chromatography (petrol/ethyl acetate 1:1) to give the DMNA carboxamide **247** as a yellow amorphous solid (200 mg, 92%): R_f = 0.43 (ethyl acetate); $[\alpha]_D^{25.6}$ −1.95 (*c* 1.02 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3489.8, 3053.4, 2931.7, 2872.1, 1724.2, 1646.8, 1529.8, 1348.8 and 783.6; δ_H(300 MHz; $CDCl_3$; Me_4Si) (mixture of rotational isomers) 1.02-2.00 (10 H, m, ArCHC*H*$_2$, ArCHCH$_2$C*H*, C*H*$_2$CH$_2$OMe), 1.40 (3 H, s, NC=OCC*H*$_3$), 1.54 (3 H, s, NC=OCC*H*$_3$), 1.66 (3 H, s, NC=OCC*H*$_3$), 1.70 (3 H, s, NC=OCC*H*$_3$), 2.47-3.25 (25 H, m, ArC*H*$_2$, C*H*C=O, C*H*$_2$OCH$_3$, NCH$_3$OC*H*$_3$, OC*H*$_3$, NC*H*$_3$OCH$_3$), 3.57 (3 H, s, NCH$_3$OC*H*$_3$), 3.60 (3 H, s, ArNC*H*$_3$), 3.80 (3 H, s, ArNC*H*$_3$), 4.06-4.15 (1 H, m, ArCH$_2$C*H*), 4.39-4.46 (1 H, m, ArC*H*), 5.26-5.36 (1 H, m, ArCH$_2$C*H*), 5.95-6.00 (1 H, m, ArC*H*), 6.90-7.68 (16 H, m, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) (mixture of rotational isomers) 20.6, 21.4, 27.1, 27.4, 27.7, 28.3, 28.7, 29.3, 29.7, 31.7, 32.0, 32.3, 33.6, 34.2, 34.6, 34.8, 44.2, 45.8, 46.7, 47.9, 48.9, 49.8, 58.4, 58.4, 61.4, 62.2, 70.5, 106.8, 108.7, 108.9, 109.0, 118.3, 118.8, 119.1, 121.0, 121.3, 125.3, 125.6, 126.2, 126.3, 127.5, 128.0, 128.0, 128.4, 132.5, 132.8, 132.9, 134.1, 136.9, 137.1, 137.9, 138.6, 148.8, 149.0, 171.6, 172.1, 172.7 and 173.0; *m/z* (ESI) 563.2855 $[M+H]^+$ $C_{31}H_{39}N_4O_6$ requires 563.2864.

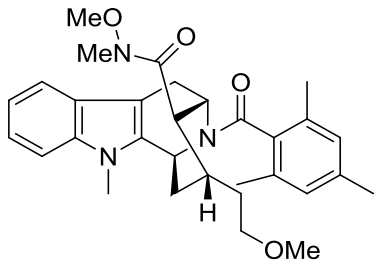
Preparation of **(6*S*,8*S*,9*S*,10*S*)-8-(2-methoxyethyl)-5-methyl-12-[2-methyl-2-(2-nitrophenyl)propanoyl]-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carbaldehyde 248**



The DMNA-protected Weinreb amide **247** (103 mg, 183 μmol) was dissolved in tetrahydrofuran (10 mL) and cooled to −78 °C. Lithium aluminium hydride (381 μL, 915 μmol) was then added dropwise and the reaction mixture stirred for two hours at −78 °C. The mixture was then allowed to warm to −30 °C and quenched with ethyl acetate (25 mL). A few drops of saturated sodium sulfate were then added and the resulting suspension left to stir for thirty minutes. The solution was filtered through Celite® and the solvents removed under reduced pressure. The crude product was purified by column chromatography (petrol/ethyl acetate 3:1) to give the aldehyde **248** as a yellow, amorphous solid (83 mg, 90%): R_f = 0.46 (ethyl acetate/petrol 3:1); $[\alpha]_D^{26.0}$ 0.00 (*c* 0.79 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3052.7, 2924.8, 2723.7, 1720.4, 1642.5, 1530.2 and 1348.3; δ_H(300 MHz; $CDCl_3$; Me_4Si) (mixture of rotational isomers) 1.14-2.00 (10 H, m, ArCHC*H*$_2$, ArCHCH$_2$C*H*, C*H*$_2$CH$_2$OCH$_3$), 1.41 (3 H, s, NCOCC*H*$_3$), 1.58 (3 H, s, NCOCC*H*$_3$), 1.63 (3 H, s, NCOCC*H*$_3$), 1.66 (3 H, s, NCOCC*H*$_3$), 2.32 (1 H, d, *J* 16.8, ArC*H*$_2$), 2.46 (1 H, d, *J* 16.8, ArC*H*$_2$), 2.55-2.72 (2 H, m, ArC*H*$_2$), 3.03-3.24 (15 H, m, ArNC*H*$_3$, OC*H*$_3$, C*H*$_2$OCH$_3$, C*H*C=O), 3.60 (3 H, s, ArNC*H*$_3$), 4.10-4.18 (1 H, m, ArCH$_2$C*H*), 4.45-4.51 (1 H, m, ArC*H*), 5.50-5.59 (1 H, m, ArCH$_2$C*H*), 5.93-5.99 (1 H, m, ArC*H*), 6.93-7.45 (12 H,

