Novel Synthetic Applications of *N*-Acyliminium Ions Toward β-Turn Mimetics and Naturally Occurring Alkaloids

by

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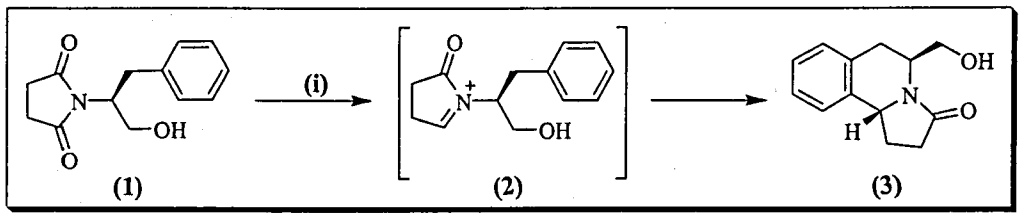
Abstract

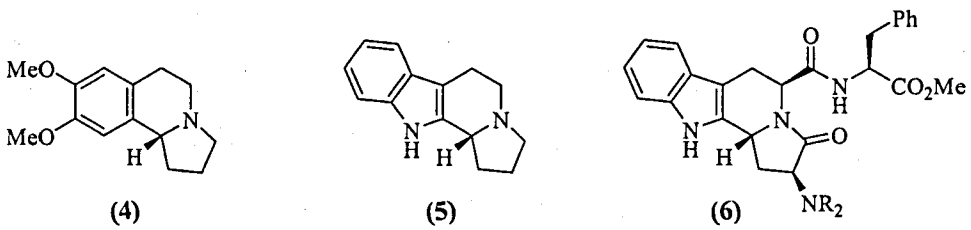
The asymmetric approach to a range of substituted indolizidine templates (**3**) from non-racemic substrates (**1**), based around the development of a diastereoselective *N*-acyliminium cyclisation strategy, is well established within our group.



(1) (2) (3)

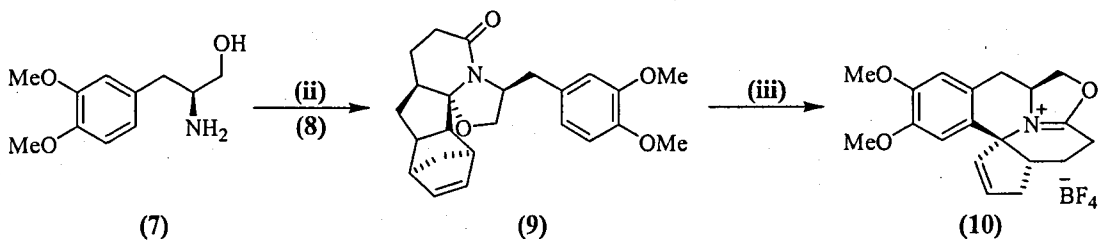
Scheme 1: Reagents; **(i)** $NaBH_4$, 2 M HCl, EtOH, 20 h.

The application of this novel methodology in target synthesis has been demonstrated by the manipulation of chiral building blocks such as (**3**). The removal of functional groups has allowed assess to therapeutically active natural products including (+)-crispine A (**4**)[1] and (+)-harmicine (**5**),[2] whilst the exploitation of their existing functionality has been utilized to form complex β-turn peptide mimics, such as (**6**).



(4) (5) (6)

The scope of this methodology has been extended with the novel *N*-acyliminium cyclisation/*retro* Diels-Alder tandem synthesis of the complex pentacyclic template (**10**), from the lactam precursor (**9**). Analogues of such templates are used as key intermediates in the synthesis of the *cephalotaxus alkaloids*.



(7) (9) (10)

Scheme 2: Reagents; **(ii)** Keto-acid (**8**), PhMe, Δ, 24 h; **(iii)** $BF_3.OEt_2$, DCM, Δ, 15 h.

[1] Allin, S. M.; Gaskell, S. N.; Towler, J. M.; Page, P. C.; McKenzie, M. J. and Martin, W. P. *J. Org. Chem.* **2007**, *72*, 8972.
[2] Allin, S. M.; Gaskell, S. N.; Elsegood, M. J. and Martin, W. P. *Tetrahedron Lett.* **2007**, *48*, 5669.

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Finally I would like to thank my family and most importantly my Mum Sheila, thank you for always believing in me and supporting me in whatever I chose to do.

Contents

1. Introduction

Abbreviations

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
AD	Asymmetric dihydroxylation
Ar	Aryl
Aq	Aqueous
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bp	Boiling point
br	Broad
Bt	Benzotriazole
BTD	Bicyclic turned dipeptide
Bu	Butyl
s-Bu	*sec*-Butyl
t-Bu	*tert*-Butyl
CCK	Cholecystokinin
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBAD	Di-*tert*-butyl azodicarboxylate
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DMAP	*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMTSF	Dimethyl(methylthio)sulfonium tetrafluoroborate
DMSO	Dimethylsulfoxide
E	Electrophile
e.e.	Enantiomeric excess
EI	Electron impact
Et	Ethyl

EDCI	1-Ethyl-3-[(dimethylamino)propyl]carbodiimide hydrochoride
FAB	Fast atom bombardment
g	Grams
GC	Gas chromatography
h	Hours
HCl	Hydrochloric acid
HOABt	1-Hydroxyazabenzotriazole
HPLC	High performance liquid chromatography
Hz	Hertz
IBTM	2-Amino-3-oxohexahydroindolizino[8,7-*b*]indole-5-carboxylate
IBX	*o*-Iodoxybenzoic acid
IR	Infra-red
J	Coupling constant
LA	Lewis acid
LC-MS	Liquid chromatography - Mass spectroscopy
LDA	Lithium diisopropylamine
m	Multiplet
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MHz	Megahertz
min	Minutes
ml	Millilitres
mmol	Millimoles
Mp	Melting point
Ms	Methanesulfonyl
MS	Mass spectroscopy
NCS	*N*-Chlorosuccinimide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear overhauser effect
Nu	Nucleophile
Ph	Phenyl
Phth	Phthalamide

PPA	Polyphosphoric acid
ppm	Part per million
i-Pr	*iso*-Propyl
py	Pyridine
Ra-Ni	Raney-nickel
Red-Al	Sodium bis(2-methoxyethyoxy)aluminium hydride
rt	Room temperature
s	Singlet
S_N1	Unimolecular nucleophilic substitution
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl (Trifyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
p-Ts	*para*-Toluenesulfonyl (Tosyl)
UV	Ultraviolet
Z	Carboxybenzyl

CHAPTER ONE:
INTRODUCTION

1.1. *N*-Acyliminium Ions in Synthesis

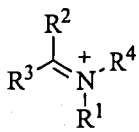
1.2. Cyclisations of *N*-Acyliminium Ion Intermediates

1.3. Chiral Bicyclic Lactams as Precursors for Asymmetric Synthesis

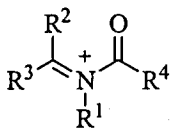
1.4. Applications of *N*-Acyliminium Ions in Alkaloid Synthesis

1.1. *N*-Acyliminium Ions in Synthesis

Advancement in chemo-, regio-, and stereoselectivity of both classical and newly developed reagents has been the basis for expansion of synthetic organic chemistry in recent history. An excellent example is the Mannich reagent **(1)** and the amidoalkylating reagent **(2)** in which the latter, also known as an *N*-acyliminium ion, had been initially designed for the purpose of Mannich-type condensations with primary amines.[1]



(1)

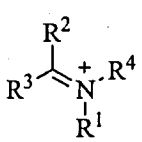


(2)

The cyclisations that proceed *via* iminium cations are well established, such as the Mannich reaction,[2] the Bischler-Napieralski reaction[3] and the Pictet-Spengler reaction,[4] and it soon became apparent that the applications of *N*-acyliminium ions would be significant due to its highly versatile reaction characteristics.[5] These have been reviewed comprehensively, the majority being of the intermolecular reaction type.[6,7] The study of intramolecular carbon-carbon forming reactions of *N*-acyliminium ions further enhances the emphasis on the reactivity and selectivity of amidoalkylative reagents.

1.1.1. Structure and Reactivity of *N*-Acyliminium Ions

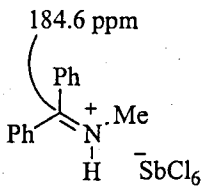
It has been well established in recent decades that the presence of a strongly electron withdrawing group at nitrogen renders the imino carbon in the Mannich-intermediate **(1)** considerably more reactive by enhancing its cationic character.



(1) R^1 = H, alkyl **(3)** R^1 = acyl **(4)** R^1 = COOR **(5)** $R^1 = CONR_2$ **(6)** R^1 = Tosyl **(7)** $R^1 = NR_2$

The *N*-acyl derivative **(3)** and the carbamate **(4)** have been the most widely exploited of these modified cations, however the use of other electronegative substituents such as the amide **(5)** and *N*-tosyl **(6)** cations have also been explored. Depending on the identity of

R^1, R^2 and R^3, numerous cyclic and linear forms can be distinguished and new variations such as the hydrazonium **(7)** have been added.[8]



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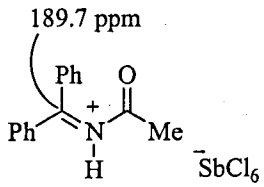
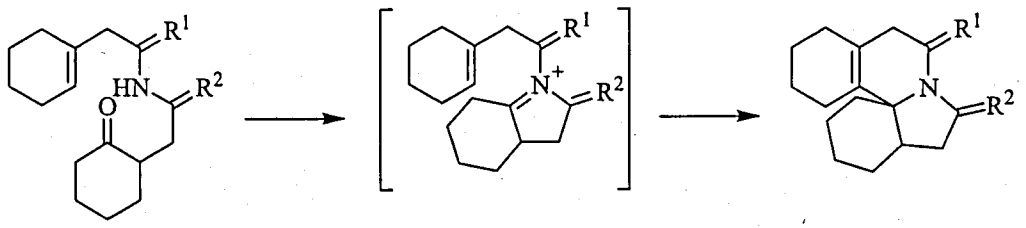


(9)

A ^{13}C NMR study of the iminium salts **(8)** and **(9)** by Würthwein *et al.* showed that the substitution of an *N*-methyl by an *N*-acetyl group gave rise to a downfield shift of the imino carbon absorption of approximately 5 ppm.[9] From this, one may anticipate that *N*-acyliminium ions are more electrophilic, i.e. more reactive than iminium ions.[10] Boekelheide *et al.* have illustrated the difference in reactivity of intramolecular reactions in the results of olefin cyclisations obtained in the synthesis of *Erythrina* alkaloids as shown in **Scheme 1**.[11] Both *N*-acyliminium ions **(11a, 11b)** generated from their respective keto amides **(10a, 10b)** proceeded to form the expected cyclisation products **(12a, 12b)**.

Scheme 1:



(10a) $R^1 = O, R^2 = H_2$
(10b) $R^1 = H_2, R^2 = O$
(13) $R^1 = H_2, R^2 = H_2$

(11a) $R^1 = O, R^2 = H_2$
(11b) $R^1 = H_2, R^2 = O$

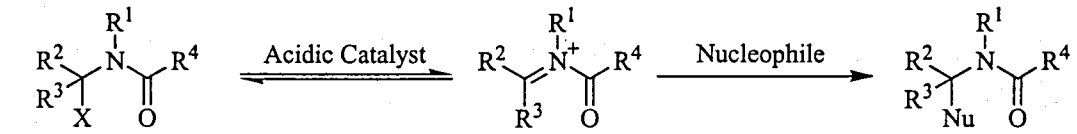
(12a) $R^1 = O, R^2 = H_2$
(12b) $R^1 = H_2, R^2 = O$

The corresponding ring closure of the iminium salt **(13)** however, led to unidentifiable products. It is important to note that these olefin cyclisations are in principle a reversible process, the reverse reaction being a Grob fragmentation.[12] The greater attribute of the *N*-acyliminium ion cyclisation is that the amide product of an *N*-acyliminium-olefin cyclisation is much less susceptible to fragmentation and hence more irreversible, in comparison to its amine counterpart from the corresponding iminium-olefin cyclisation.

1.1.2. Mechanistic Aspects of *N*-Acyliminium Ion Chemistry

When applied to organic synthesis, *N*-acyliminium ions are almost always generated *in situ*, in view of their limited stability and high reactivity. The mechanistic scheme, which applies to most amidoalkylation reactions, is shown in **Scheme 2.**[13]

Scheme 2:



X = Cl, RCO_2, RSO_2, N_3, RO, RS

(14) **(15)** **(16)**

The *N*-acyliminium ion **(15)** is formed in equilibrium with its precursor **(14)** through the influence of an acidic catalysis. The subsequent reaction of a nucleophile with the *N*-acyliminium ion yields the product **(16)** in an irreversible process. This scheme closely resembles that of an S_N1 process. A study by Zaugg and Martin distinguished two extreme kinetic situations: [6a]

i. The formation of the *N*-acyliminium ion is rate limiting,
ii. The reaction with the nucleophile is rate limiting.

The former case would suggest that a more stable *N*-acyliminium ion leads to a faster reaction, whereas in the latter the opposite is true. The rate of amidoalkylation is also influenced by the nature of the leaving group and the solvent, as well as the acidic catalyst structure.

In *N*-acyliminium chemistry, an important side reaction is the formation of an enamide. This can be a reversible process when preformed in an acidic medium; however this is not always the case. The enamide formed can act as a nucleophile and further react with the *N*-acyliminium species still present, to give dimeric structures. These problems of enamide formation and subsequent side reactions arise if the *N*-acyliminium ion is not trapped fast enough by the nucleophile. This may occur if:

- The nucleophile is not very reactive,
- There is too much steric hindrance,
- Stereoelectronic factors are unfavourable (for intramolecular processes),
- A medium-sized or large ring is to be formed.[13]

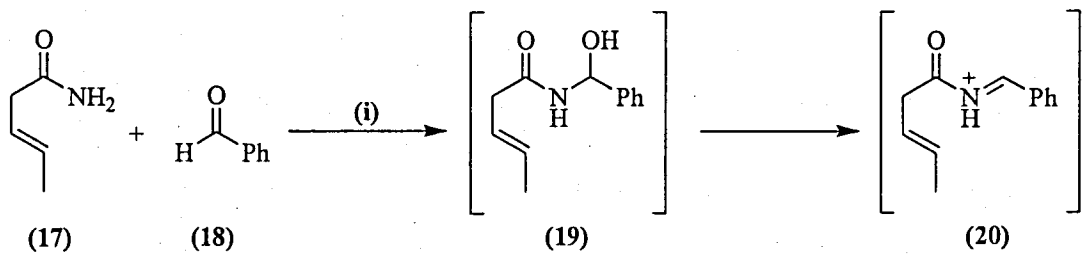
1.1.3. Generation of *N*-Acyliminium Ions and their Precursors

Whereas iminium salts are frequently isolable, their *N*-acyliminium counterparts are far more reactive and seldom, if ever, isolated.[5] There are five major synthetic pathways to form *N*-acyliminium ions *in situ* for applications in elaborate organic synthesis.

1.1.3.1. Heterolysis of α-Oxygenated Amides

Heterolysis of α-substituted amides is the most common method for the generation of synthetically useful *N*-acyliminium ions, the α-substituent being an oxygen moiety in the majority of cases, although a variety of other leaving groups have been employed, including bisamides, α-chloroalkyl amides and α-thioalkylamides; an example is the amidoalkylation outlined in **Scheme 3**.[14]

Scheme 3:



(17) (18) (19) (20)

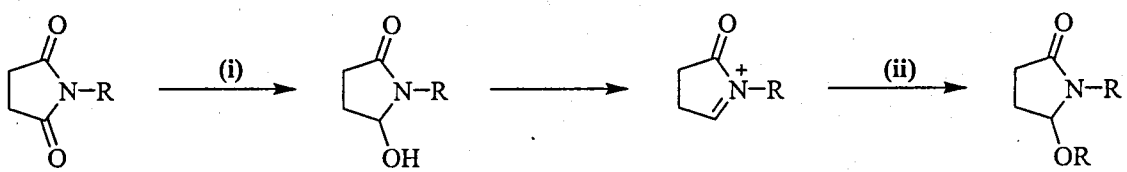
Reagents: (i) $MeSO_3H$, P_2O_5, 35 °C, 18 h.

The addition of an amide **(17)** to an aldehyde **(18)** or ketone under conditions of acid catalysis can be used to prepare the α-oxygenated amides **(19)**. Generally, Brönsted or Lewis acids are used to generate the corresponding *N*-acyliminium ions **(20)** from the α-oxyalkyl amide precursors.

The reduction of cyclic imides **(21)** in the presence of an alcohol affords the corresponding hydroxy lactam **(22)** and/or the alkoxy lactam **(24)**, which are useful

precursors of cyclic *N*-acyliminium species **(23)** **(Scheme 4)**.[15] Such reductions of imides are often highly regiospecific in the presence of other functionality.[16]

Scheme 4:



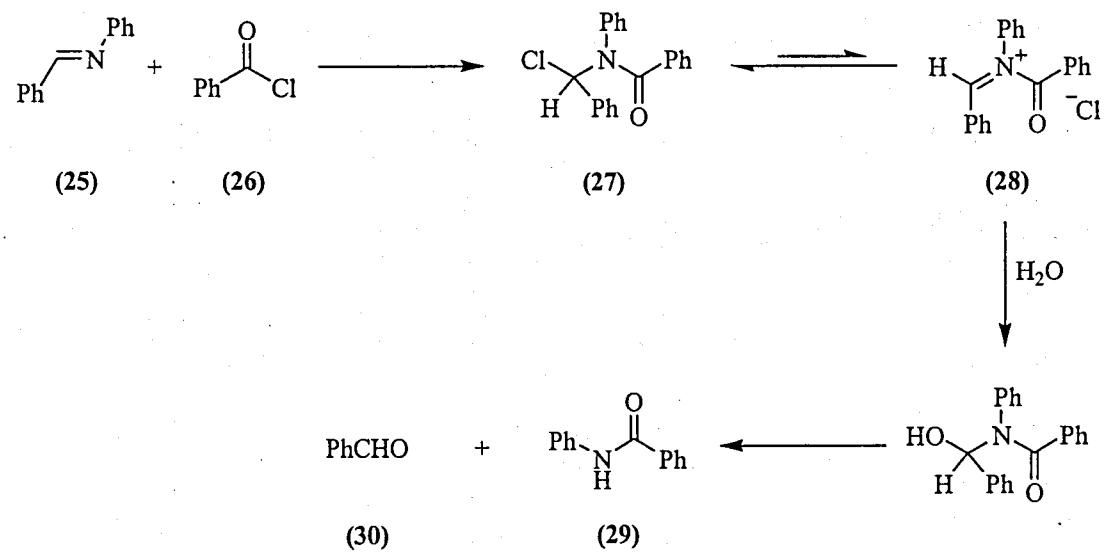
(21) **(22)** **(23)** **(24)**

Reagents: (i) $NaBH_4$, H^+; (ii) ROH.

1.1.3.2. *N*-Acylation of Imines

Imines are readily prepared in high yield by condensation of an aldehyde or ketone with a primary amine. In 1914, James and Judd reported the first acylation of an imine with a reactive carboxylic acid derivative such as an acid chloride or anhydride when they reacted benzaniline **(25)** with benzyl choride **(26)** **(Scheme 5)**.[17]

Scheme 5:



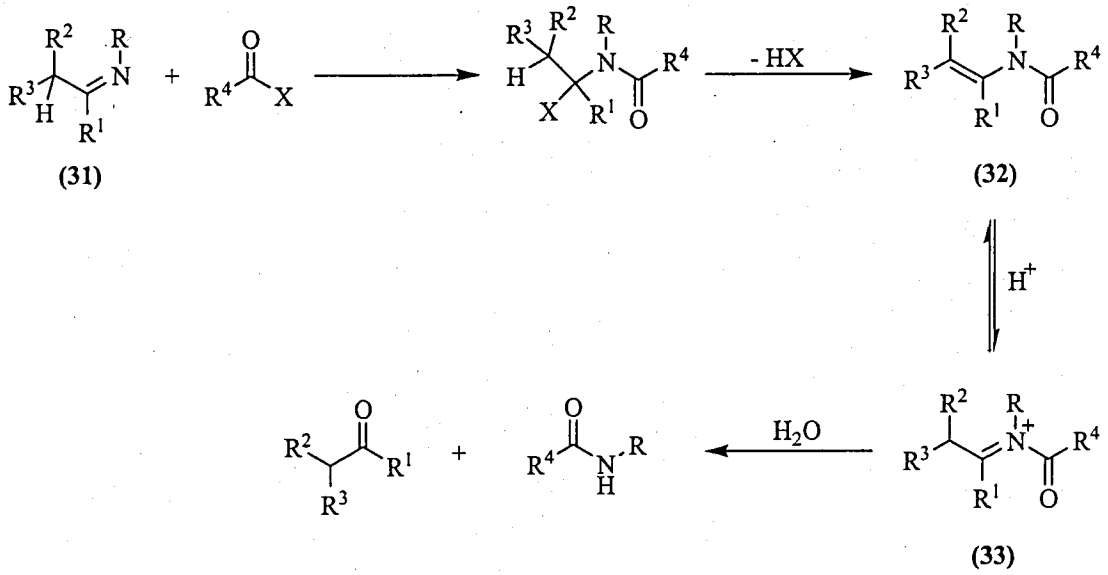
(25) **(26)** **(27)** **(28)** **(30)** **(29)**

The crystalline precursor **(27)** was readily hydrolyzed in water to give benzanilide **(29)** and benzaldehyde **(30)**. The lability of the carbon-chlorine bond illustrates the propensity to *N*-acyliminium ion **(28)** formation in this system.

1.1.3.3. Electrophilic Addition to Enamides

Enamides (**32**) are easily formed *via* acylation of an imine (**31**) with an acid chloride or anhydride followed by elimination. Enamides are stable compounds under neutral or basic conditions. When reacted with Brönsted acids they give rate-determining protonation at carbon, which leads to hydrolysis in aqueous medium (**Scheme 6**). The *N*-acyliminium ion (**33**) is the intermediate formed after protonation of the enamide.[13]

Scheme 6:

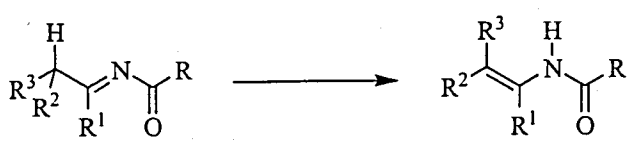


(31) (32) (33)

1.1.3.4. *N*-Protonation of *N*-Acylimines

N-acylimine protonation is in principle, a route to acyliminium ions, however it is more of mechanistic interest rather than a general synthetic method. This is due to the limitations in preparing *N*-acylimines (**34**) themselves and their relative instability. If possible they tautomerise to the corresponding enamide (**35**) (**Scheme 7**), unless there are no α-hydrogen atoms available.

Scheme 7:

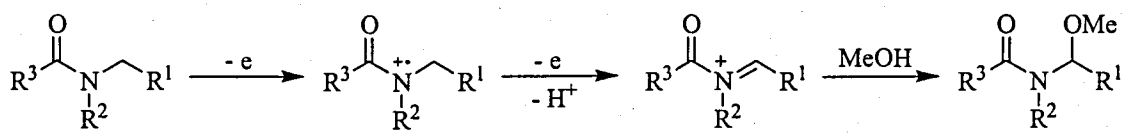


(34) (35)

1.1.3.5. Oxidation of Amides

The removal of a hydride from the α-carbon of an amide **(36)** formally leads to an *N*-acyliminium ion **(37)**. The most important way to effect this transformation has been established by many research groups as the electrochemical method, which involves two single-electron transfer steps as shown in **Scheme 8.**[7]

Scheme 8:



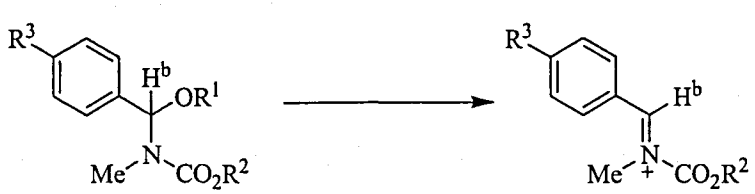
(36) **(37)** **(38)**

This electrochemical oxidation is conducted in the presence of a nucleophile, usually methanol, in order to trap the *N*-acyliminium ion as soon as it is generated as the α-methoxyalkyl amide **(38)**. This reaction is effective for a large variety of amides and carbamates and there are few reports of other methods for the formation of *N*-acyliminium ions *via* hydride abstraction of amides.

1.1.4. Observation of *N*-Acyliminium Ions by NMR Spectroscopy

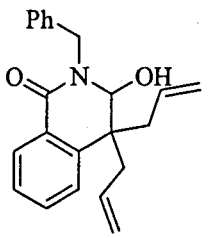
It has been previously mentioned that *N*-acyliminium ions are almost always generated *in situ* due to their limited stability and high reactivity. Consequently, the observation of a transient *N*-acyliminium intermediate in dynamic NMR has been reported only twice.[8] It has been shown in a specially designed experiment by Yamamoto *et al.*, that alkoxycarbamate **(39)** at –55 °C in the presence of triflic anhydride produced a clean ^{13}C NMR spectrum of the intermediate **(40)** shown in **Scheme 9.**[18]

Scheme 9:



(39) **(40)**

More recently, it was discovered that treatment of the bis(homoallyl)hydroxylactam **(41)** with boran trifluoride diethyl etherate at 25 °C produced the ^{13}C NMR spectrum of the *N*-acyliminium species **(42)**.[19]



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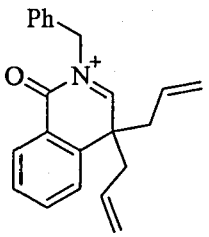
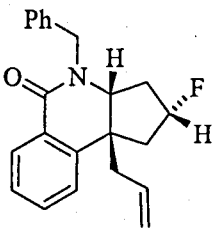


(42)



(43)

This intermediate was slowly (1 hour) converted to the fluoro compound **(43)**. The reasons for this unexpected stability are not entirely clear although the spectral data suggests that the greater electron withdrawing ability of the amide carbonyl group in comparison to carbamate could be a factor.[8]

1.2. Cyclisations of *N*-Acyliminium Ion Intermediates

The reactions of *N*-acyliminium ions with tethered π-nucleophiles have been established as an excellent method for the preparation of complex nitrogen heterocycles. Since the introduction of *N*-acyliminium methodology as a versatile tool, the γ-lactam derivatives have prominently featured in the field of intramolecular carbon-carbon bond formation.

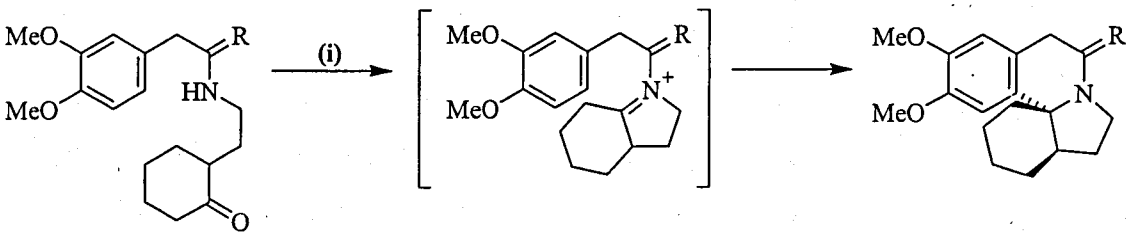
1.2.1. Reactions of Benzenoid Nucleophiles

Intramolecular amidoalkylations have been applied to a wide variety of aromatic nucleophiles and have been shown to be highly effective with benzene rings, as well as derivatives substituted with moderate deactivating groups.[20] The major breakthrough of *N*-acyliminium cyclisations with benzene nucleophiles came in the 1950's and was conducted by Belleau[21] and Mondon,[22] who both lead the pioneering work in the syntheses of the *Erythrina* isoquinoline alkaloids.

1.2.1.1. Synthesis of Erythrinanes

Belleau illustrated the enhanced reactivity of an *N*-acyliminium variant of the Mannich reaction in the formation of the erythrinane **(45)**, as shown in **Scheme 10** with a successful cyclisation from the *N*-acyliminium species **(44)**. The corresponding iminium ion **(46)** had previously failed under "various conditions".[23]

Scheme 10:



R = O
R = H_2

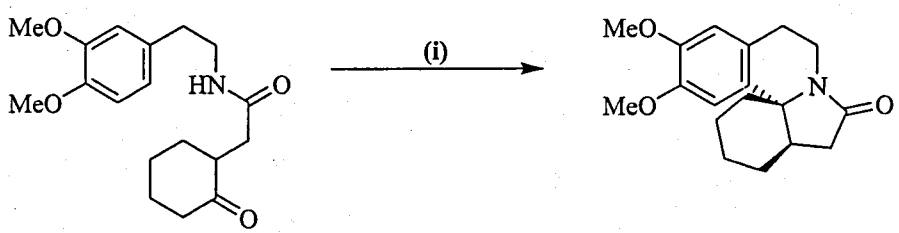
(44) R = O
(46) R = H_2

(45) R = O
R = H_2

Reagents: **(i)** P_2O_5, PPA, 100 °C, 3 h (93 %).

The alternative "Mondon-type" cyclisation, which differs only by the position of the lactam carbonyl as shown in **Scheme 11**, is similar to that of Belleau as both modes are completely stereoselective for the *cis*-fused configuration.

Scheme 11:



Reagents: **(i)** H_3PO_4, H_2O/MeOH, Δ, 1 h (65 %).

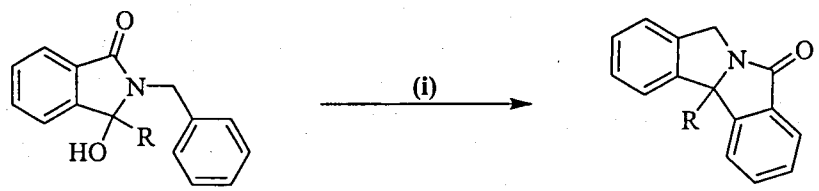
The stereochemical outcome is a result of the steric effects that arise in the orthogonal approach of the π-orbital of the arene nucleophile to the plane of the iminium ion[23] and this pattern is general for a diverse range of substrates.[20]

1.2.1.2. Effects of Substituents on the Iminium Ion

The nature of the substituent on the iminium unit does not have a great impact on the outcome of an *N*-acyliminium cyclisation. However more reactive intermediates, such as those bearing an electron-withdrawing group on carbon or those devoid of steric hindrance may lead to increased yields and/or allow milder conditions.

Winn and Zaugg used various hydroxyisoindolinones as *N*-acyliminium precursors to determine the influence of iminium carbon substituents on cyclisation **(Scheme 12)**.[24]

Scheme 12:



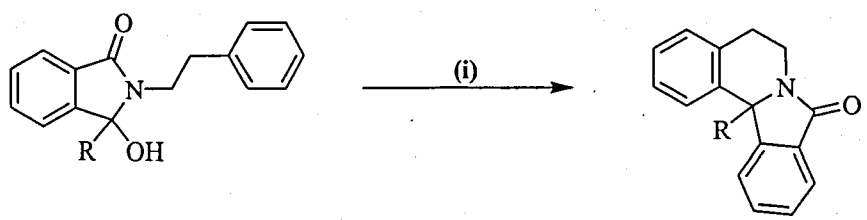
(47) R = Ph
(48) R = H

R = Ph (75 %)
R = H (0 %)

Reagents: **(i)** PPA, 135 °C, 4 h.

With standard substituents such as phenyl or hydrogen, there were cases of differential reactivity. The more reactive *N*-acyliminium species bearing an electron withdrawing phenyl group **(47)** leads to enhanced cyclisation yields in comparison to those observed for its hydrogen group counterpart **(48)**, which fails to cyclise. However, the ring strain exhibited during formation of the five-membered ring is also a contributing factor, as the corresponding cyclisations to six-membered derivatives occur with good yields for both phenyl **(49)** and hydrogen **(50)** substitution **(Scheme 13)**.

Scheme 13:



(49) R = Ph
(50) R = H

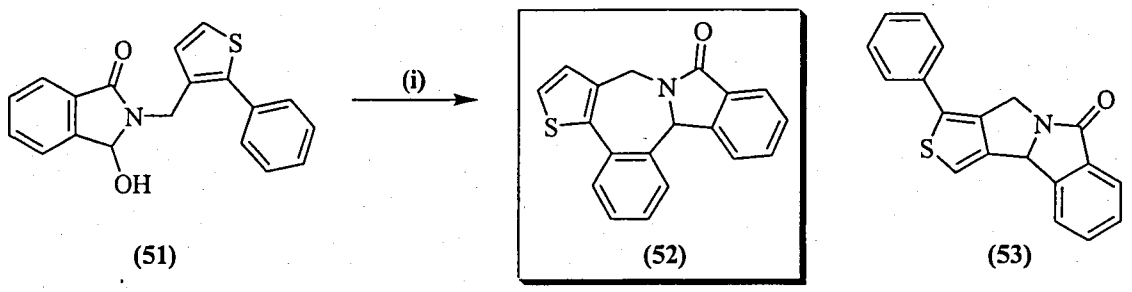
R = Ph (65 %)
R = H (84 %)

Reagents: **(i)** H_2SO_4, 2 h.

1.2.1.3. Formation of Five and Seven-Membered Rings

The formation of five-membered rings by *N*-acyliminium ion cyclisation onto arenes can be problematic in comparison to its six-membered equivalent due to considerable ring strain during formation, as demonstrated in the previous example. This difficulty is also illustrated by the preference for cyclisation of the phenyl substituent of **(51)** to generate a new seven-membered system **(52)**, in favour of the completing cyclisation of the more nucleophilic thiophene to form a 5,5-fused product **(53)** **(Scheme 14)**.[25]

Scheme 14:

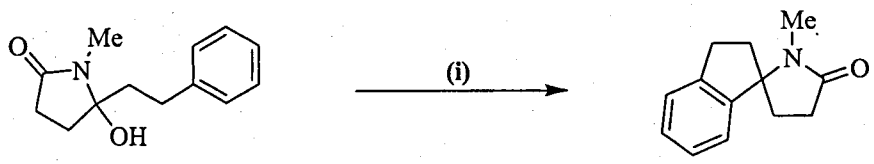


(51) **(52)** **(53)**

Reagents: **(i)** TFA (80 %).

Alternatively, five-membered rings are more readily formed from spirocyclisation of *N*-acyliminium intermediates as shown in **Scheme 15**.[26]

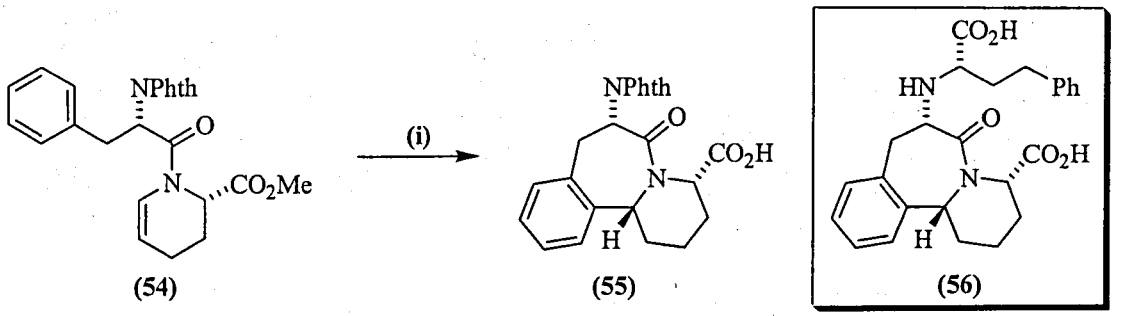
Scheme 15:



Reagents: **(i)** TFA, Δ (69 %).

The formation of seven-membered rings in arene cyclisations can also be troublesome, however there are a number of successful examples.[20] One such example is the synthesis of an extremely potent inhibitor of angiotensin-converting enzyme **(56)** using an *N*-acyliminium intermediate generated from an *N*-acyl enamine **(54)** to construct the fused tricyclic core **(55)** **(Scheme 16)**.[27]

Scheme 16:



(54) (55) (56)

Reagents: (i) TfOH, DCM, 24 h (77 %).

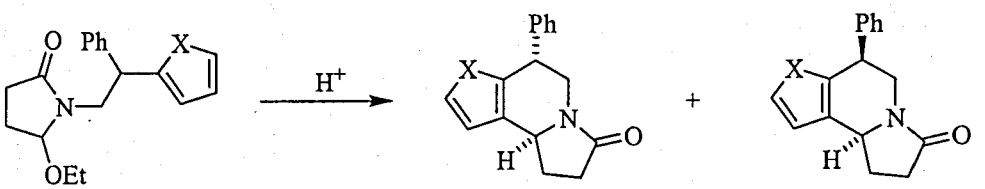
1.2.2. Reactions of Heterocyclic Nucleophiles

N-acyliminium ion cyclisations of heterocyclic nucleophiles for the most part, mirror that of their benzenoid counterparts. The π-rich heteroarenes, such as furan, pyrrole and indole are at the higher end of the reactivity spectrum comparable to phenyl derivatives, where as π-deficient compounds such as pyridine are significantly attenuated.[20]

1.2.2.1. Cyclisations of Thiophenes and Furans

Heterocyclic cyclisations that generate new six-membered rings are very tolerant and often proceed better than their phenyl counterparts **(Scheme 17)**.[28]

Scheme 17:

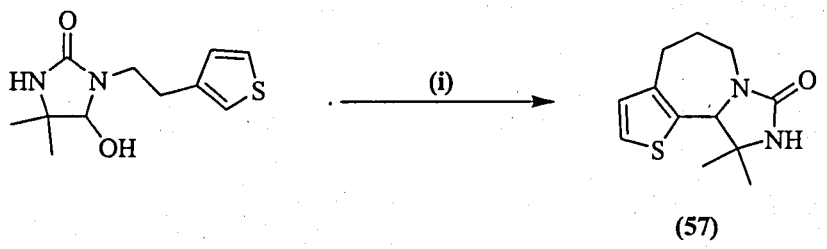


X = NMe 74:26 (96 %)
X = S 96:4 (47 %)

In comparing reactions of thiophene nucleophiles with its phenyl equivalent, it is found that the thiophene is more reactive when its α-position is involved. In cases when the heterocycle is linked to the *N*-acyliminium segment by its 3-position, regiochemistry of the cyclisation can be an issue. When the thiophene 2-position is available however,

regiospecific cyclisation readily occurs at this site as shown in **Scheme 18** and in this case, allow access a seven-membered product **(57)**.[29]

Scheme 18:

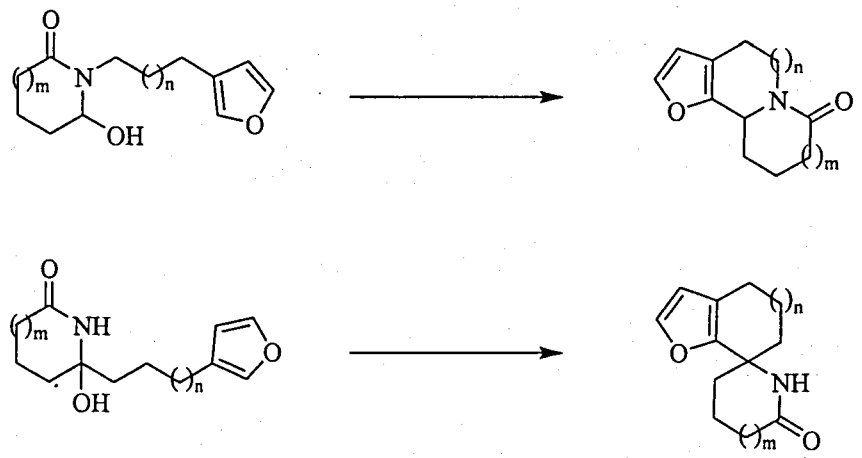


(57)

Reagents: **(i)** TFA, Δ, 1 h (65 %).

Tanis *et al.* have explored furan-based *N*-acyliminium cyclisations extensively. The products obtained are highly dependent on the furan tether position, the tether length and the substituents on the furan 5-position as shown in **Scheme 19**.[30]

Scheme 19:

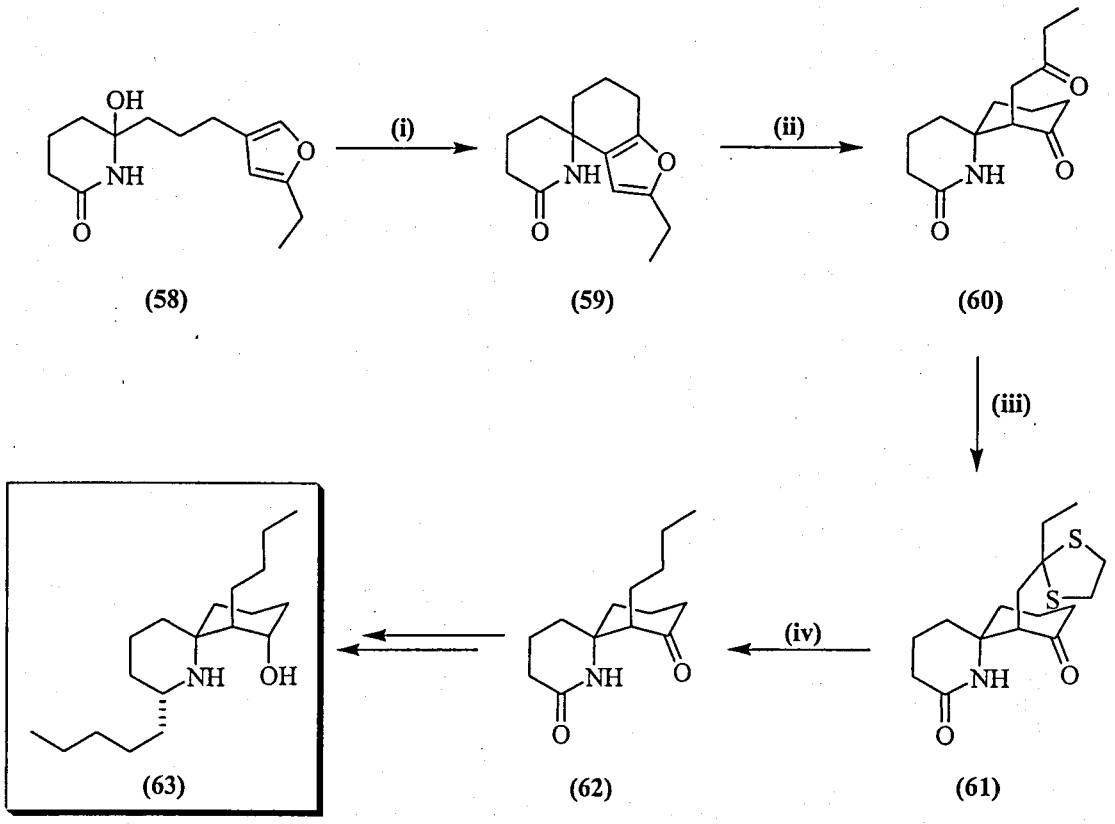


This outcome and the ability to form spirocycles reflects the lower nucleophility of the furan β-position in comparison to the α-position and has been applied in a formal synthesis of (±)-perhydrohistrionicotoxin **(63)** **(Scheme 20)**, which selectively binds to part of the cholinergic receptor that regulates the ion transport mechanism.[30]

The desired spirocyclic intermediate **(59)** was formed upon treatment of the *N*-acyliminium precursor **(58)** with formic acid. Oxidative ring opening of the furan with *m*-chloroperoxybenzoic acid and subsequent reduction of the ene-dione gave the

target dione **(60)**. Selective thioketalisation afforded **(61)**, which was desulfurised under Raney nickel conditions to give the spirocyclic amide **(62)** and thus completed the formal synthesis of the target (±)-perhydrohistrionicotoxin **(63)**.

Scheme 20:



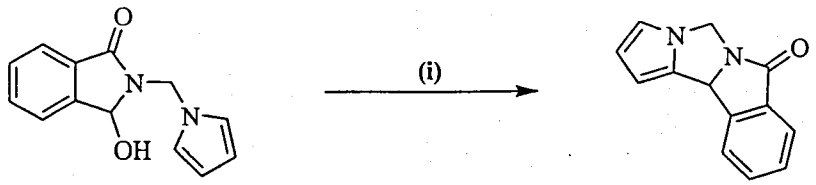
Reagents: **(i)** HCO_2H, cyclohexane (72 %); **(ii)** *m*-CPBA then Pd/C, H_2, EtOAc (70 %); **(iii)** TMSOTf, $TMSS(CH_2)_2STMS$ (67 %); **(iv)** Raney-nickel, EtOH, Δ (78 %).

1.2.2.2. Cyclisations of Pyrroles and Pyridines

N-acyliminium ion precursors linked to an *N*-substituted pyrrole at the α-position react cleanly at the β-position as previously shown in **Scheme 17**.[28] However when linked to the pyrrole nitrogen, *N*-acyliminium ion cyclisation at the α-position can occur to form five, six, seven and eight-membered ring systems.[20] Some examples are shown below.

As previously discussed, the formation of five-membered rings by *N*-acyliminium ion cyclisation onto arenes can be problematic, however **Scheme 21** shows a new, highly strained five-membered ring **(65)** produced, with difficultly as indicated by the low yield, *via* the *N*-acyliminium ion cyclisation of **(64)**.[31]

Scheme 21:

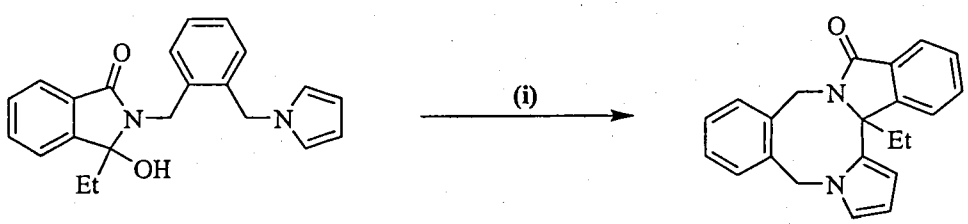


(64) (65)

Reagents: (i) HCO_2H, 3 d (27 %).

In the case of **(66)** **(Scheme 22)**, attack of the pyrrole over the competing phenyl group gives a new eight-membered ring **(67)** in excellent yield and under extremely mild conditions (1 hour, 23 °C).[32] Both examples highlight the high reactivity of the pyrrole nucleus for *N*-acyliminium cyclisations.