m, Ar*H*), 7.53-7.73 (4 H, m, Ar*H*), 9.23 (1 H, s, C=O*H*), 9.66 (1 H, s, C=O*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) (mixture of rotational isomers) 21.8, 23.8, 25.9, 26.1, 27.8, 27.9, 28.7, 29.3, 29.3, 33.2, 33.3, 34.1, 34.5, 44.0, 44.3, 46.6, 46.9, 48.8, 49.3, 56.9, 57.2, 58.4, 69.5, 69.9, 105.8, 108.2, 108.9, 109.2, 117.9, 118.5, 119.2, 119.3, 121.4, 121.6, 125.4, 125.8, 125.8, 126.0, 127.7, 127.8, 128.0, 128.4, 132.5, 132.7, 133.5, 134.6, 136.9, 137.1, 138.0, 138.4, 148.7, 149.2, 172.0, 172.3, 202.1 and 202.6; *m/z* (ESI) 504.2487 $[M+H]^+$ $C_{29}H_{34}N_3O_5$ requires 504.2493.

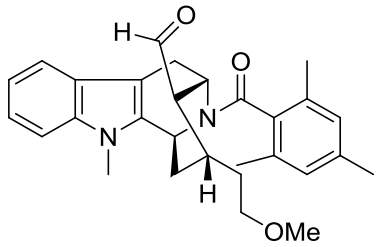
Preparation of **(6*S*,8*S*,9*S*,10*S*)-12-(mesitylcarbonyl)-*N*-methoxy-8-(2-methoxyethyl)-*N*,5-dimethyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carboxamide 254**



Amine **206** (150 mg, 404 µmol) was dissolved in dichloromethane (5 mL) under a nitrogen atmosphere and triethylamine (68 µL, 485 µmol) was added. 2,4,6-Trimethylbenzoyl chloride (81 µL, 485 µmol) was then added and the reaction mixture left to stir for twenty-two hours. The resulting solution was concentrated under reduced pressure and the residue partitioned between ethyl acetate (25 mL) and saturated sodium bicarbonate (25 mL). The phases were separated and the organic portion washed with saturated sodium bicarbonate (2 x 25 mL) and then saturated sodium chloride (25 mL). The organic portion was then dried ($MgSO_4$),

filtered and solvents removed under reduced pressure to give the crude amide. This was then subject to column chromatography (petrol/ethyl acetate 9:1 to ethyl acetate) to give the trimethylbenzoyl carboxamide **254** as a mixture of two rotamers (ratio of 4:1) as a beige, amorphous solid (178 mg, 85%). The pair of rotamers were separable by chromatography but then re-equilibrated during collection of the fractions: R_f = 0.46, 0.56 (ethyl acetate); $[\alpha]_D^{24.7}$ +0.75 (*c* 1.33 in $CHCl_3$); v_{max}(film)/cm^{-1} 3482.5, 3051.9, 2927.2 and 1627.5; δ_H(300 MHz; $CDCl_3$; Me_4Si) (mixture of rotational isomers) 1.22-2.16 (20 H, m, ArCHC*H*$_2$, ArCHCH$_2$C*H*, C*H*$_2$CH$_2$OMe), 1.61 (3 H, s, ArC*H*$_3$), 1.98 (3 H, s, ArC*H*$_3$), 2.20 (6 H, s, ArC*H*$_3$, ArC*H*$_3$), 2.32 (3 H, s, ArC*H*$_3$), 2.35 (3 H, s, ArC*H*$_3$), 2.78-2.86 (2 H, m, ArC*H*$_2$), 2.89-3.28 (8 H, m, ArC*H*$_2$, C*H*C=O, C*H*$_2$OMe), 3.01 (3 H, s, NC*H*$_3$OCH$_3$), 3.09 (3 H, s, OC*H*$_3$), 3.12 (3 H, s, OC*H*$_3$), 3.18 (3 H, s, NC*H*$_3$OCH$_3$), 3.30 (3 H, s, ArNC*H*$_3$), 3.37 (3 H, s, NCH$_3$OC*H*$_3$), 3.65 (3 H, s, ArNC*H*$_3$), 3.79 (3 H, s, NCH$_3$OC*H*$_3$), 4.14-4.23 (1 H, m, ArCH$_2$C*H*), 4.55-4.61 (1 H, m, ArC*H*), 5.55-5.65 (1 H, m, ArCH$_2$C*H*), 6.16-6.26 (1 H, m, ArC*H*), 6.67 (1 H, br s, Ar*H*), 6.77 (1 H, br s, Ar*H*), 6.81 (1 H, br s, Ar*H*), 6.83 (1 H, br s, Ar*H*), 6.97-7.05 (2 H, m, Ar*H*), 7.08-7.19 (3 H, m, Ar*H*), 7.23 (1 H, d, *J* 7.9, Ar*H*), 7.35 (1 H, d, *J* 7.9, Ar*H*) and 7.43 (1 H, d, *J* 7.5, Ar*H*); δ_C(75 MHz; $CDCl_3$; Me_4Si) (mixture of rotational isomers) 18.5, 19.0, 19.4, 19.5, 21.2, 21.3, 22.8, 22.9, 27.5, 27.6, 29.0, 29.5, 29.8, 32.1, 33.8, 34.0, 35.0, 36.7, 43.0, 44.4, 48.8, 49.1, 50.2, 50.3, 58.5, 58.5, 61.3, 62.1, 70.5, 70.7, 107.2, 108.4, 109.0, 109.0, 118.6, 118.9, 119.1, 119.2, 121.3, 121.4, 126.2, 126.4, 128.1, 128.3, 128.6, 128.6, 132.7, 133.0, 133.5, 133.7, 133.9, 134.0, 134.0, 134.1, 137.1, 137.2, 138.2, 138.2, 168.5, 168.5, 171.9 and 172.9; *m/z* (ESI) 518.3008 $[M+H]^+$ $C_{31}H_{40}N_3O_4$ requires 518.3013.

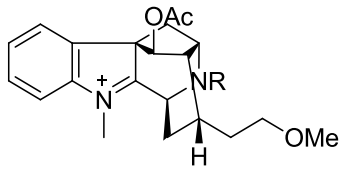
Preparation of **(6*S*,8*S*,9*S*,10*S*)-12-(mesitylcarbonyl)-8-(2-methoxyethyl)-5-methyl-6,7,8,9,10,11-hexahydro-5*H*-6,10-epiminocycloocta[*b*]indole-9-carbaldehyde 255**



The trimethylbenzoyl-protected Weinreb amide **254** (178 mg, 344 μmol) was dissolved in tetrahydrofuran (20 mL) and cooled to −78 °C. Lithium aluminium hydride (728 μL, 1.74 mmol) was then added dropwise and the reaction mixture stirred for two hours at −78 °C. The mixture was then allowed to warm to −30 °C and quenched with ethyl acetate (40 mL). A few drops of saturated sodium sulfate were then added and the resulting suspension left to stir for thirty minutes. The solution was filtered through Celite® and the solvents removed under reduced pressure. The crude product was purified by column chromatography (petrol/ethyl acetate 7:3) to give the aldehyde **255** as a white, amorphous solid (142 mg, 89%) as a pair of rotamers (1:1 ratio). The pair of rotamers were separable by chromatography but re-equilibrated during collection of the fractions: R_f = 0.42, 0.58 (ethyl acetate/petrol 3:2); $[\alpha]_D^{26.0}$ +1.51 (*c* 0.66 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3433.7, 3051.8, 2921.4, 2855.4, 2733.6, 1720.2, 1634.5 and 737.0; δ_H(300 MHz; $CDCl_3$; Me_4Si) (mixture of rotational isomers) 1.30-1.68 (5 H, m, C*H*$_2$CH$_2$OCH$_3$, ArCHC*H*$_2$), 1.61 (3 H, s, ArC*H*$_3$), 1.71-1.85 (2 H, m, ArCHC*H*$_2$), 1.88-1.94 (1 H, m, ArCHC*H*$_2$), 1.96 (3 H, s, ArC*H*$_3$), 2.03-2.17 (2 H, m, ArCHCH$_2$C*H*), 2.21 (3 H, s,