Scheme 22:

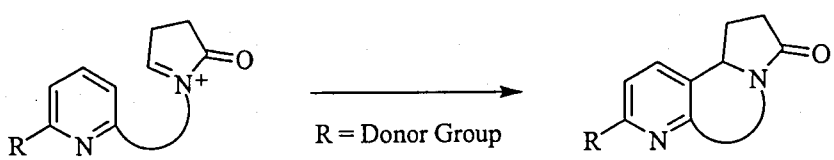


(66) (67)

Reagents: (i) TFA, DCM, 1 h (92 %).

In contrast, the pyridine ring is considerably less reactive toward electrophiles due to its electron-withdrawing nature and has received limited attention in cationic π-cyclisation reactions, despite its prevalence in a variety of biologically active heterocycles. Pawda has reported the intramolecular cyclisation of activated pyridines of type **(68)** with tethered *N*-acyliminium ions as detailed in **Scheme 23**.[33]

Scheme 23:

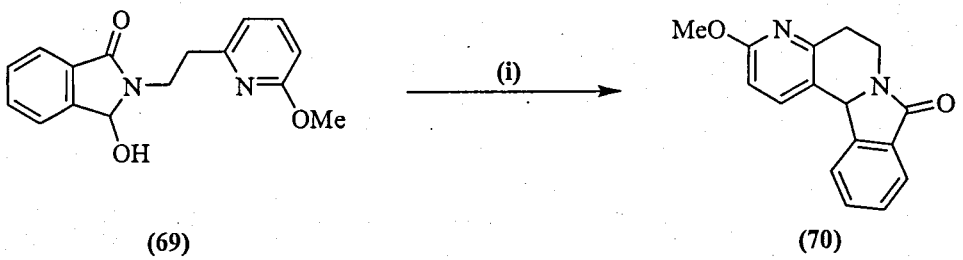


(68)

An example of such is the cyclisation of lactam **(69)** as shown in **Scheme 24**, which upon treatment with a variety of Lewis acids including $BF_3.OEt_2$, $TiCl_4$, and $SnCl_4$

resulted only in the recovery of starting materials. The synthesis of **(70)** was achieved however, with catalytic amounts of protic acid in refluxing benzene in 70 % yield.

Scheme 24:



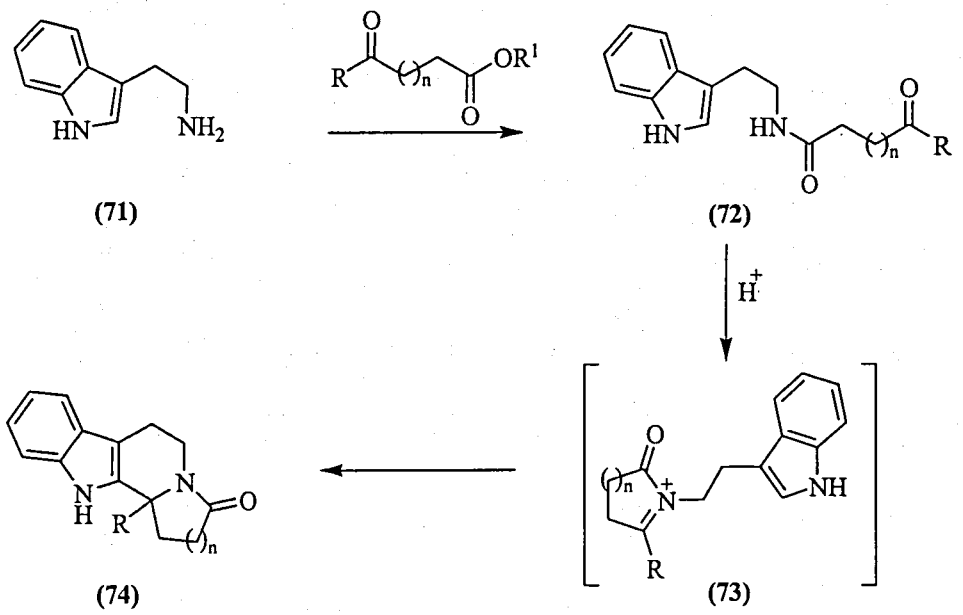
(69) **(70)**

Reagents: (i) *p*-TsOH, benzene, Δ (70 %).

1.2.2.3. Cyclisations of Indoles

The work of several research groups has illustrated the versatility of *N*-acyliminium cyclisations with indole nucleophiles and its applications in the total synthesis of various indole alkaloids. The highly reactive nature of the indole π-nucleophile allows these cyclisations to stand out as a unique collection of examples.

Scheme 25:



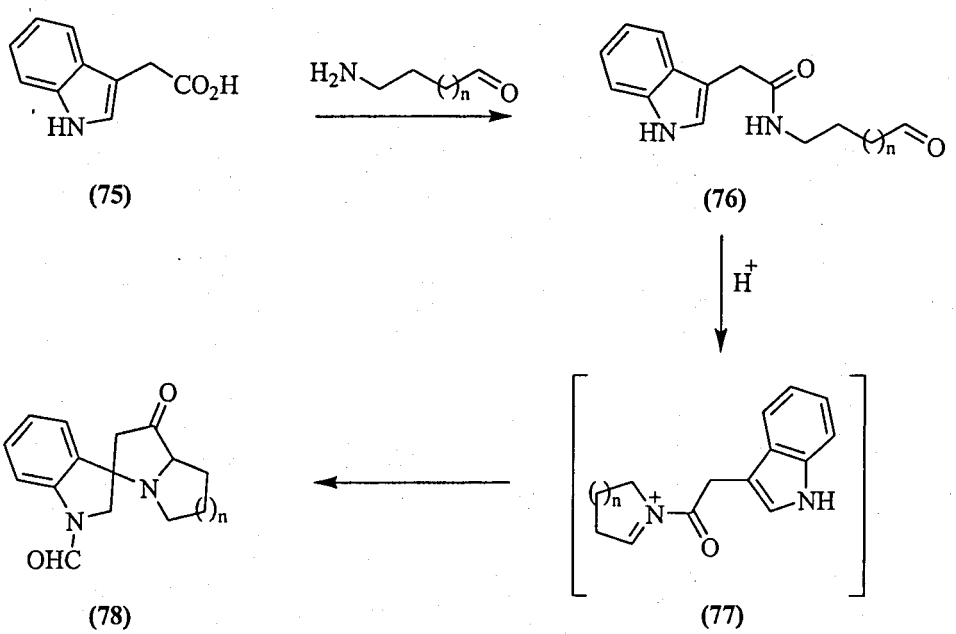
(71) **(72)** **(73)** **(74)**

In the vast majority of cases, the essential step is the coupling of an oxo-carboxylic acid with tryptamine **(71)** and acid catalysed ring closure of the so formed oxo-amide **(72)**

into the desired template **(74)** *via* the *N*-acyliminium species **(73)** **(Scheme 25)**.[13] As can be expected in cases where different stereoisomers may be formed, mixtures of both RC-N diastereoisomers are obtained, the composition dependent on the location of additional substituents in the *N*-acyliminium portion.

Exceptions to this method are the indole alkaloids synthesised by Van Tamelen *et al.*[34] and Wenkert *et al.*[35] starting from indole-3-acetic acid **(75)** and an amine to form the amide precursor **(76)**, which is cyclised by acid-catalysed formation of the *N*-acyliminium ion **(77)** and subsequent ring closure to **(78)** **(Scheme 26)**.

Scheme 26:

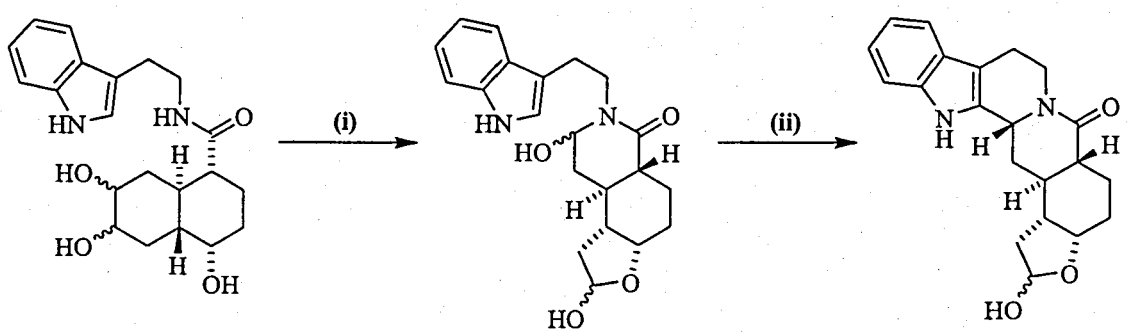


Unlike the previous reaction, where bond formation is only observed at the 2-position of the indole ring, the greater stability of the γ-lactam influences the cyclisation to yield the spiro-structure **(78)** as the more stable product *via* bond formation at the 3-position.

The distinct difference in behaviour between the two *N*-acyliminium ions **(73)** and **(77)** is extremely useful for exerting regiocontrol in this type of bond formation and cyclisation.[13] Van Tamelen *et al.* demonstrated this in an early example of an *N*-acyliminium ion cyclisation with an indole π-nucleophile as the key step in the total synthesis of (±)-yohimbine **(Scheme 27)**.[36] The precursor **(80)**, a trapped dialdehyde

formed by oxidation of **(79)** using sodium metaperiodate, reacts with phosphoric acid to yield the polycyclic lactam **(81)** in 60 % yield with high stereoselectivity.[20]

Scheme 27:



(79) **(80)** **(81)**

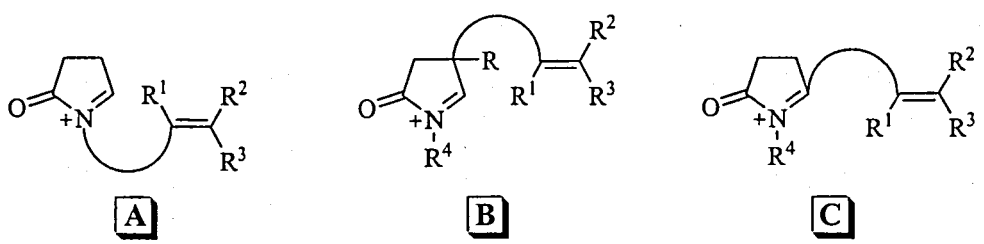
Reagents: **(i)** $NaIO_4$; **(ii)** H_3PO_4, Δ (60 %).

1.2.3. Reactions of Alkenes and Related Species

Although Belleau reported the first *N*-acyliminium cyclisation with an alkene nucleophile in 1957,[37] it was two decades later when Speckamp pioneered the field, by capitalising on a diverse range of *N*-acyliminium precursors through imide partial reduction. The introduction of mild condition, such as formic acid at room temperature, was an important step forward in this area.[13]

1.2.3.1. Standard Alkenes

With respect to the position of the tethered alkene π-nucleophile, three types of cyclisation can be distinguished as shown below.[13]

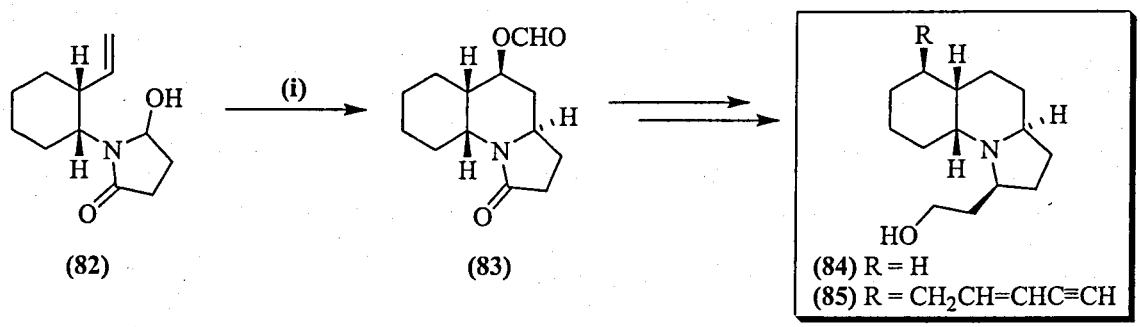


A **B** **C**

Ring closure of type A lead to high yields of single isomers, as exemplified in the synthesis of depentylperhydrogephyrotoxin **(84)** by Hart. The key step involved the

treatment of the *N*-acyliminium precursor **(82)** with formic acid, which gave the lactam core structure **(83)** as a single diastereoisomer, the observed stereochemistry being controlled by $A^{(1,3)}$ strain as shown below in **Scheme 28.**[38]

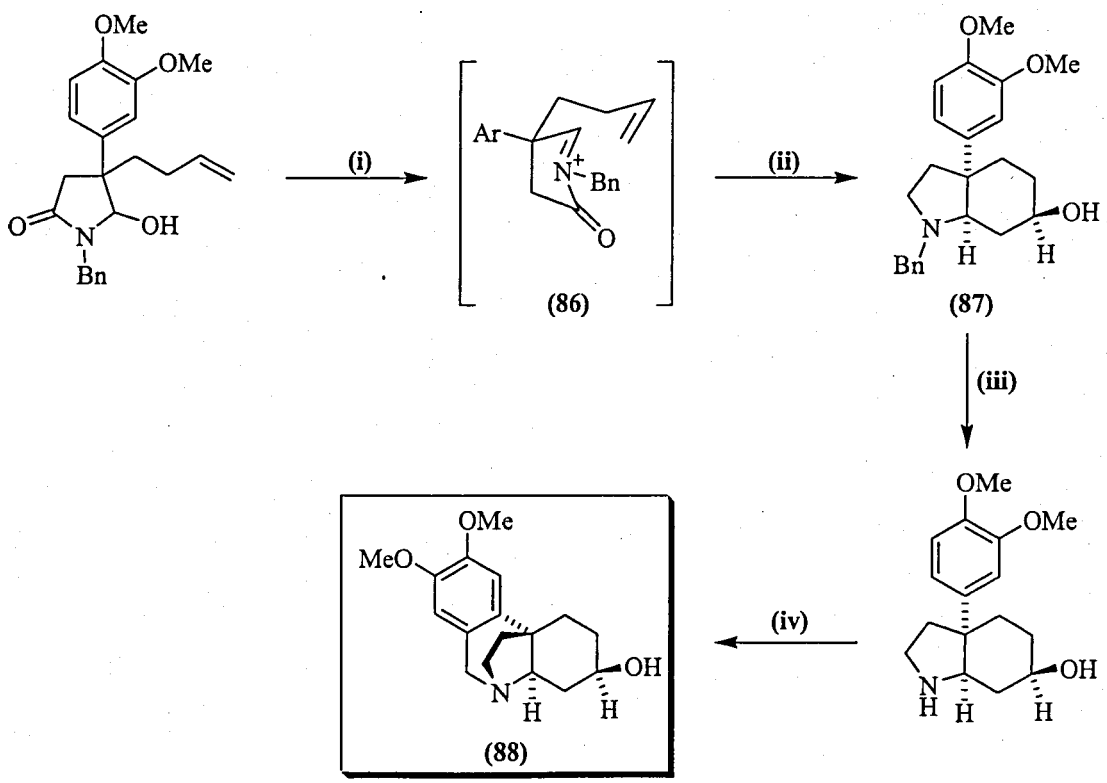
Scheme 28:



Reagents: **(i)** HCO_2H, 30 min (85 %).

Depentylperhydrogephyrotoxin **(84)** is an analogue of gephyrotoxin **(85)**; an alkaloid isolated from the skin extracts of the neotropical frog *Dendrobates histrionicus* which has shown some interesting pharmacological properties.[39]

Scheme 29:



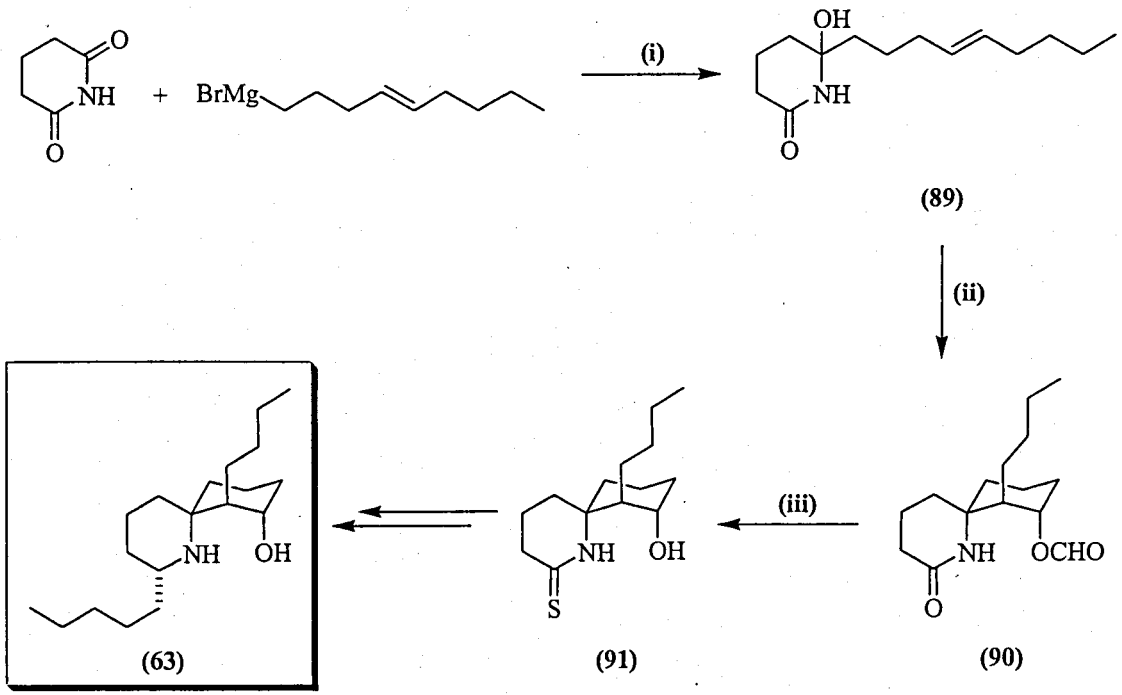
Reagents: **(i)** HCO_2H, 20 h; **(ii)** $LiAlH_4$, THF, Δ, 3 h; **(iii)** PtO_2, H_2, *i*-PrOH, 48 h (66 %); **(iv)** HCO_2H (50 %).

In the second type of ring closure B, mixtures of diastereoisomers are expected, the composition of which is dependent on substituent R.

Thus, in the synthesis of the mesembrine alkaloid *dl-epi*-di-hydromaritidine **(88)** by Speckamp and Wijnberg, shown above in **Scheme 29**, the *cis*-fused-ocatahydroindole isomer **(87)** resulting from transition state **(86)** is preferred, in which the bulky aromatic group occupies the equatorial position.[40]

When an alkene is directly linked to the iminium carbon as in type C, *N*-acyliminium ion spirocyclisation can ensue. This reaction has been demonstrated in the stereoselective formal total synthesis of perhydrohistrionicotoxin **(63)** **(Scheme 30)**.[41]

Scheme 30:



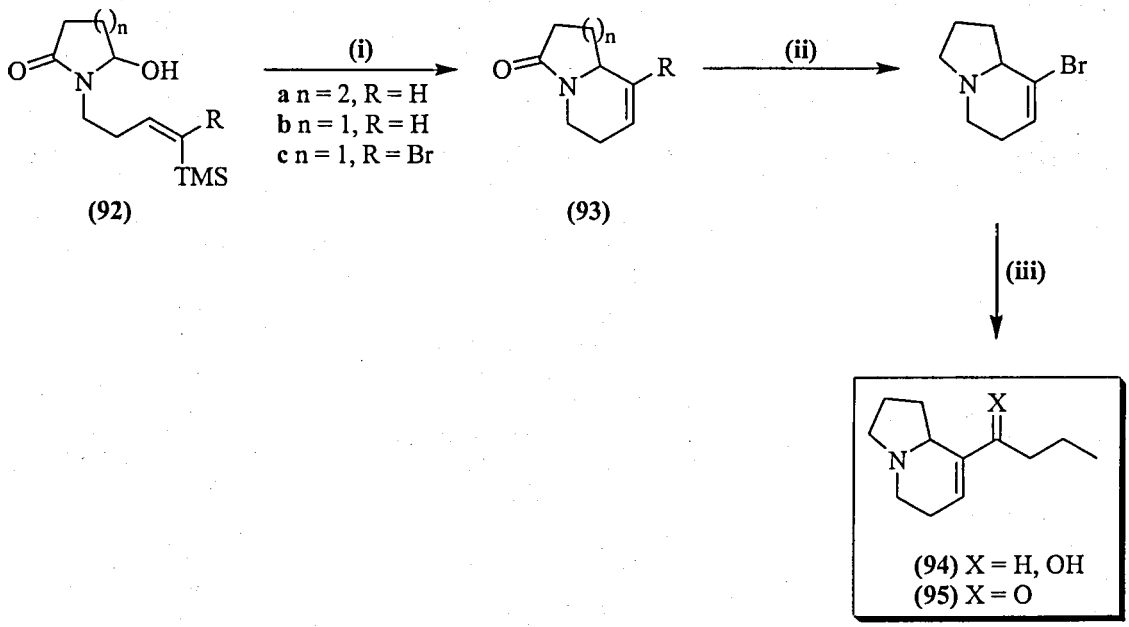
Reagents: **(i)** THF, 20 h; **(ii)** HCO_2H, Δ, 8 d (23 %); **(iii)** P_2S_5, benzene, Δ, 1 h then NaOH, 1 h (88 %).

In the key step of the synthesis **(89)** to **(90)**, three asymmetric centres are formed in a single operation *via* a 6-*endo*-trig, *N*-acyliminium-olefin cyclisation. The resulting spiro formate ester **(90)** was converted to the spirothiolactam alcohol **(91)**, which is a known precursor of perhydrohistrionicotoxin **(63)**.

1.2.3.2. Vinylsilanes

The *N*-acyliminium ion cyclisation of vinylsilane nucleophiles is directed toward the silicon-bearing alkene carbon because of the stabilisation of the resultant carbocation by the "β-silyl effect". Although not as reactive as the analogous allylsilanes and vinyl thioesters, vinylsilane nucleophiles have been utilised in the preparation of several nitrogen containing heterocycles.[20] Early examples of silicon-directed cyclisations were conducted as an extension of the Mannich reaction in the synthesis of quinolizidines **(93a)** and indolizidines **(93b)** as shown in **Scheme 31**.[42]

Scheme 31:



Reagents: **(i)** TFA, 15 min; **(ii)** $LiAlH_4$, Et_2O, Δ, 2 h (67 %); **(iii)** *s*-BuLi, THF, −78 °C, butanal (86 %).

The additional reactivity of the *N*-acyliminium ion was significant in cyclisations of electron-deficient vinylsilanes, which had failed to react with the corresponding iminium derivatives. Dissolution of the hydroxylactams **(92a)** and **(92b)** under acidic conditions produced clean cyclisation within 15 minutes at room temperature to afford the quinolizidine **(93a)** (91 % yield) and indolizidine **(93b)** (93 % yield), respectively.

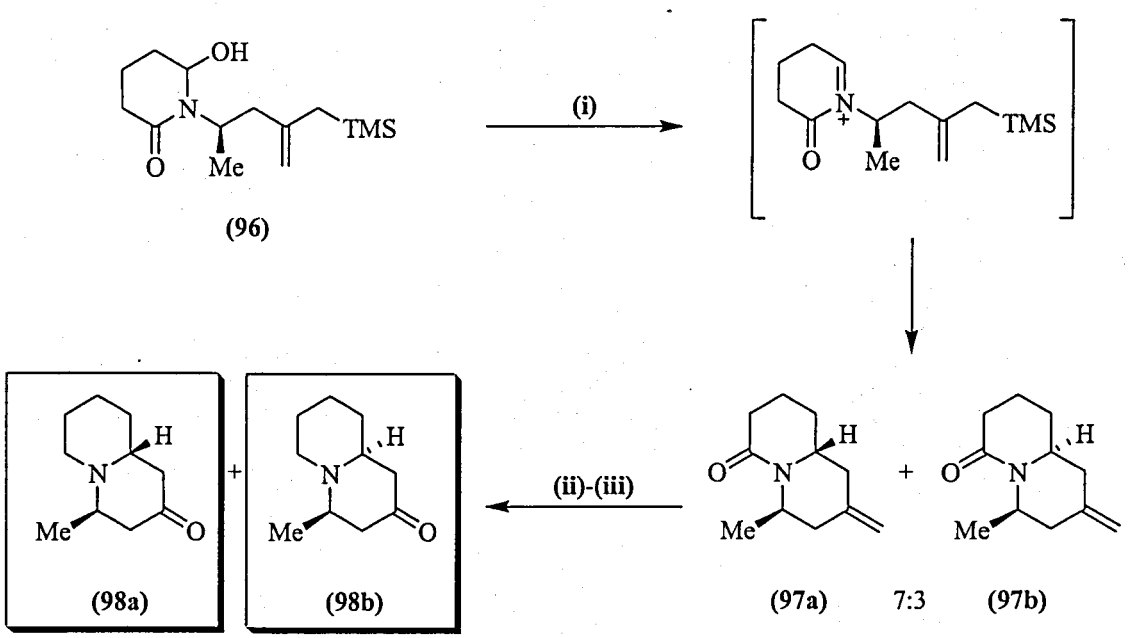
To demonstrate the synthetic opportunities presented by functionalised alkene cyclisation products, the bromoindolizidine intermediate **(93c)** was employed in the efficient synthesis of the *Elaeocarpus* alkaloids, elaeokanine B **(94)** and A **(95)**.

Reduction of **(93c)** followed by treatment with *sec*-butyl lithium and butanal afforded elaeokanine B **(94)** as a 1:1 mixture of diastereoisomers in 86 % yield. Subsequent Swern oxidation provided racemic elaeokanine A **(95)** in 56 % yield.[42]

1.2.3.3. Allylsilanes and Allylstannanes

Allylsilanes are normally exemplary participants in *N*-acyliminium ion cyclisations, the β-effect of the silicon atom allowing excellent regiocontrol with electrophiles at the γ-position. Diastereoselectivity of such reactions however, can be an issue. The use of terminal alkenes with nitrogen-linked allylsilanes has been useful in the synthesis of quinolizidines derivatives such as (+)-myrtine **(98a)** and (–)-epimyrtine **(98b)** as shown below in **Scheme 32.**[43]

Scheme 32:



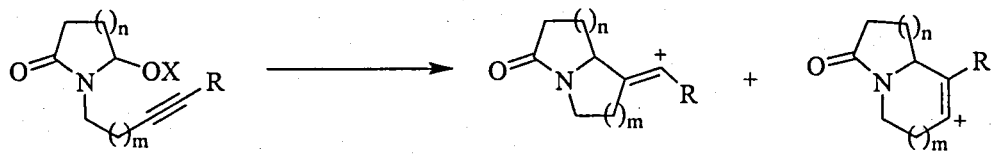
Reagents: **(i)** TFA, DCM, 0 °C 6 h (99 %); **(ii)** $LiAlH_4$, THF, Δ, 2.5 h (99 %); **(iii)** $NaIO_4$, OsO_4, AcOH, 23 h (36 %).

Treatment of the hydroxylactam **(96)** with trifluoroacetic acid gave the bicyclic compounds **(97a)** and **(97b)** as a 7:3 mixture of diastereoisomers in quantitative yield. Reduction of the lactam carbonyl followed by oxidation of the olefinic bond leads to a mixture of (+)-myrtine **(98a)** and (–)-epimyrtine **(98b)**, which were separated by flash chromatography to give the optically pure natural alkaloids.

1.2.4. Reactions of Alkynes

Participation of the alkyne function as a nucleophilic terminator for *N*-acyliminium ion cyclisations has been applied in a wide number of syntheses. Ring closure may proceed through an *exo* **(99)** or *endo* **(100)** vinyl cation intermediate, which is captured by solvent or an available anion as shown in **Scheme 33**.

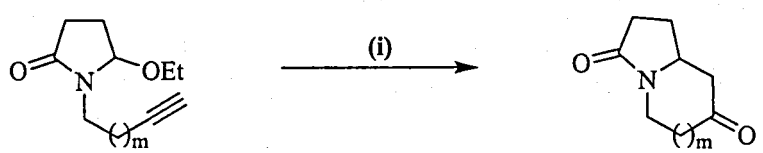
Scheme 33:



(99) **(100)**

In view of the energy difference between these two possible intermediates, in general *endo*-dig cyclisation is strongly favoured even in the case of macrocyclic formation **(102e)** as shown in **Scheme 34**, by the ring closure of ω-alkoxy lactams **(101)** bearing a terminal alkyne.[20]

Scheme 34:



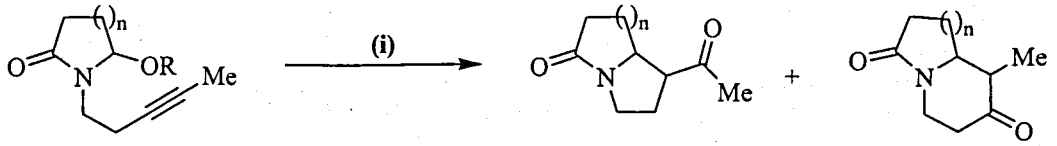
(101) **(102)**

	m	Time	Yield (%)
a	0	??	0
b	1	3d	97
c	2	5d	90
d	3	14d	80
e	10	20d	82

Reagents: **(i)** HCO_2H, Aqueous work up.

Only in the case of electronically unbiased acetylenes such as **(103)** and **(105)**, where ring strain effects influence the order of stability of linear and bent vinyl cations, do different results occur **(Scheme 35)**.

Scheme 35:



(103) n = 1
(105) n = 2

(104a) n = 1
(106a) n = 2

(104b) n = 1
(106b) n = 2

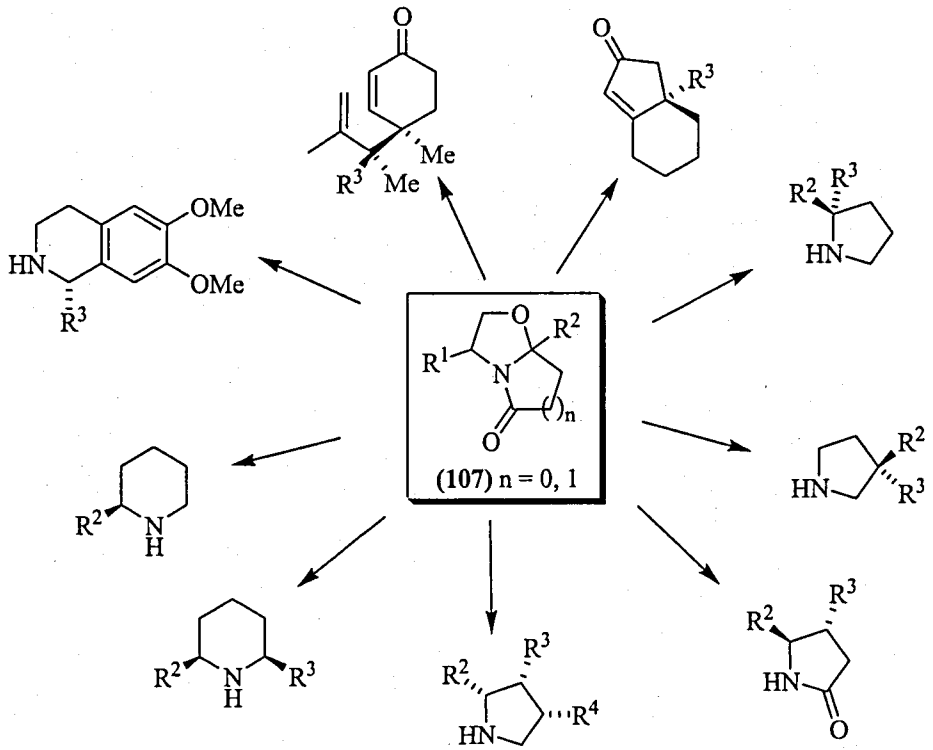
Reagents: **(i)** HCO_2H, 5 d.

Thus in the case of **(103)** (n = 1), *N*-acyliminium cyclisation in formic acid results in a 10:90 mixture of products **(104a)** and **(104b)** in favour of the *endo* regioisomer. In contrast, the one-carbon homologue **(105)** generates mostly the *exo* product **(106a)** in a ratio 85:15, presumably due to the reduced ring strain of the resulting indolizidine **(106a)** in comparison to the *endo* pyrrolizidine product **(106b)**.[44]

1.3. Chiral Bicyclic Lactams as Precursors for Asymmetric Synthesis

The chiral bicyclic lactam **(107)** has proven to be an exceptional building block for the formation of a wide variety of enantiomerically pure carbocycles and heterocycles.

Scheme 36:

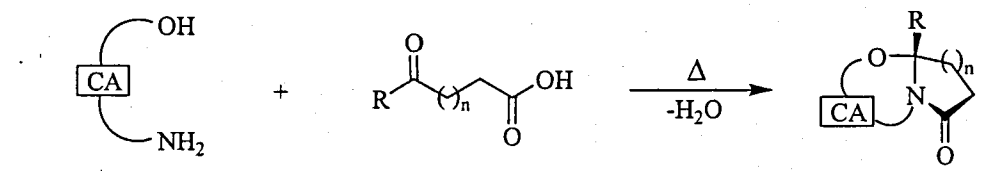


The ability of non-racemic bicyclic lactams to generate new quaternary carbon compounds with excellent control over the absolute stereochemistry, as well as access to a variety of other structural features has been widely utilised in total synthesis.[45]

Two general methods have been developed for the synthesis of bicyclic lactams.[46]

Cyclodehydration of an optically pure amino alcohol **(108)** with a keto acid **(109)** has been used to generate lactams such as **(110)** as shown in **Scheme 37**.

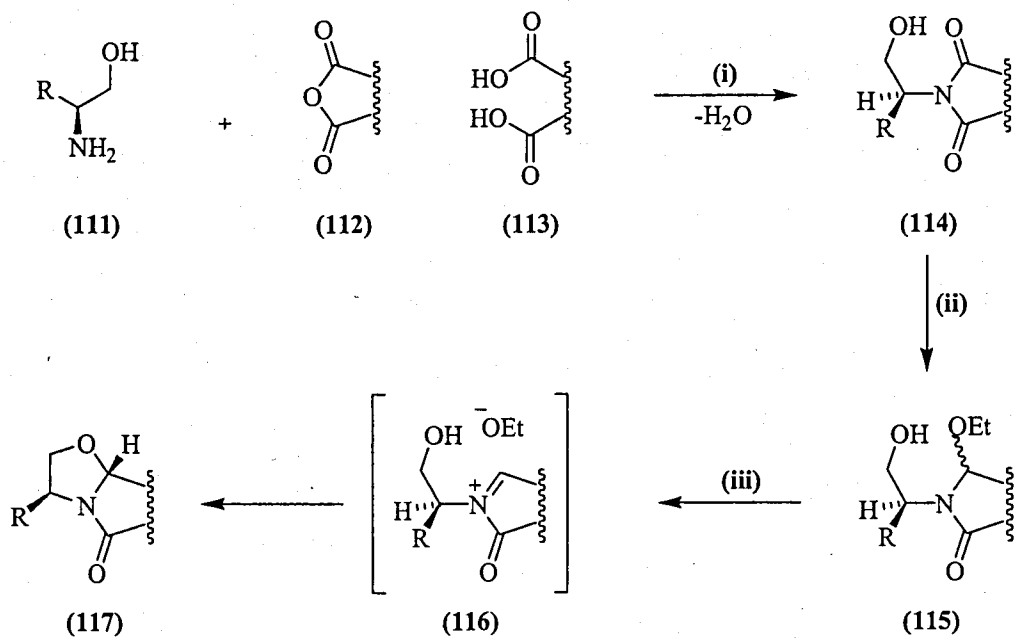
Scheme 37:



(108) CA = Chiral Auxiliary **(109)** n = 1, 2 **(110)** n = 1, 2

The second route, which involves an *N*-acyliminium species, is related to the work by Speckamp **(Scheme 38)**.[13,47]

Scheme 38:



(111) **(112)** **(113)** **(114)** **(115)** **(116)** **(117)**

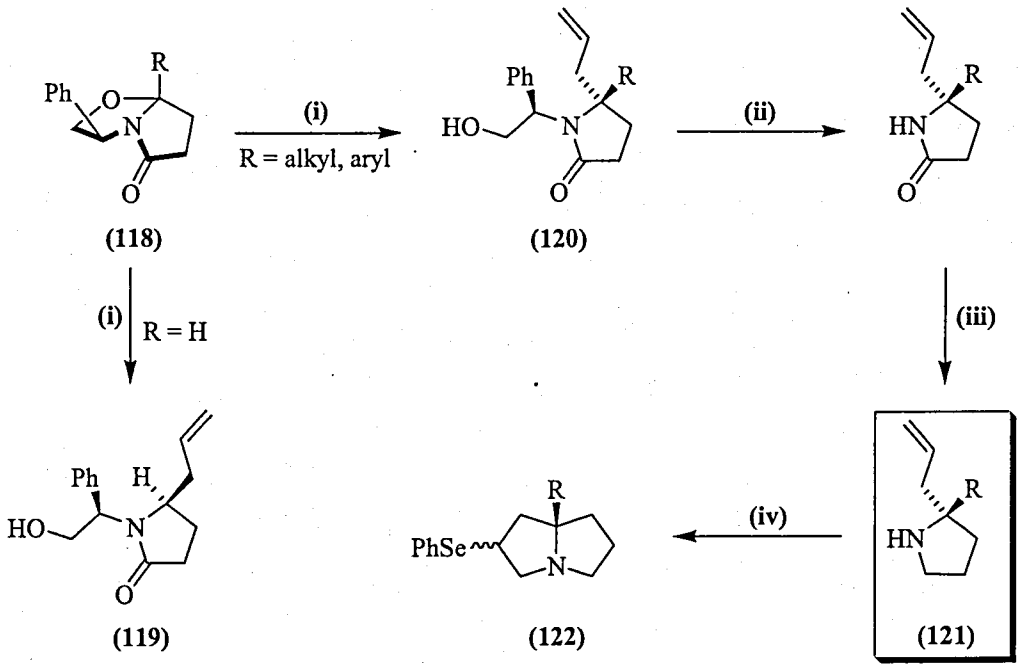
Reagents: **(i)** PhMe, Δ; **(ii)** $NaBH_4$, 6 N HCl, EtOH, 6 h (82 %); **(iii)** Benzene, *p*-TsOH, Δ, 2 h (73 %).

Condensation of an optically pure amino alcohol **(111)** with a cyclic anhydride **(112)** or dicarboxylic acid **(113)** afforded the imide **(114)**. Addition of a hydride source in ethanol generated the corresponding ethoxylactam **(115)**, which upon treatment with acid produced **(117)** *via* the *N*-acyliminium intermediate **(116)**.[46,48]

1.3.1. Construction of Pyrrolidines and Pyrrolidinones

The addition of allylsilanes at the angular position of 5,5-bicyclic lactams **(118)** is possible under strong Lewis acid conditions to furnish the disubstituted pyrrolidinones **(119)** and **(120)** as illustrated below in **Scheme 39**.[49]

Scheme 39:



Reagents: **(i)** Allyltrimethylsilane, $TiCl_4$, DCM, −78 °C to rt; **(ii)** Li, NH_3, EtOH, −33 °C; **(iii)** $LiAlH_4$; **(iv)** $(PhSe)_2$, $(NH_4)_2S_2O_8$, MeCN, Δ.

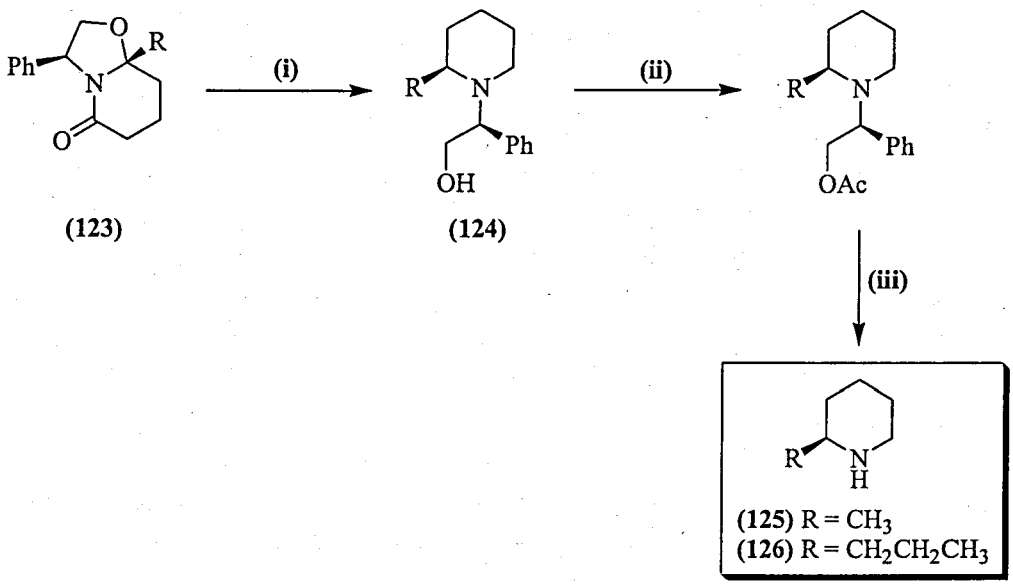
When R was an alkyl or acyl group, the products **(120)** are formed with retention of configuration at the angular position due to the *endo* attack at the bicyclic lactam. Conversely, when the angular substituent was hydrogen, the observed stereochemistry results from *exo* entry to give an inversion of configuration in the product **(119)**. Dissolving metal cleavage of the chiral auxiliary in **(120)** followed by further reduction

generates the pyrrolidine **(121)**, which acts as a key cyclisation precursor to the backbone of the pyrrolizidine alkaloids **(122)**.[49b]

1.3.2. Construction of Piperidines

Due to the success of 5,5-bicyclic lactams **(118)** in the preparation of enantiomerically pure pyrrolidines **(121)**, it was felt this procedure could be applied to the related 5,6-lactams **(123)** in the synthesis of 2-substituted piperidines **(124)** **(Scheme 40)**.

Scheme 40:



(123) **(124)**

(125) R = CH_3
(126) R = $CH_2CH_2CH_3$

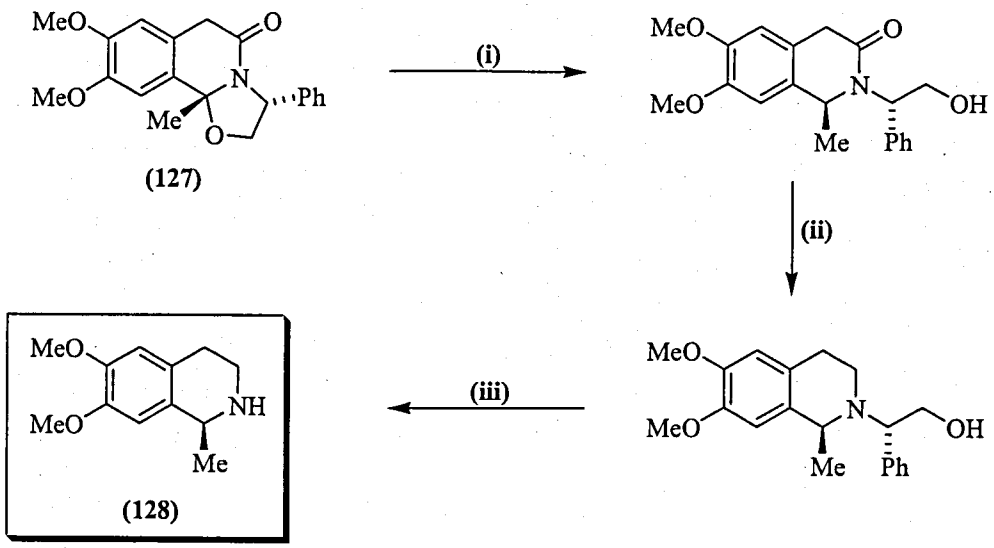
Reagents: (i) Red-Al, THF, Δ; (ii) Ac_2O, DMAP, DCM; (iii) $Pd(OH)_2$, H_2, MeOH.

Red-Al reduction of a variety of alkyl 5,6-bicyclic lactams **(123)** generated the piperidine derivatives **(124)** in good yield and with high diastereoselectivity, with retention of configuration at the angular substituent. The efficient and versatile nature of this piperidine synthesis has been exemplified in the total synthesis of (–)-pipecoline **(125)** and (+)-coniine **(126)**.[50]

1.3.3. Construction of Tetrahydroisoquinolines

Similarly substituted tetrahydroisoquinolines, such as (–)-salsolidine **(128)**, have been synthesised from the appropriately benzo-fused bicyclic lactams **(127)** **(Scheme 41)**, following the previously described reduction protocol for piperidines.[51]

Scheme 41:

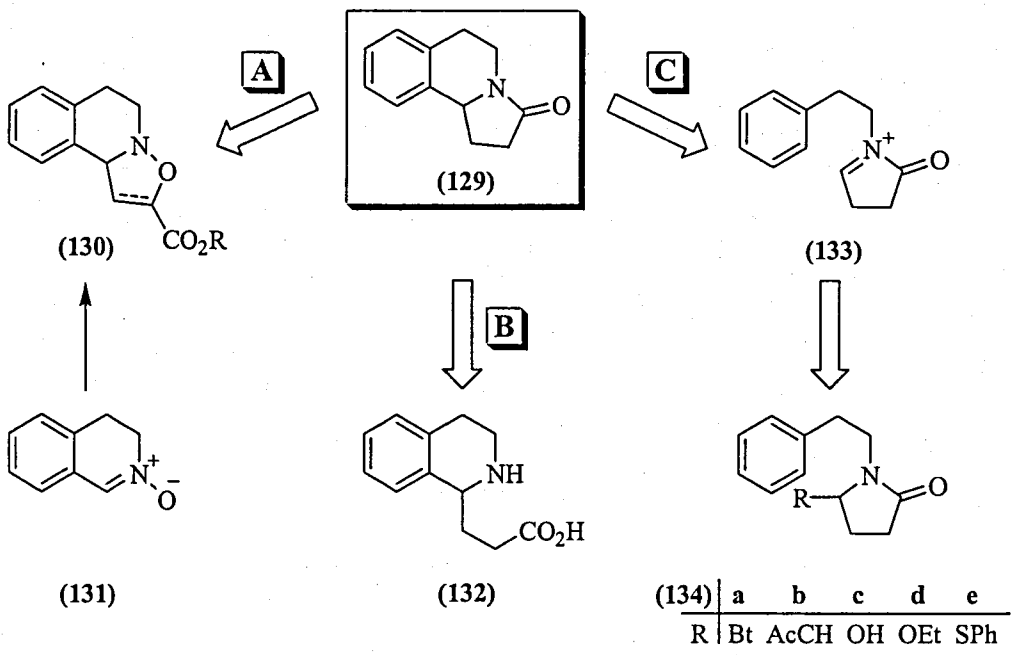


Reagents: **(i)** Red-Al, THF (85 %); **(ii)** $LiAlH_4$ (50 %); **(iii)** Pd/C, H_2, MeOH (97 %).