ArCH_3), 2.22 (3 H, s, ArCH_3), 2.30 (6 H, s, ArCH_3), 2.44-2.50 (1 H, m, CHC=O), 2.53 (1 H, d, *J*, 16.6, ArCH_2), 2.68 (1 H, d, *J* 17.0, ArCH_2), 2.70-2.78 (1 H, m, ArCH_2), 2.93 (1 H, dd, *J* 16.8, 7.0, ArCH_2), 3.10 (3 H, s, OCH_3), 3.12 (3 H, s, OCH_3), 3.15-3.27 (5 H, m, CHC=O, CH_2OCH$_3$), 3.33 (3 H, s, ArNCH_3), 3.68 (3 H, s, ArNCH_3), 4.18-4.25 (1 H, m, ArCH$_2$CH), 4.59-4.65 (1 H, m, ArCH), 5.77-5.85 (1 H, m, ArCH$_2$CH), 6.20-6.26 (1 H, m, ArCH), 6.69 (1 H, br s, ArH), 6.77 (1 H, br s, ArH), 6.85 (2 H, br s, ArH), 7.00-7.09 (2 H, m, ArH), 7.11-7.22 (3 H, m, ArH), 7.26 (1 H, d, *J* 7.9, ArH), 7.33 (1 H, d, *J* 7.5, ArH), 7.40 (1 H, d, *J* 7.5, ArH), 9.49 (1 H, d, *J* 1.9, C=OH) and 9.76 (1 H, d, *J* 1.5, C=OH); δ_C(75 MHz; $CDCl_3$; Me_4Si) (mixture of rotational isomers) 18.4, 19.0, 19.4, 19.5, 21.2, 21.2, 22.5, 23.9, 26.2, 26.6, 29.1, 29.6, 33.4, 33.6, 34.7, 36.4, 42.9, 43.0, 49.1, 50.1, 57.9, 58.5, 58.5, 58.6, 69.7, 70.1, 106.4, 107.6, 109.2, 109.3, 118.2, 118.6, 119.3, 119.4, 121.6, 121.7, 125.9, 126.1, 128.2, 128.7, 128.7, 128.7, 132.3, 132.6, 133.4, 133.6, 133.7, 134.0, 134.0, 134.0, 137.1, 137.2, 138.5, 138.5, 168.8, 168.8, 201.9 and 202.5; *m/z* (ESI) 459.2640 $[M+H]^+$ $C_{29}H_{35}N_2O_3$ requires 459.2642.

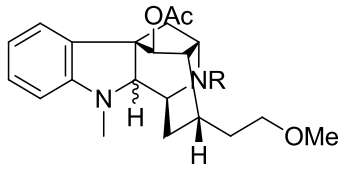
General method for cyclisation onto the indole 3-position



The appropriate amine-protected aldehyde (x mg) was dissolved in glacial acetic acid, acetic anhydride and concentrated hydrochloric acid (x mL, 3:3:0.2 v/v ratio) at 0 °C and hydrogen chloride gas, generated by dropping concentrated sulfuric

acid onto sodium chloride, was bubbled through the reaction solution to the point of saturation. The reaction was kept at 0 °C for six hours and re-saturated with hydrogen chloride gas every two hours. The mixture was then allowed to warm to room temperature and left to stir for sixteen hours. The solvents were removed under reduced pressure to give the iminium salt typically as a brown foam. To check for successful cyclisation a portion of the iminium salt was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate (10 mL). The organic portion was then dried ($MgSO_4$), filtered and the solvents removed under reduced pressure to give the carbinolamine as a single diastereoisomer.

General methods for indolenine iminium ion reduction



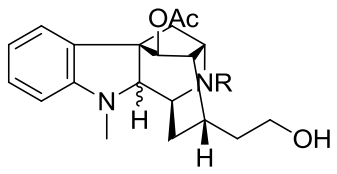
A typical hydrogenation procedure:

Pd/C (x mg, 10% by weight) was added to a solution of the iminium salt (x mg) in dichloromethane (0.1x mL), the reaction flask was evacuated and placed under an atmosphere of hydrogen gas (1 atm.). The reaction mixture was left to stir for sixteen hours. The reaction mixture was filtered through Celite® washing with dichloromethane. The solvents were removed under reduced pressure to give the crude product as a mixture of diastereoisomers.

A typical hydride reduction procedure:

The iminium salt was dissolved in tetrahydrofuran, cooled to −78 °C and the hydride reducing agent added. The reaction mixture was stirred at −78 °C for two hours and then allowed to warm to room temperature at which point it was quenched with methanol. The solvents were removed under reduced pressure and the residue partitioned between ethyl acetate and saturated sodium chloride. The organic portion was washed with saturated sodium chloride, dried ($MgSO_4$), filtered and solvents removed under reduced pressure to give the product as a mixture of diastereoisomers.

General method for methyl ether deprotection



The starting material was taken up in dichloromethane and cooled to −78 °C at which point boron tribromide (4.25 eq., 1 M solution in dichloromethane) was added dropwise. The reaction mixture was allowed to warm to room temperature over six hours and then stirred for a further sixteen hours. The reaction was quenched by the addition of water and stirred for thirty minutes. The phases were then separated and the aqueous portion extracted with ethyl acetate. The combined organics were washed with saturated sodium chloride, dried ($MgSO_4$),

filtered and the solvents removed under reduced pressure to give the crude alcohol product which was then purified by column chromatography.

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