1.3.4. Construction of Substituted Pyrroloisoquinolines

The pyrroloisoquinoline ring system **(129)** has received significant interest in recent years as a major structural motif of the *Erythrina* alkaloids. Katritzky[52] suggests that there are three major routes reported for the synthesis of such systems **(Scheme 42)**.

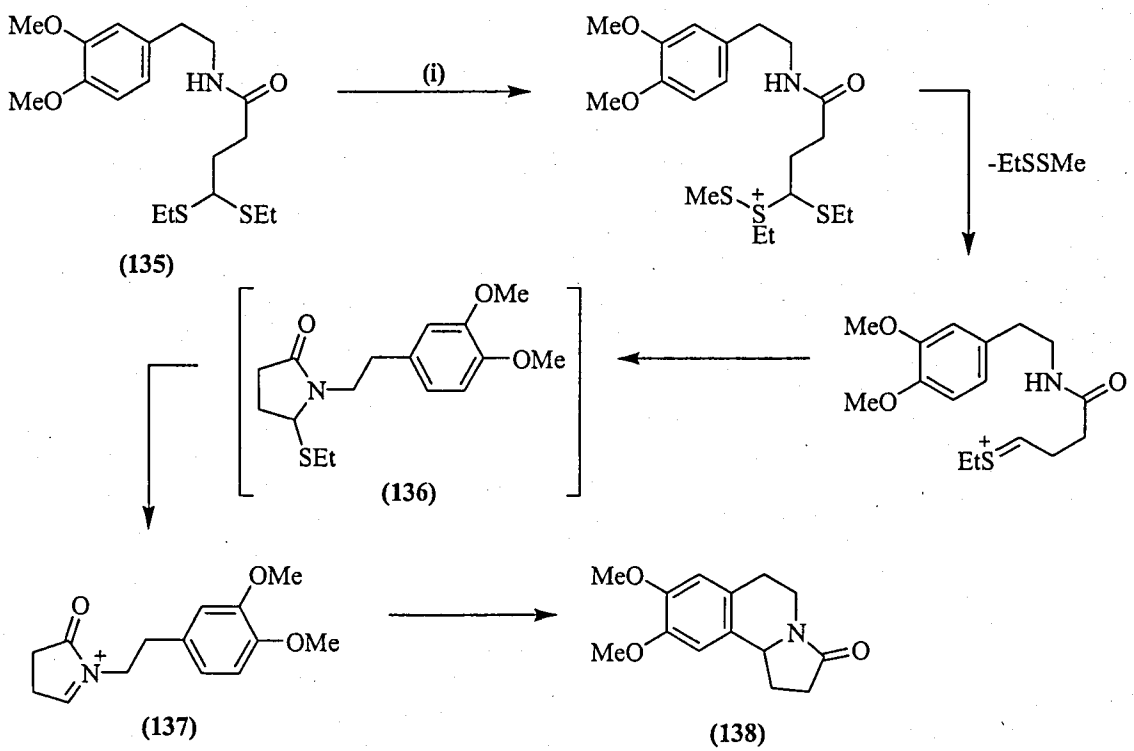
Scheme 42:



Route A involves the carbon-nitrogen bond formation *via* reduction of the intermediate **(130)**, obtained by the 1,3 cycloaddition of nitrones **(131)** with electron deficient alkenes. Burdisso *et al.* have extensively explored this method with studies into the steric interactions of nitrone cycloadditions with ethylenes,[53] whilst Huisgen and Seidl have investigated reactions with various acetylenes to generate functionalised pyrroloisoquinolines.[54] Orito *et al.* reported the synthesis of these templates by intramolecular condensation of intermediate **(132)** with the elimination of water as shown in route B.[55] Katritzky *et al.* established novel methodology by utilising route C, which involved cyclisation of an *N*-acyliminium cation **(133)** generated by loss of a benzotriazolyl anion **(134a)** in the presence of titanium tetrachloride.[52] Other research groups have explored this route, involving carbon-carbon bond formation from cyclisation of *N*-acyliminium ions generated by protonation of an enamide **(134b)**[56] or by elimination of a hydroxy **(134c)**,[57] ethoxy **(134d)**[58] or phenylthio group **(134e)**.[59]

Padwa *et al.* have recently reported the synthesis of alkyl-thio-substituted five-membered lactams **(136)** by treatment of amido-substituted thioacetals **(135)** with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) as shown in **Scheme 43**.[60]

Scheme 43:

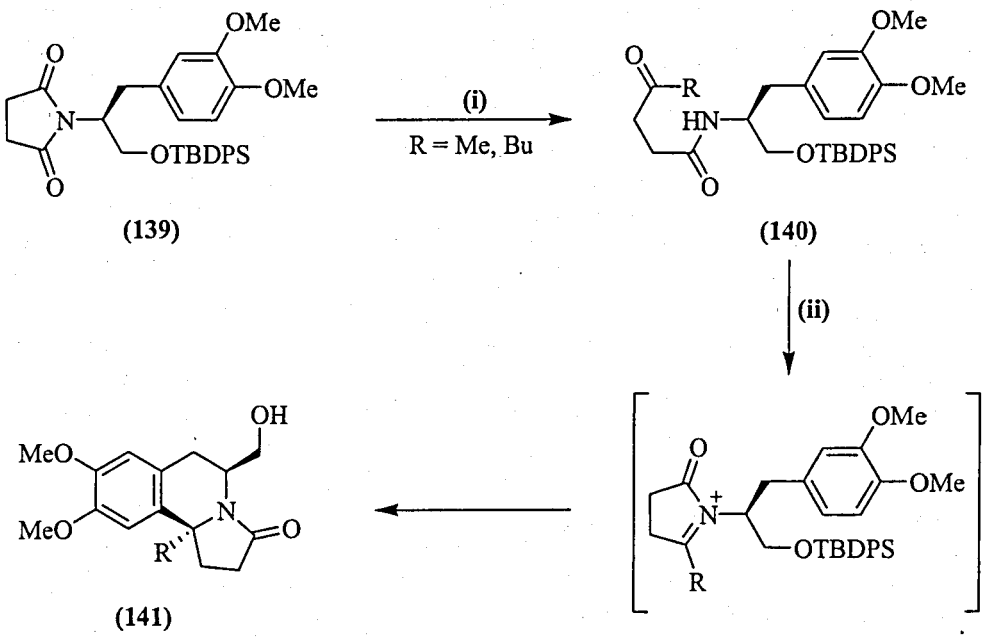


Reagents: (i) DMTSF (2 equiv), DCM, 12 h (64 %).

Such lactams **(136)** act as transient intermediates and upon further reaction with DMTSF, generate an *N*-acyliminium ion **(137)** that undergoes subsequent cyclisation with the tethered aromatic ring to produce the pyrroloisoquinoline template **(138)**.

Additional methods include the stereoselective synthesis of pyrrolo[2,1-*a*]isoquinolines **(141)** by Lete *et al. via* a tandem organolithium addition/*N*-acyliminium ion cyclisation as shown in **Scheme 44**.[61]

Scheme 44:

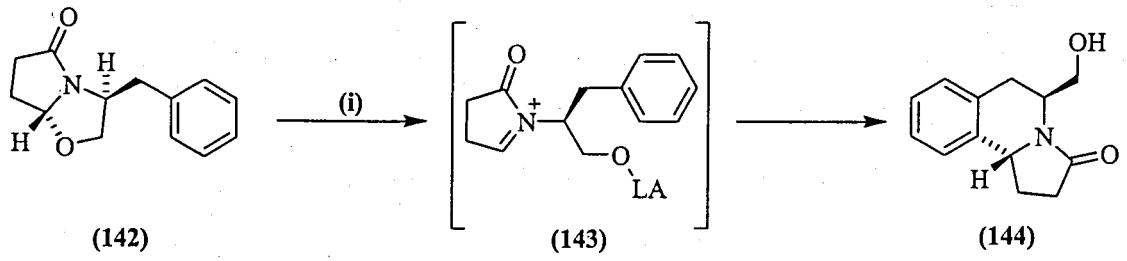


Reagents: **(i)** RLi, THF, −78 °C, 6 h; **(ii)** $BF_3.OEt_2$, DCM, Δ, 4 d.

The chiral succinimide **(139)** was reacted with organolithiums (methyl or butyl lithium) to generate the corresponding oxoamide **(140)**, which upon treatment under Lewis acid conditions undergoes stereoselective cyclisation to afford the *trans*-pyrroloisoquinolines **(141)** with no trace of the related *cis*-diastereoisomer.

More recently, Allin *et al.* reported a novel, highly stereoselective approach to the tricyclic core of the erythrinane ring system in which the key step involved an asymmetric intramolecular *N*-acyliminium mediated cyclisation.[62] Treatment of the bicyclic lactam **(142)** with the Lewis acid activator titanium tetrachloride gave the target pyrroloisoquinoline ring system **(144)** as a single diastereoisomer, with inversion of stereochemistry at the newly formed chiral centre **(Scheme 45)**.

Scheme 45:



(142) (143) (144)

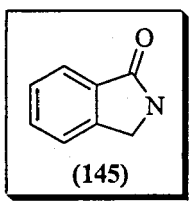
Reagents: (i) Lewis acid, DCM, −10 °C, 20 h.

It is presumed that the cyclisation, to yield the product **(144)** proceeds *via* the *N*-acyliminium ion intermediate **(143)**.

1.4. Applications of *N*-Acyliminium Ions in Alkaloid Synthesis

The formation of optically pure heterocyclic templates from non-racemic substrates is now a standard, and widely applied technique in the synthesis of a number of therapeutically active natural and unnatural compounds. The applications of functionalised chiral bicyclic lactams as useful precursors for asymmetric synthesis has been described in preceding sections, and the *N*-acyliminium cyclisation has been applied with excellent success in the synthesis of a wide range of both simple and complex chiral polycyclic alkaloids.

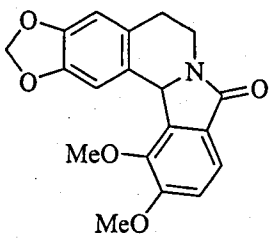
1.4.1. Stereoselective Synthesis of the Isoindolinone Ring System



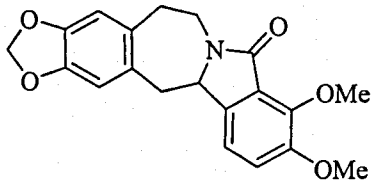
(145)

The isoindolinone ring system **(145)** is an interesting synthetic target due to actual and potential biological activities of many of its derivatives.[63] In addition, the fused heterocyclic isoindolinone moiety is present in several naturally occurring chiral alkaloids; including lennoxamine[64] **(147)** and neuvamine[65] **(146)**, which was the first

isoindolisoquinoline isolated from the natural source, the *Berberis Darwinii Hook* found in Southern Chile.



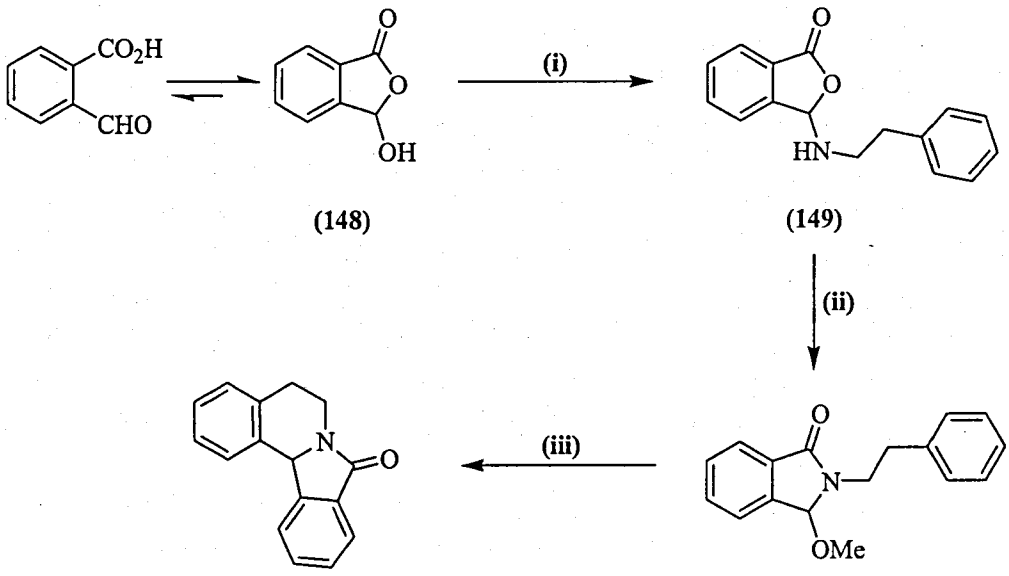
(146)



(147)

Heaney and Shuhaibar reported the use of α-methoxyisoindolones **(150)** as useful acyliminium precursors in the synthesis of the isoindolinone template **(151)** **(Scheme 46)**.[66] The aminol lactone **(149)** was formed in quantitative yield from the reaction of β-phenylethylamine with 3-hydroxyphthalide **(148)**, which upon treatment with thionyl chloride followed by methanol gave the methoxyisoindolone intermediate **(150)**. Treatment of **(150)** with titanium tetrachloride in dichloromethane gave the expected isoindoloisoquinoline derivative **(151)** in quantitative yield and constitutes a novel synthesis of the nuevamine skeleton **(146)**.

Scheme 46:



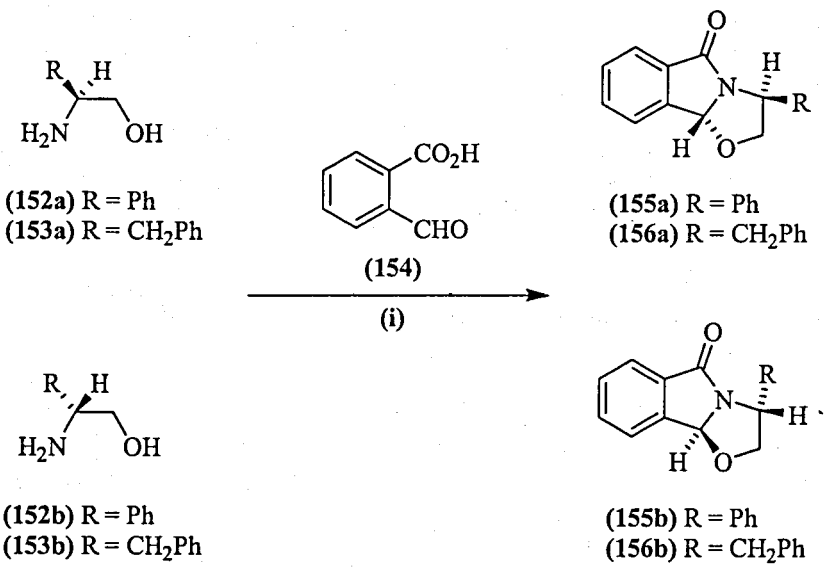
(148) (149) (150) (151)

Reagents: **(i)** β-Phenylethylamine, PhMe, Δ, 4 h; **(ii)** $SOCl_2$ then MeOH; **(iii)** $TiCl_4$, DCM, −78 °C, 2 h.

Several other research groups have reported the synthesis of chiral ring-fused isoindolinone targets *via* *N*-acyliminium ion cyclisations, however few have addressed the issue of stereocontrol during the reaction. Allin *et al.* have recently developed a facile new two-step procedure for the synthesis of chiral ring-fused isoindolinones, with extremely high levels of diastereoselectivity, from readily available starting materials.[67]

Condensation of enantiomerically pure amino alcohols phenylglycinol **(152a/b)** and phenylalaninol **(153a/b)** with 2-formylbenzoic acid **(154)** produced the desired *trans*-tricyclic γ-lactams **(155a/b)** and **(156a/b)** respectively, with excellent diastereoselectivity **(Scheme 47, Table 1)**.[68]

Scheme 47:



Reagents: (i) PhMe, Δ.

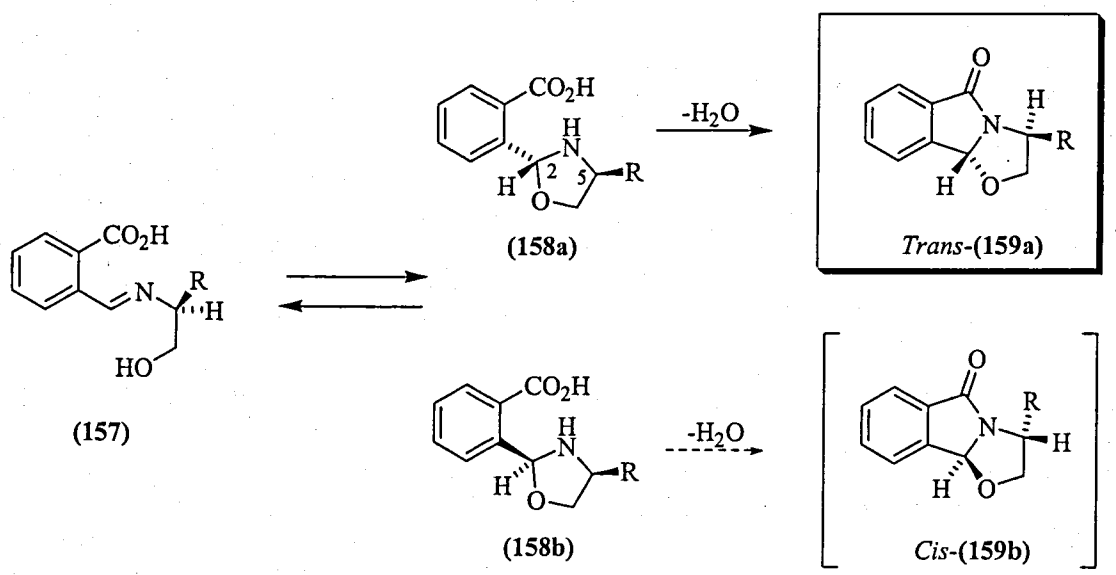
Table 1:

Substrate	R	Yield (%)	Diastereoselectivity
(152a)	Ph	70	**(155a)**, exclusive
(152b)	Ph	70	**(155b)**, exclusive
(153a)	CH_2Ph	72	**(156a)**, exclusive
(153b)	CH_2Ph	71	**(156b)**, exclusive

A mechanism has been proposed by Allin to explain the stereochemical outcome of the reaction outlined in **Scheme 48**.[68] The hydroxyimine **(157)** could undergo a reversible

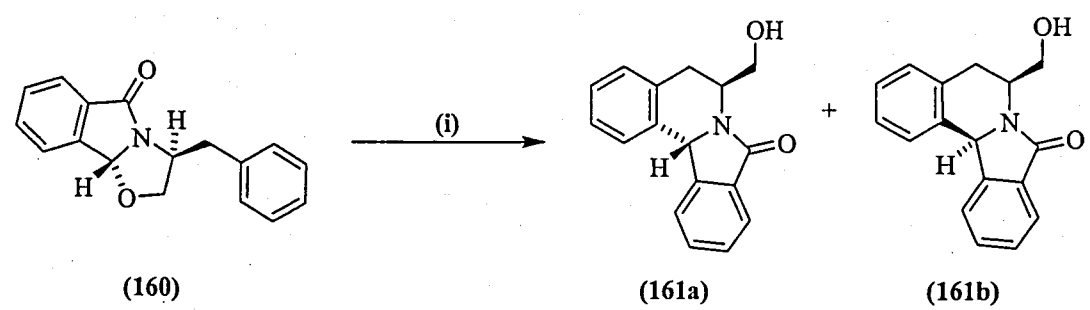
cyclisation to produce both the *trans*-**(158a)** and *cis*-**(158b)** oxazolidines (referring to the stereochemistry at C-2 and C-5). Ring closure of **(158a)** with the loss of water yields the observed *trans*-tricyclic lactam **(159a)**. The cyclisation to **(159b)** however, appears from simple molecular modelling studies to be highly disfavoured due to the remote orientation of the reactive functional groups.

Scheme 48:



The potential of tricyclic lactam **(160)** to act as a suitable precursor for intramolecular *N*-acyliminium ion cyclisation was demonstrated upon treatment with a Lewis acid activator. Nucleophilic attack of the aromatic substituent formed the desired tetracyclic isoindolinone target as a mixture of two diastereoisomers **(161a/b) (Scheme 49).**[67]

Scheme 49:



Reagents: **(i)** Lewis acid, DCM, −10 °C, 20 h.

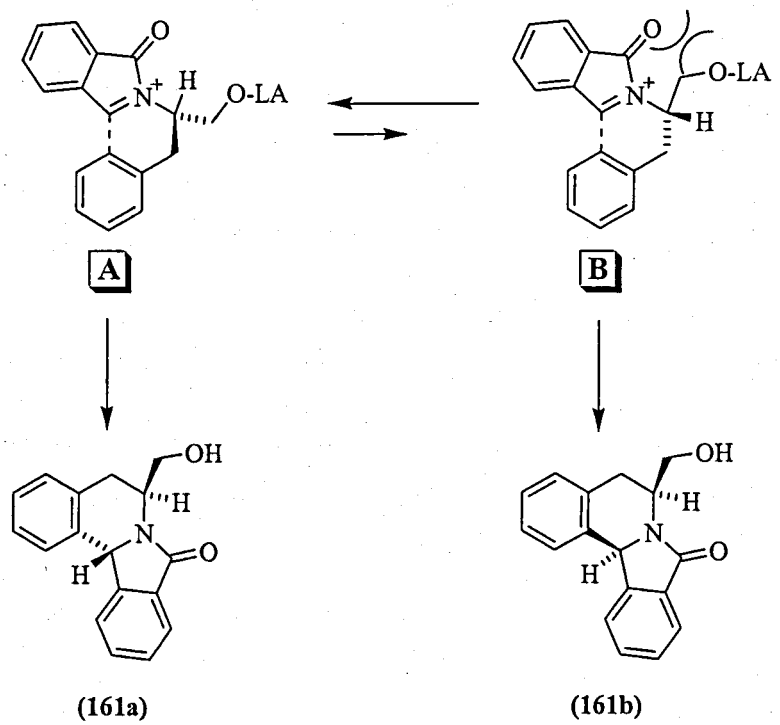
An extremely high degree of diastereoselectivity can be achieved in this reaction as displayed in **Table 2**, particularly with trimethylsilyl triflate as the Lewis acid activator.

Table 2:

Entry	Activator	Yield (%)	(161a) : (161b)
a	$SnCl_4$	98	2:1
b	$TiCl_4$	93	2:1
c	$BF_3.OEt_2$	99	3:1
d	H_2SO_4	80	6:1
e	TMSOTf	97	≥49:1

The stereochemical outcome of the reaction was rationalised by invoking the conformational models highlighted in **Scheme 50**. In transition state A, leading to the favoured diastereoisomer **(161a)**, the carbonyl moiety would be "eclipsed" in a 1,3-fashion by the hydrogen atom at the chiral centre.

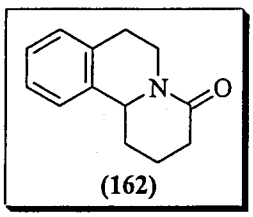
Scheme 50:



In the alternative transition state B (leading to the minor diastereoisomer **(161b)**) however; an unfavourable 1,3-interaction between the carbonyl group and the more bulky Lewis acid complexed oxymethyl group exists. The possibility of an additional seven-membered chelate generated from the amide oxygen atom and the alkoxy group

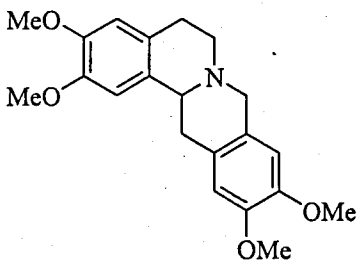
with a metal counter-ion, could make transition state B initially seem more favourable. However from consideration of the results shown in **Table 2**, it is clear that if chelation does occur, it leads to lower levels of diastereoselectivity probably due to an increased contribution of a chelated transition state similar in structure to B.[67]

1.4.2. Stereoselective Synthesis of Benzoquinolizidine Derivatives

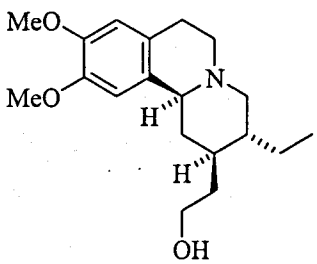


(162)

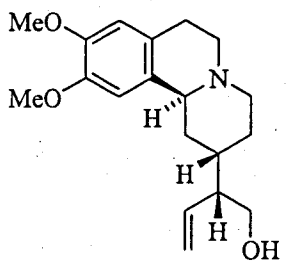
The benzo[*a*]quinolizidine ring system **(162)** is of considerable significance since this heterocyclic motif is present within a wide range of pharmacologically active compounds. Some examples include the protoberberine alkaloid xylopinine **(163)**,[69] which has shown potential as an antimicrobial agent whilst (–)-protoemetinol **(164)**[70] and more recently alangine **(165)**,[71] isolated from *Alangium lamarckii* act as potent inhibitors of HIV-1 reverse transcriptase.



(163)



(164)

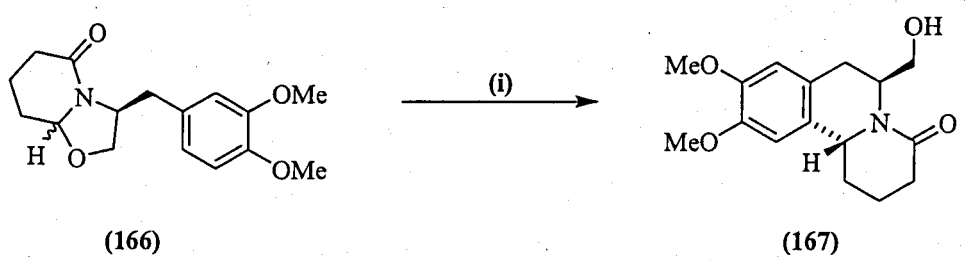


(165)

Based on their stereoselective approach to the pyrroloisoquinoline[62] and isoindoloinone[67] ring systems, Allin *at al.* envisaged that a suitably bicyclic lactam **(166)** could act as a precursor toward the tetrahydroisoquinoline core **(162)** of such compounds. This approach involved the introduction of asymmetry during the key ring-forming step *via* an *N*-acyliminium intermediate **(Scheme 51)**.[72] Synthesis of the desired bicyclic lactam **(166)** followed the method previously described by Amat.[73] Separation of the lactam diastereoisomers and subsequent cyclisation upon treatment

with titanium tetrachloride produced exclusively the *trans*-product **(167)** in both cases, evidence to support the proposed mechanism involving an *N*-acyliminium intermediate.

Scheme 51:

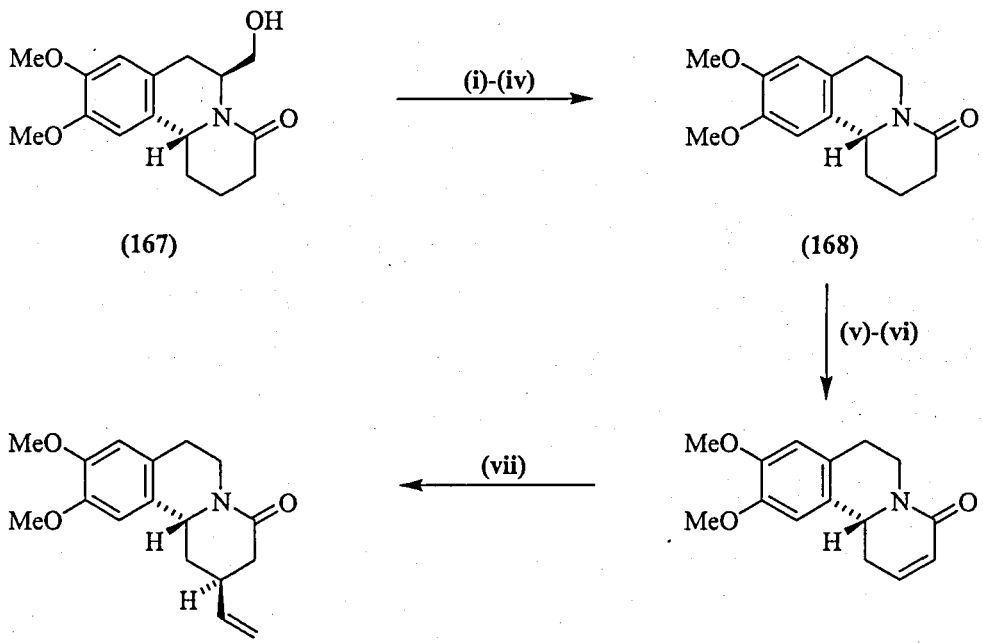


(166) **(167)**

Reagents: **(i)** $TiCl_4$, DCM, −10 °C, 20 h (65 %).

In collaboration with Amat, Allin *et al.* developed complimentary routes to functionalised benzoquinolizidine derivatives that allow the preparation of targets with complete control of relative stereochemistry.[74] The first method is through conjugate addition to an α,β-unsaturated tetrahydroisoquinoline substrate **(169) (Scheme 52).**

Scheme 52:

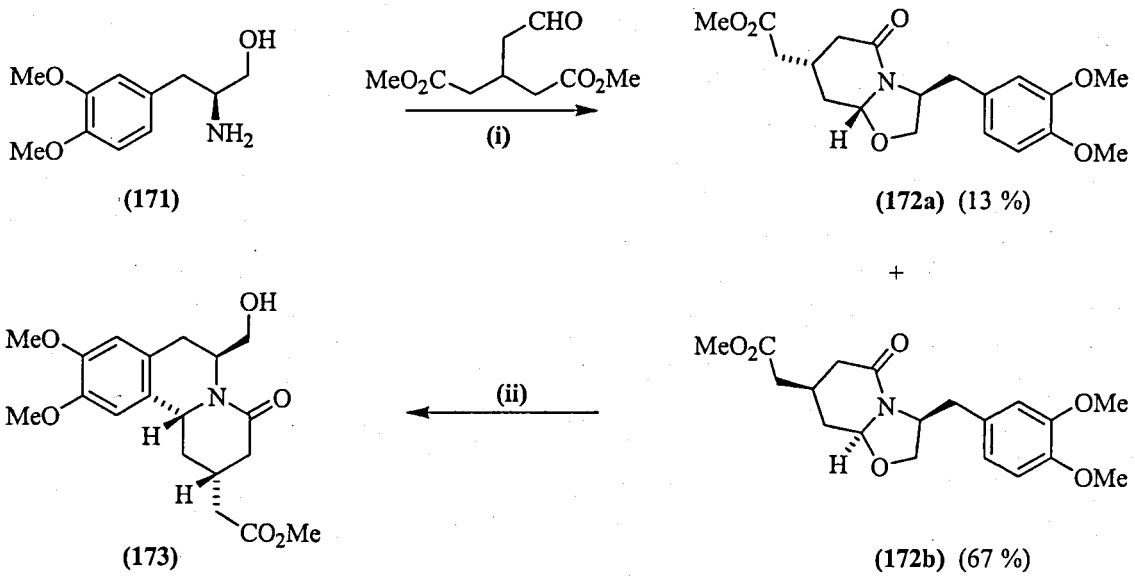


(167) **(168)** **(169)** **(170)**

Reagents: **(i)** IBX, DMSO, 24 h (70 %); **(ii)** $NaClO_2$, NaH_2PO_4, MeCN, *t*-BuOH, H_2O, 18 h (86%); **(iii)** $(PhSe)_2$, PBu_3, DCM, 18 h (76 %); **(iv)** *n*-Bu_3SnH, AIBN, PhMe, 80 °C, 2 h (81 %); **(v)** LDA, PhSeBr, THF, −78 °C, 24 h; **(vi)** $NaIO_4$, $NaHCO_3$, MeOH, H_2O, 18 h (61 %); **(vii)** Vinyl MgBr, CuCN, TMSCl, THF, −78 °C, 24 h (67 %).

Removal of the hydroxymethyl substituent present in the tetrahydroisoquinoline skeleton **(167)** was accomplished in four steps *via* the acylselenide followed by radical decarbonylation **(Scheme 52)**. Treatment of **(168)** with lithium diisopropylamine and phenylselenylbromide followed by oxidation, generated the α,β-unsaturated substrate **(169)**, which allowed conjugate addition of vinylmagnesium bromide to form the desired product as the single *trans*-diastereoisomer **(170)** as observed in alangine **(165)**.

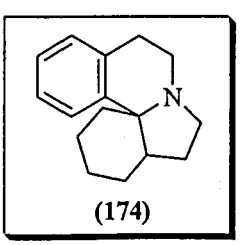
Scheme 53:



Reagents: **(i)** PhMe, Δ, 24 h (80 %); **(ii)** $TiCl_4$, DCM, −78 °C, 3 d (36%).

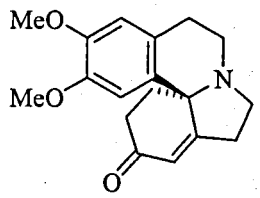
The alternative route that incorporates functionality at an earlier stage, involved the stereoselective cyclocondensation of a chiral amino alcohol **(171)** with the prochiral glutarate as shown in **Scheme 53**. This approach lead to the formation of separable functionalised bicyclic lactams **(172a/b)**. The major *N*-acyliminium precursor **(172b)**, on treatment with titanium tetrachloride gave the benzoquinolizidine derivative **(173)** containing *cis* relative stereochemistry as required in protoemetinol **(164)**.[74]

1.4.3. Stereoselective Synthesis of the *Erythrina* Alkaloids

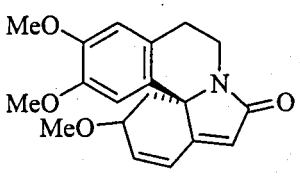


(174)

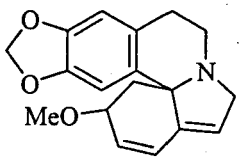
The genus *Erythrina* is common in tropical and sub-tropical regions and the alkaloids have been used in indigenous medicine.[75] Members of the *Erythrina* family have shown curare-like and hypnotic activity, and a number of pharmacological effects including sedative, hypotensive, neuromuscular blocking and central nervous system activity have been associated with its tetracyclic template **(174)**,[76] examples of which include (–)-3-demethoxyerythratidinone **(175)**, erysotramidine **(176)** and erythraline **(177)**.



(175)



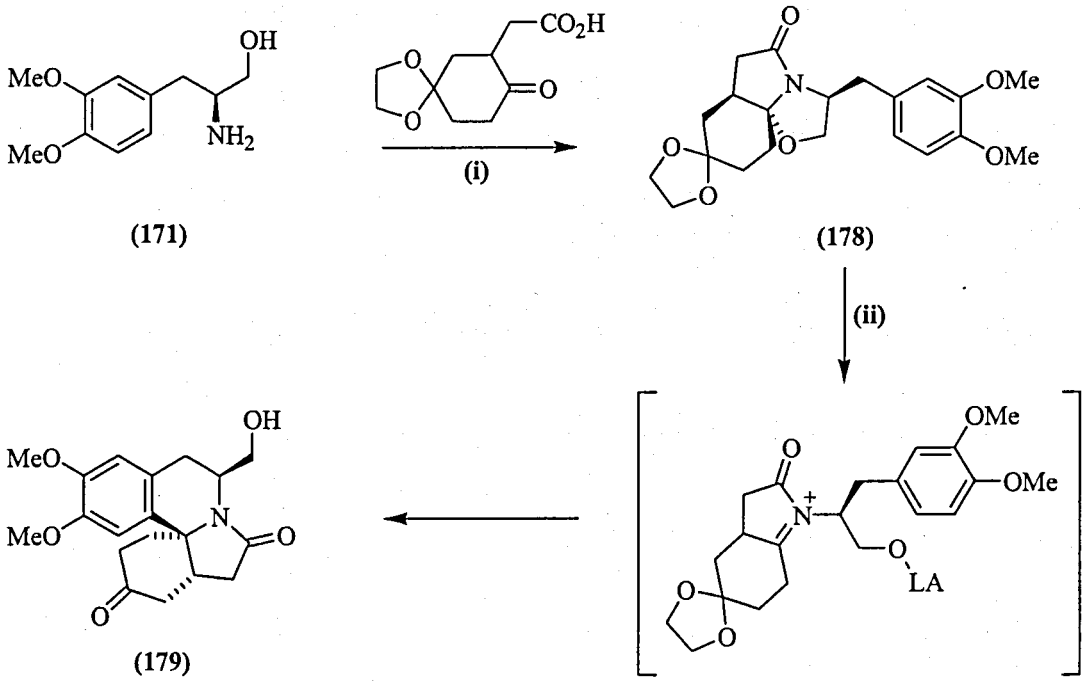
(176)



(177)

Recently, Allin *et al.* have extended their initial methodology toward the pyrrolo isoquinoline ring system, a key structural subunit of the *Erythrina* alkaloids, towards a functionalised tetracyclic core **(179)** in a highly stereoselective manner (**Scheme 54**).[77]

Scheme 54:



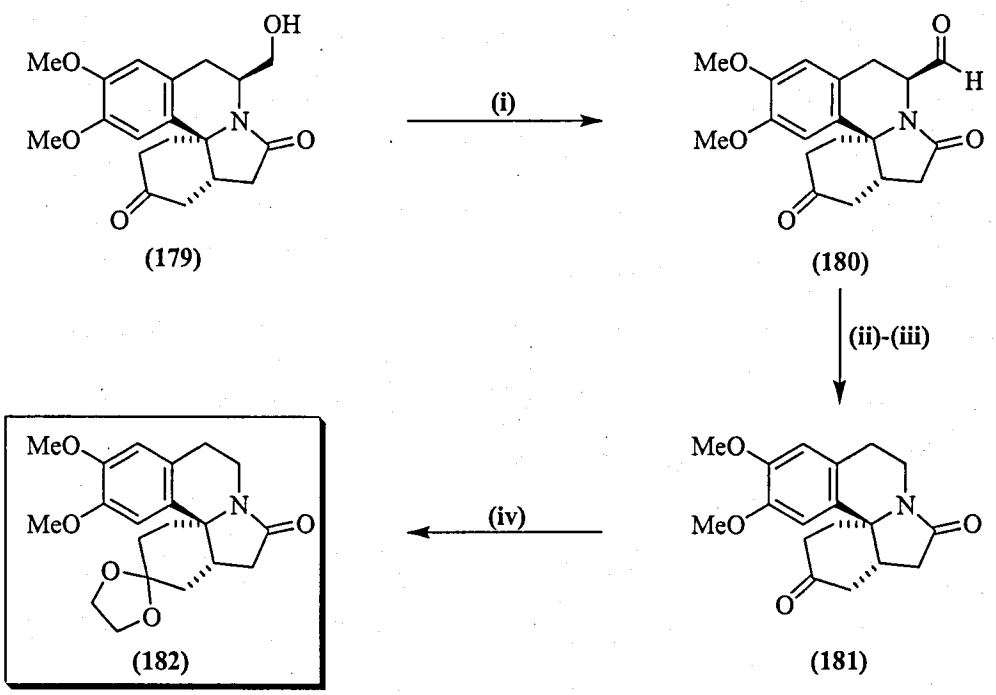
(171) **(178)** **(179)**

Reagents: **(i)** PhMe, Δ, 48 h (63%); **(ii)** $TiCl_4$, DCM, −78 °C, 20 h (92 %).

The formation of the required tricyclic lactam **(178)** followed similar methodology to that previously described by Allin *et al*,[62] with the condensation of a suitable β-amino alcohol **(171)** and the required keto-acid substrate under Dean-Stark conditions in 63 % yield. Treatment of the lactam **(178)** with an excess of titanium tetrachloride at low temperature produced the key tetracyclic product **(179)** with deprotection of the ketal protecting group in 92 % yield and with excellent diastereoselectivity.

Removal of the pendant hydroxymethyl auxiliary from template **(179)** was achieved in a three-step procedure by initial oxidation of the primary alcohol with Dess-Martin periodinane to provide aldehyde **(180)** **(Scheme 55)**. The aminoketone **(181)** was then completed by a rhodium-catalysed decarbonylation protocol to access the corresponding enamide and its subsequent reduction by catalytic hydrogenation.[77]

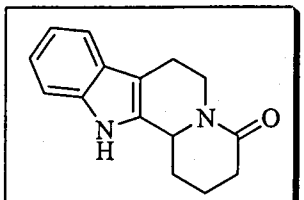
Scheme 55:



Reagents: **(i)** Dess-Martin periodinane, DCM (93 %); **(ii)** $Rh(PPh_3)_2(CO)Cl$, dppp, *p*-xylene, Δ, 4 d (61 %); **(iii)** Pd/C, H_2, EtOH (79 %); **(iv)** Ethylene glycol, *p*-TsOH, PhMe, Δ.

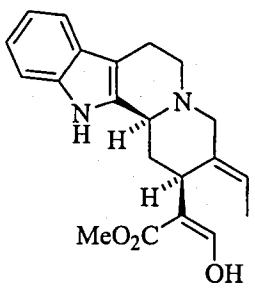
The formal asymmetric synthesis of (–)-3-demethoxyerythratidinone **(175)**, the natural enantiomer isolated from *Erythrina lithosperman* in 1973 by Barton,[78] was completed by re-protection of the ketone using ethylene glycol to give intermediate **(182)**[77] which had been converted by others to the natural product in a four-step sequence.[79]

1.4.4. Stereoselective Synthesis of Indole Alkaloids

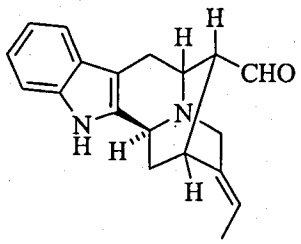


(183)

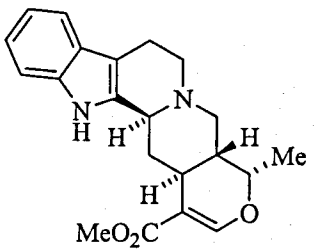
The indolo[2,3-*a*]quinolizine ring system **(183)** is of great interest since this heterocyclic skeleton is found within a plethora of highly bioactive indole alkaloids, including geissoschizine **(184)**,[80] vellosimine **(185)**[81] and ajmalicine **(186)**.[82]



(184)



(185)

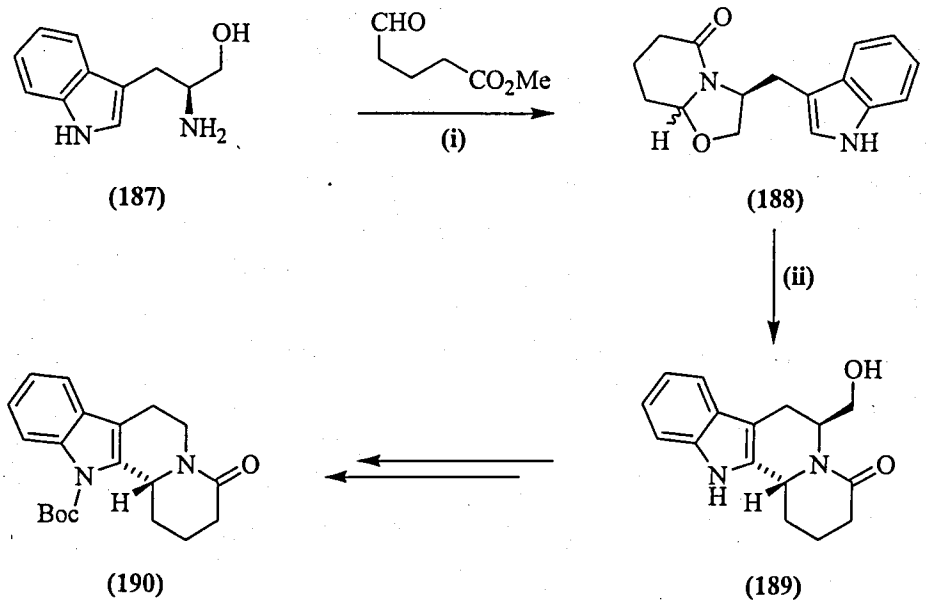


(186)

Recent approaches to the construction of this heterocyclic target system by other groups have included the Mannich reaction,[83] Bischler-Napieralski reaction,[84] Fischer indole synthesis[85] and the Pictet-Spengler reaction.[86] Allin *et al.* have recently developed a stereoselective synthesis of the indolo[2,3-*a*] quinolizine ring system **(183)**,[87] based on the general approach to a range of non-racemic heterocycles, as detailed in this section.

Synthesis of the required bicyclic lactam **(188)** followed the method previously used by Allin. Dean-Stark condensation of (*S*)-tryptophanol **(187)** with an appropriate keto-ester for 48 hours, which under these reaction conditions generated the expected bicyclic lactam in 69 % yield as a 5:1 mixture of diastereoisomers **(188)** **(Scheme 56)**. Treatment of the mixture of isomers **(188)** with hydrochloric acid in ethanol at room temperature for 20 hours gives an excellent 95 % yield of the expected *trans*-cyclic product **(189)** as a single diastereoisomer.[87]

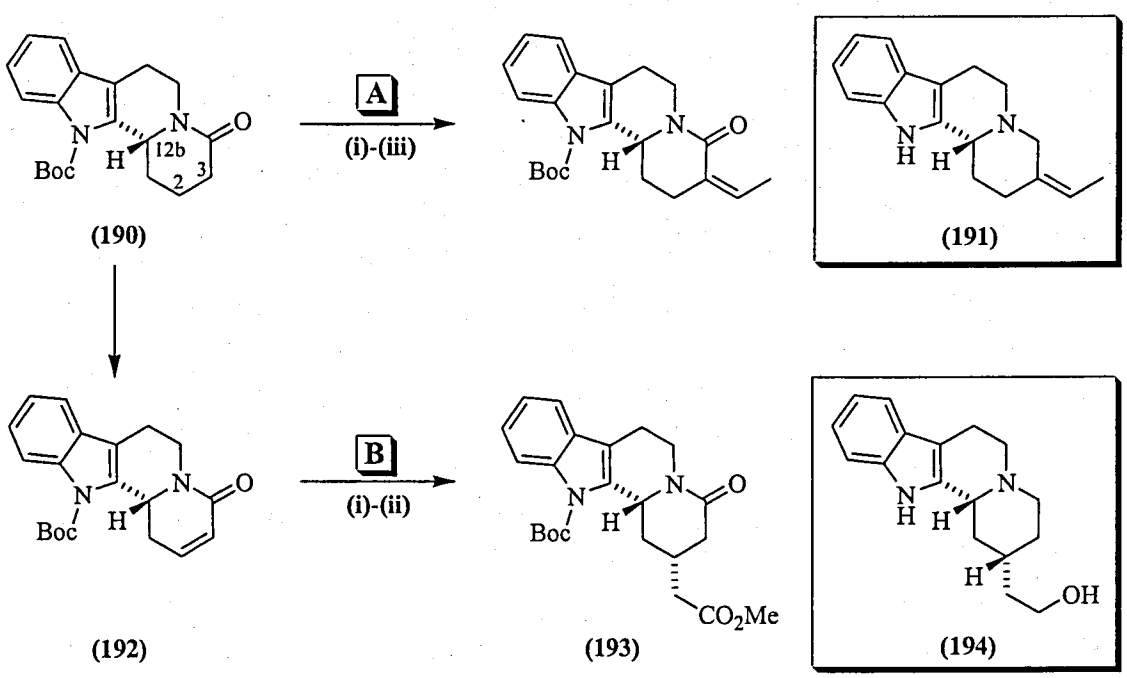
Scheme 56:



Reagents: **(i)** PhMe, Δ, 48 h (69 %); **(ii)** 2 M HCl, EtOH, 20 h (95 %).

From this structure **(189)** the key building block **(190)** is easily generated, which due to the presence of the lactam carbonyl allows several avenues for functionalisation *en route* to natural product targets **(Scheme 57)**.

Scheme 57:

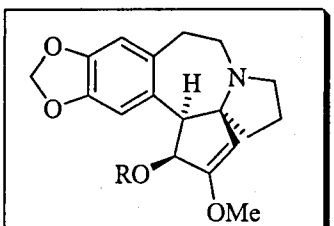


Reagents: **A (i)** LDA, MeCHO, THF, −78 °C, 24 h; **(ii)** Et_3N, MsCl, DCM, 3 h; **(iii)** DBN, THF, 16 h (65 %); **B (i)** Methyl-1,3-dithiolane-2-carboxylate, *n*-BuLi, THF, −78 °C, 24 h (47 %); **(ii)** $NiCl_2$, $NaBH_4$, THF/MeOH, 4 h (73 %).

Route A utilises the formation of a lithium enolate to introduce an ethylidene substituent at the 3-position *via* a three-step aldol/elimination procedure. This has been applied in the total asymmetric synthesis of (*R*)-(+)-deplancheine **(191)**, an alkaloid isolated from the New Caledonian plant *Alstonia deplanchei*, with an *e.e.* >95 %.[88]

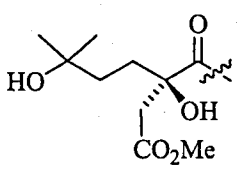
Alternatively, the introduction of α,β-unsaturation to give **(192)** allows access to the 2-position *via* Michael addition, as demonstrated in route B with the asymmetric synthesis of the indole alkaloid derivative (+)-12*b*-epidevinylantirhine **(194)**.[89] Upon the addition of lithiated methyl 1,3-dithiolane-2-carboxylate to substrate **(192)**, the exclusive formation of the addition product **(193)** was observed as a single diastereoisomer in 47 % yield. Further transformation involving desulfurisation, deprotection and reduction completed the desired target **(194)** displaying *cis* relative stereochemistry at positions 2 and 12b.

1.4.5. Stereoselective Synthesis of the *Cephalotaxus* Alkaloids

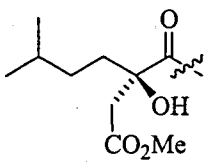


(195) R = H Cephalotaxine

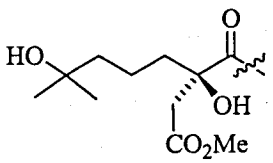
R =



(196) Harringtonine



(197) Deoxyharringtonine



(198) Homoharringtonine

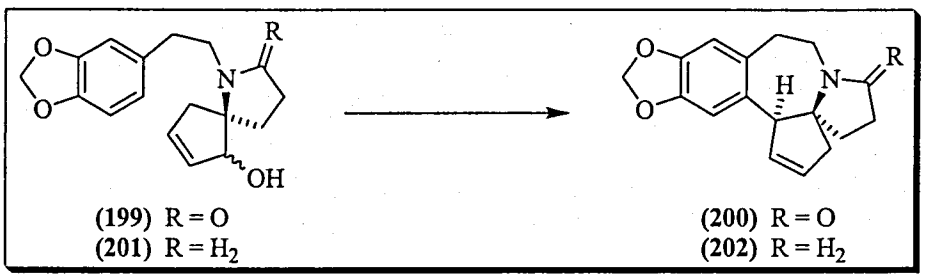
We recognised that an extension of the methodology used in the construction of the isoindolinone, benzoquinolizidine, erythrinane and indolo[2,3-*a*]quinolizine ring systems would be its application toward the synthesis of (–)-caphalotaxine **(195)**, the parent compound of the *Cephalotaxus* alkaloids.

Interest in the members of the *Cephalotaxus* alkaloids has remained high since their isolation in 1963 by Paudler[90] and subsequent characterisation in the 1960s and 1970s.[91]

The evergreen plum-yews of the genus *Cephalotaxus*, which are indigenous to south-east Asia, produce a range of structurally related polycyclic homoerythrina alkaloids of which (–)-cephalotaxine **(195)** is the most abundant member.[92] Whilst cephalotaxine itself is largely biologically inactive, significant interest has been paid to its ester derivatives, especially harringtonine **(196)**, deoxyharringtonine **(197)** and homoharringtonine **(198)**, which have been found to be highly effective for the treatment of acute human leukemia and are currently undergoing advanced clinical trials.[93] More recently, homoharringtonine **(198)** has shown potential as a potent agent against strains of the chloroquinine-resistant *Plasmodium f.* malaria parasite.[94]

The natural source of this alkaloid remains limited and some species of the Asian shrub from which it is extracted are now endangered. For these reasons, this structurally unique class of alkaloids, of which a 1-azaspiro[4.4]-nonane moiety fused to a benzazepine system is a common feature, have stimulated a large number of studies directed towards the total synthesis of these compounds.

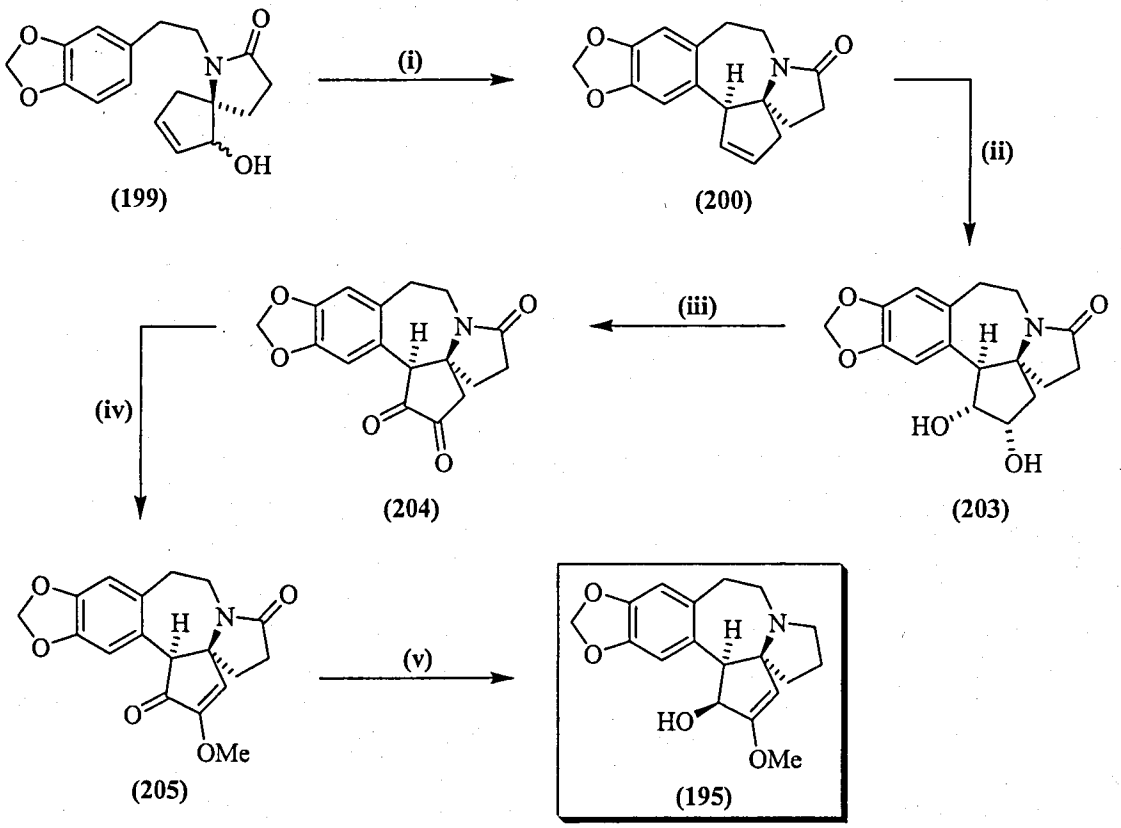
Scheme 58:



Over the last 40 years, a number of racemic synthetic approaches to the core pentacyclic ring system of cephalotaxine **(195)** have been developed. However, to date it is surprising to find that only six syntheses of optically pure (–)-cephalotaxine **(195)**[95] have been reported in which the polycyclic core alkenes **(200)** and **(202)** are common intermediates. The most significant work in this area has focused on the formation of the spirocyclic allylic alcohols **(199)** and **(201)** as key intermediates, followed by subsequent intramolecular cyclisation as shown in **Scheme 58**, which was initially applied by Kuehne *et al.* in the synthesis of (±)-cephalotaxine **(195)**.[96]

Treatment of the key allylic alcohol intermediate **(199)** with stannic chloride in dichloromethane and nitromethane resulted in cyclisation to the desired tetracyclic lactam core **(200)** in quantitative yield. With this core olefin **(200)** in hand, functionalisation toward cephalotaxine **(195)** was achieved by oxidation with osmium tetraoxide to the corresponding diol **(203)**, followed by further oxidation with dimethyl sulfide, *N*-chlorosuccinimide and triethylamine at –42 °C to the lactam diketone **(204)** in 89 % yield **(Scheme 59)**.

Scheme 59:

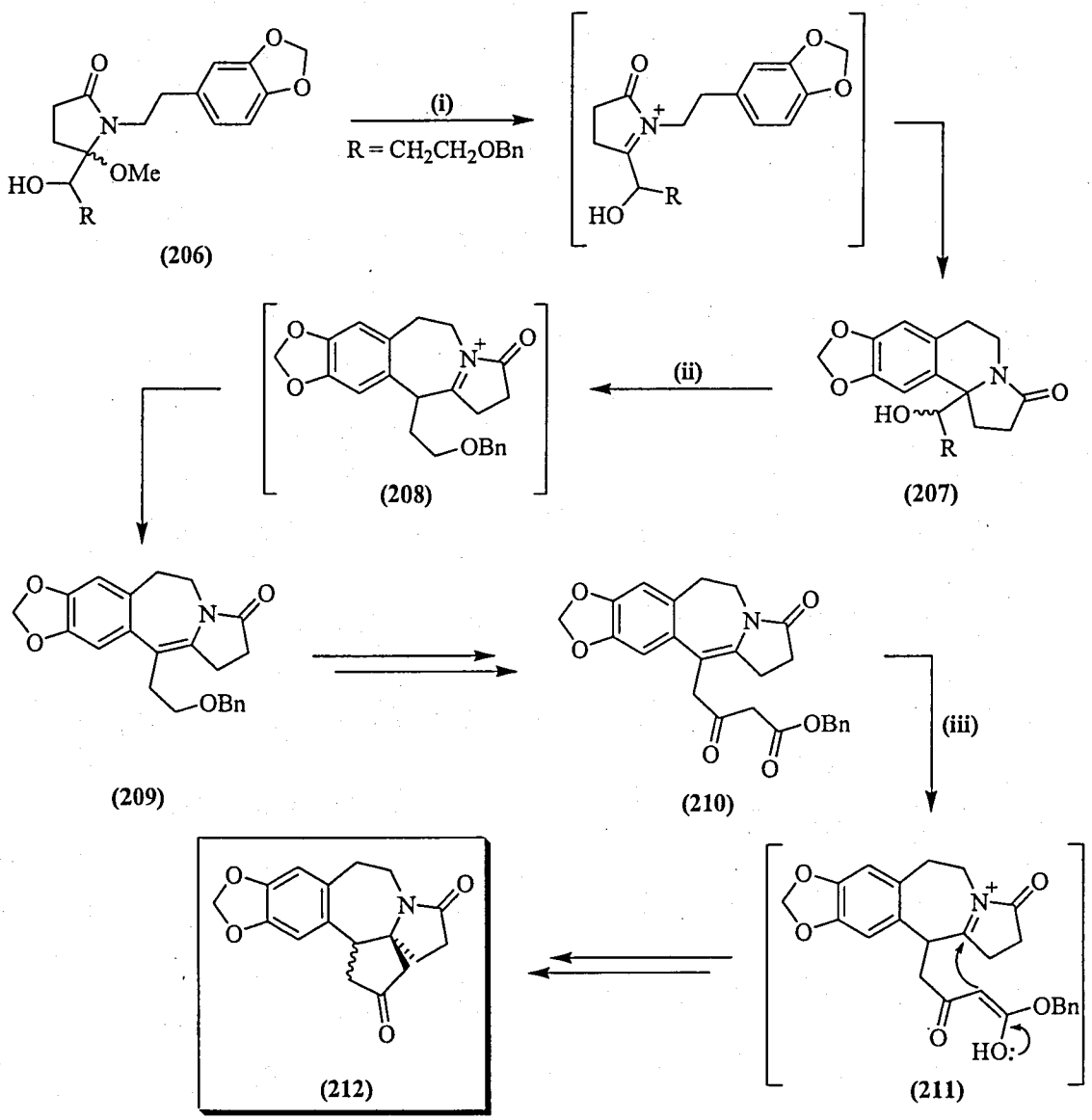


Reagents: **(i)** $SnCl_4$, $MeNO_2$, DCM, –78 °C, 1 h (100 %); **(ii)** OsO_4, NMO, THF, 24 h (99 %); **(iii)** Me_2S, NCS, Et_3N, DCM, –42 °C, 2.5 h (89 %); **(iv)** TMSOMe, TfOH, DCM, 24 h (97 %); **(v)** $LiAlH_4$, THF, Δ, 1 h (88 %).

Finally, the sterically less hindered ketone was converted to the enol ether **(205)** with trimethylsilyl methyl ether and triflic acid, followed by reduction with lithium aluminium hydride to provide racemic cephalotaxine **(195)** in 88 % yield. This pioneering methodology has since been utilised in three of the six reported total asymmetric syntheses of (–)-cephalotaxine **(195)** using optically active spirocyclic allylic alcohol substrates.[95a-c]

To the best of our knowledge, only one formal total synthesis of (±)-cephalotaxine **(195)** based on *N*-acyliminium ion chemistry has been achieved to date. The key steps in the synthesis reported by Nagasaka *et al.*[97] include the formation of pyrroloisoquinoline **(207)**, the ring-expansion to pyrrolobenzazepine **(209)** and the construction of the cyclopentapyrrolobenzazepine ring system **(212)**, a key intermediate in Hanaoka's synthesis,[98] all derived from sequential *N*-acyliminium ion intermediates (**Scheme 60**).

Scheme 60:



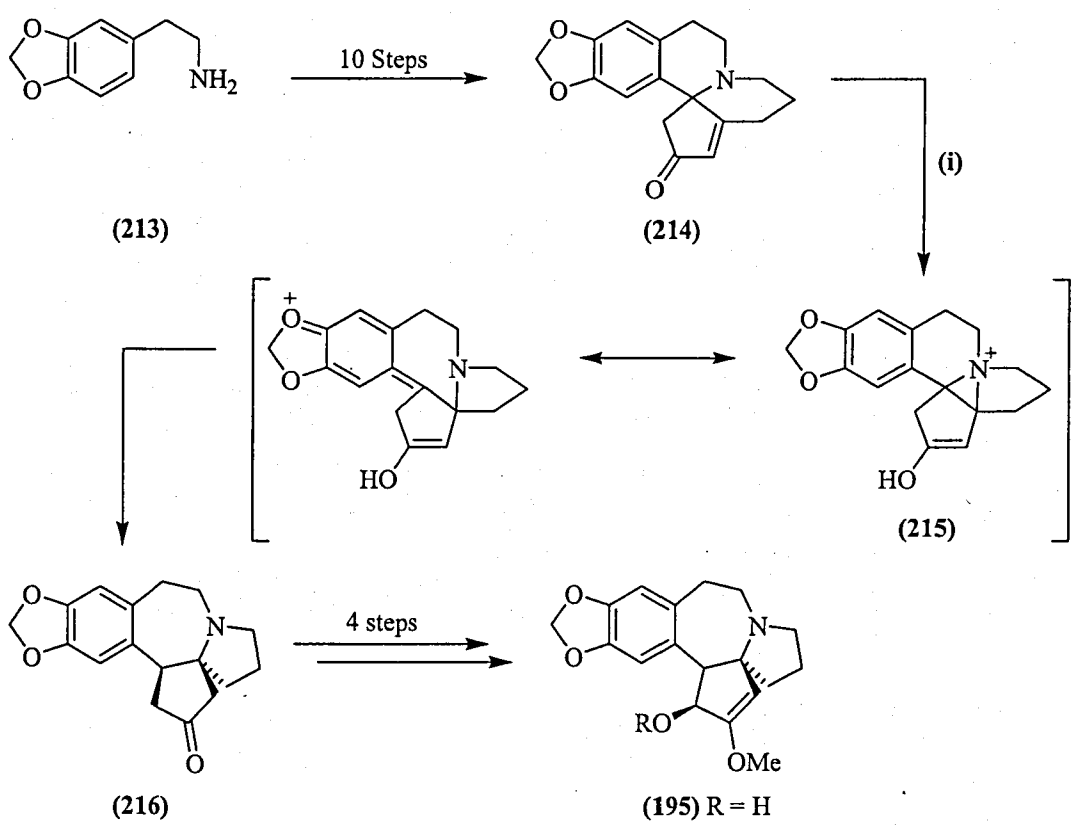
Reagents: (i) $BF_3.OEt_2$, DCM, –45 °C (80 %); (ii) SO_2Cl_2, Et_3N, $CHCl_3$, py, –78 °C (76 %); (iii) $TiCl_4$, DCM (71 %).

The synthesis of building block **(207)** as a tertiary *N*-acyliminium ion equivalent from the methoxylactam **(206)** proceeded smoothly under Lewis acid conditions to afford the

pyrroloisoquinoline **(207)** in excellent yield as a 2:1 mixture of diastereoisomers. Chlorosulfonylation of the crude mixture, followed by migration of the aromatic ring allowed the successful ring-expansion to pyrrolobenzazepine **(209)** *via* the acyliminium ion **(208)** in 76 % yield. The final key step, the intramolecular cyclisation of β-keto-ester **(210)** occurred upon exposure with titanium tetrachloride through the formation of intermediate **(211)**. Subsequent debenzylation completed the formal synthesis and gave the target pentacyclic ketone **(212)** in a 1:4.3 ratio (*cis:trans*).

In 2003, an interesting novel synthesis of (±)-cephalotaxine **(195)** involving a similar pentacyclic intermediate **(216)** was detailed by Li and Wang **(Scheme 61)**,[99] which was based on the postulated biogenesis of cephalotaxine **(195)** reported by Parry *et al.*[100]

Scheme 61:



(213) **(214)** **(215)** **(216)** **(195)** R = H

Reagents: **(i)** Zn, AcOH, 100 °C (65 %).

The synthesis commenced with the Bischler-Napieralski cyclisation of the phenylethylamine **(213)** followed by structural modification over a further nine steps to form the key intermediate pentacyclic amino enone **(214)** in good yield. Upon exposure

to zinc dust in warm acetic acid, amino enone **(214)** underwent a transannular reductive skeletal rearrangement *via* the transient bridged aziridinium species **(215)** to generate the unique fused benzazepine system **(216)**, which was easily converted to cephalotaxine **(195)** in four additional steps. This key transformation may be regarded as a novel biomimetic synthesis in terms of its unique pentacyclic ring construction and offers a new and efficient formation of this class of alkaloid.

We envisage an asymmetric route to the key homo-erythrinane **(214)** described by Li and Wang, or derivative of such, *via* a stereoselective *N*-acyliminium cyclisation from a suitable polycyclic lactam precursor. Thus, subsequent skeletal rearrangement and structural modification would allow a non-racemic entry toward (–)-cephalotaxine **(195)**. The progress toward the proposed synthesis of this highly desirable structural unique template is reported in the proceeding sections.

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CHAPTER TWO:
RESULTS AND DISCUSSION

2.1. Asymmetric Cyclisations of Chiral *N*-Acyliminium Ion Precursors

2.2. Application in the Synthesis of Naturally Occurring Alkaloids

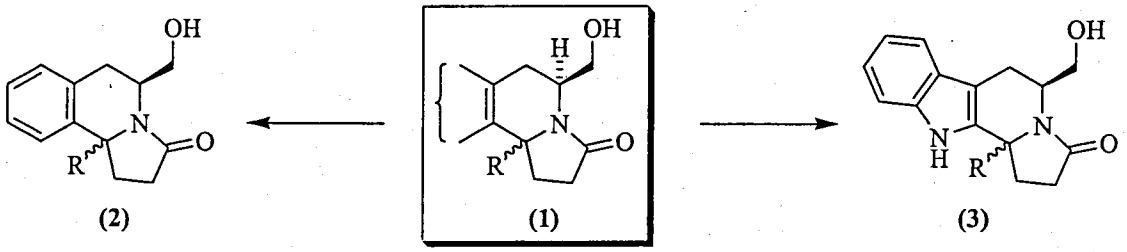
2.3. Application as Potential Building Blocks for Peptide Mimics

2.4. Application Toward the Synthesis of Cephalotaxine

2.1. Asymmetric Cyclisations of Chiral *N*-Acyliminium Ion Precursors

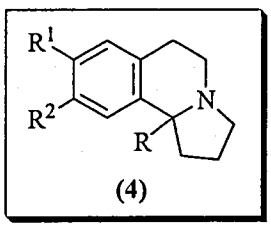
As detailed in Section 1, the high versatility exhibited by *N*-acyliminium species is well documented and has created an active interest in these compounds as useful synthetic intermediates to access various chiral fused-ring targets. The methodology developed by Allin *et al*, in which substituted bicyclic lactams act as *N*-acyliminium ion precursors in the synthesis of enantiomerically pure heterocyclic templates, is also well established.[1]

Scheme 1:



Our initial investigations focused on the construction and manipulation of substituted chiral indolizidines **(1)**, a key structural subunit present in both the pyrroloisoquinoline **(2)**[1b] and the indolizino[8,7-*b*]indoles **(3)**[2] model systems **(Scheme 1)**.

2.1.1. Stereoselective Synthesis of Pyrrolo[2,1-*a*]isoquinolines



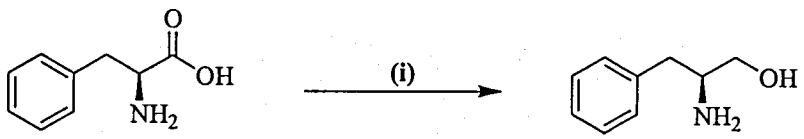
Interest in the pyrroloisoquinoline ring system of general structure **(4)** is well documented as a skeletal motif for the *Erythrina* alkaloids. However its core structure is not restricted to just one class of alkaloid and has been utilised as intermediates in the synthesis of various compounds, including cephalotaxine as detailed in Section 1.4.5.

As previously mentioned, it was recognised by Allin and James that a duly substituted bicyclic lactam could act as a precursor for the stereoselective synthesis of the

pyrroloisoquinoline template **(10)**. This short reaction sequence detailed in **Scheme 4** was used as an experimental introduction to the concept of *N*-acyliminium chemistry.

The synthesis of the pyrroloisoquinoline ring system **(10)** by Allin and James required the initial preparation of an optically pure amino alcohol **(6)**. This was generated in quantitative yields by reduction of the corresponding amino acid, *L*-phenylalanine **(5)** with lithium borohydride and trimethylsilylchloride, as shown in **Scheme 2.**[3]

Scheme 2:

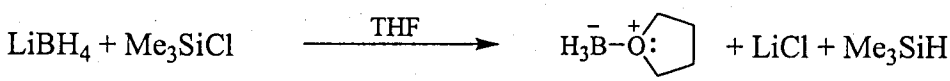


(5) **(6)**

Reagents: **(i)** $LiBH_4$, TMSCl, THF, 24 h (99 %).

The reaction is believed to proceed through a borane-tetrahydrofuran complex **(7)** in which borane exists as a Lewis acid-base species with the ether oxygen **(Scheme 3)**. In the presence of excess trimethylsilylchloride, it is this complex which is envisaged to act as the required reducing agent.

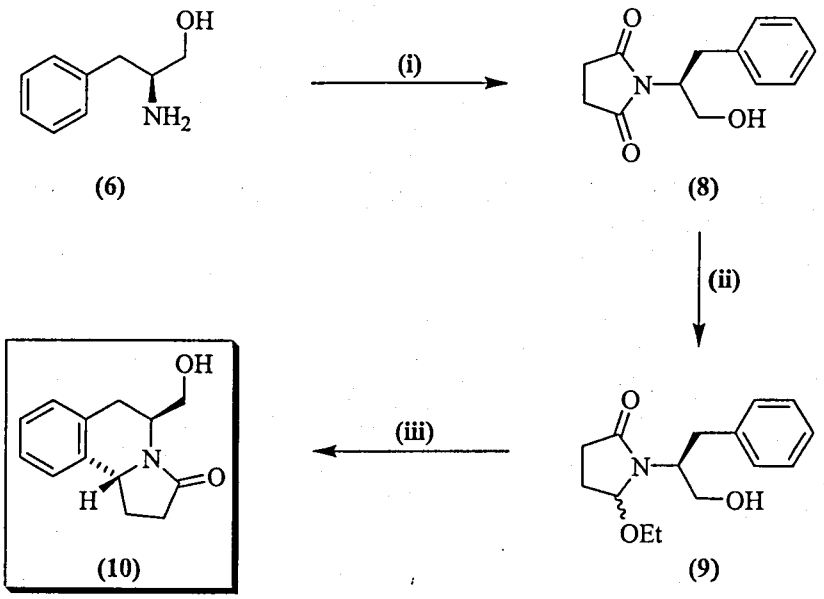
Scheme 3:



(7)

Scheme 4 outlines the stereoselective synthesis of the pyrroloisoquinoline ring system **(10)** from the *N*-acyliminium precursor **(8)**, which is formed by condensation of the β-amino alcohol **(6)** with succinic anhydride in the presence of triethylamine. Following reduction of the imide **(8)** with sodium borohydride in ethanol, the intermediate ethoxy lactam **(9)**, which exhibited no sign of direct *N*-acyliminium cyclisation under the protic acid conditions, was treated with titanium tetrachloride to undergo clean conversion to the cyclic template **(10)**. The desired heterocycle **(10)** was obtained as a single diastereoisomer in 44 % yield, which is very respectful when compared to the literature value of 53 %, previously published by Allin and James.[1b]

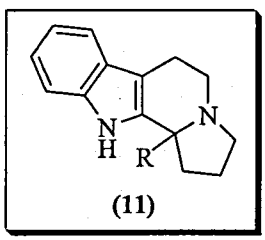
Scheme 4:



Reagents: **(i)** Succinic anhydride, Et_3N, PhMe, Δ, 18 h (62 %); **(ii)** $NaBH_4$, 2 M HCl, EtOH, 20 h; **(iii)** $TiCl_4$, DCM, −78 °C to rt, 20 h (44 %).

This methodology has since been applied in the synthesis of a range of substituted pyrroloisoquinoline derivatives[1b] and the indolizino[8,7-*b*]indole ring system.[2]

2.1.2. Stereoselective Synthesis of Indolizino[8,7-*b*]indoles

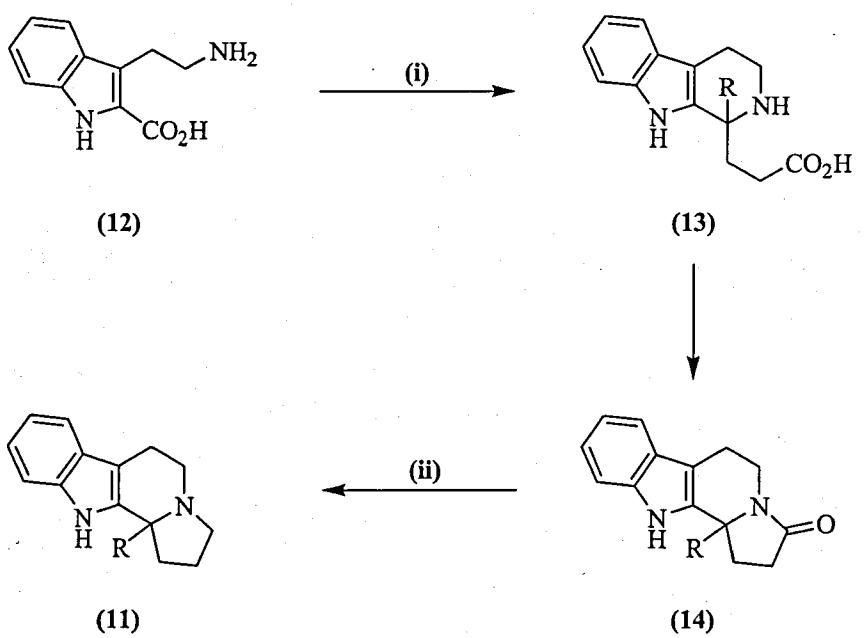


The initial applications of this chemistry allowed access to the pyrroloisoquinoline system **(10)** by a stereoselective attack of an electron-rich aromatic nucleophilic at the planar *N*-acyliminium ion intermediate. By substitution of the aromatic ring with an increasing electronegative indole π-nucleophile, it was envisaged that the tetracyclic core of a new class of physiologically active compounds **(11)**, could be accessed in novel fashion.[2]

Indolizino[8,7-*b*]indoles of general structure **(11)** have attracted great interest as synthetic intermediates in the pharmaceutical industry. Indeed, a number of these indoles are known to exhibit analgesic and anti-inflammatory activity in their own right,[4] however they have been widely used as a core building block for more complex alkaloids which possess diuretic properties.[5]

A typical method for the preparation of indolizino[8,7-*b*]indole derivatives **(11)** is the condensation of a tryptamine derivative **(12)** with a keto-acid or keto-ester species. An example of such is the diverse range of tetrahydro-β-carbolines **(14)** prepared by a modified Pictet-Spengler reaction demonstrated in **Scheme 5**. The resulting secondary amine **(13)** formed during condensation then reacts intramolecularly with loss of water and subsequent ring closure to give the desired indolizino[8,7-*b*]indole **(14)**.[6]

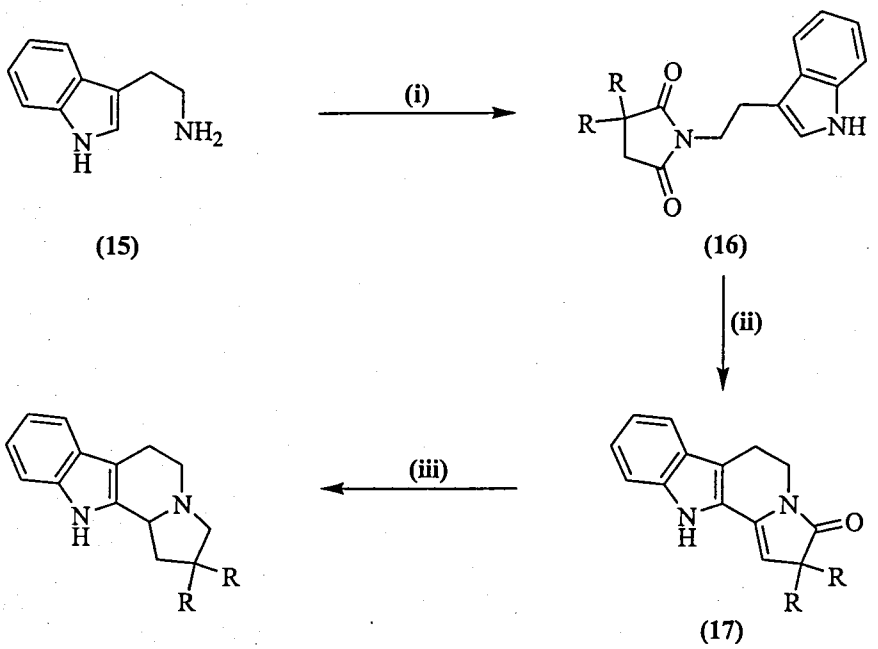
Scheme 5:



Reagents: **(i)** $RCOCH_2CH_2CO_2H$, Δ; **(ii)** $LiAlH_4$, THF.

Alternatively, tryptamine **(15)** can be converted to the corresponding imide **(16)** by reaction with succinate esters and cyclisation to the β-carboline derivative **(17)**, accomplished under Bischler-Napieralski conditions as shown in **Scheme 6**.[7]

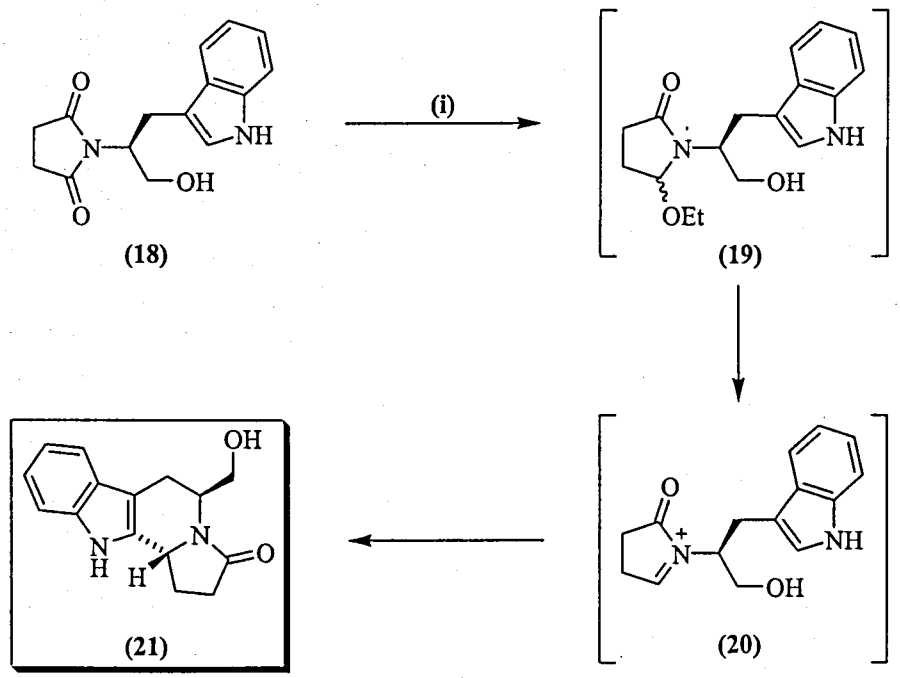
Scheme 6:



Reagents: (i) $EtO_2COCH_2CR_2CO_2Et$, Δ; (ii) P_2O_5, PhMe, Δ; (iii) PtO_2, H_2, AcOH.

Our approach to the indolizino[8,7-*b*]indole template **(21)** shown in **Scheme 7**, mirrors the synthesis of the pyrroloisoquinoline equivalent **(10)** previously applied by our group, with excellent levels of stereocontrol.

Scheme 7:

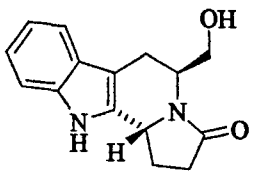


Reagents: (i) $NaBH_4$, 2 M HCl, EtOH, 20 h (85 %).

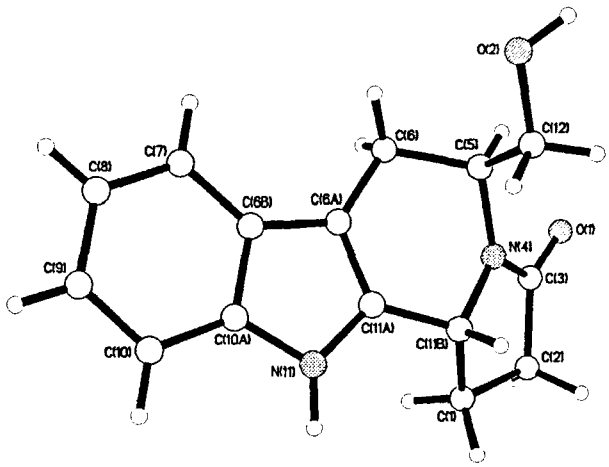
Subjecting imide **(18)** to the typical sodium borohydride reduction conditions as described earlier in **Scheme 4**, *en route* to the expected ethoxylactam precursor **(19)**, resulted in direct cyclisation *via* the *N*-acyliminium ion **(20)** to the target β-carboline **(21)** as a 9:1 mixture of diastereoisomers and in an excellent 85 % yield. To date the ethoxy lactam intermediate **(19)** has not been isolated.[2]

Presumably, under the acidic reaction conditions, the increased nucleophilicity of the indole ring is able to attack the *N*-acyliminium ion generated *in situ* and cyclise directly. The major isomer **(21)** was isolated from the mixture by recystallisation and the relative stereochemistry was confirmed by X-ray crystallography, with the hydrogen atoms at positions 5 and 11b situated in a *trans* relationship **(Figure 1)**.

Figure 1: Single Crystal X-Ray Structure of (21).

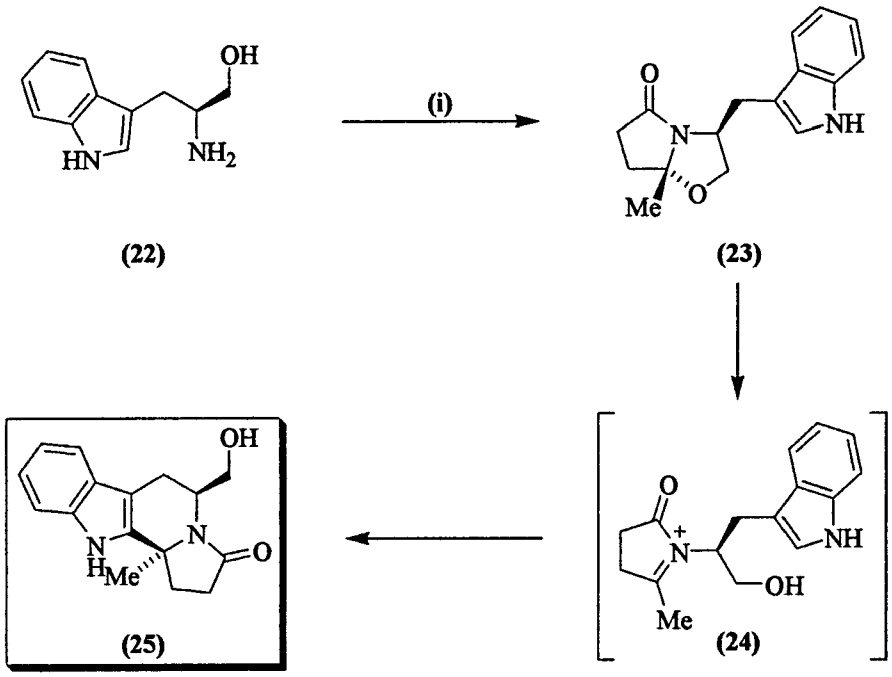


(21)



An approach to the analogous indolizino[8,7-*b*]indole ring system **(25)** has also been investigated that proceeds *via* the bicyclic lactam **(23)**, which acts as an *N*-acyliminium ion precursor **(Scheme 8)**.[2] The β-amino alcohol **(22)** of *L*-tryptophan was reacted under Dean-Stark conditions with levulinic acid for 48 hours. Under these reaction conditions the expected bicyclic lactam **(23)** was only isolated in 3 % yield, the major product being the target indolizino[8,7-*b*]indole derivative **(25)** formed as a single diastereoisomer in 55 % yield.

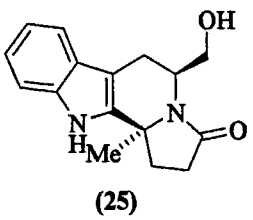
Scheme 8:

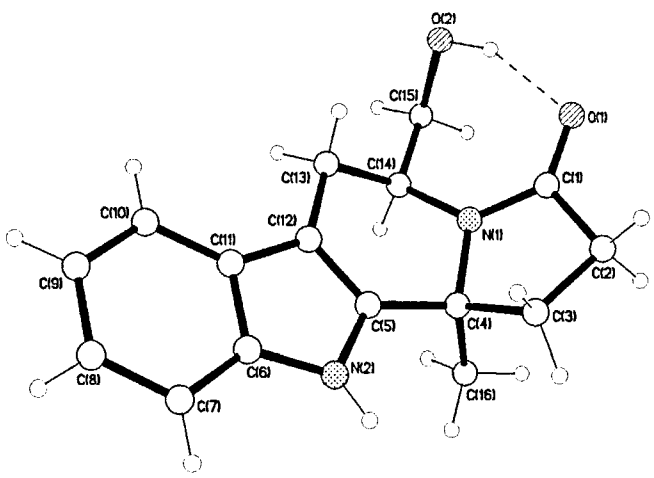


Reagents: (i) Levulinic acid, PhMe, Δ, Dean-Stark, 48 h (55 %).

The stereochemistry of the heterocyclic product (**25**) has been confirmed as the *anti* configuration with respect to the angular methyl substituent and the hydroxymethyl auxiliary by X-ray crystallography as shown in **Figure 2**. Effectively, retention of configuration at the methyl-bearing chiral centre is observed if one considers the bicyclic lactam (**23**) as an intermediate.[2]

Figure 2: Single Crystal X-Ray Structure of (25).





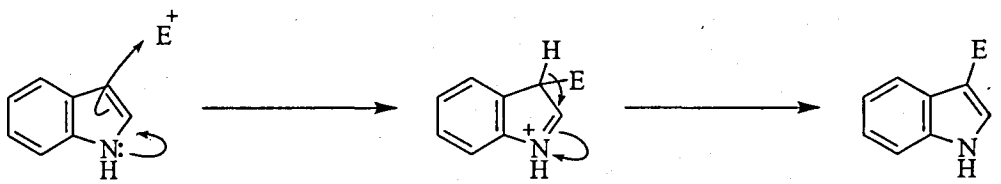
One could however, envisage an alternate mechanism to explain the formation of **(25)** which avoids the intermediacy of the bicyclic lactam **(23)**; a stereoselective Pictet-Spengler condensation of the β-amino alcohol and keto-acid substrate that results in the initial formation of a tetrahydro-β-carboline derivative and then undergoes lactam formation to yield **(25)** in the final step.[8] To date, no intermediates have been observed by us that would support this hypothesis with our substrates.

2.1.3. Cyclisations Involving Indole – Proposed Mechanism

The chemistry of indole is, in many ways that of a reactive pyrrole ring with a relatively unreactive benzene ring attached, in that electrophilic substitution almost always occurs on the pyrrole ring. However, indole and pyrrole differ in one important aspect, that is electrophilic substitution is preferred in the 3-position with almost all reagents. Examples include halogenation, nitration, sulfonation, Friedel-Crafts acylation and alkylation which all occur cleanly at this position.

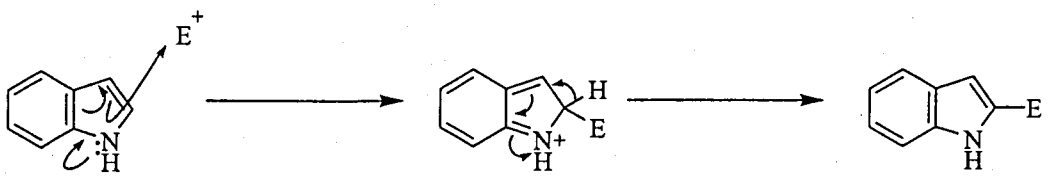
A simple explanation is that reaction at the 3-position involves the isolated enamine system in the five-membered ring and hence does not disturb the aromaticity of the benzene ring **(Scheme 9)**.

Scheme 9:



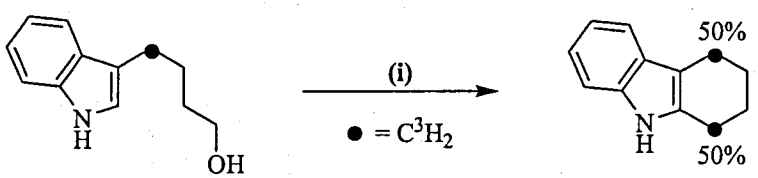
The positive charge in the intermediate is, of course, delocalised round the benzene ring, however its main stabilisation is from the nitrogen atom. It is not possible to get reaction at the 2-position without seriously disturbing the aromaticity of the benzene ring **(Scheme 10)**.

Scheme 10:



If the 3-position is blocked, reaction will occur at the 2-position, which seems to suggest that electrons can be taken the 'wrong way' round the five-membered ring. An intramolecular Friedel-Crafts alkylation experiment involving a tritium (radioactive ^3H) labelled substrate next to the ring has shown that this is not so simple **(Scheme 11).**

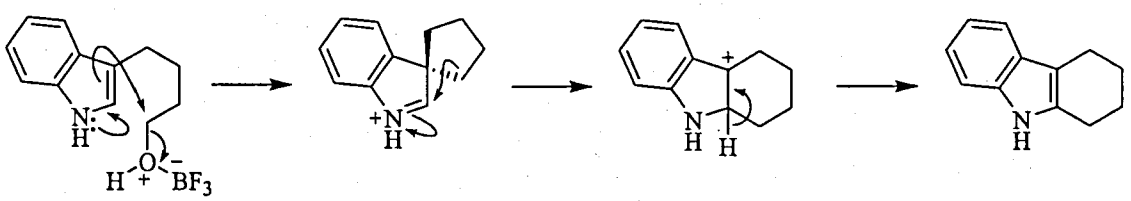
Scheme 11:



Reagents: **(i)** BF_3.

The resulting product showed exactly 50 % of the label where it is expected and 50 % where it is not, which indicates the reaction must have a symmetrical intermediate for this result to occur. The obvious candidate arises from attack at the 3-position, the so called *spiro* compound, in which the five-membered ring is at a right angle to the indole ring with each CH_2 group having an equal chance of migrating as shown in **Scheme 12.**

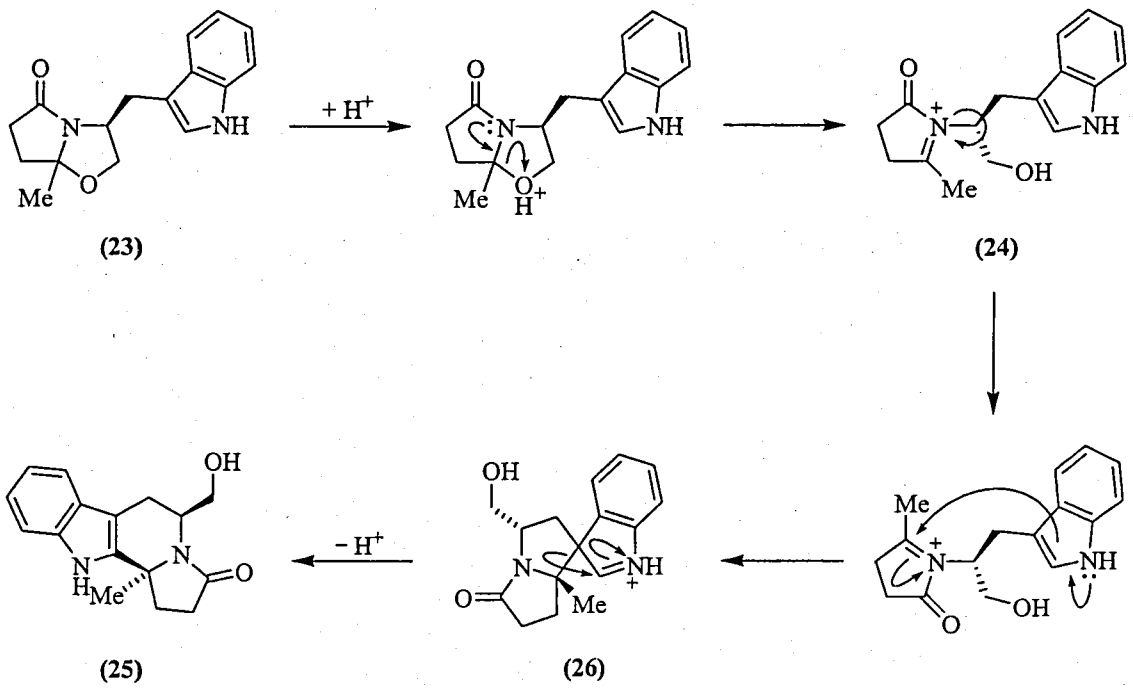
Scheme 12:



The migration is a pinacol-like rearrangement; it is thought that most substituent's in the 2-position occur *via* this migration, but some attack directly with disruption of the aromatic ring.[9]

The condensation reaction to produce the target β-carboline product **(25)** is envisaged to initially proceed *via* the bicyclic lactam intermediate **(23)**, as its presence in the reaction mixture would suggest **(Scheme 13)**.

Scheme 13:

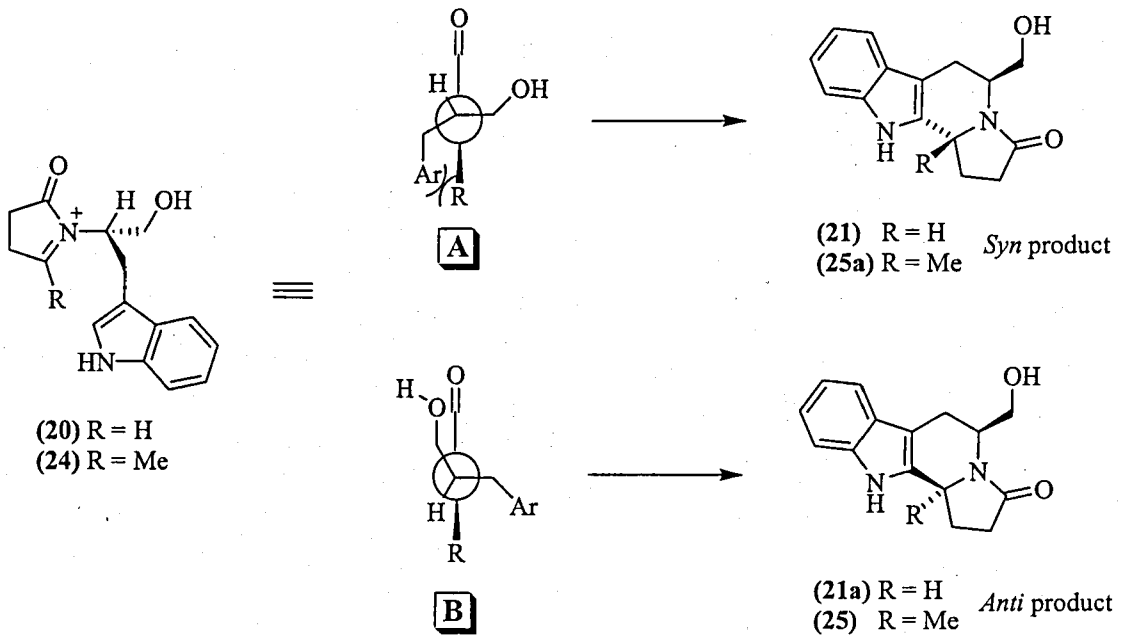


Rotation about the iminium bond in the resultant *N*-acyliminium species **(24)** to the more favourable conformation is then assumed, which is followed by stereoselective intramolecular attack of the indole, initially occurring at the 3-position to generate the *spiro* compound **(26)**. Bond migration to the 2-position followed, resulting in the target heterocycle **(25)**.

2.1.4. Rationalisation of the Observed Stereochemical Outcome

The stereochemistry observed in the cyclised products **(10)**, **(21)** and **(25)** has been rationalised by invoking the conformational models detailed in **Figure 3**, in which formation of the ethoxy lactam **(19)** and bicyclic lactam **(23)** leads to the formal *N*-acyliminium ion intermediates **(20)** and **(24)** respectively.[10]

Figure 3: Proposed Conformational Models.

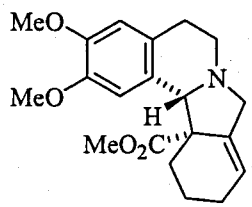


In conformation **A** (R = H), leading to the favoured *syn*-isomer **(21)**, the carbonyl moiety is "eclipsed" in a 1,3-fashion by the hydrogen atom at the β-amino alcohol chiral centre. The angular hydrogen atom at the iminium carbon provides no significant steric bulk to interfere with the steric positioning of the large indole (Ar) or hydroxymethyl substituents. Rotation about the extra-annular C-N bond leads to the alternative conformation **B** (R = H), which would form the minor diastereoisomer **(21a)**. In this scenario an unfavourable 1,3-interaction exists between the carbonyl and hydroxymethyl groups.

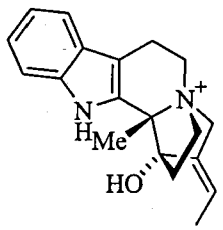
With the *N*-acyliminium species **(24)**, the steric influence exercised by the angular methyl substituent (R = Me) at the iminium carbon over-rides the conformational effect previously noted and leads to the major diastereoisomer **(25)** of opposite relative stereochemistry. Steric interactions between the angular methyl and the indole moiety (**A**, R = Me) can be envisaged, however bond rotation about the extra-annular C-N bond leads to conformation **B** (R = Me) with minimised steric interactions from the iminium carbon substituent, which generate the observed diastereoisomer **(25)** exclusively, with retention of stereochemistry.[1b]

2.2. Application in the Synthesis of Naturally Occurring Alkaloids

Having demonstrated the potential for *N*-acyliminium cyclisation chemistry in the construction of both the pyrrolo[2,1-*a*]isoquinoline and indolizino[8,7-*b*]indole ring systems, we aimed to establish the synthetic utility of this methodology in target synthesis. The tetracyclic skeleton of both these chiral building blocks is present in the structures of several interesting heterocyclic targets, examples of which include (+)-jamtine **(27)**[11] and (–)-subincanadine B **(28)**[12] as illustrated below.



(27)



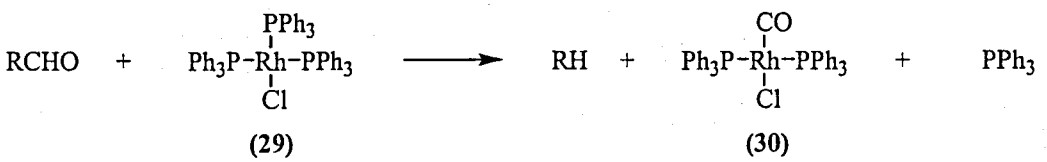
(28)

However, conditions to remove both the pendent hydroxymethyl moiety and the lactam carbonyl from the respective chiral templates are essential to achieve such targets. This section outlines the methodology adopted by us to perform these transformations and the application toward some simple, therapeutically interesting alkaloids.

2.2.1. Removal of the Hydroxymethyl Auxiliary

Methodology for the successful removal of the hydroxymethyl auxiliary has received extensive attention in our group due to its application in the synthesis of both the *Erythrina*[13] and indole[14] alkaloids. The initial work in this area focused on the decarbonylation of aldehydes using complexes of rhodium, as developed by Tsuji and Ohno in their studies with chlorotris(triphenylphosphine)rhodium **(29)**, more commonly known as Wilkinson's catalyst **(Scheme 14)**.[15]

Scheme 14:

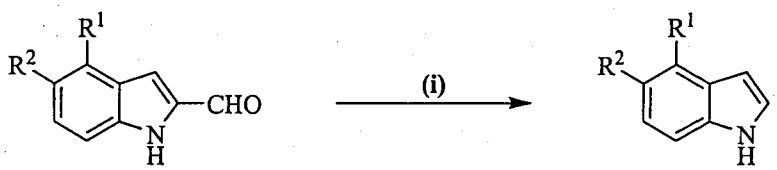


(29) **(30)**

Typically, the decarbonylation reaction requires stoichiometric quantities of rhodium in refluxing benzene, toluene or *p*-xylene, however the same research group discovered that at temperatures in excess of 200 °C, the decarbonylation of aldehydes proceeds smoothly with the chlorocarbonylbis(trisphenylphosphine)rhodium complex **(30)** in only catalytic amounts.

Kruse and Meyer investigated a further modification of this procedure on the decarbonylation of indole-2-carboxaldehydes **(31)** under mild conditions, whereby chlorobis[1,2-bis(diphenylphoshino)propane]rhodium was prepared *in situ* from catalytic **(30)** and 1,3-bis(diphenylphosphino)propane (dppp) without the usual requirement for high temperatures **(Scheme 15)**.[16]

Scheme 15:

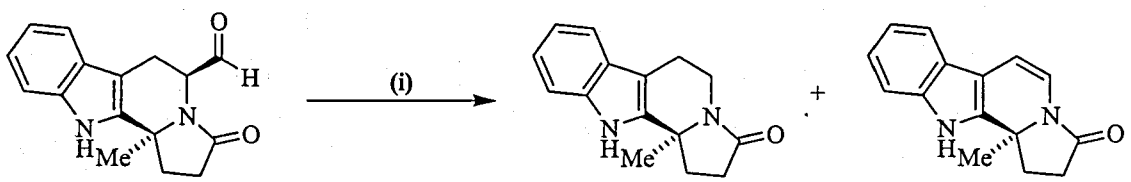


(31)

Reagents: **(i)** $Rh(PPh_3)_2(CO)Cl$, dppp, *p*-xylene, Δ, 24 h.

This route was initially applied by Allin *et al.* using the aldehyde derivative **(32)** formed by mild oxidation of the indolizino[8,7-*b*]indole template **(25)** with *o*-iodoxybenzoic acid (IBX) in dimethyl sulfoxide **(Scheme 16)**.[2]

Scheme 16:



(32) **(33)** **(34)**

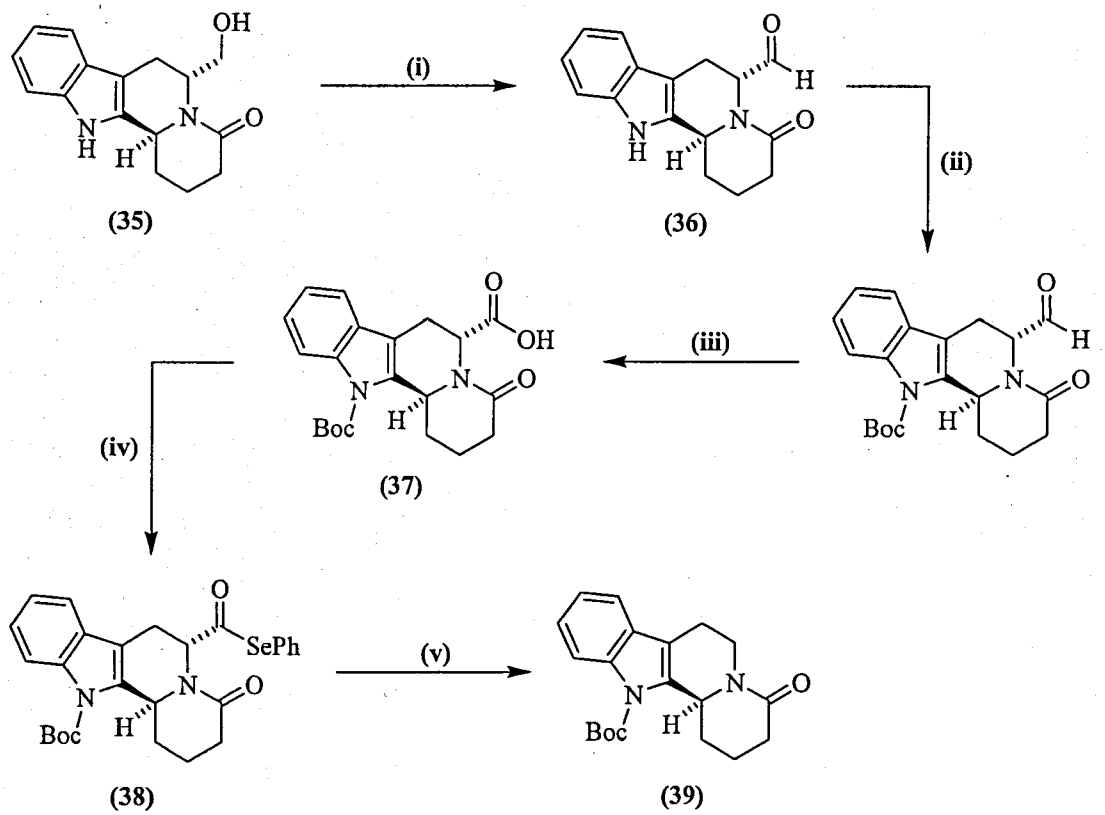
Reagents: **(i)** $Rh(PPh_3)_2(CO)Cl$, dppp, *p*-xylene, Δ, 5 d.

The subsequent decarbonylation procedure under the conditions described by Kruse and Meyer[16] resulted in a mixture of products, which required catalytic hydrogenation to

convert the unwanted enamine **(34)** to the target lactam **(33)**. Due to the additional steps, extended reaction times (8 days) and evidence for some degree of racemisation when applied to indolo[2,3-*a*]quinolizine templates,[17] an alternate procedure for the removal of the hydroxymethyl auxiliary was sought.

A large number of radical chain decarbonylation reactions are reported in the literature, of which the trialkylstanne-induced decarbonylation of phenyl seleno esters appeared advantageous to our group.[18] Allin and co-workers have since applied this procedure in the synthesis of several complex indole alkaloids, and is highlighted in **Scheme 17**.[1d]

Scheme 17:

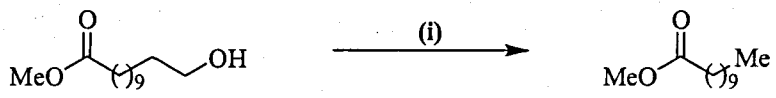


Reagents: **(i)** IBX, DMSO; **(ii)** Di-*t*-butyl dicarbonate, Et_3N, DMAP, THF; **(iii)** $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, MeCN, *t*-BuOH, H_2O; **(iv)** $(PhSe)_2$, PBu_3, DCM; **(v)** *n*-Bu_3SnH, AIBN, PhMe, 80 °C.

Compound **(35)** was oxidised to the carboxylic acid derivative **(37)** *via* the corresponding aldehyde **(36)**, from which the acylselenide **(38)** was generated and subsequently underwent a tin-mediated deacylation to yield the indolo[2,3-*a*]quinolizine ring system **(39)** with a high level of enantiomeric purity.

However a more direct route reported by Krafft,[19] which was highly appealing to us due to its simplicity, was that in the presence of Raney nickel in refluxing toluene, primary alcohols gave rise to new deoxygenated compounds containing one less carbon. For example, heating a solution of methyl 12-hydroxydodecanoate **(40)** with Raney nickel for 3.5 hours provided a 73 % isolated yield of methyl undecanoate **(41)** **(Scheme 18).**

Scheme 18:

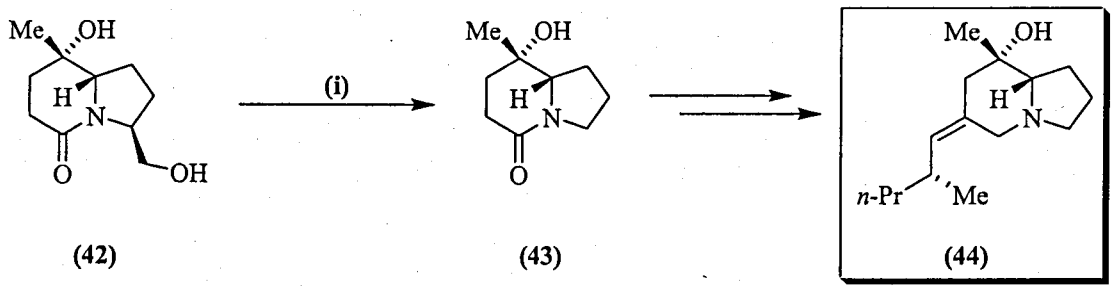


(40) **(41)**

Reagents: **(i)** Raney-nickel, PhMe, Δ, 3.5 h (73 %).

Krafft proposed that the dehydroxymethylation procedure involves a reversible dehydrogenation (i.e. oxidation) of the alcohol to the aldehyde, followed by an irreversible decarbonylation. Martin has since applied this procedure developed by Krafft to remove a superfluous hydroxymethyl group during a formal synthesis of pumiliotoxin 251D **(44)** **(Scheme 19).**[20] Heating a mixture of **(42)** and Raney nickel (W-2) in refluxing toluene produced the bicyclic lactam **(43)**, a known precursor to the allopumiliotoxin alkaloid, in 71 % yield.

Scheme 19:



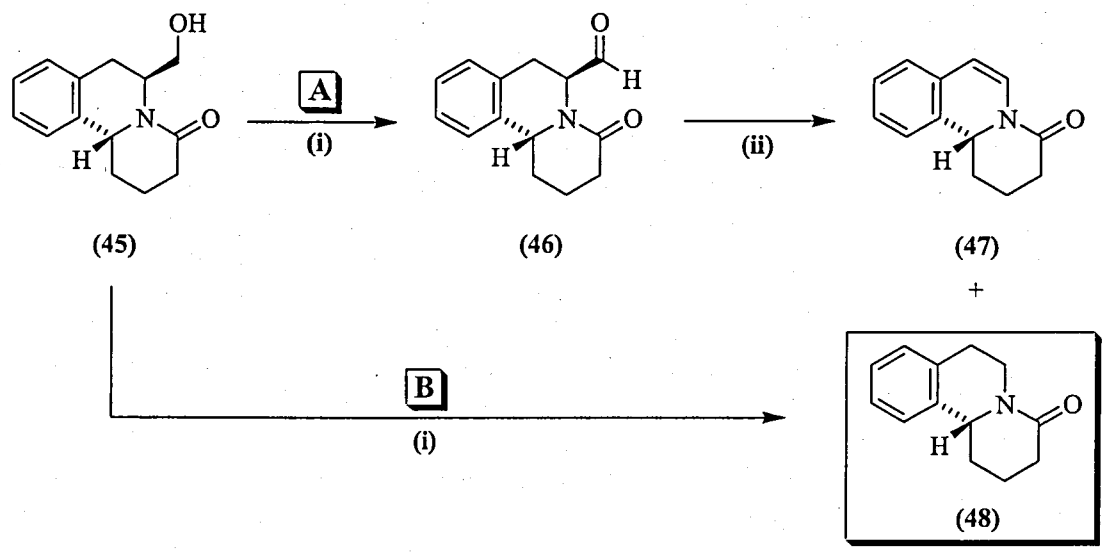
(42) **(43)** **(44)**

Reagents: **(i)** Raney-nickel, PhMe, Δ, 4 h (71 %).

The quality of Raney nickel was critical to the successful removal of the pendant hydroxymethyl group. The use of commercially available catalyst failed to promote the reaction to completion, even after prolonged heating. Alternatively, freshly prepared catalyst effected the conversion in 4 hours.[21]

Our application of these reaction conditions with a range of heterocyclic substrates developed within our group began with the formation of **(48)** from the tetrahydroisoquinoline building block **(45)** **(Scheme 20)**. The target lactam **(48)** had previously been synthesised in our group *via* route A as an inseparable mixture containing the enamide **(47)** using the rhodium catalysed decarbonylation method described earlier in this section from aldehyde **(46)**.

Scheme 20:

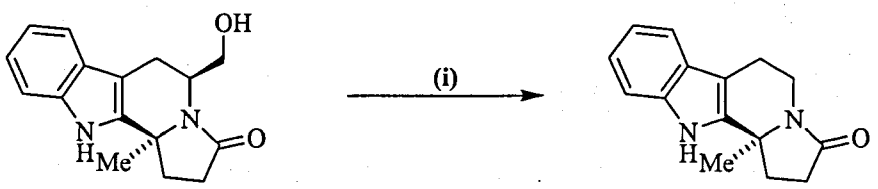


Reagents: **A (i)** Dess-Martin periodinane, DCM, 20 h; **(ii)** $Rh(PPh_3)_2(CO)Cl$, dppp, *p*-xylene, Δ, 72 h; **B (i)** Raney-nickel, PhMe, Δ, 4 h (44%).

This was seen as a suitable test reaction for the new methodology and upon subjecting compound **(45)** to freshly prepared Raney nickel (W-2) in refluxing toluene for 4 hours under Dean-Stark conditions, the desired compound **(48)** was isolated in 44 % yield with no trace of the corresponding enamide **(47)**. With this encouraging result, we proceeded to broaden the scope of this technique toward the more complex indolizino[8,7-*b*]indole substrate **(25)** in order to investigate its diversity and potential use in natural product synthesis.

Our initial attempts represented the most direct route to the desired free indole decarbonylation product **(33)** from the indolizino[8,7-*b*]indole building block **(25)** as outlined in **Scheme 21.**

Scheme 21:

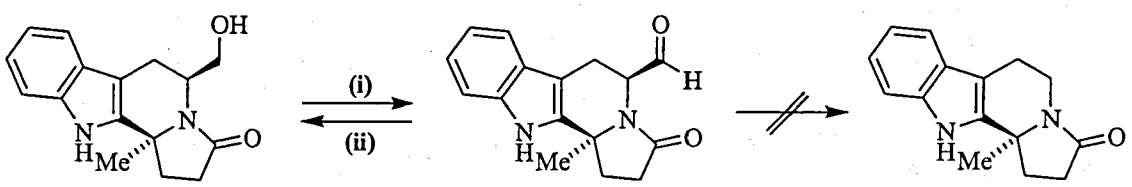


(25) (33)

Reagents: (i) Raney-nickel, PhMe, Δ.

Treatment of alcohol **(25)** under the Raney nickel conditions however, liberated only starting material after prolonged heating for 24 hours. With the mechanism proposed by Krafft in mind,[19] we attempted to gain more insight into this process by subjecting the corresponding aldehyde **(32)**, formed by oxidation of **(25)** with IBX, to the analogous reaction conditions **(Scheme 22)**.

Scheme 22:



(25) (32) (33)

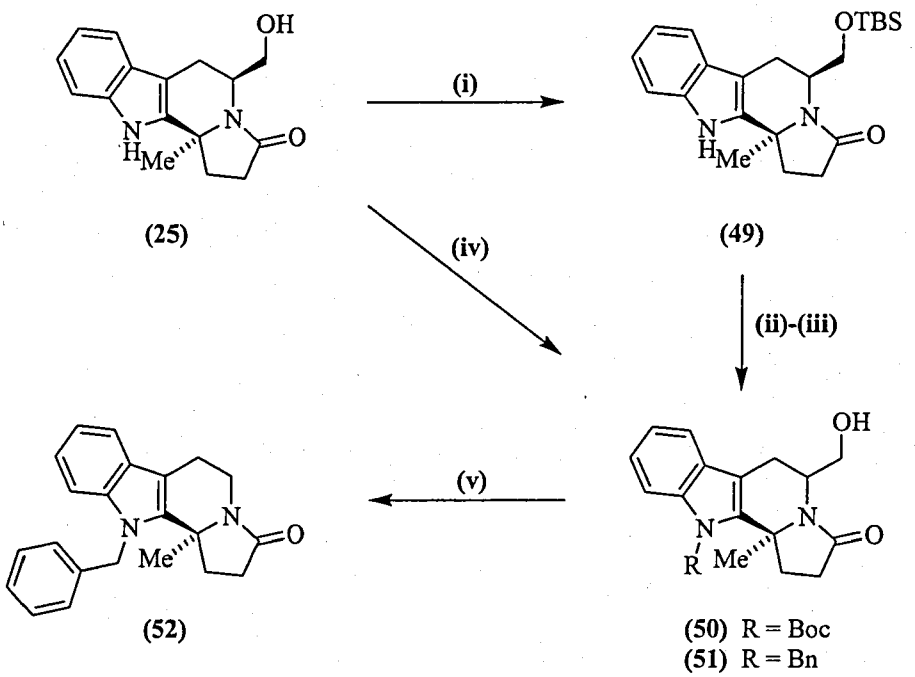
Reagents: (i) IBX, DMSO, 24 h (49%); (ii) Raney-nickel, PhMe, Δ.

Upon treatment of aldehyde **(32)** with Raney nickel in refluxing toluene, it was perhaps unsurprising to us to isolate exclusively the reduction product **(25)**, as the dehydrogenation step is a reversible process under these conditions. This result does however indicate that it was the rate-determining decarbonylation step that failed to proceed and not the initial dehydrogenation.

Our next approach was to attempt the Raney-nickel induced decarbonylation on various *N*-protected indolizino[8,7-*b*]indole derivatives to prevent any co-ordination between the nickel catalyst and indole nitrogen, which may potentially hinder the process **(Scheme 23)**. The first candidate was the *tert*-butyloxycarbonyl (Boc) protected carbamate **(50)**, which was considered due to the ease of its removal. The hydroxyl group was initially converted to the silyl ether **(49)** to avoid any unwanted side

reactions, which allowed protection of the indole with di-*tert*-butyl dicarbonate, triethylamine and catalytic dimethylaminopyridine in 92 % yield. Subsequent removal of the silyl group in the presence of tetrabutylammonium fluoride (TBAF) afforded the desired substrate **(50)** after 5 minutes, which when subjected to Raney-nickel, resulted only in a mixture of starting material and the free indole **(25)**.

Scheme 23:

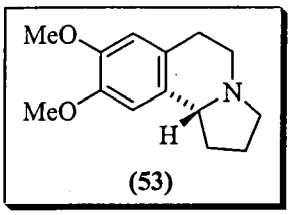


Reagents: **(i)** TBSCl, imidazole, DMAP, DCM, 4 h (81 %); **(ii)** Di-*t*-butyl dicarbonate, Et_3N, DMAP, THF, 24 h, (92 %); **(iii)** TBAF, THF, 5 min (97 %); **(iv)** NaH, BnBr, DMF, 3 h (62 %); **(v)** Raney-nickel, PhMe, Δ, 4 h (77 %).

In view of this result, we utilised the more stable benzyl-protected derivative **(51)**, formed directly from **(25)** by deprotonation with sodium hydride and treatment with benzyl bromide, which to our delight successfully decarbonylated to the target amide **(52)** in the presence of Raney-nickel under reflux in a respectable 77 % yield.

From these initial studies, we aimed to demonstrate the potential application of this methodology toward a range of simple natural products, which would significantly decrease the reaction time and increase efficiency when compared to previous procedures detailed in this section.

2.2.2. Total Synthesis of (*R*)-(+)-Crispine A

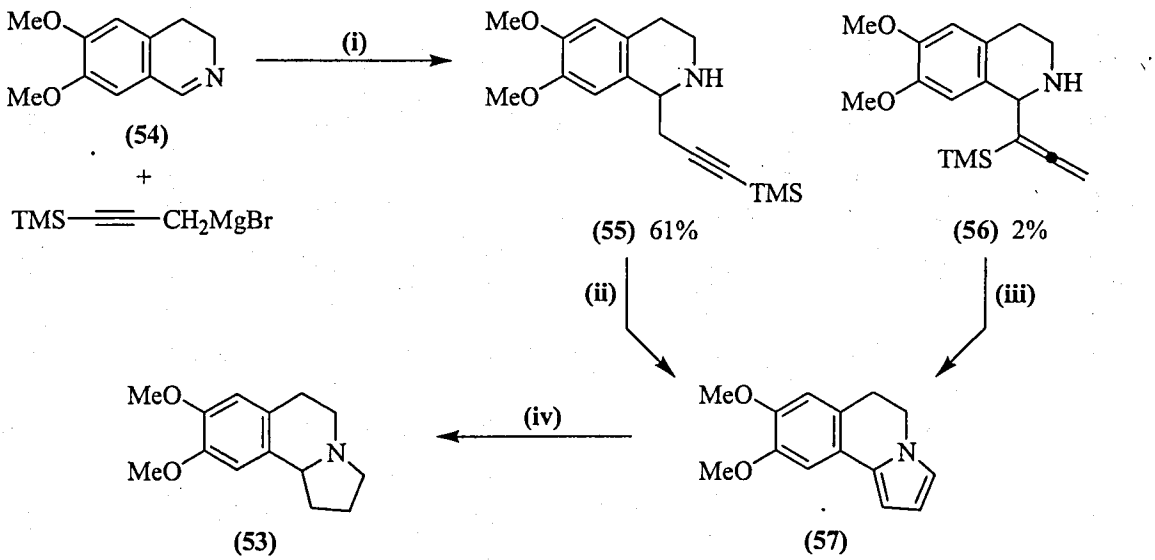


(53)

The pyrrolo[2,1-*a*]isoquinoline alkaloid (*R*)-(+)-crispine A **(53)**, isolated in 2002 by Zhao and co-workers from the welted thistle *Carduus crispus* Linn, has been applied in Chinese folk medicine for the treatment of cold, stomach ache and rheumatism since ancient times. More recently, pharmacological screening has revealed a cytotoxic activity against SKOV3, KB and HeLa human cancer cell lines.[22]

Due to the renewed interest in this molecule, three total syntheses of (±)-crispine A **(53)** have been published to date.[23] The first of these by Knölker and Agarwal, utilised a novel three-step pyrrole synthesis from the isoquinoline **(54)** **(Scheme 24)**.[23a]

Scheme 24:



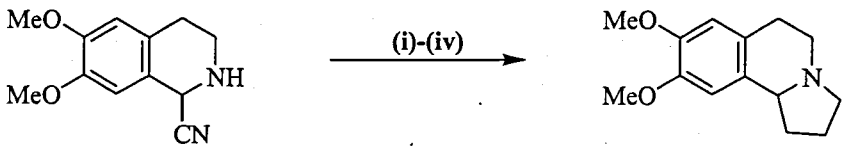
Reagents: **(i)** $BF_3.OEt_2$, THF; **(ii)** AgOAc, DCM; **(iii)** AgOAc, acetone, Δ; **(iv)** Rh/C, H_2, AcOH/MeOH, 8 d (66 %).

The Lewis addition promoted addition of 3-trimethylsilylpropargylmagnesium bromide to **(54)** afforded the propargyl compound **(55)** and allene **(56)** in 61 % and 2 % yields respectively. The silver(I)-promoted oxidative cyclisation of the homopropargylamine

(55) in dichloromethane at room temperature and subsequent chemoselective hydrogenation of the pyrrole ring (57) provided (±)-crispine A (53) in 66 % yield.

In 2006, Meyer and Opatz reported a facile one-pot synthesis of (±)-crispine A (53) based on the conjugate addition of a deprotonated α-amino nitrile to an α,β-unsaturated carbonyl compound (**Scheme 25**).[23b] Deprotonation of amino nitrile (58) with potassium hexamethyldisilazide (KHMDS), followed by 1,4-addition to acrolein and reduction of the resulting unstable intermediate with sodium cyanoborohydride in acidic solution, furnished racemic crispine A (53) in a relatively low 13 % yield.

Scheme 25:

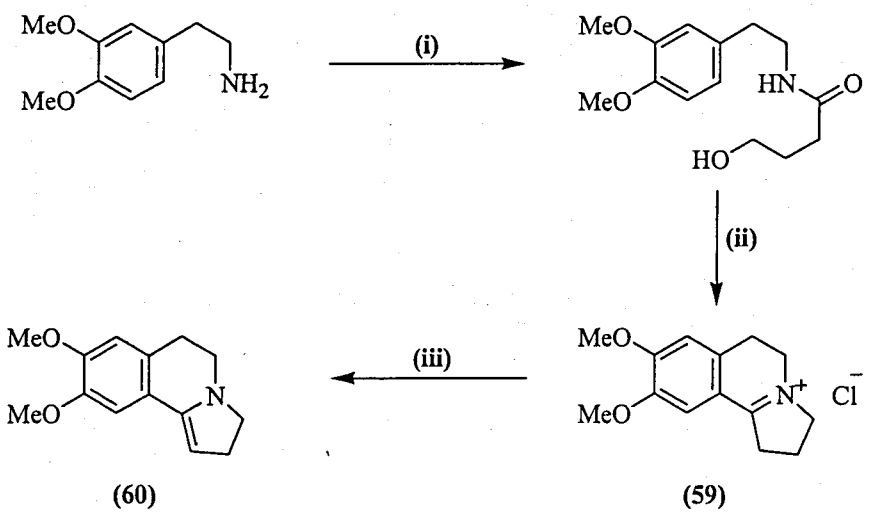


(58) (53)

Reagents: (i) KHMDS; (ii) Acrolein; (iii) AcOH/EtOH; (iv) $NaCNBH_3$.

The first enantioselective synthesis of this alkaloid was reported in 2005 by Czarnocki and co-workers, in which the key synthetic step involved an asymmetric transfer hydrogenation of enamine (60) generated from the iminium salt (59), to introduce chirality (**Scheme 26**).[24]

Scheme 26:

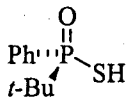


(60) (59)

Reagents: (i) γ-butyrolactone, *p*-xylene, Δ (95 %); (ii) $POCl_3$, Δ (95 %); (iii) Hydroxide (67 %);

The successful synthesis of (+)-crispine A was concluded to be enantiomerically pure within the detection limits of a ^{1}H NMR spectroscopic method using (*R*)-(+)-*tert*-butylphenylphosphinothiolic acid **(61)** as a chiral additive **(Figure 4)**.

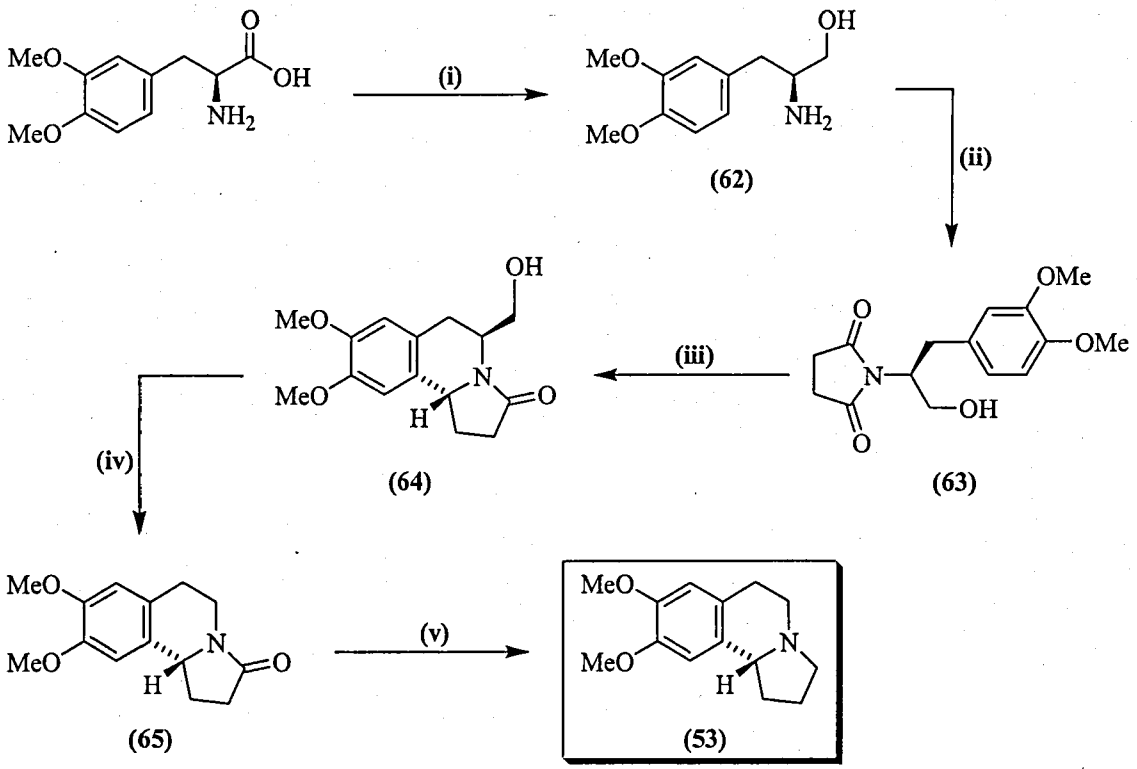
Figure 4: Structure of (*R*)-(+)-*tert*-butylphenylphosphinothiolic acid (61).



(61)

Our approach to (+)-crispine A **(53)** involved the asymmetric synthesis of the pyrroloisoquinoline derivative **(64)** *via* an *N*-acyliminium ion cyclisation as the key step **(Scheme 27)**. Imide **(63)**, prepared as previously reported from β-amino alcohol **(62)** and succinic anhydride was subjected to a sodium borohydride reduction that resulted in direct cyclisation to the tricyclic lactam **(64)** as a single diastereoisomer.

Scheme 27:

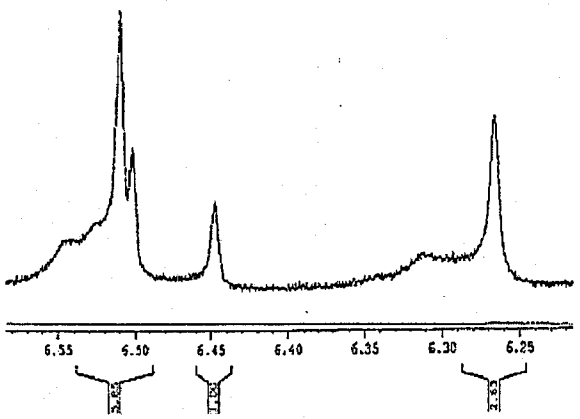


Reagents: **(i)** $LiBH_4$, TMSCl, THF, 24 h (91 %); **(ii)** Succinic anhydride, Et_3N, PhMe, Δ, 18 h (71 %); **(iii)** $NaBH_4$, 2 M HCl, EtOH, 20 h, (78 %); **(iv)** Raney-nickel, PhMe, Δ, 4 h (98 %); **(v)** $LiAlH_4$, THF, Δ, 3 h, then rt, 12 h (76 %).

Presumably, under the acidic reaction conditions, the electron rich methoxy-substituted aryl ring is able to cyclise directly onto the *N*-acyliminium intermediate generated *in situ*. The relative stereochemistry of this advanced intermediate has been confirmed as the expected *trans*-diastereoisomer by single crystal X-ray analysis and is consistent with the conformation models previously rationalised on template systems.[1b] With this cyclic template in hand, we applied the method developed by Kraft,[19] and tested by us, involving a Raney nickel induced decarbonylative removal of the hydroxymethyl functionality. The quality of the Raney nickel in this approach is known to be a critical factor in its success and in our hands, the decarbonylation of **(64)** proceeded smoothly in an impressive 98 % yield to give the corresponding lactam **(65)**. Reductive removal of the lactam carbonyl group was achieved using lithium aluminium hydride, thus completing the synthesis of crispine A **(53)**.

The enantiomeric excess of **(53)** was determined using the ^{1}H NMR spectroscopic method detailed by Czarnocki and Drabowicz,[24] who kindly furnished us with an amount of the chiral shift reagent (*R*)-(+)-*tert*-butylphenylphosphinothiolic acid **(61)**, and was shown to be a disappointingly low value of 50 % *e.e.* **(Figure 5)**.

Figure 5:

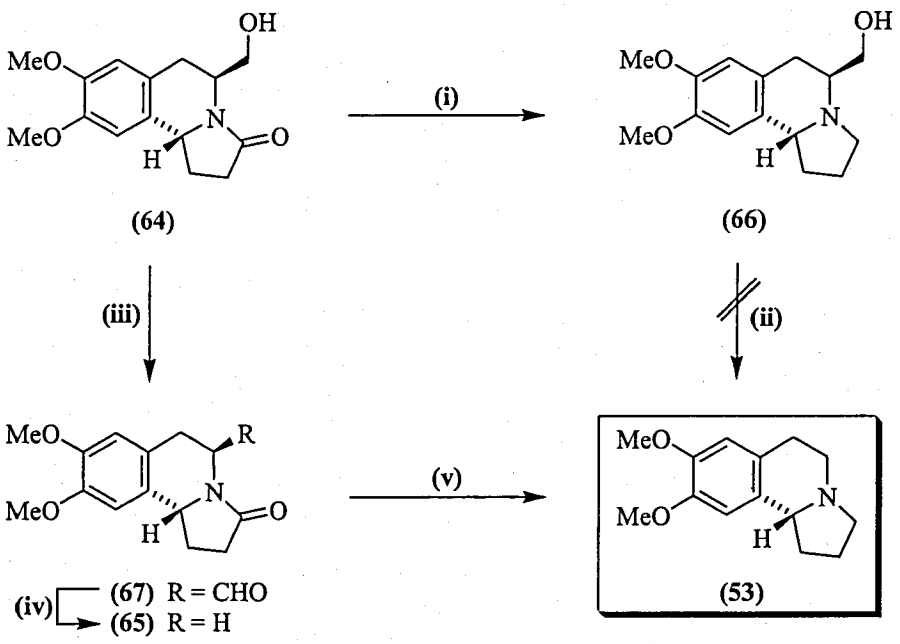


The diagnostic signal in the ^{1}H NMR spectrum used in the determination was the aromatic C(10) proton which, in the presence of the chiral shift reagent, shows distinct, well separated singlet peaks for the enantiomers at 6.27 and 6.45 ppm. In our case, although the level of product *e.e.* was moderate, the major enantiomer was confirmed as the desired (*R*)-crispine A **(53)**.

Although the use of Raney nickel allows for a rapid and high yielding access to crispine A **(53)** from lactam **(64)**, epimerisation of the benzylic stereocentre was occurring at some point in the two-step sequence and thus compromising the enantiomeric purity of the final product.

As an alternative approach, we chose to reverse the order of synthetic transformation and firstly removed the lactam carbonyl to yield amine **(66)** **(Scheme 28)**. No epimerisation was evident during this step within the limits of ^{1}H NMR spectroscopy, however subsequent attempts to remove the hydroxymethyl group to form **(53)** using Raney-nickel resulted only in decomposition of the starting material.

Scheme 28:

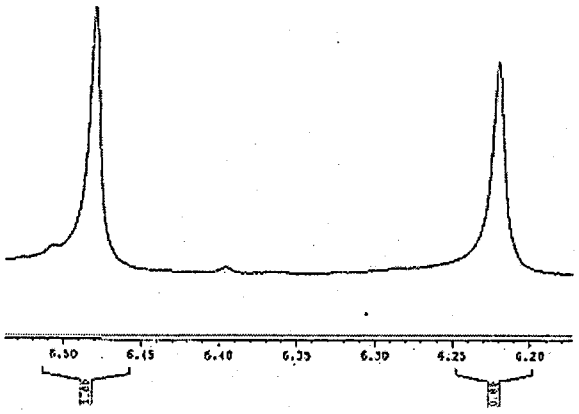


Reagents: **(i)** $LiAlH_4$, THF, Δ, 3 h, then rt, 12 h (97 %); **(ii)** Raney-nickel, PhMe, Δ, 4 h; **(iii)** IBX, EtOAc, Δ, 4 h (99 %); **(iv)** $Rh(PPh_3)_2(CO)Cl$, dppp, *p*-xylene, Δ, 10 d (46 %); **(v)** $LiAlH_4$, THF, Δ, 3 h, then rt, 12 h (58 %).

This issue was ultimately overcome in collaboration with a colleague through the application of a rhodium-induced decarbonylation sequence **(Scheme 28)** previously applied by our group in the work on the *Erythrina* alkaloid series.[13] The template compound **(64)** was oxidised to aldehyde **(67)** in excellent yield using IBX in ethyl acetate under reflux, followed by a rhodium-induced decarbonylation over 10 days to give the amide **(65)**. The target (*R*)-(+)-crispine A **(53)** was achieved following lactam reduction using lithium aluminium hydride in 58 % yield. Compound **(53)** was shown to

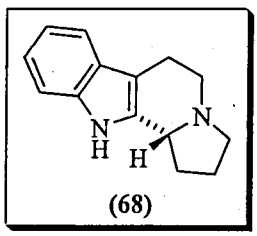
have an *e.e.* greater than 95 % using the ^{1}H NMR spectroscopic technique previously described, as shown in **Figure 6**.

Figure 6:



The optical rotation of our product was determined to be + 95.2 (*c* 1.5, MeOH) and was comparable to that reported by Zhao of the natural product isolate [+ 91.0 (MeOH)].[22]

2.2.3. Total Synthesis of (*R*)-(+)-Harmicine

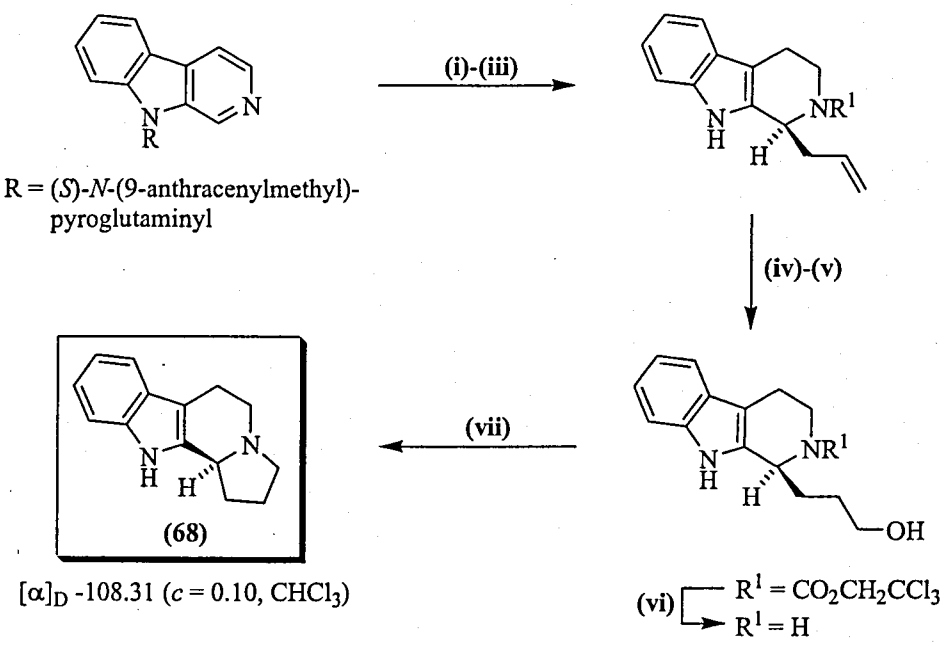


(68)

Leishmaniasis, a disease spread by the bite of the sand fly, is found in tropical and sub-tropical regions, affecting some 12 million people in 88 countries. Symptoms of this disease vary from skin sores to fever, anaemia and damage to the spleen and liver. Common therapies have included the use of antimony containing drugs, although less toxic treatments are currently in development.[25] Preliminary screening of the leaf extracts from the Malaysian plant *Kopsia griffithii* by Kam and Sim showed strong anti-leishmania activity, which was ascribed to the basic fractions containing the indolizidino[8,7-*b*]indole alkaloid, harmicine **(68)**.[26]

Ohsawa and co-workers previously reported the asymmetric synthesis of *ent*-harmicine **(68)** **(Scheme 29)** and assigned the absolute configuration of the natural product as *R*.[27]

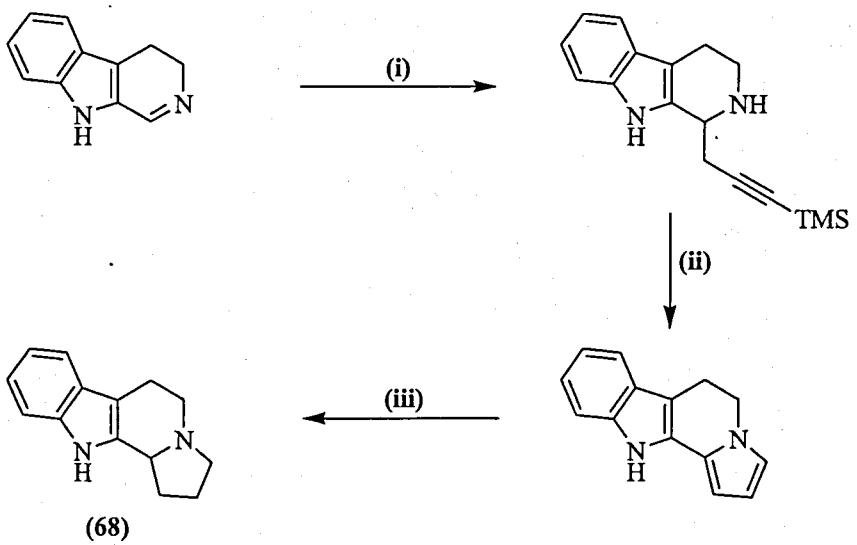
Scheme 29:



Reagents: **(i)** $Bu_3SnCH_2CH{=}CH_2$, $ClCO_2CH_2CCl_3$; **(ii)** NaOH, THF/H_2O; **(iii)** Et_3SiH, TFA (91 %); **(iv)** BH_3, 2 h; **(v)** NaOH, H_2O_2 (79 %); **(vi)** Zn, AcOH, 1 h (77 %); **(vii)** PPh_3, DEAD, DCM, 3 h (84 %).

Knölker and Agarwal have also generated harmicine in racemic form, by utilising the same three-step pyrrole synthesis described for the preparation of the pyrroloisoquinoline alkaloid crispine A **(53) (Scheme 30).**[28]

Scheme 30:

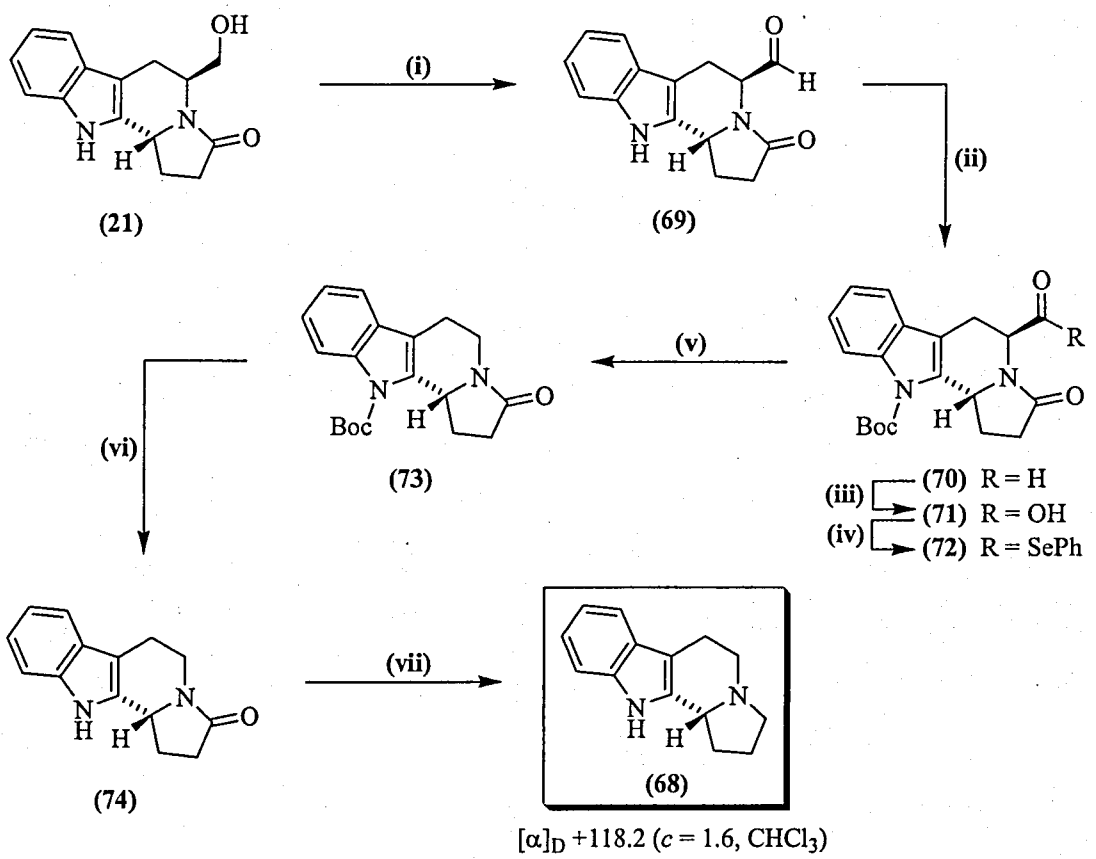


Reagents: **(i)** $TMSC{\equiv}CCH_2MgBr$, $BF_3.OEt_2$, THF 15 h (68 %); **(ii)** AgOAc, DCM, 14 h (77 %); **(iii)** Rh/C, H_2, AcOH/MeOH, 8d (88 %).

Our approach to (+)-harmicine **(68)** began with the highly stereoselective synthesis of the indolizidino[8,7-*b*]indole framework **(21)** as previously described in Section 2.1.2. *via* application of an *N*-acyliminium cyclisation **(Scheme 31)**.

With the cyclic template in hand, our synthesis again required the removal of the hydroxymethyl auxiliary group. Due to the potential epimerisation at the benzylic stereocentre experienced with both the Raney nickel and rhodium induced decarbonylation techniques when applied to indole derivatives, we opted for a tin-mediated deacylation route that has been successfully utilised by our group in recent natural product syntheses, with no signs of racemisation.

Scheme 31:



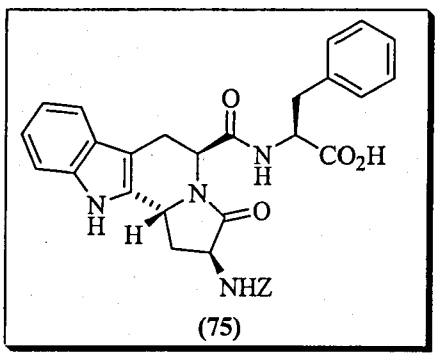
$[\alpha]_D$ +118.2 (c = 1.6, $CHCl_3$)

Reagents: **(i)** IBX, DMSO, 24 h (72 %); **(ii)** Di-*t*-butyl dicarbonate, Et_3N, DMAP, THF, 18 h (98 %); **(iii)** $NaClO_2$, NaH_2PO_4, cyclohexene, MeCN, *t*-BuOH, H_2O, 17 h (79%); **(iv)** $(PhSe)_2$, PBu_3, DCM, 24 h (66 %); **(v)** *n*-Bu_3SnH, AIBN, PhMe, 80 °C, 4 h (90 %); **(vi)** TBAF, THF, Δ, 2 h (69 %); **(vii)** $LiAlH_4$, THF, Δ, 3h, then rt, 12 h (80 %).

Compound **(21)** was oxidised to the carboxylic acid derivative **(71)** *via* the aldehyde **(70)**; from **(71)** we generated the acyl selenide **(72)** and successfully performed a

deacylation in the presence of tri-*n*-butyl tin hydride and azobisisobutyronitrile to give the core indolizidino[8,7-*b*]indole ring system (**73**). Deprotection of the indole nitrogen gave (**74**), from which reductive removal of the lactam carbonyl group completed the synthesis of the natural product (*R*)-(+)-harmicine (**68**), in 80 % yield by treatment with lithium aluminium hydride.[29] The optical rotation of our target compound was determined to be + 118.2 (*c* 1.6, $CHCl_3$) and was comparable to that reported by Kam and Sim for the natural product isolate [+ 119 (*c* 0.086, $CHCl_3$)].[26]

2.3. Application as Potential Building Blocks for Peptide Mimics



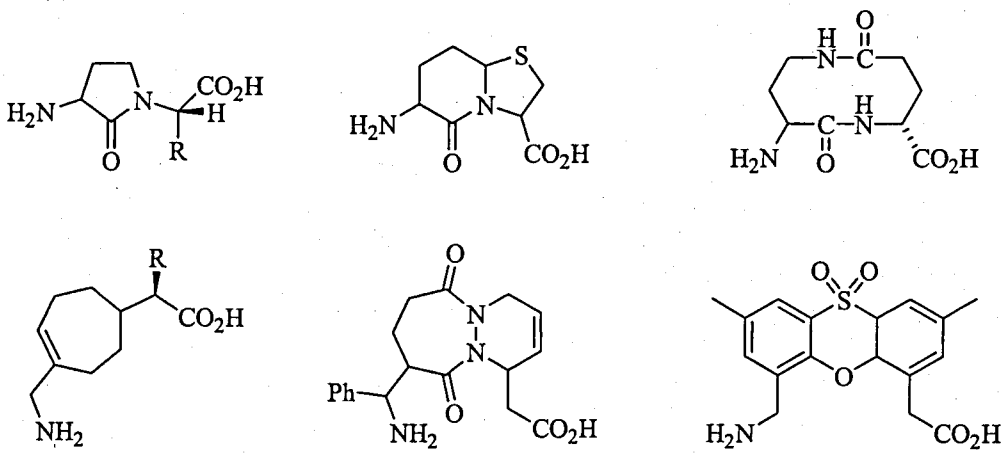
(75)

Having successfully demonstrated the application of our novel *N*-acyliminium chemistry toward simple natural product targets by the removal of functionality from chiral indolizidine templates, we envisaged the elaboration of these core building blocks toward more complex targets, through exploitation of the carbonyl group reactivity. Functionalised indolizino[8,7-*b*]indoles such as (**75**), have displayed the ability to mimic β-turn activity and shown high binding affinity and selectivity for CCK_1 receptors, due to the constrained framework of the lactam backbone. [30]

Considerable attention has been paid toward peptide and protein secondary structure mimics, in particular the β-turn motif that describes an amino acid chain in which the two central residues function to reverse the direction of chain propagation. Due to the frequent appearance of the reverse turns on the external surface of protein molecules, they have been postulated as *loci* for receptor binding and antibody recognition.[31] However, most biologically active peptides are highly flexible molecules and the number of possible conformations complicates attempts to relate structural parameters and activities. Due to these problems, major efforts in recent years have been devoted to

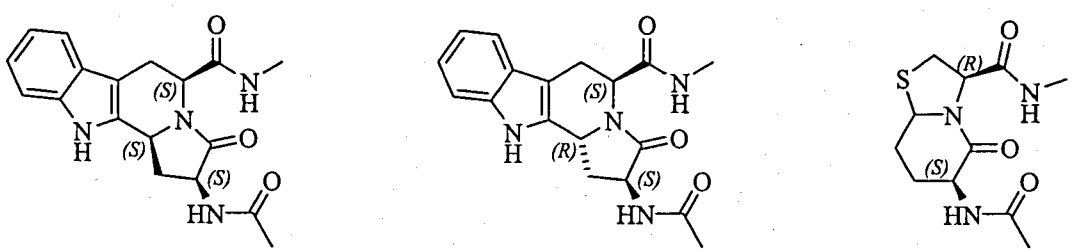
the development of templates that mimic or stabilise these secondary structural features, several of which are shown below in **Figure 7**.[32]

Figure 7:



Extensive research in this field has been conducted by González-Muñiz *et al.* with the synthesis and molecular-dynamic studies of the 2-amino-3-oxohexahydroindolizino [8,7-*b*]indole-5-carboxylate (IBTM) derivatives **(76)** and **(77)**, which have displayed a conformational behaviour similar to that of the bicyclic turned dipeptide (BTD) **(78)**, a competent type-II′ β-turn mimic **(Figure 8)**. Their findings indicate that the ability to fix the desired torsion angles within the bicyclic framework is highly dependent on the stereochemistry at the 11b chiral centre, with the (*R*)-isomer **(77)** showing fewer variations and hence a greater ability to adopt a reverse turn when compared to its (*S*)-counterpart **(76)**.[33]

Figure 8:

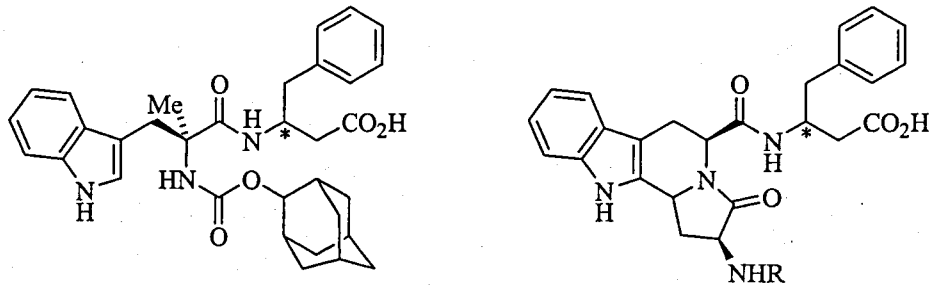


(76) **(77)** **(78)**

In order to investigate whether a turn-like conformation was adopted at the CCK receptor site, a new series of constrained depeptoid derivatives **(81)** and **(82)** was

developed by incorporation of the IBTM skeleton into the known receptor antagonists **(79)** and **(80)** (CCK_2 and CCK_1 selective, respectively) **(Figure 9)**.[34]

Figure 9:



(79) (PD-140547) (*, *S*)
(80) (PD-140548) (*, *R*)

(81) R = Z
(82) R = Boc

Cholecystokinin (CCK) is a peptide hormone and neurotransmitter, which has been implicated in the regulation of gastrointestinal functions and behaviour by interaction with specific receptors. Two CCK receptor subtypes have been characterised: CCK_1 receptors that predominate in the periphery and CCK_2 receptors located in the central nervous system (CNS). Changes in CCK levels found in the tissues and sera of patients with various disease states, including schizophrenia and eating disorders, models of Parkinson's disease, cancer, anxiety and pain, indicate the potential utility of CCK receptor ligands as therapeutic agents.[30]

The results of this investigation demonstrated that compounds **(81)** and **(82)** containing an 11b*R* configuration showed a higher CCK_1 binding potency of one to two orders of magnitude compared to the corresponding 11b*S* isomers. Due to the greater ability of 11b*R* conformers to mimic a type II′ reverse turn, these results indicate that a turn-like conformation within the dipeptoid backbone is favourable for CCK_1 receptor recognition, and that the high degree of constraint imposed by the IBTM framework is not tolerated by CCK_2 receptor binding sites, making them highly selective.

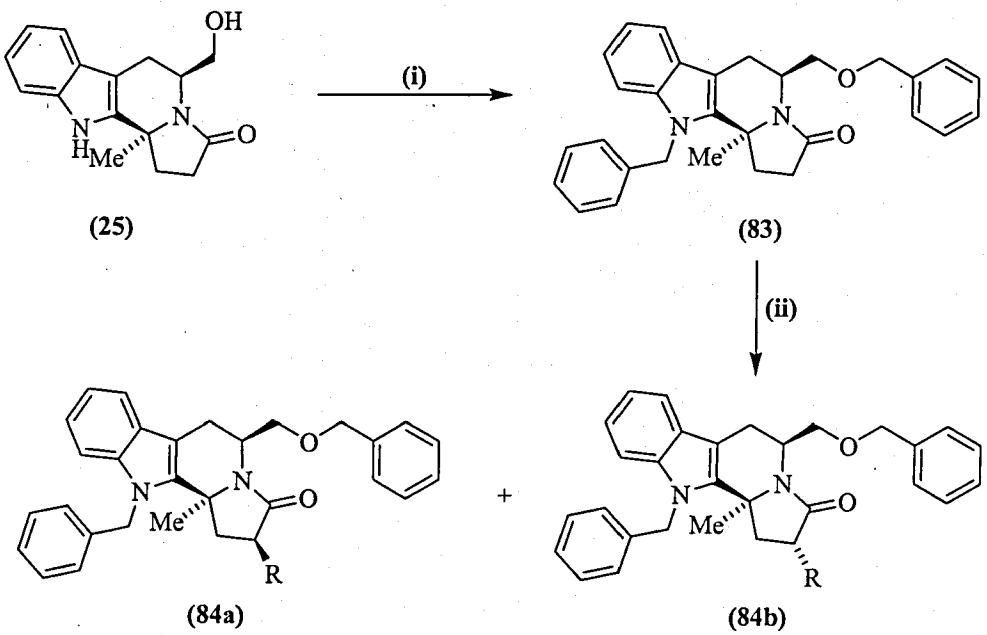
2.3.1. Enolate Addition Studies

The presence of the lactam carbonyl group within the structural building blocks **(21)** and **(25)** provides a handle for regiospecific derivatisation through the exploitation of enolate addition chemistry. It was envisaged that the presence of asymmetry in the

molecule could also exhibit some level of stereocontrol for the incorporation of an *N*-terminal moiety and provide a novel route to constrained peptides such as **(75)** with the ability to adopt a β-turn conformation.

An initial study was undertaken involving the alkylation of the indolizine[8,7-*b*]indole template **(25)** using simple electrophiles of varying steric bulk, in order to evaluate the effects on the stereoselective outcome. The procedure is outlined in **Scheme 32.**

Scheme 32:



Reagents: **(i)** NaH, BnBr, DMF, 3 h (72 %); **(ii)** LDA, RX, THF, −78 °C to rt, 16 h.

Protection of the acidic protons present on the indole nitrogen and the hydroxyl group was initially required to avoid any unwanted side-reactions at either position during treatment with the hindered base. Deprotonation of **(25)** with sodium hydride followed by treatment with benzyl bromide afforded the bis-protected compound **(83)** in 72 % yield. With the protected indolizine[8,7-*b*]indole **(83)** in hand, we turned our attention toward the proposed functionalisation of our substrate. Enolisation of **(83)** was achieved with lithium diisopropylamine (LDA), which upon addition of the desired electrophile produced the target compound **(84)** as a mixture of diastereoisomers, the ratio of which was determined from the crude ^{1}H NMR spectrum.

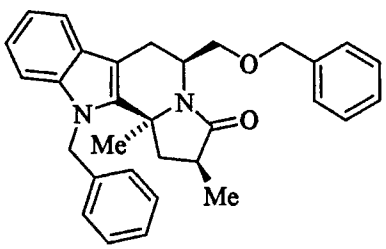
The results are summarised below in Table 1:

Entry	R	X	Product	Yield (%)	Ratio (a:b)
1	Me	I	**85 a/b**	67	4:1
2	Et	I	**86 a/b**	70	1:8
3	*i*-Pr	I	**87 a/b**	79	1:10
4	Bn	Br	**88 a/b**	52	1:2

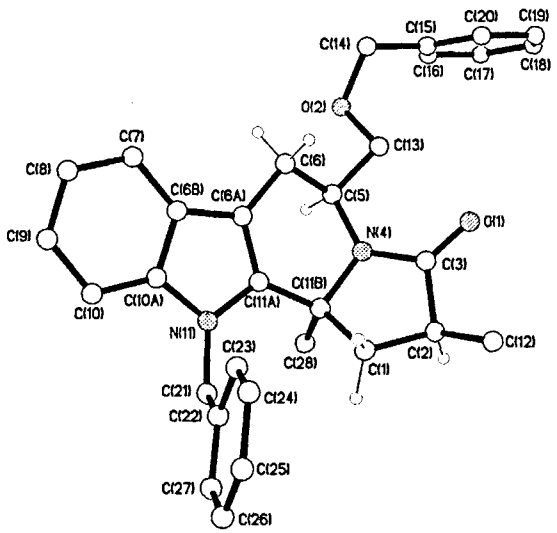
From the results, it was evident that reactions of substrate **(83)** with alkyl iodides (Entries 1-3) show an increase in stereoselectivity with increasing steric bulk of the electrophile. It was surprising to discover that the stereoselectivity of the alkylation with benzyl bromide (Entry 4) was significantly reduced in this case. This could be due to the planar nature of the benzyl electrophile decreasing the steric interactions at this angle of electrophilic attack. The increased reactivity of the electrophile could also lead to lower selectivity for alkylation, as is the case with the alkylation of pyridinones.[35]

The relative stereochemistry at the newly formed chiral centre was determined by single crystal X-ray analysis for the major isomers from the methyl, isopropyl and benzyl alkylation reactions **(Figure 10, 11 and 12 respectively)**.

Figure 10: Single Crystal X-Ray Structure of (85a).



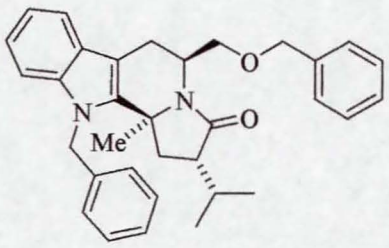
(85a)



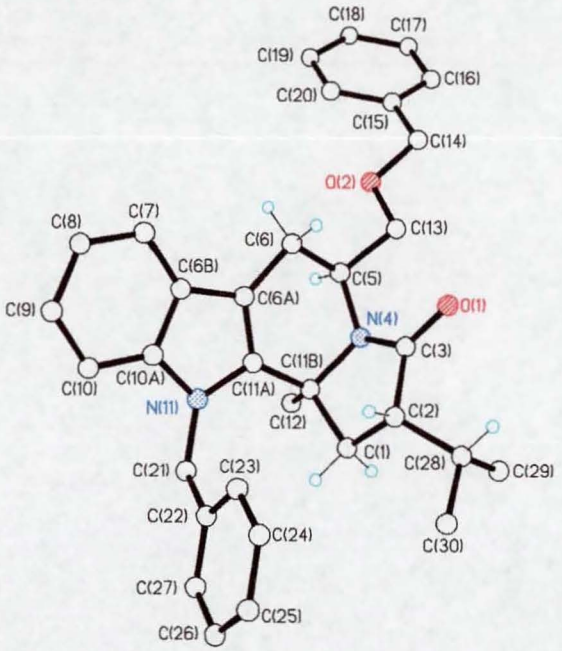
Interestingly, the major diastereoisomer from the methyl alkylation was formed in a 4:1 ratio in favour of the *anti* isomer with respect to the angular methyl substituent and the

C-2 alkyl group **(85a) (Figure 10)**. When the steric bulk of the electrophile was increased to isopropyl, the diastereoisomeric ratio increased to 10:1, however the major product of the reaction was that formed from electrophilic attack at the opposite face, displaying *syn* relative stereochemistry **(87b) (Figure 11)**.

Figure 11: Single Crystal X-Ray Structure of (87b).

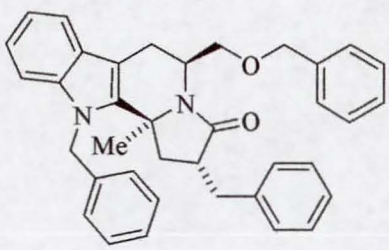


(87b)

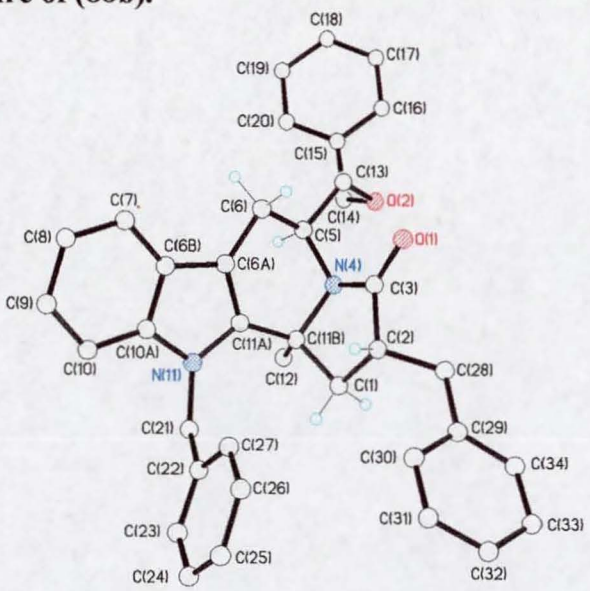


This trend continued in the benzyl alkylation in which the *syn* isomer **(88b)** was again favoured as the major product **(Figure 12)**, however the stereoselectively was greatly reduced to a 2:1 ratio in this case, as previously stated.

Figure 12: Single Crystal X-Ray Structure of (88b).

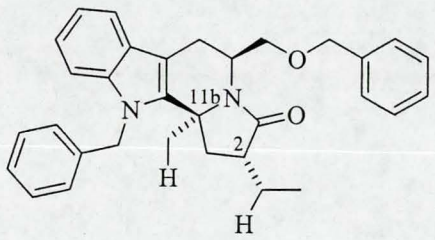


(88b)



This trend was also evident in the ethyl alkylation where 1D nOe studies suggest the presence of a *syn* relationship between the alkyl groups at positions 2 and 11b of the favoured product **(86b)** formed in an 8:1 ratio **(Figure 13)**.

Figure 13: 1D nOe Interactions for (86b).



(86b)

The presence of a nOe between the protons situated on the methyl group at position 11b and the ethyl group at position 2 was consistent with the proposed structure. As we were unable to isolate the minor diastereoisomer we were unable to carry out a comparative nOe study.

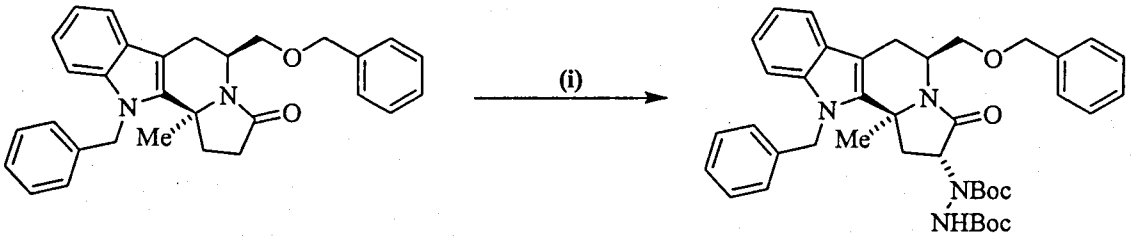
It is assumed that the stereochemical outcome of these alkylation reactions is due to the "concave" nature of the chiral indolizidine ring structure. The sterically smaller methyl electrophile is able to manoeuvre into this space and attack at the top face of the molecule. As the steric bulk of the electophile increase, the interaction with the bicyclic ring structure consequently increases and retards attack from the top face of the molecule, as is the case for the ethyl, isopropyl and benzyl electrophiles.

With potential β-turn polypeptide targets such as **(75)** in mind,[30] we turned our attention toward the electrophilic α-amination of our indolizine[8,7-*b*]indole enolate precursor **(83)**. The introduction of an amine functionality adjacent to a carbonyl group using electrophilic aminating agents is a topical area of research, particular with respect to the synthesis of α-amino acids,[36] and the formation of a new chiral C-N bond is key to our synthesis of enantiomerically pure β-turn mimetics.

The initial choice of aminating agent was a commercially available diazene dicarboxylate due to the high reactivity and large steric bulk. It was intended that, in

tandem with the asymmetry present in our substrates, the steric size would induce high levels of stereoselectivity as shown in **Scheme 33**.

Scheme 33:

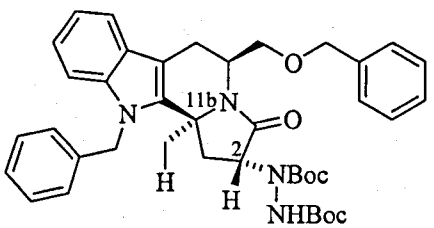


(83) **(89)**

Reagents: **(i)** LDA, DBAD, THF, −78 °C to rt, 16 h, (82 %).

Treatment of the bis-protected indolizine[8,7-*b*]indole derivative **(83)** with LDA at −78 °C and subsequent addition of di-*tert*-butyl azodicarboxylate (DBAD) formed exclusively the target α-aminocarbonyl compound **(89)** as a single diastereoisomer. A nOe study was conducted to confirm the relative stereochemistry present at the newly formed chiral centre generated from α-amination **(Figure 14)**.

Figure 14: 1D nOe Interactions for (89).



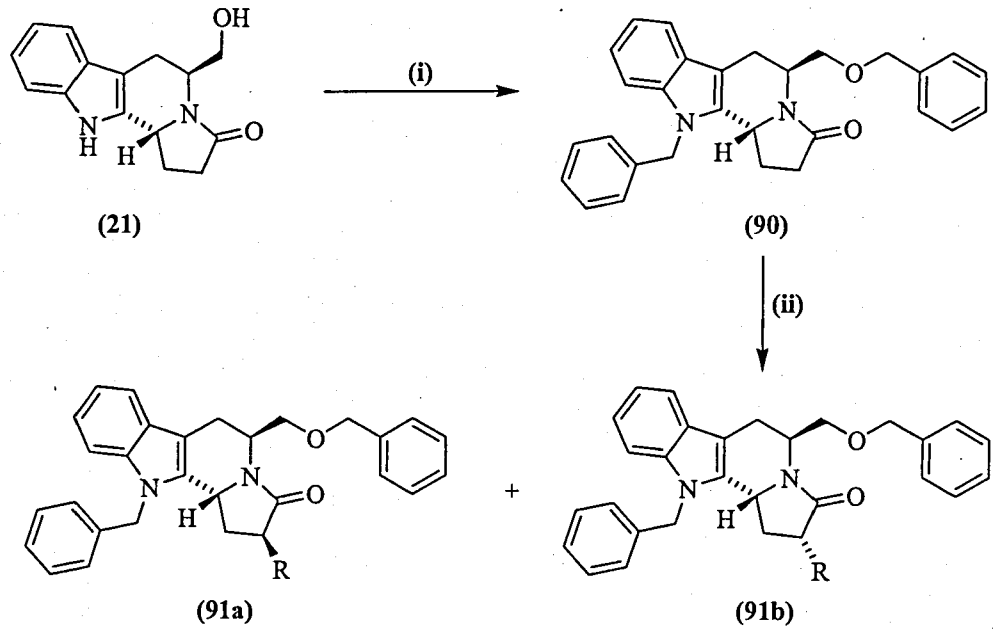
(89)

As with the major product of the ethyl alkylation **(86b)**, the absence of a nOe between the protons situated on the methyl group and position 2 suggests the amine moiety adopts a *syn* conformation with respect to the 11b methyl group. As we were unable to isolate the minor diastereoisomer we were unable to carry out a comparative nOe study. It should be noted that the observation of *syn* relative stereochemistry is consistent with the trend previously observed for the alkylation of **(83)** with large electrophiles.

Following these initial investigations into the α-addition of precursor **(25)**, we deemed it would be interesting to observe the effect, if any, on diastereoselectivity and face

selectivity of the enolate addition using the analogous *syn*-indolizine[8,7-*b*]indole template **(21)** **(Scheme 34)**.

Scheme 34:



Reagents: **(i)** NaH, BnBr, DMF, 3 h (97 %); **(ii)** LDA, RX, THF, −78 °C to rt, 16 h.

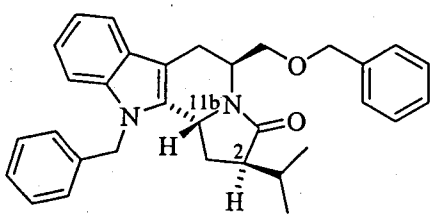
Protection of the indole nitrogen and the primary alcohol group was again necessary to avoid any unwanted side-reactions at either position during treatment with base. Protection of **(21)** with sodium hydride followed by benzyl bromide afforded the bis-protected compound **(90)** in quantitative yield. Treatment of the indolizine[8,7-*b*] indole derivative **(90)** with LDA and the desired electrophile under the standard protocol generated compound **(91)** as a mixture of diastereoisomers, the ratio of which was again determined from the crude ^{1}H NMR spectra.

The results are summarised below in Table 2:

Entry	R	X	Product	Yield (%)	Ratio (a:b)
5	*i*-Pr	I	**92 a/b**	58	3:1
6	Bn	Br	**93 a/b**	58	1:1
7	DBAD	-	**94 a/b**	57	6:1

As we expected, the diastereoselectivities observed for both the alkylation and amination procedures of **(90)** were lower in comparison to their 11b methyl counterpart **(83)**. It is reasonable to propose that this is due to the reduction of steric bulk provided by the angular methyl substituent, hence decreasing the interaction with the attacking electrophile. The relative stereochemistry of the major isomer formed from the isopropyl alkylation (Entry 5) was determined by 1D nOe studies (**Figure 15**).

Figure 15: 1D nOe Interactions for (92a).



(92a)

The absence of a nOe between the protons situated at positions 2 and 11b of product **(92a)** is consistent with the proposed *trans* relationship. As we were unable to isolate the minor diastereoisomer we were unable to carry out a comparative nOe study.

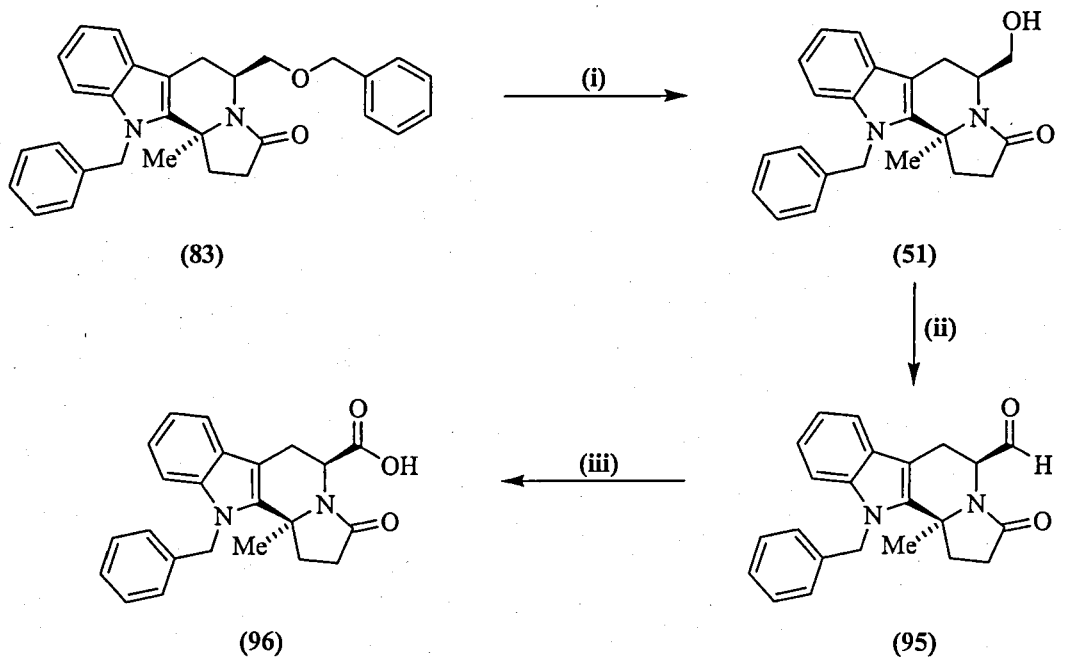
In conclusion, we have discovered that the electrophilic addition of the indolizine[8,7-*b*] indole template is a highly stereoselective process which increases significantly with the size of the electrophile. The relative stereochemistry of these addition products is highly dependent on the stereochemistry present at the 11b asymmetric centre, with the enolate addition of sterically large carbophiles forming products containing a *syn* relative stereochemistry between the newly introduced α-substituent and the group at ring junction 11b. In addition, we have also found that the steric bulk of the 11b substituent exerts some influence on the diastereoselective ratio of the enolate addition.

2.3.2. Manipulation of the Hydroxymethyl Auxiliary

To determine the potential of the α-aminated compounds **(89)** and **(94)** as β-turn mimics, the *C*-terminal hydroxyl group required modification to be consistent with the known IBTM β-turn mimic **(75)** reported by González-Muñiz *et al.*[30] However the poor resolution of these compounds in the ^{1}H NMR, due to the slow rotation about the planar carbamate groups made assignment difficult. For this reason, a test study was carried

out on the core indolizine[8,7-*b*]indole derivative **(83)**, as shown in **Scheme 35**, to avoid the need for elevated temperature ^{1}H NMR experiments and give a detailed understanding of the conversion required.

Scheme 35:



(83) **(51)** **(95)** **(96)**

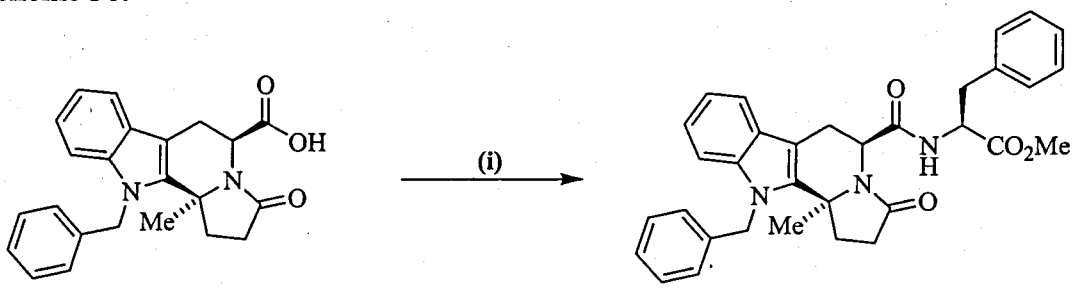
Reagents: **(i)** Pd/C, H_2, EtOH, 50 psi, 4 d (78 %); **(ii)** IBX, DMSO, 24 h, (65 %); **(iii)** $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, MeCN, *t*-BuOH, H_2O, 17 h (75 %).

Initial selective debenzylation of the hydroxymethyl auxiliary was achieved under standard hydrogenolysis conditions in the presence of a palladium catalyst to yield the desired alcohol **(51)**. A variety of methods have previously been attempted within our group for the direct oxidation of indolizine[8,7-*b*]indole alcohol derivatives to the corresponding carboxylic acid which include, Jones oxidation, pyridinium dichromate and treatment with potassium permanganate, however all have failed to produce the target carboxylic acid. Due to these previous difficulties, we utilised the more established two-step procedure involving formation of the aldehyde **(95)** by mild oxidation of **(51)** with IBX followed by further oxidation to the carboxylic acid derivative **(96)** using sodium chlorite.

An appropriate coupling reaction between the indolizine[8,7-*b*]indole acid derivative **(96)** and an amino ester was then envisaged which allows control of the new

asymmetric centre by consideration of the substrate chirality. This is an important consideration as the stereochemistry at this position has shown significant influence towards receptor selectivity, as seen in the known antagonists **(79)** and **(80)** (CCK_2 and CCK_1 selective, respectively) shown in **Figure 9**.[34] In this case, (*S*)-phenylalanine methyl ester hydrochloride **(97)** was coupled to the carboxylic acid **(96)** in the presence of 1-ethyl-3-[(dimethylamino)propyl] carbodiimide hydrochoride (EDCI) with 1-hydroxyazabenzotriazole acting as a racemisation suppressant, to generate the desired dipeptide compound **(98)** as shown in **Scheme 36**.

Scheme 36:



(96) **(98)**

Reagents: **(i)** *L*-Phenylalanine methyl ester hydrochloride **(97)**, EDCI, HOABt, NMM, DCM, −15 °C, 3 h (77 %).

With an established procedure in place to modify the hydroxymethyl auxiliary to a dipeptide moiety, we aimed to demonstrate the synthetic potential of this methodology towards a range of chiral α-aminated lactams and allow a highly controlled synthesis of a range of potential β-turn mimics.

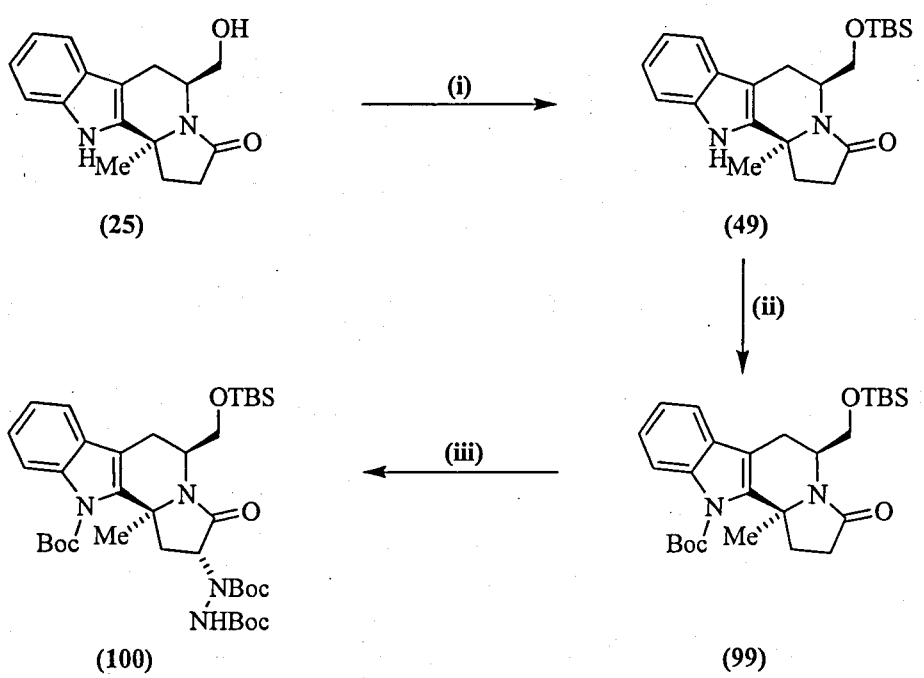
2.3.3. The *Anti*-Indolizino[8,7-*b*]indole Polypeptide

Before the derivatavation of the *anti*-aminated template **(89)** was attempted, the initial protecting group strategy of the tetracyclic template **(25)** was revised. It was felt that the 4 day reaction time required to successfully remove the benzyl ether and the harsh conditions necessary to deprotect a benzylic indole group could be optimised with an improved choice of protecting group.

The hydroxyl moiety was initially protected as the *tert*-butyldimethylsilyl ether **(49)** upon treatment of the template **(25)** with imidazole, catalytic 4-dimethylaminopyridine and *tert*-butyldimethylsilylchloride, which was successful in 81 % yield **(Scheme 37)**.

Subsequent Boc protection of the indole was achieved in near quantitative yield by treatment with triethylamine, 4-dimethylaminopyridine and di-*tert*-butyl dicarbonate to form the bis-protected substrate **(99)**, which could be selectively deprotected at either position under the appropriate conditions. The enolate of **(99)**, formed upon treatment with LDA, was then reacted with the DBAD under the standard protocol to provide the α-aminated compound **(100)** exclusively as a single diastereoisomer in 89 % yield.

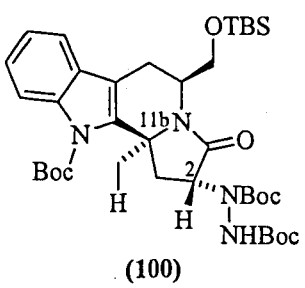
Scheme 37:



Reagents: (i) TBSCl, imidazole, DMAP, DCM, 4 h (81 %); (ii) Di-*t*-butyl dicarbonate, Et_3N, DMAP, THF, 18 h, (92 %); (iii) LDA, DBAD, THF, −78 °C to rt, 16 h, (89 %).

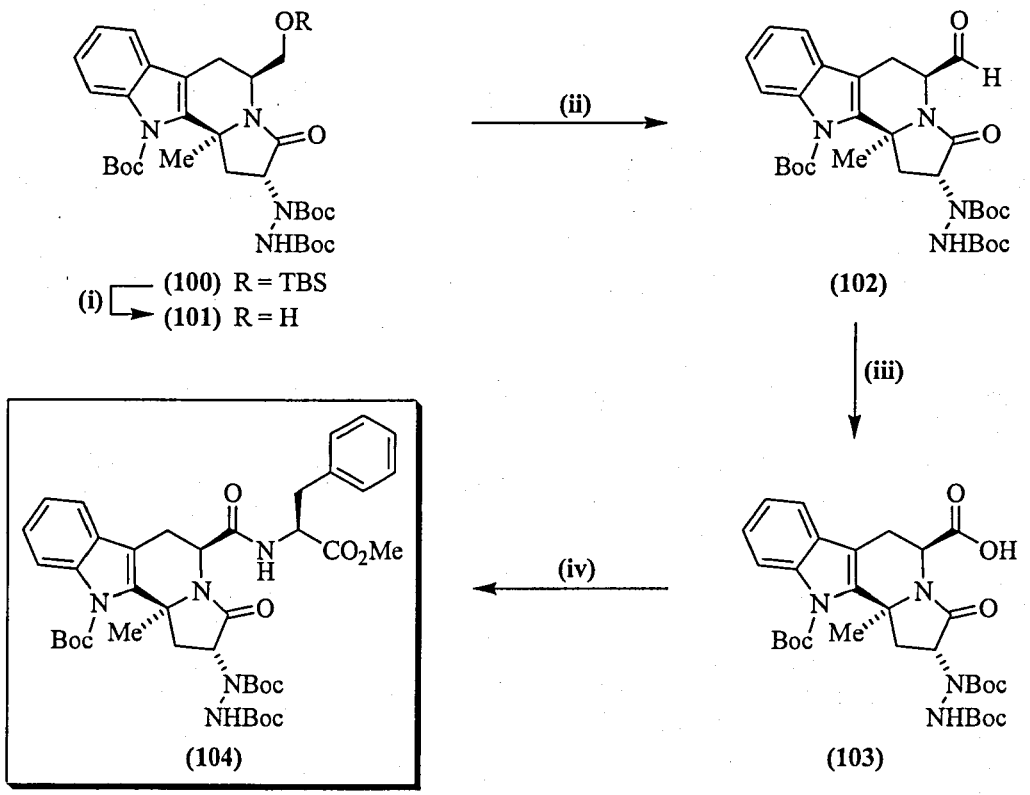
The nOe interactions displayed by the isolated product **(100)** were consistent with the trends previously observed for the α-substitution of **(83)** and indicated the expected *syn* relative stereochemistry between the angular methyl and hydrazine groups **(Figure 16)**.

Figure 16: 1D nOe Interactions for (100).



Treatment of **(100)** with TBAF in tetrahydrofuran efficiently formed the free alcohol **(101)** in quantitative yield as shown in **Scheme 38**. The free hydroxyl **(101)** was then oxidised to the aldehyde **(102)** in 94 % yield by treatment with IBX in refluxing ethyl acetate, a protocol successfully established by Finney and More.[37]

Scheme 38:

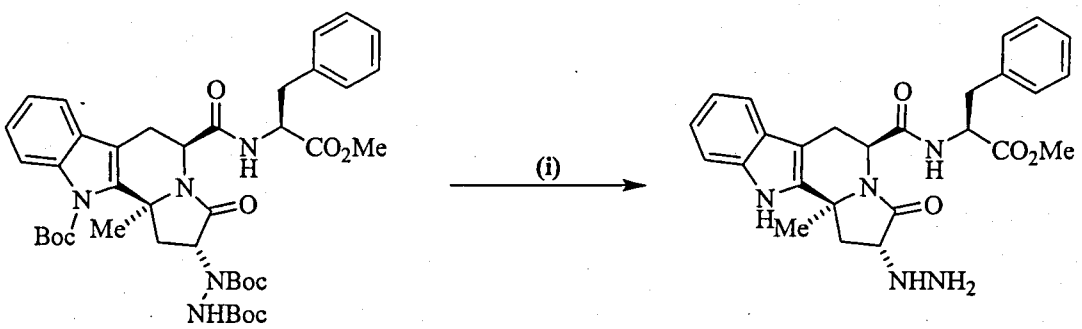


Reagents: **(i)** TBAF, THF, 5 min (98 %); **(ii)** IBX, DMSO, 20 h (97 %); **(iii)** $NaClO_2$, NaH_2PO_4, 1-methyl-cyclohexene, MeCN, *t*-BuOH, H_2O, 17 h (83 %); **(iv)** *L*-Phenylalanine methyl ester hydrochloride **(97)**, EDCI, HOABt, NMM, DCM, −15 °C, 3 h (46 %).

Oxidation to the carboxylic acid **(103)** was achieved with sodium chlorite, which was consequently reacted with the amine moiety of the (*L*)-phenylalanine methyl ester **(97)** in the presence of EDCI and 1-hydroxyazabenzotriazole to generate the peptide **(104)**.

The Boc protecting groups present in **(104)** were easily removed in the presence of trifluoroacetic acid as shown in **Scheme 39**; however purification of the resultant amine derivative **(105)** proved difficult.

Scheme 39:



(104) (105)

Reagents: (i) TFA, DCM, 30 min.

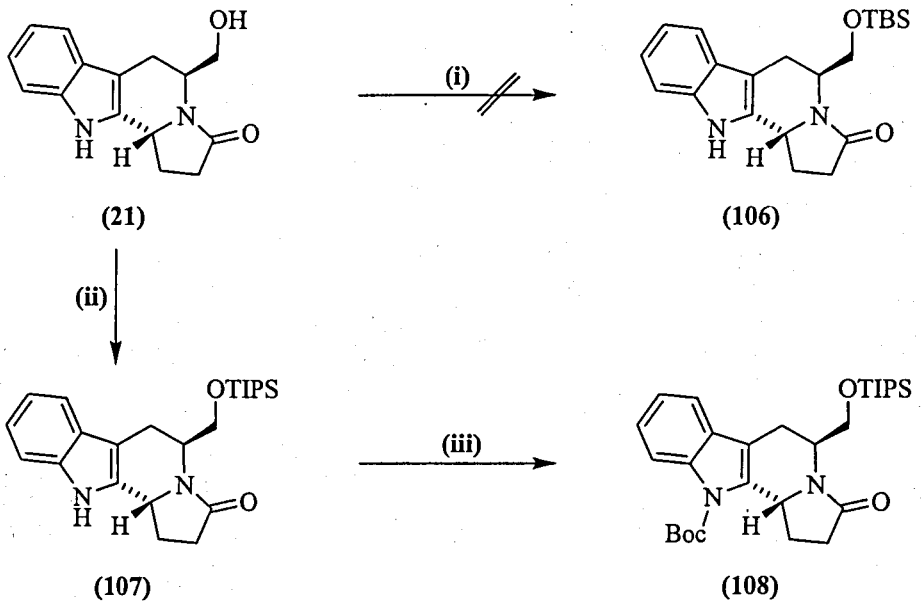
The (2*R*,5*S*,11b*S*,3′*S*) constrained dipeptoids **(104)** and **(105)** still represent a novel stereochemical configuration to the reported IBTM frameworks probed by González-Muñiz for type-II and type-II′ β-turn activity,[30] and have the potential to exhibit a turn-like conformation and perhaps display affinity for the CCK receptor subtype.

2.3.4. The *Syn*-Indolizino[8,7-*b*]indole Polypeptide

As detailed earlier in this section, extensive studies conducted by González-Muñiz and co-workers have shown that the 11b*R* IBTM skeletons, such as **(75)** have a greater ability to adopt a type-II′ β-turn conformation and exhibit a higher binding affinity for CCK_1 receptors by one or two orders of magnitude when compared to their 11b*S* counterparts. With this in mind, we attempted to apply the methodology shown previously to the 11b*R*-indolizino[8,7-*b*]indole building block **(21)**, in the hope of generating a functionalised polypeptide which displays the stereochemical requirements of the known type-II′ β-turn IBTM mimic and selective CCK_1 receptor antagonist **(75)**, constructed by González-Muñiz *et al.*[30]

With the core indolizino[8,7-*b*]indole **(21)** prepared in asymmetric fashion as detailed in Section 2.1.2, the next step was protection of the hydroxymethyl auxiliary as the *tert*-butyldimethylsilyl ether **(106)** **(Scheme 40)**. An initial problem was the poor solubility of our substrate **(21)** in the reaction solvent, dichloromethane. For this reason, the silyl protection was performed under analogous conditions replacing the solvent with *N*,*N*-dimethylformamide, a common medium for this style of protection.

Scheme 40:

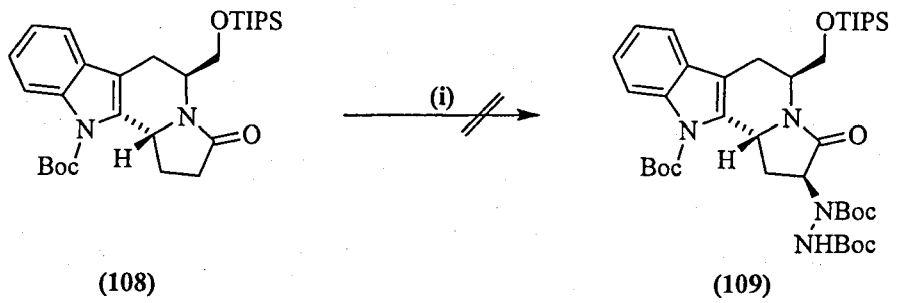


Reagents: (i) TBSCl, imidazole, DMAP, DCM, 24 h; (ii) TIPSCl, imidazole, DMF, 6.5 h (98 %); (iii) Di-*t*-butyl dicarbonate, Et_3N, DMAP, THF, 16 h, (73 %).

Under these revised conditions, the silyl protection proved unsuccessful on numerous attempts, with only starting material recovered. An alternate triisopropylsilyl protecting agent was then attempted under similar basic conditions in *N,N*-dimethylformamide, which successfully formed the corresponding triisopropylsilyl ether **(107)** in excellent 98 % yield as shown in **Scheme 40**.

With a silyl protected indolizino[8,7-*b*]indole **(107)** in hand, protection of the indole was achieved as previously detailed using a Boc protecting group formed by treatment with di-*tert*-butyl dicarbonate to give the bis-protected compound **(108)** in 92 % yield. Substrate **(108)** was then subjected to the amination conditions previously applied to its 11b*S*-methyl-counterpart as described in Section 2.3.3, however only starting material was isolated from the reaction **(Scheme 41)**. The reaction was repeated several times with increased levels of base and electrophile, with all attempts proving unsuccessful.

Scheme 41:

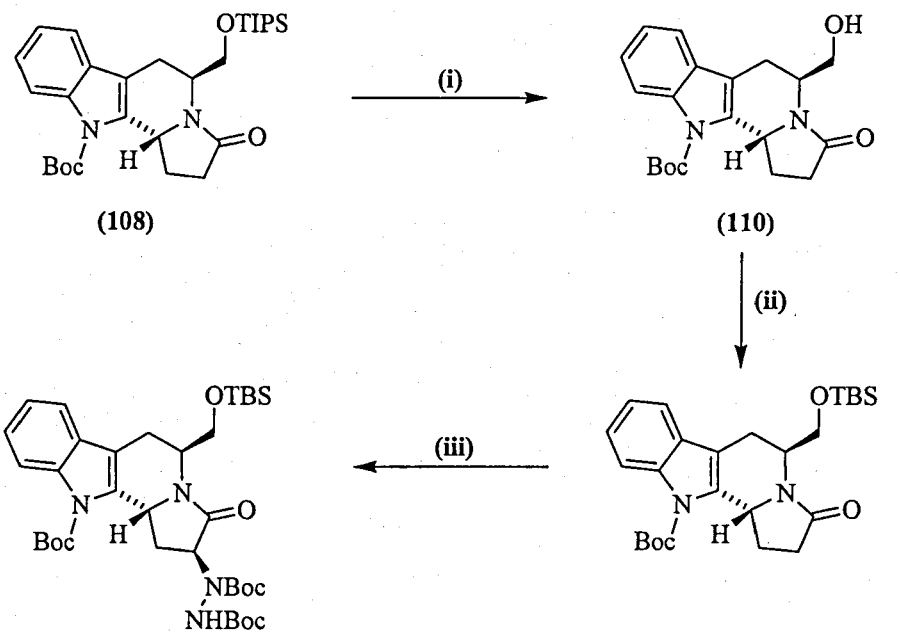


(108) (109)

Reagents: (i) LDA,.DBAD, THF, −78 °C to rt, 16 h.

We reasoned that this unexpected lack of reactivity was due to the increased steric influence of the triisopropylsilyl group. From the trends displayed in our alkylation studies detailed in Section 2.3.1, we envisage that the sterically large DBAD electrophile would attack from the top face of our substrate **(108)** as it is unable to manoeuvre within the concave lactam. It is possible that this alternate protecting group is hindering this mode of attack and thus preventing the formation of the product **(109)**.

Scheme 42:

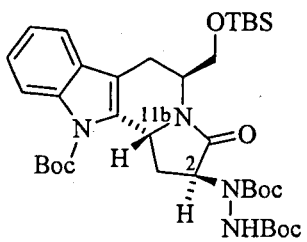


(108) (110) (111) (112)

Reagents: (i) TBAF, THF, 10 min (72 %); (ii) TBSCl, imidazole, DMAP, DCM, 4 h, (85 %); (iii) LDA, DBAD, THF, −78 °C to rt, 16 h, (86 %).

To consolidate this theory, the triisopropylsilyl derivative **(108)** was converted to the corresponding *tert*-butyldimethylsilyl ether **(111)** by means of TBAF induced deprotection to restore the alcohol **(110),** and subsequent treatment with *tert*-butyldimethylsilylchloride under basic conditions **(Scheme 42).** The *tert*-butyl dimethylsilyl ether **(111)** was then treated with LDA at –78 °C to generate the desired enolate and upon addition of the DBAD electrophile, to our delight formed the target α-aminocarbonyl as a 6:1 mixture of diastereoisomers. A nOe study was conducted on the major diastereoisomer **(112)** to confirm the relative stereochemistry present at the newly formed α-aminated chiral centre **(Figure 17).**

Figure 17: 1D nOe Interactions for (112).

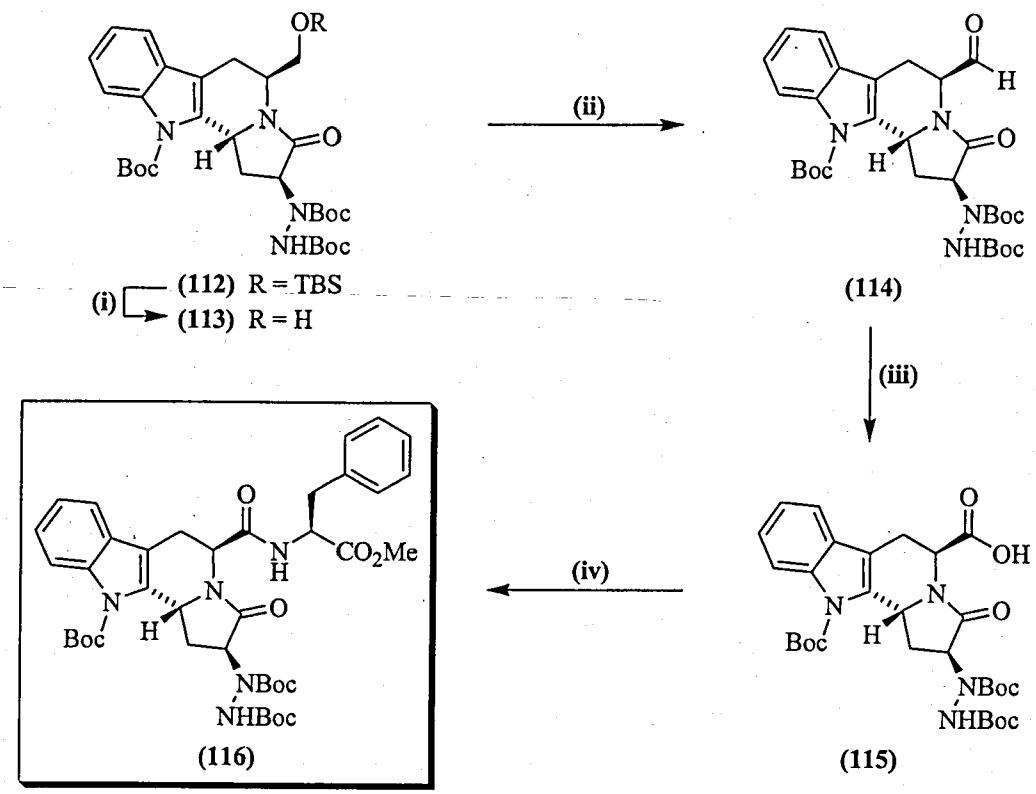


(112)

The absence of a nOe between the hydrogen atoms situated at positions 2 and 11b suggests they are situated in a *trans* relationship. As we were unable to isolate the minor diastereoisomer we were unable to carry out a comparative nOe study. This result continues the trend of the expected *syn* addition of sterically large carbophiles with respect to the substituent at the 11b ring junction.

With the desired aminated compound in hand, **(112)** was then subjected to the same derivatisation methodology detailed earlier. The silyl protecting group was efficiently removed in the presence of TBAF at room temperature and the resultant hydroxyl moiety **(113)** was successfully oxidised to the carboxylic acid **(115)** *via* the aldehyde **(114)** upon treatment with IBX followed by sodium chlorite **(Scheme 43).** Coupling of the acid substrate **(115)** with the (*S*)-amino ester **(97)** was achieved in 64 % yield with the carbodiimide coupling agent EDCI to complete the formation of polypeptide **(116).**

Scheme 43:



Reagents: **(i)** TBAF, THF, 20 min (72 %); **(ii)** IBX, EtOAc, Δ, 5 h (94 %); **(iii)** $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, MeCN, *t*-BuOH, H_2O, 17 h (85 %); **(iv)** *L*-Phenylalanine methyl ester hydrochloride **(97)**, EDCI, HOABt, NMM, DCM, −15 °C, 3 h (64 %).

This synthesis demonstrates the versatility of the indolizino[8,7-*b*] indole building block **(21)** with a stereoselective α-amination and subsequent manipulation to produce the constrained polypeptoid **(116)**, which incorporates all the stereochemical requirements displayed by the known type II′ β-turn mimetic **(75)**. It has been shown that the type of β-turn is critical for maintaining good selectivity for the CCK_1 receptor.[30] Thus the restricted dipeptoid analogue **(116)**, containing a type II′ β-turn backbone, is apparently devoid of affinity for the CCK_2 receptor and therefore could represent a new potent and selective CCK_1 receptor antagonist.

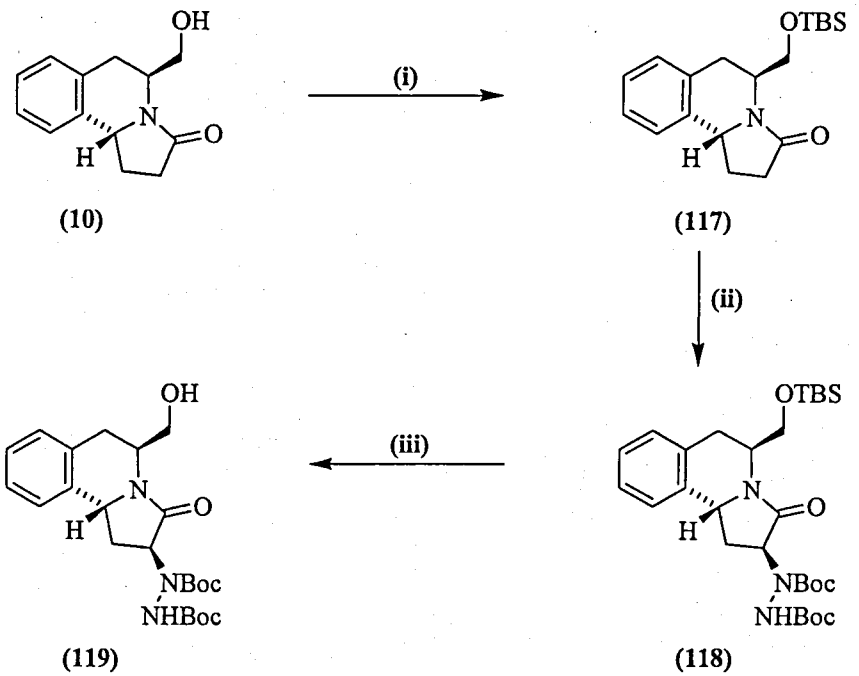
2.3.5. The *Syn*-Pyrrolo[2,1-*a*]isoquinoline Polypeptide

To the best of our knowledge, the application of substituted chiral pyrroloisoquinoline derivatives as potential CCK receptor antagonists has not been explored, which is surprising due to the structural similarities with the indolizino[8,7-*b*]indole ring system.

The pyrroloisoquinoline **(10)** contains the necessary bicyclic framework responsible for the type II′ β-turn activity possessed by the IBTM derivatives utilised by González-Muñiz and in theory, could act as a potent and selective CCK_1 receptor antagonist.[30] With this in mind, we envisaged a stereoselective synthesis of a new type of constrained polypeptide, which incorporates the pyrroloisoquinoline framework **(10)** and has the potential to mimic a β-turn conformation and show selective affinity for the CCK receptor subtype.

The pyrrolo[2,1-*a*]isoquinoline building block **(10)**, which is formed in an asymmetric fashion as detailed in Section 2.1.1. was converted to the silyl ether **(117)** in the presence of imidazole, 4-dimethylaminopyridine and *tert*-butyldimethylsilylchloride in quantitative yield as shown in **Scheme 44**.

Scheme 44:

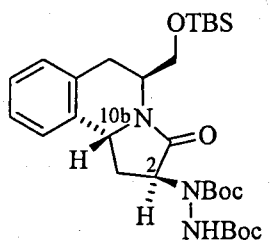


Reagents: **(i)** TBSCl, imidazole, DMAP, DCM, 4 h (99 %); **(ii)** LDA, DBAD, THF, −78 °C to rt, 16 h (88 %); **(iii)** TBAF, THF, 5 min (40 %).

Subsequent α-amination upon enolisation of **(117)** with LDA and treatment with DBAD at −78 °C successfully generated the desired product as a 15:1 mixture of diastereoisomers within the limits of ^{1}H NMR spectroscopy. The nOe interactions displayed by the major product **(118)** shown in **Figure 18**, were consistent with the

trends observed for the *syn*-indolizino[8,7-*b*]indole analogue **(112)**, indicating a *syn* addition product with respect to the substituent's at positions 2 and 10b.

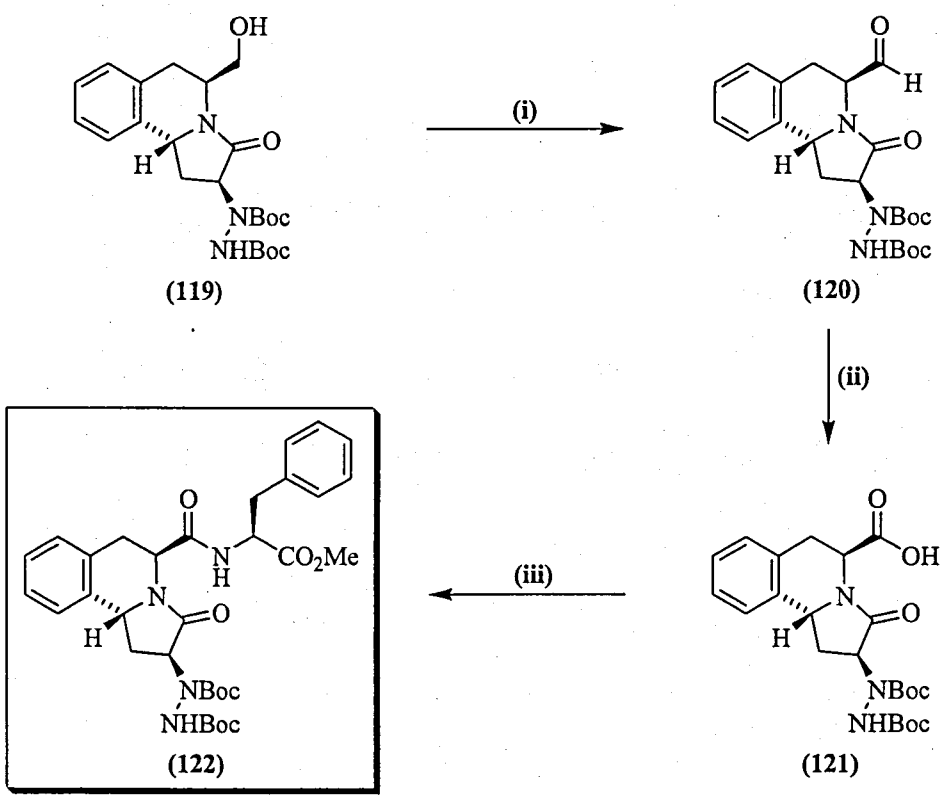
Figure 18: 1D nOe Interactions for (118).



(118)

Deprotection of the silyl ether **(118)** was achieved upon treatment with TBAF at room temperature to generate the free alcohol derivative **(119)**, which was subsequently oxidised to the aldehyde **(120)** in the presence of IBX as detailed in **Scheme 45**.

Scheme 45:

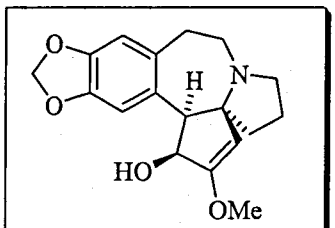


Reagents: **(i)** IBX, DMSO, 24 h (61 %); **(ii)** $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, MeCN, *t*-BuOH, H_2O, 17 h (80 %); **(iii)** *L*-Phenylalanine methyl ester hydrochloride **(97)**, EDCI, HOABt, NMM, DCM, −15 °C, 3 h (57 %).

Oxidation to the carboxylic acid **(121)** was achieved using sodium chlorite in acetonitrile and *tert*-butanol and isolated by column chromatography in 80 % yield, which was then utilised in the EDCI induced coupling process with (*S*)-phenylalanine methyl ester hydrochloride **(97)** in the presence of a racemisation suppressant to form the polypeptide **(122)**.

This synthesis represents the development of a novel constrained dipeptoid **(122)** which effectively incorporates the pyrroloisoquinoline framework into the known receptor antagonists **(79)** and **(80)** shown in **Figure 9**,[34] in a highly stereoselective fashion. This (2*S*,5*S*,11b*R*,3′*S*) peptide derivative **(122)** also displays the required stereochemistry properties necessary for β-turn activity and is comparable to the known type II′ β-turn IBTM mimetic **(75)**. The construction of this new phenyl derivative **(122)** could also give some insight into the effects of the aromatic substituent on receptor affinity and selectivity when compared to its indole analogue **(116)**.

2.4. Application Toward the Synthesis of Cephalotaxine



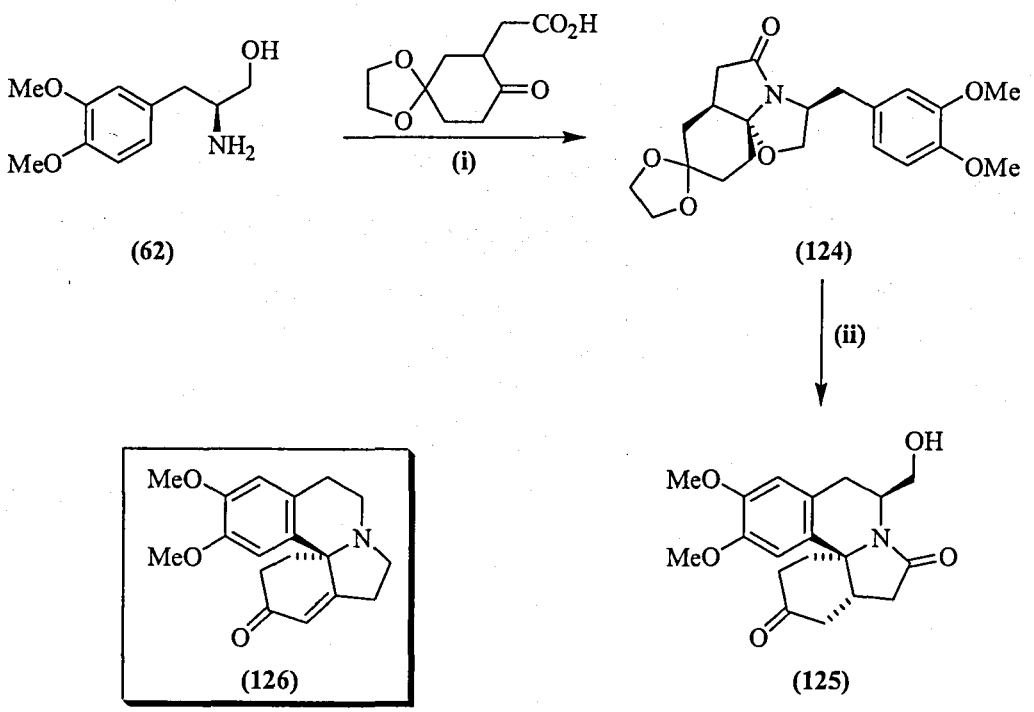
(123)

The application of *N*-acyliminium ion cyclisations toward a range of heterocyclic templates has been described in detail throughout this thesis. We have demonstrated the diverse nature of these key building blocks toward both simple natural products and more complex rigid polypeptides with potential β-turn activity. In our ongoing attempts to extend this novel methodology toward new polycyclic ring systems, we undertook the asymmetric synthesis of the pentacyclic enone **(127)**, a key precursor in the synthesis of cephalotaxine **(123)** by Li and Wang detailed earlier in Section 1.4.5.[38]

Allin *et al.* had previously reported the formation of a cyclic ketone **(125)** as a key structural template in the synthesis of (–)-3-demethoxyerythratidinone **(126)**, from a

ketal protected lactam **(124)** as shown below in **Scheme 46.**[13b] In this synthesis, the required β-amino alcohol **(62),** prepared quantitatively from the readily available amino acid, was subjected to condensation with a cyclic keto-acid under Dean-Stark conditions in toluene for 48 hours to generate the desired lactam **(124)** as a single diastereoisomer.

Scheme 46:

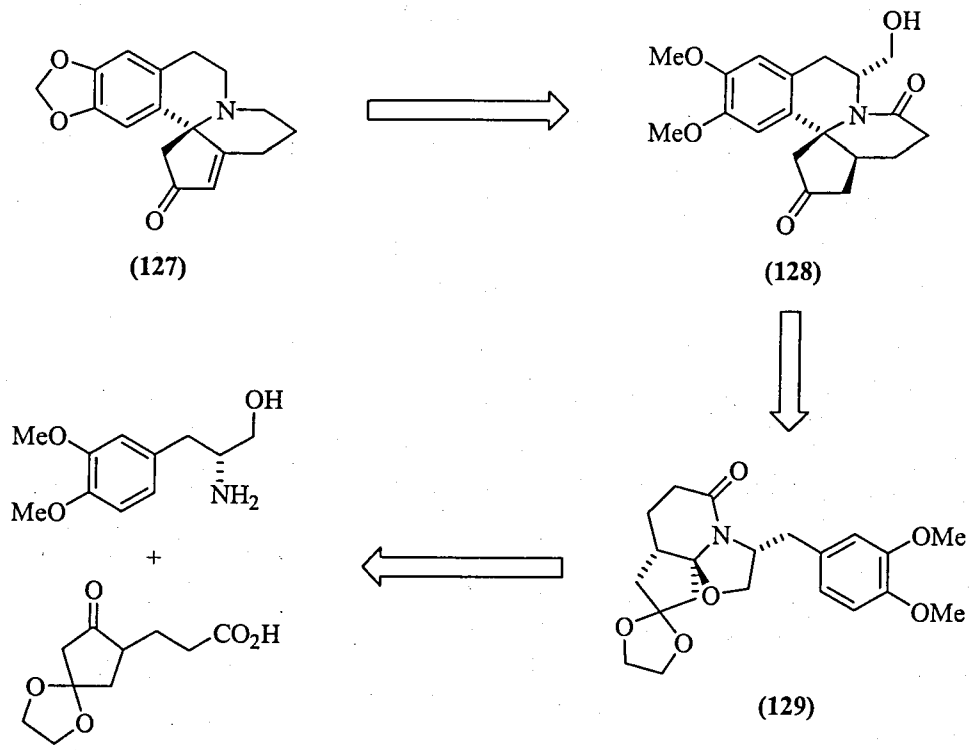


Reagents: **(i)** PhMe, Δ, Dean-Stark, 48 h (63 %); **(ii)** $TiCl_4$, DCM, −78 °C, 48 h (92 %).

The exclusive formation of this isomer from the racemic keto-acid requires the epimerisation of the stereogenic centre adjacent to the ketone, and this fact has been noted in the preparation of similar polycylic lactams for use as *N*-acyliminium precursors. On treating lactam **(124)** with excess titanium tetrachloride at low temperatures, the tetracyclic product **(125)** was isolated in an excellent 92 % yield, and perhaps not unexpectedly, had been accompanied by the concomitant deprotection of the ketal protecting group.

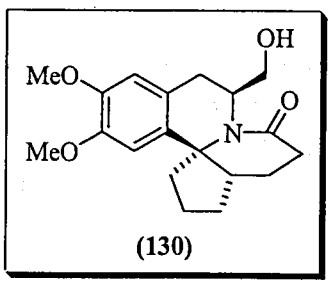
As shown in the retrosynthetic **Scheme 47,** we envisaged a similar route toward the structural related tetracyclic system **(128)** in which the tricyclic lactam **(129)** could be generated by cyclocondensation of the chiral amino alcohol with the pro-chiral functionalised keto-acid.

Scheme 47:



We believed this chiral lactam **(129)** could act as a suitable *N*-acyliminium ion precursor in the asymmetric synthesis of building block **(128)**, which under these acidic conditions would also liberate the carbonyl group in the same step, as previously seen in the synthesis of (–)-3-demethoxyerythratidinone **(126)**.[13b] This ketone functionality could then be easily manipulated to form the target amino enone **(127)** and onward towards a novel synthesis of (–)-cephalotaxine **(123)**.

2.4.1. Stereoselective Synthesis of a Tetracyclic Model System

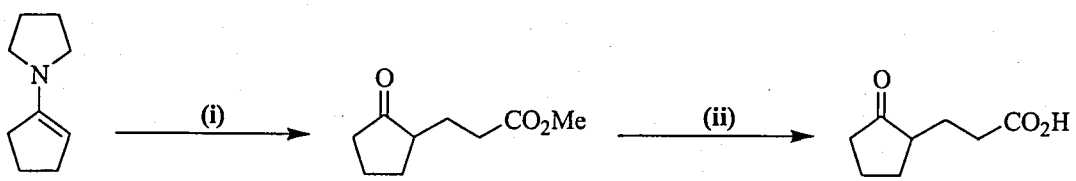


In order to determine the potential of our *N*-acyliminium chemistry towards the synthesis of the cyclic ketone **(128)** and hence (–)-cephalotaxine **(123)**, it was first

deemed necessary to investigate if the formation of this particular tetracyclic ring system **(130)** was favoured using our methodology. Our synthesis mirrored that of the *Erythrina* alkaloids by Allin *et al.* described in Section 1.4.3. in which condensation of a chiral amino alcohol with a racemic cyclic keto-acid substrate provided a tricyclic lactam with high levels of diastereoselectivity.[13]

The desired keto-ester **(132)** required for condensation had previously been synthesised by Stork *et al.* and employed the alkylation of an appropriate enamine **(131)**.[39] As shown in **Scheme 48**, this was used to great effect by treatment of pyrrolidine enamine **(131)** and methyl acrylate in refluxing dioxane to yield the target keto-ester **(132)** in 79 % yield. Hydrolysis of the ester **(132)** with lithium hydroxide gave the corresponding target keto-acid **(133)** in quantitative yield.

Scheme 48:



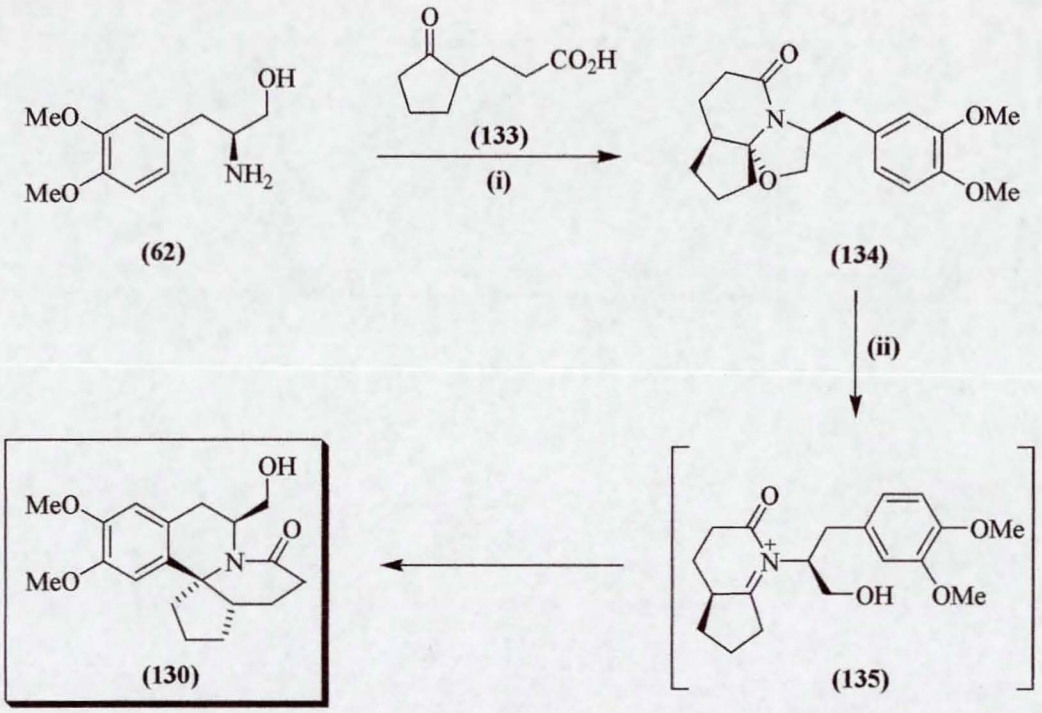
(131) **(132)** **(133)**

Reagents: **(i)** Methyl acrylate, dioxane, Δ, 3.5 h (79 %); **(ii)** LiOH, THF/H_2O, 20 h (99 %).

Condensation of the amino alcohol **(62)** and racemic keto-acid **(133)** in toluene for 48 hours under Dean-Stark conditions generated the desired tricyclic lactam **(134)** as a single diastereoisomer in an excellent 76 % yield as illustrated in **Scheme 49**.

Exposure of the lactam **(134)** to the Lewis acid activator, titanium tetrachloride, in dichloromethane over 48 hours generated the reactive *N*-acyliminium ion intermediate **(135)**, which then underwent intramolecular cyclisation to exclusively afford the tetracyclic model template **(130)** in 68 % yield as a single diastereoisomer.

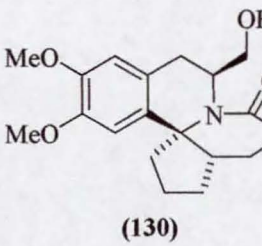
Scheme 49:

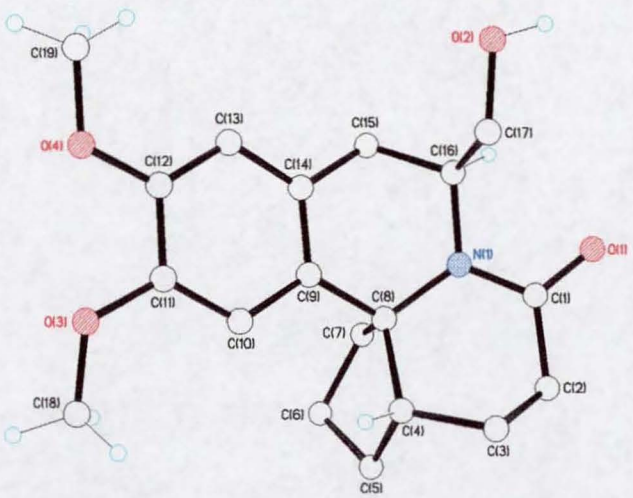


Reagents: **(i)** PhMe, Δ, Dean-Stark, 48 h (76 %); **(ii)** $TiCl_4$, DCM, −78 °C, 48 h (68 %).

The relative stereochemistry of the pentacyclic tetrahydroisoquinoline skeleton **(130)** was confirmed by single crystal X-ray crystallography **(Figure 19)**.

Figure 19: Pentacyclic Template (130).

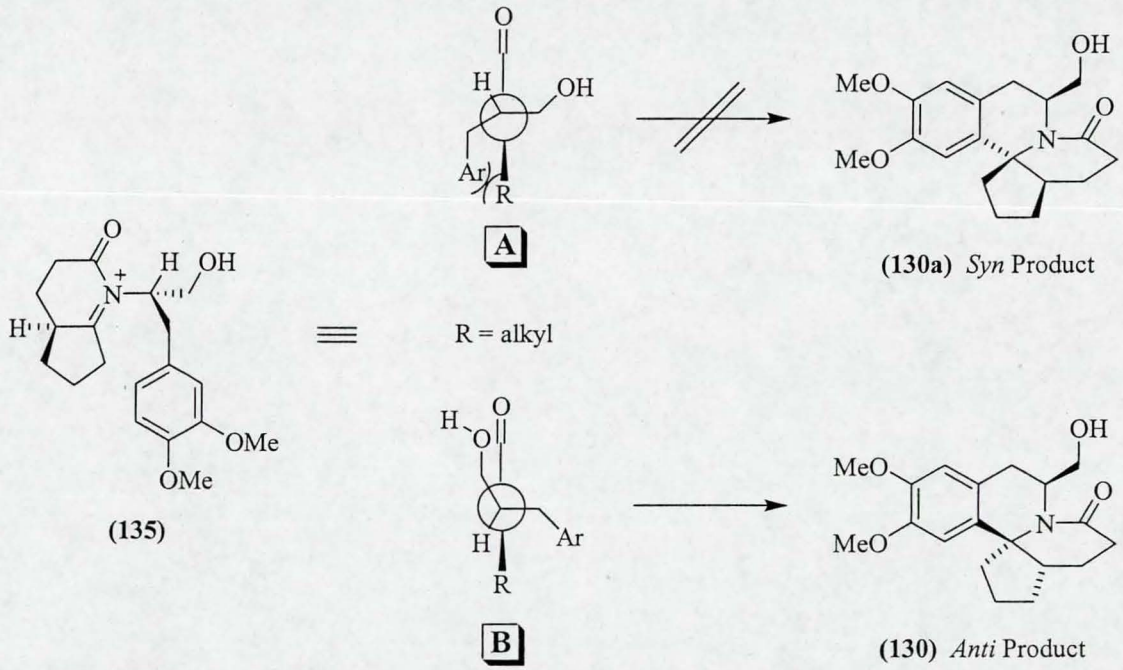




We were pleased to observe that the stereochemical outcome of the cyclisation could be rationalised using the same conformational models previously proposed for the related synthesis of the pyrroloisoquinoline and indolizino[8,7-*b*]indoles ring systems. As

highlighted in **Figure 20**, Lewis acid activation of the tricyclic lactam substrate **(134)** leads to the formation of a formal *N*-acyliminium species **(135)**.

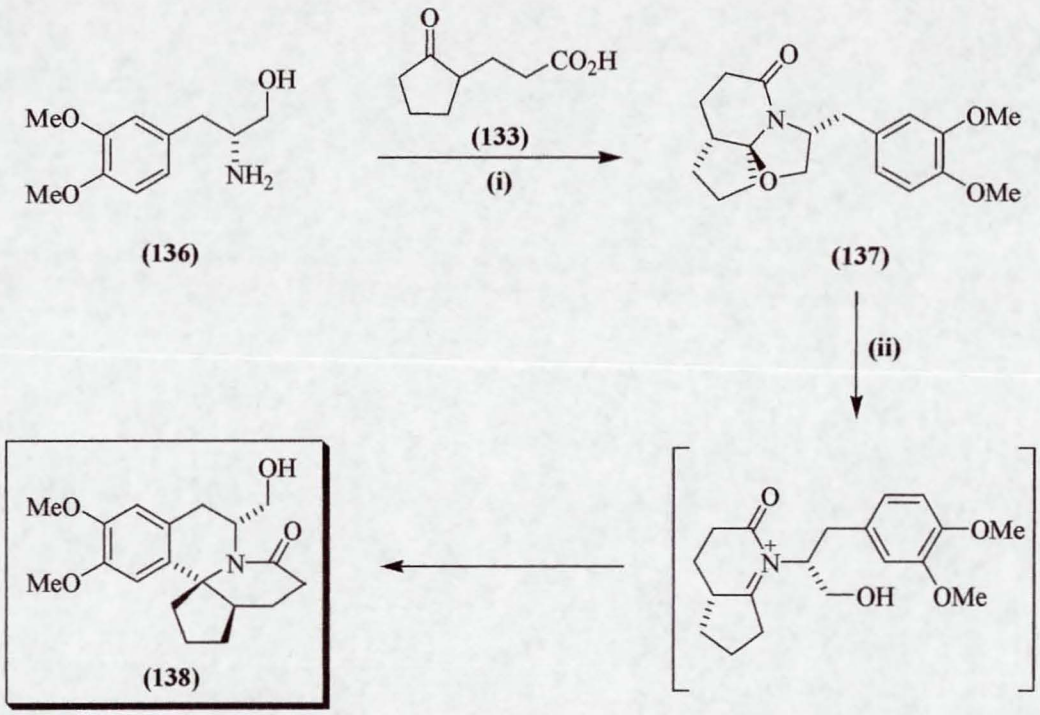
Figure 20: Proposed Conformational Models.



In the proposed conformation A, one can envisage steric interactions between the angular alkyl group, R, and the benzyl moiety, which may disfavour the formation of the *syn*-product **(130a)**. This steric influence exercised by the angular alkyl substituent at the iminium carbon atom over-rides the unfavourable 1,3-interaction that exists between the carbonyl and hydroxyl groups in conformation B and leads to the observed *anti*-diastereoisomer **(130)** with retention of stereochemistry. The presence of the additional chiral centre within the *N*-acyliminium species may also contribute to this stereochemical outcome, as it has been shown that the related erythrinane systems exhibit high levels of stereoselectivity for a *cis*-fused configuration.

The cyclised compound **(130)** obtained from 3-(3,4-dimethoxyphenyl)-*L*-alanine possesses the opposite stereochemistry to that of naturally occurring (–)-cephalotaxine **(123)**. For this reason, the process was repeated using the *D*-amino alcohol **(136)** in order to ensure the transfer of chirality and afford enantiomer **(138)**, which contained the relative stereochemistry required for (–)-cephalotaxine **(123)** **(Scheme 50)**.

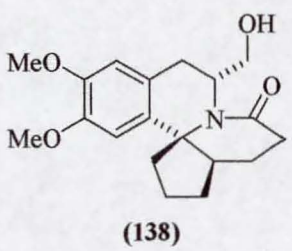
Scheme 50:

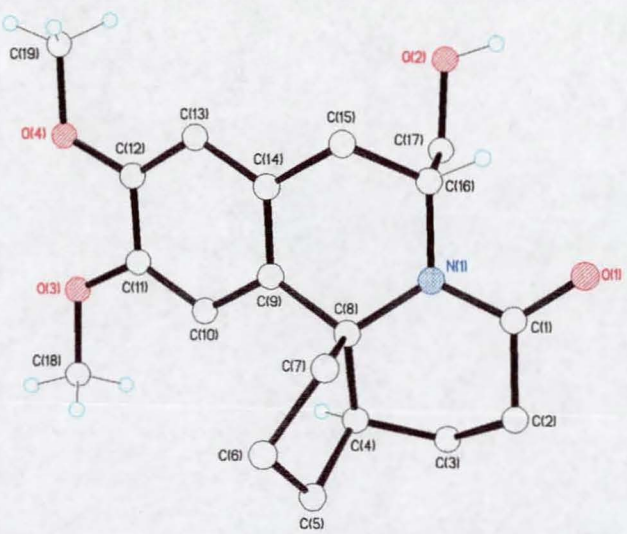


Reagents: **(i)** PhMe, Δ, Dean-Stark, 48 h (71 %); **(ii)** $TiCl_4$, DCM, −78 °C, 48 h (73 %).

The procedure was repeated under the exact conditions as previously stated with the tricyclic lactam **(137)** formed exclusively as a single diastereoisomer in 71 % yield and the cyclised product **(138)** isolated in 73 % yield. The relative stereochemistry of **(138)** was again confirmed by X-ray crystallography **(Figure 21)**.

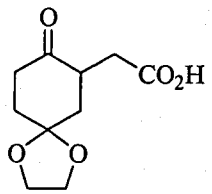
Figure 21: Pentacyclic Template (138).



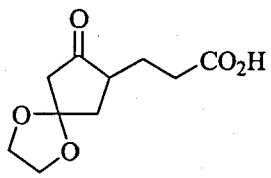


2.4.2. Synthesis of an Appropriate Keto-Acid Substrate

With the successful application of our *N*-acyliminium methodology with the model tetracyclic skeletons **(130)** and **(138)**, we turned our attention to the formation of a more functionalised ketone derivative that was suitable for a ring expansion/contraction procedure. Our initial focus was on the preparation of a protected keto-acid derivative such as **(140)**, which could undergo cyclocondensation with an amino alcohol to generate the lactam precursor **(129)**, described previously in **Scheme 47**.



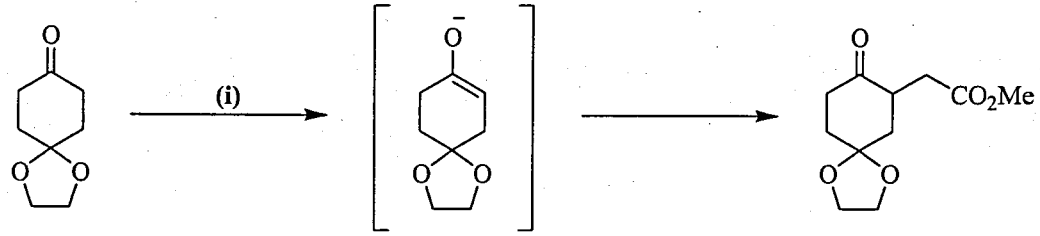
(139)



(140)

The related keto-acid **(139)** utilised in the synthesis of (–)-3-demethoxyerythratidinone **(126)** **(Scheme 46)** was prepared by the enolate addition of methyl bromoacetate to the 1,4-protected cyclohexanone **(141)**, which posed no problem of regioselectivity due to the symmetrical nature of the substrate **(Scheme 51)**.[13b]

Scheme 51:

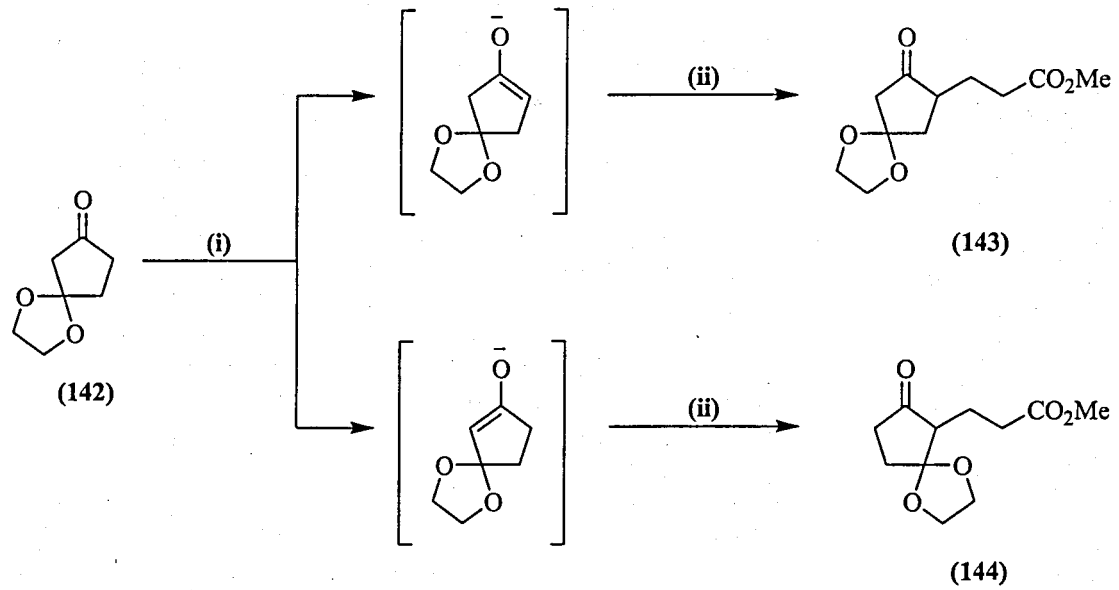


(141)

Reagents: (i) KHMDS, THF, methyl bromoacetate, −78 °C to rt, 16 h.

The electrophilic alkylation of the 1,3-cyclopentadione derivative **(142)** however, is more problematic, as shown in **Scheme 52**, due to the potential formation of multiple regioisomers **(143)** and **(144)**.

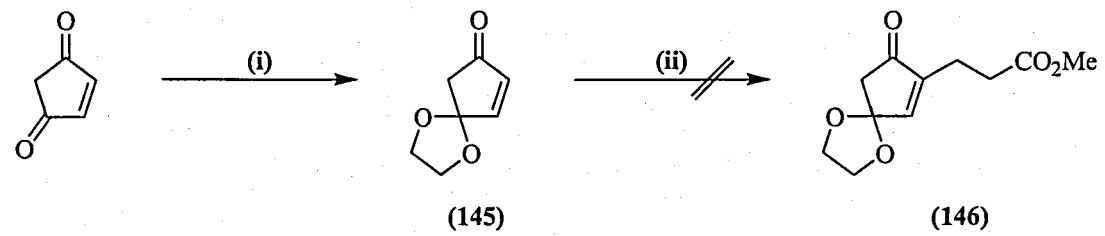
Scheme 52:



Reagents: **(i)** LDA, THF, −78 °C; **(ii)** Methyl-3-bromopropionate, rt.

With this in mind, our initial approach was to substitute the protected 1,3-cyclopentene dione **(145)** regioselectively at the 4-position using a Baylis-Hillman procedure **(Scheme 53)**. This also had the advantage of incorporating α,β-unsaturation into substrate **(146)**, which is a feature of the target enone **(127)**. This could however, be removed if the additional functionality proved problematic during condensation with the amino alcohol.

Scheme 53:



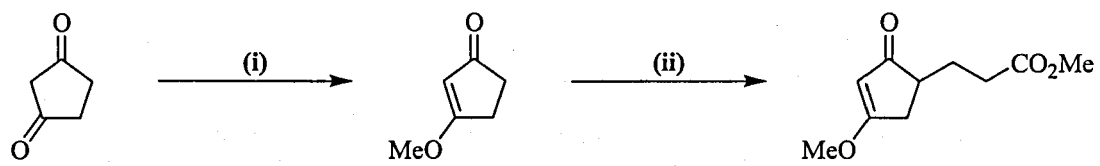
Reagents: **(i)** Ethylene glycol, *p*-TsOH, PhMe, Δ, 15 h (64 %); **(ii)** DABCO, methyl acrylate, THF.

Treatment of the mono-protected cyclopentene dione **(145)** with methyl acrylate in the presence of catalytic 1,4-diazabicyclo[2.2.2]octane (DABCO) however, produced only starting materials after vigorous stirring for 7 days at room temperature. The reaction was repeated under more extreme conditions including stoichiometric quantities of

DABCO, elevated temperatures, extended reaction times and microwave conditions,[40] which all failed to generate the desired compound.

After this initial setback, an alternate approach was attempted using the vinyl ether derivative of 1,3-cyclopentadione **(148)**, in which the 2-position is effectively blocked, allowing substitution at the desired 4-position **(Scheme 54)**. The vinyl ether **(148)** was readily obtained from 1,3-cyclopentanedione **(147)** following the procedure described by Chandrasekhar and Reddy in 72 % yield.[41] Alkylation of the protected ketone **(148)** was then achieved using LDA and methyl-3-bromopropionate at –78 °C to generate the ester **(149)** as part of a complex mixture.

Scheme 54:

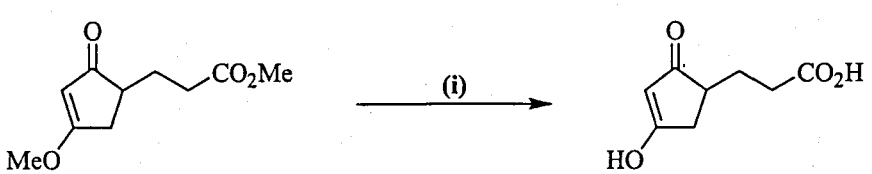


(147) **(148)** **(149)**

Reagents: **(i)** Trimethyl orthoformate, *p*-TsOH, MeOH, PhMe, Δ, 80 min (72 %); **(ii)** LDA, methyl-3-bromo propionate, THF, −78 °C to rt, 16 h, (22 %).

Isolation of the desired compound was eventually achieved by column chromatography in 22 % yield while monitoring the isolated fractions by LC-MS. The complex mixture generated in this reaction highlights the problems associated with alkylation's involving methyl-3-bromopropionate due to the potential side-reactions including; alkylation at the ester carbonyl and possible enolisation of the ester electrophile. Hydrolysis of the isolated methyl ester **(149)** was subsequently achieved with lithium hydroxide to form the desired carboxylic acid **(150)** in 55 % yield, as shown in **Scheme 55**.

Scheme 55:



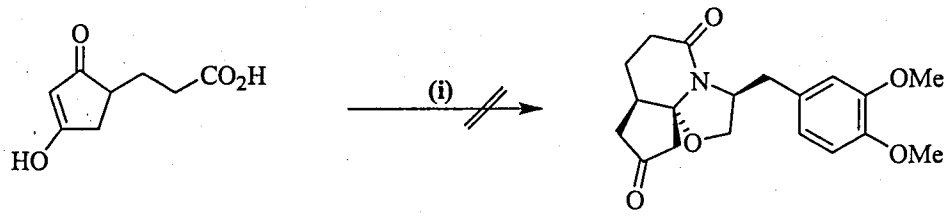
(149) **(150)**

Reagents: **(i)** LiOH, THF/H_2O, 20 h (55 %).

2.4.3. Attempted Synthesis of the Tricyclic Ketone

With the desired substrate **(150)** in hand, we attempted the formation of the functionalised tricyclic lactam **(151)**, which would act as our *N*-acyliminium precursor **(Scheme 56)**. The condensation was performed with amino alcohol **(62)** and the keto-acid **(150)** substrates under the Dean-Stark conditions previously applied in our test study, detailed in Section 2.5.1.

Scheme 56:



(150) **(151)**

Reagents: **(i)** *L*-Dimethoxyphenylalaninol **(62)**, PhMe, Δ, Dean-Stark, 48 h.

However to our disappointment, no trace of the desired lactam **(151)** was evident, with only starting materials recovered after prolonged heating in toluene. Attempts to increase the reaction temperature with the use of xylene and mesitylene also proved fruitless, as did attempts to condense the keto-ester precursor **(149)**.

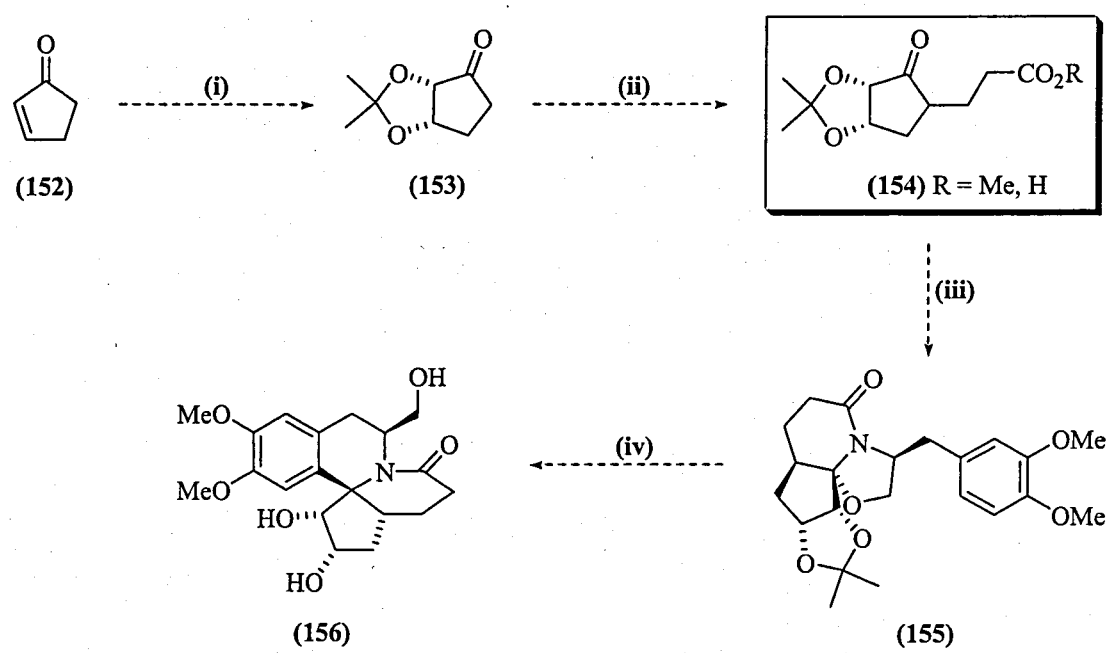
We propose that under these conditions the amino alcohol **(62)** favours attack in a 1,4-fashion over the desired 1,2-addition, and is then immediately eliminated to revert back to the starting materials, which is supported by trace amounts of what appeared to be a conjugate addition product in the LC-MS, however this was not isolated.

2.4.4. An Alternate Approach Towards a Tetracyclic Diol

Due to the problems associated with condensation of the amino alcohol **(62)** and a 1,3-diketo-acid equivalent **(150)**, we designed a different approach to overcome the problem of 1,4-addition whilst still providing a functionalised substrate **(154)** **(Scheme 57)**. As a solution to the previous problems associated with 1,4-addition to the 1,3-diketone substrates, we focused our efforts on the formation of an analogous 1,3-keto-alcohol, which could be oxidised to the ketone at a later stage. We reasoned

that a suitable condensation precursor **(154)** could be generated through a kinetically controlled enolate alkylation of the protected diol **(153)** formed by an asymmetric dihydroxylation of the readily available 2-cyclopentene-1-one **(152)**.

Scheme 57:

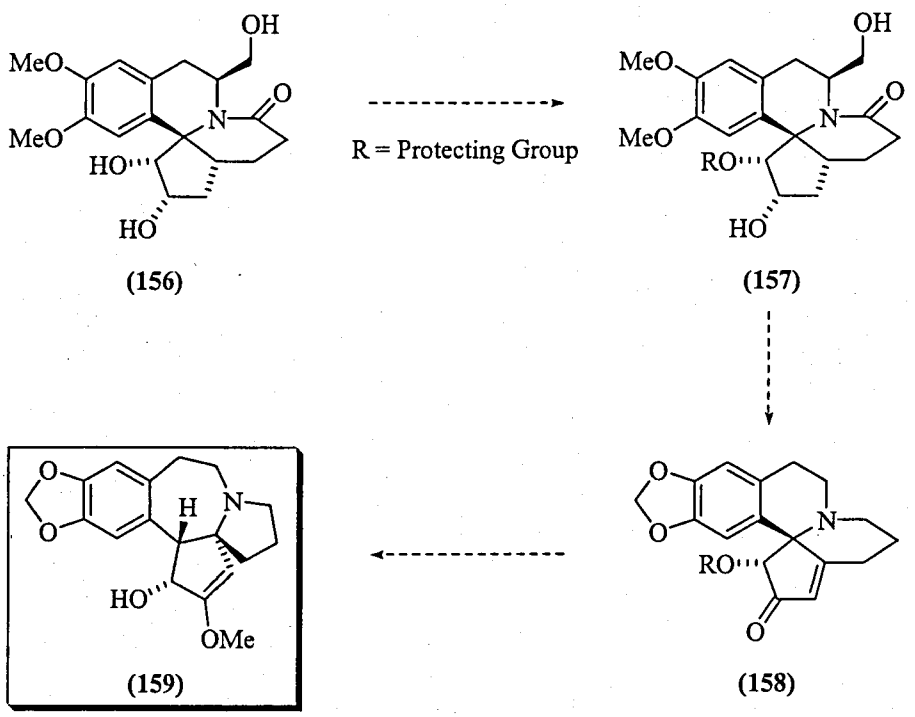


Reagents: **(i)** AD-mix-β, *t*-BuOH/H_2O; **(ii)** LDA, methyl-3-bromopropionate, THF, −78 °C to rt; **(iii)** *L*-Dimethoxy phenylalaninol **(62)**, PhMe, Δ, Dean-Stark; **(iv)** $TiCl_4$, DCM, −78 °C.

Cyclocondensation of this keto-acid **(154)** with amino alcohol **(62)** in refluxing toluene could generate the highly functionalised *N*-acyliminium ion precursor **(155)**. We envisaged that upon treatment of **(155)** with a Lewis acid activator such as titanium tetrachloride, the heterocyclic template **(156)** could be generated *via* a stereoselective *N*-acyliminium ion cyclisation with probable removal of the ketal protecting group under the acidic conditions.

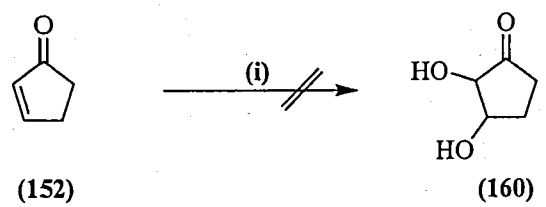
With a suitable protecting group strategy to prepare the mono-protected diol **(157)** and subsequent oxidation to generate the enone derivative **(158)** as shown in **Scheme 58**, we could incorporate the required chiral hydroxyl group present in the (+)-cephalotaxine target **(159)** with complete stereocontrol and present a novel introduction of this asymmetric centre.

Scheme 58:



To the best of our knowledge the dihydroxylation of 2-cyclopentene-1-one **(152)** to diol **(160)** had not previously been reported in the literature, and it was perhaps unsurprising to us when this conversion failed under various conditions including AD-mix,[42] ruthenium tetraoxide,[43] and potassium permanganate[44] **(Scheme 59)**.

Scheme 59:

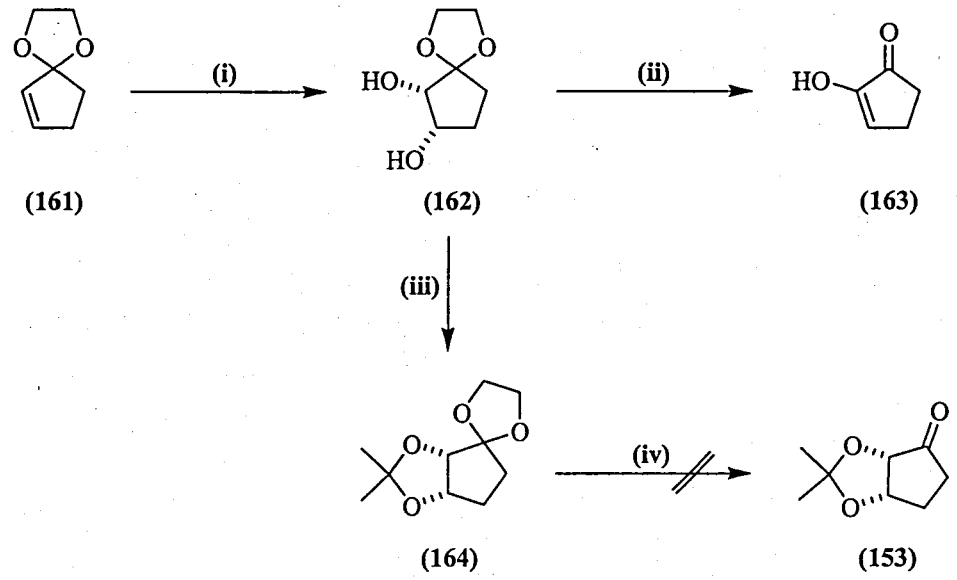


Reagents: **(ia)** AD-mix-β, *t*-BuOH/H_2O, 25 h; **(ib)** $RuCl_3$, $NaIO_4$, H_2SO_4; **(ic)** $KMnO_4$, $MgSO_4$, EtOH, H_2O.

The lack of success of this reaction was put down to the reduced reactivity of the olefin moiety in the presence of a conjugated ketone. With this in mind, the protected analogue 2-cyclopenten-1-one ethylene ketal **(161)** was subjected to the same conditions and successful afforded the diol **(162)** in both a racemic (potassium permanganate)[44] and asymmetric fashion (AD-mix) in 41 and 94 % yields respectively **(Scheme 60)**. With

the free diol **(162)** in hand we attempted to remove the acetal protecting group and subsequently protect the diol to obtain the desired substrate **(153)**.

Scheme 60:

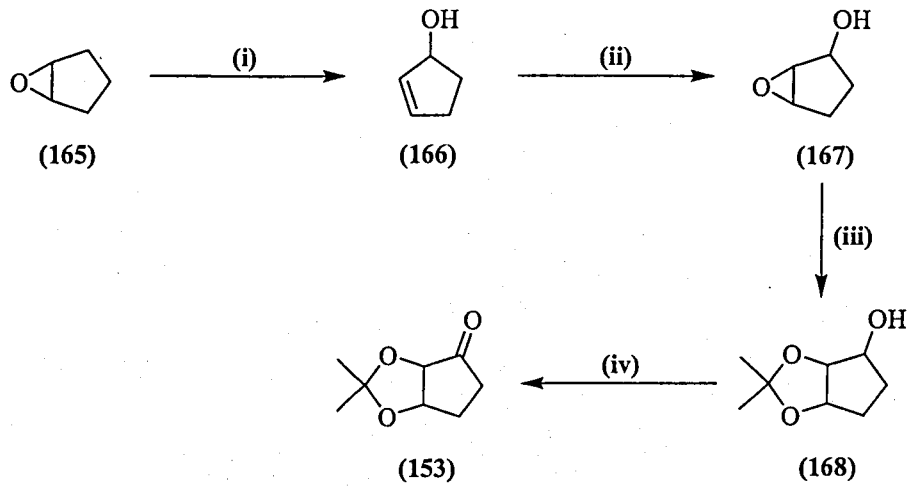


Reagents: **(i)** AD-mix-β, *t*-BuOH/H_2O, 25 h (94%); **(ii)** Perchloric acid, acetone/H_2O; **(iii)** Dimethoxypropane, $BF_3.OEt_2$, 30 min (79 %); **(iv)** Perchloric acid, acetone/H_2O.

However, exposure of **(162)** to protic acid conditions including both *p*-tosic acid and perchloric acid at various temperatures only generated the elimination product **(163)**. An alternate route reported by Cocu detailed the protection of diol **(162)** with dimethoxypropane to give **(164)** followed by treatment with perchloric acid in acetone to selectively remove the ketone-protecting group and generate **(153)**,[44] however this was unsuccessful in our hands.

Synthesis of the target ketone **(153)** was achieved however, by an alternate strategy involving an epoxide intermediate **(167)** as shown in **Scheme 61**. 2-Cyclopentene-1-ol **(166)** was formed from the readily available oxirane **(165)** as described by Mordini *et al.* in the presence of LDA and potassium *tert*-butoxide in an excellent 88 % yield.[45] The allylic alcohol **(166)** was significantly more reactive than its enone counterpart **(152)** and successfully underwent epoxidation in the presence of *m*-CPBA to form **(167)** in 68 % yield.

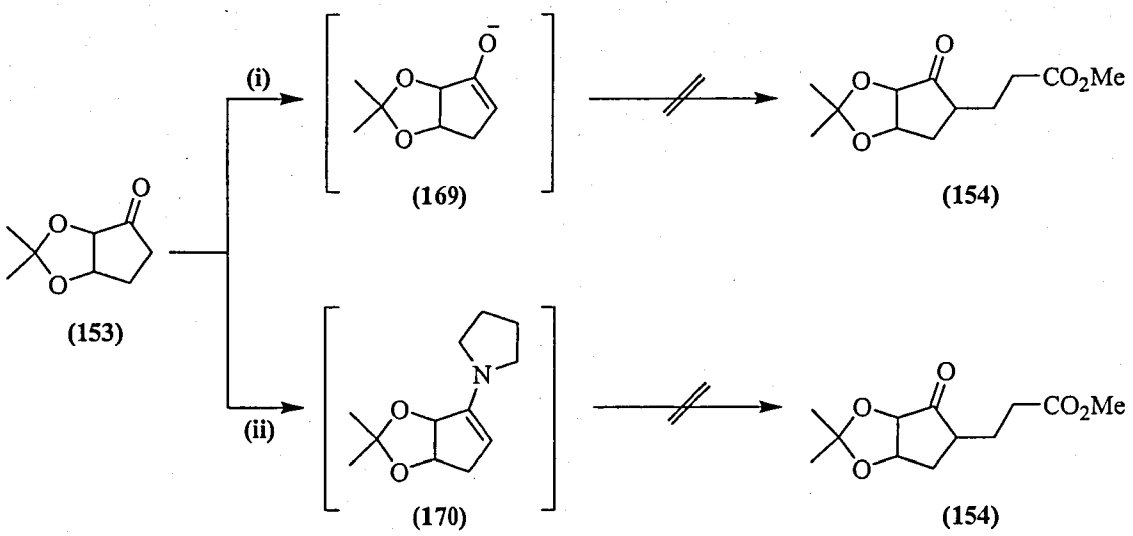
Scheme 61:



Reagents: **(i)** LDA, *t*-BuOH, −78 °C to 0 °C, 90 min (88 %); **(ii)** *m*-CPBA, DCM, 2 h (68 %); **(iii)** $BF_3.OEt_2$, acetone, 1 h (81 %); **(iv)** Dess-Martin periodinane, DCM, 3 h (90 %).

Treatment of the epoxide **(167)** with Lewis acid in acetone quickly produced the desired 1,3-dioxolane **(168)**,[46] which was then transformed into the target ketone **(153)** upon oxidation with Dess-Martin periodinane. It was expected that treatment of the ketone **(153)** with the hindered base LDA at low temperatures would generate the kinetic enolate **(169)** and allow regioselective alkylation to yield substrate **(154)** **(Scheme 62)**. To our disappointment however, only a complex mixture was obtained which was inseparable by chromatography methods.

Scheme 62:



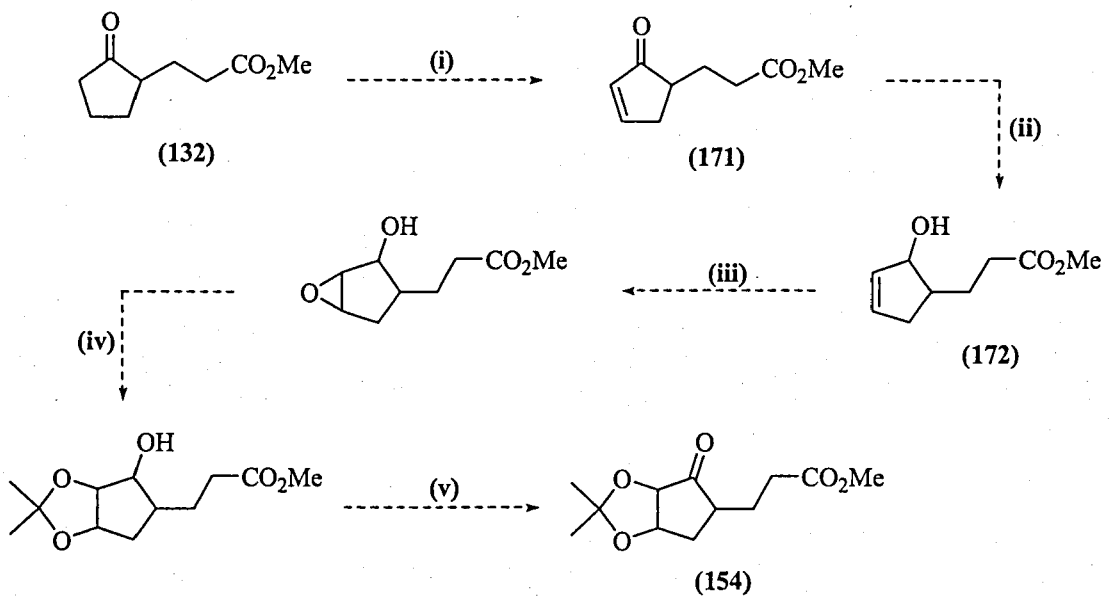
Reagents: **(i)** LDA, THF, −78 °C, then methyl-3-bromopropionate, rt, 16 h; **(ii)** Pyrrolidine, Dean-Stark, then methyl acrylate, PhMe, Δ, 15 h.

It has been shown by Stork that enamines derived from unsymmetrical ketones lead to substitution on the less substituted carbon when reacted with alkyl halides.[39] With this in mind we attempted to generated enamine **(170)** by reaction of **(153)** with pyrrolidine, and undergo a Michael addition to methyl acrylate, however this was also unsuccessful.

2.4.5. Manipulation of the Keto-ester Test Substrate

Having spent a significant amount of time investigating the enolate addition of functionalised cyclopentanes with little success, it seemed advantageous at this point to attempt to manipulate substrate **(132)**, previously used in our model systems, in a similar fashion to that shown in **Scheme 63**. This keto-ester **(132)** already incorporates the desired propionate side chain and hence avoids the problems associated with its introduction *via* enolate chemistry. This approach had previously been avoided due to the additional steps required to generate the allylic alcohol **(172)** from **(132)**, and the potential for several regioisomers when introducing α,β-unsaturation.

Scheme 63:

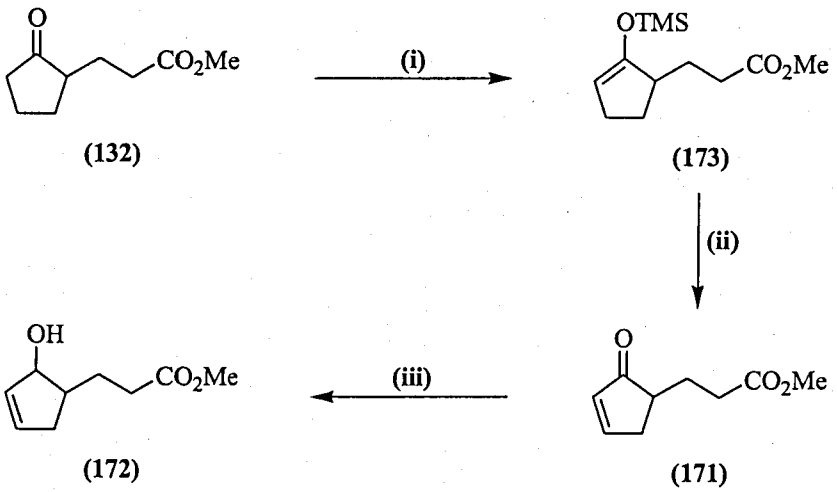


Reagents: **(i)** Unsaturation method; **(ii)** $NaBH_4$, $CeCl_3$, EtOH; **(iii)** *m*-CPBA, DCM; **(iv)** $BF_3.OEt_2$, acetone **(v)** Dess-Martin periodinane, DCM.

To achieve our desired enone product **(171)** in favour of the other potential compounds, we utilised a palladium (II)-catalysed dehydrosilylation of the silyl enol ether **(175)**.[47] It was reasoned that regioselective formation of the desired enolate could be achieved

under kinetically controlled conditions as shown in **Scheme 64**. To our delight, deprotonation of the keto-ester **(132)** with LDA at low temperature and trapping of the enolate with chlorotrimethylsilane afforded exclusively the kinetic product **(173)**, which was then converted to the desired α,β-unsaturated regioisomer **(171)** in the presence of palladium (II) acetate in a modest 39 % yield with trace amounts of the keto-ester **(132)**.

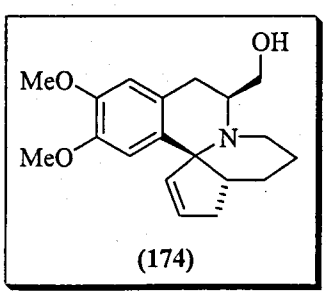
Scheme 64:



Reagents: **(i)** LDA, THF, TMSCl, −78 °C to rt, 4 h (99 %); **(ii)** $Pd(OAc)_2$, 1,4-benzoquinone, MeCN, 4 h (39%); **(iii)** $NaBH_4$, $CeCl_3$, EtOH.

However upon subjecting enone **(171)** to the Luche reduction conditions, a 1:1 mixture of products was obtained which appeared to be consistent with the allylic alcohol **(172)** and the analogous alcohol. Due to the difficulties encountered when separating these compounds, together with the low yields and high expense associated with the dehydrosilylation of **(173)**, we turned our attentions to an alternate strategy.

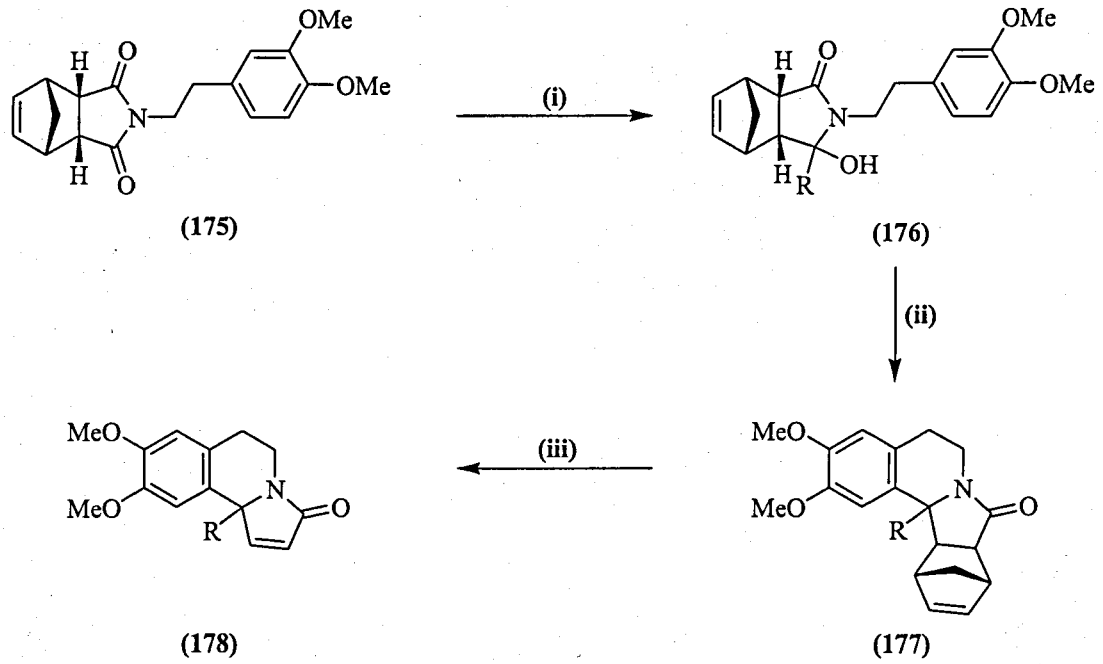
2.4.6. Synthesis of a Tetracyclic Olefin *via* a Diels-Alder Strategy



(174)

Lete and co-workers recently reported an interesting synthesis of polyfunctionalised α,β-unsaturated lactams of type **(178)** in which a masked olefin moiety was contained in the imide precursor **(175)**, in the form of a Diels-Alder adduct **(Scheme 65)**.[48]

Scheme 65:

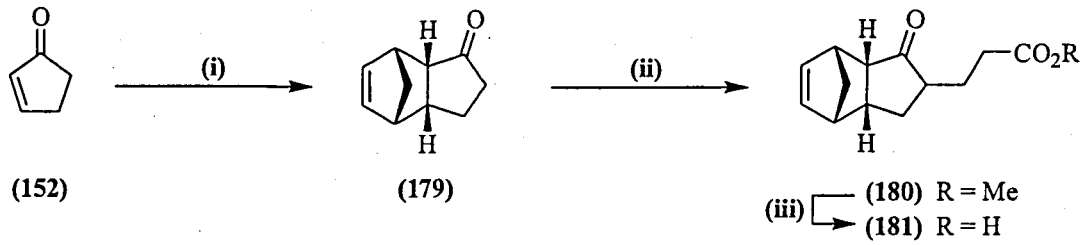


Reagents: **(i)** RLi, −78 °C, 6 h; **(ii)** TFA, DCM, Δ, 24 h; **(iii)** Δ, 1mm Hg, 10 min.

Treatment of the protected imide **(175)** with *n*-butyl lithium or methyl lithium at low temperatures afforded the corresponding hydroxy lactams **(176)** as diastereomeric mixtures, in good yields. Subsequent *N*-acyliminium cyclisation of **(176)** under protic acid conditions formed the respective lactams **(177)**, which when heated at 500 °C under reduced pressure, afforded the α,β-unsaturated pyrroloisoquinolinones **(178)** in almost quantitative yields, by a *retro* Diels-Alder reaction. With all previous attempts to introduce a protected diol moiety into our keto-acid substrate proving unsuccessful, it was felt that this masked alkene strategy could be used to our advantage.

The endo ketone **(179)** had previously been prepared in quantitative yields by Little *et al. via* a Diels-Alder cycloaddition of cyclopentadiene with cyclopentenone **(152)** in the presence of a boron trifluoride diethyl etherate.[49] With this cycloadduct **(179)** readily accessible to us, we attempted to introduce the necessary propionate side chain **(Scheme 66)**.

Scheme 66:



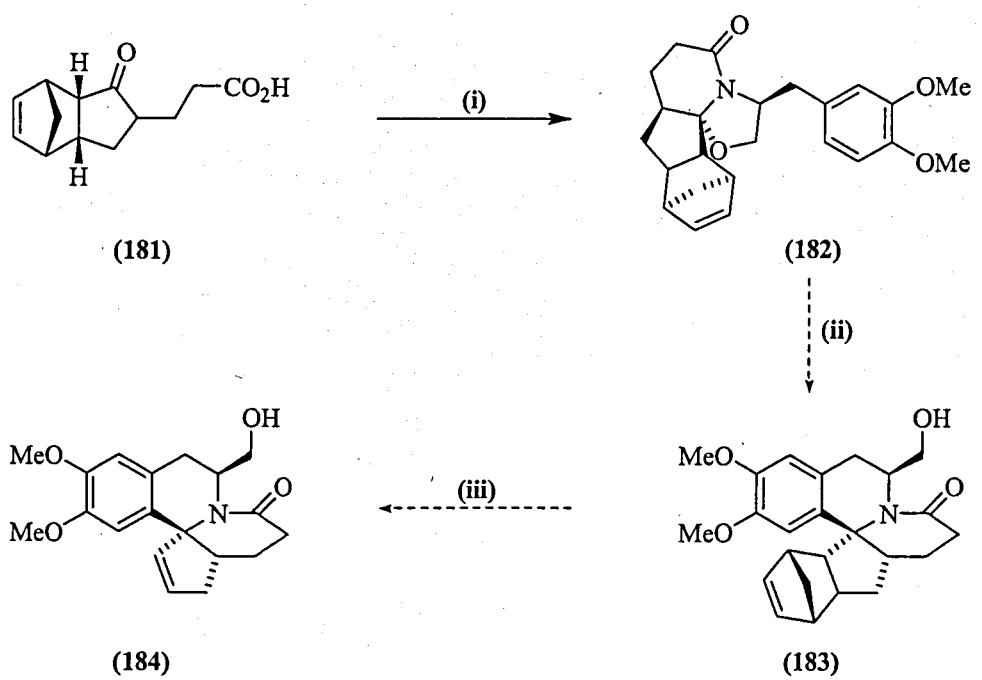
(152) (179)

Reagents: (i) Cyclopentadiene, $BF_3.OEt_2$, Et_2O, 24 h (99 %); (ii) LDA, THF, methyl-3-bromopropionate, −78 °C to rt, 16 h (66 %); (iii) LiOH, THF/H_2O, 90 min (99 %).

To our delight, treatment of **(179)** with LDA at –78 °C followed by the addition of the methyl-3-bromopropionate electrophile, resulted in the formation of our desired keto-ester **(180)** in a respectable 66 % yield as a single diastereoisomer. Subsequent hydrolysis to the corresponding carboxylic acid **(181)** was achieved quantitatively in the presence of lithium hydroxide, to yield the target condensation substrate.

The protected polycyclic lactam **(182)** was then successfully prepared as a single diastereoisomer by cyclocondensation of the racemic keto-acid **(181)** and chiral amino alcohol **(62)** under Dean-Stark conditions, as shown in **Scheme 67**.

Scheme 67:



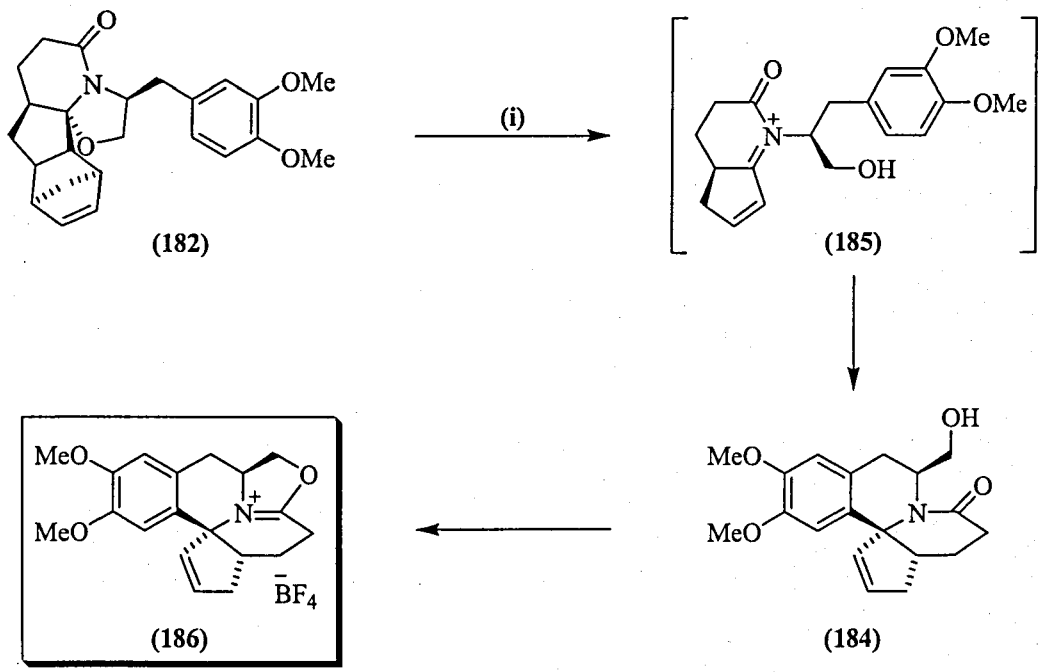
(181) (182) (184) (183)

Reagents: (i) *L*-Dimethoxyphenylalaninol **(62)**, PhMe, Δ, Dean-Stark, 48 h (45 %); (ii) $TiCl_4$, DCM; (iii) Δ, 1mm Hg.

With our functionalised lactam **(182)** in hand, we visualised an asymmetric *N*-acyliminium ion cyclisation upon treatment with Lewis acid at low temperature to form **(183)** bearing a masked olefin, that could be released in the final step by a *retro* Diels-Alder reaction to give the alkene building block **(184)**.

However, treatment of the *N*-acyliminium ion precursor **(182)** with titanium tetrachloride at –78 °C failed to produce the desired product **(183)** and resulted only in the degradation of the starting materials. Attempts to generate the *N*-acyliminium intermediate with an alternate Lewis acid, boron trifluoride diethyl etherate, was also unsuccessful at low temperatures with only starting materials recovered. In a further attempt to drive this synthesis, the temperature was elevated by performing the reaction in refluxing dichloromethane, which after 24 hours under these revised conditions, produced the unexpected alkene iminium salt **(186)** shown in **Scheme 68**.

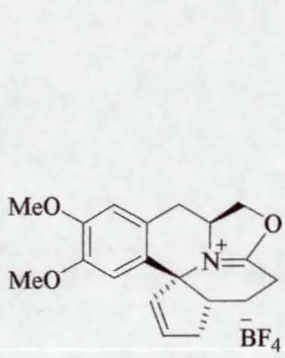
Scheme 68:



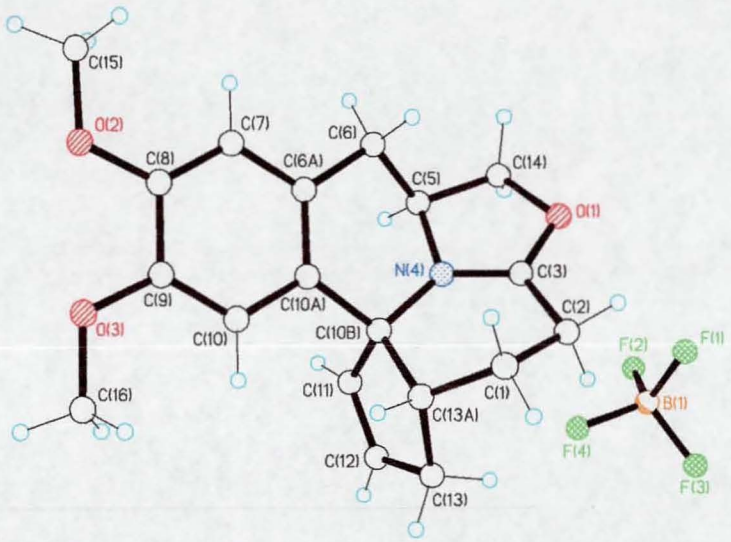
Reagents: **(i)** $BF_3.OEt_2$, DCM, Δ, 15 h (91 %).

The complete structure of the iminium salt **(186)** was determined by single crystal X-ray crystallography and also confirmed the relative stereochemistry of this highly functionalised intermediate, which followed the trends observed in the model tetracyclic system with effective retention of configuration **(Figure 22)**.

Figure 22: Single Crystal X-Ray Structure of (186):

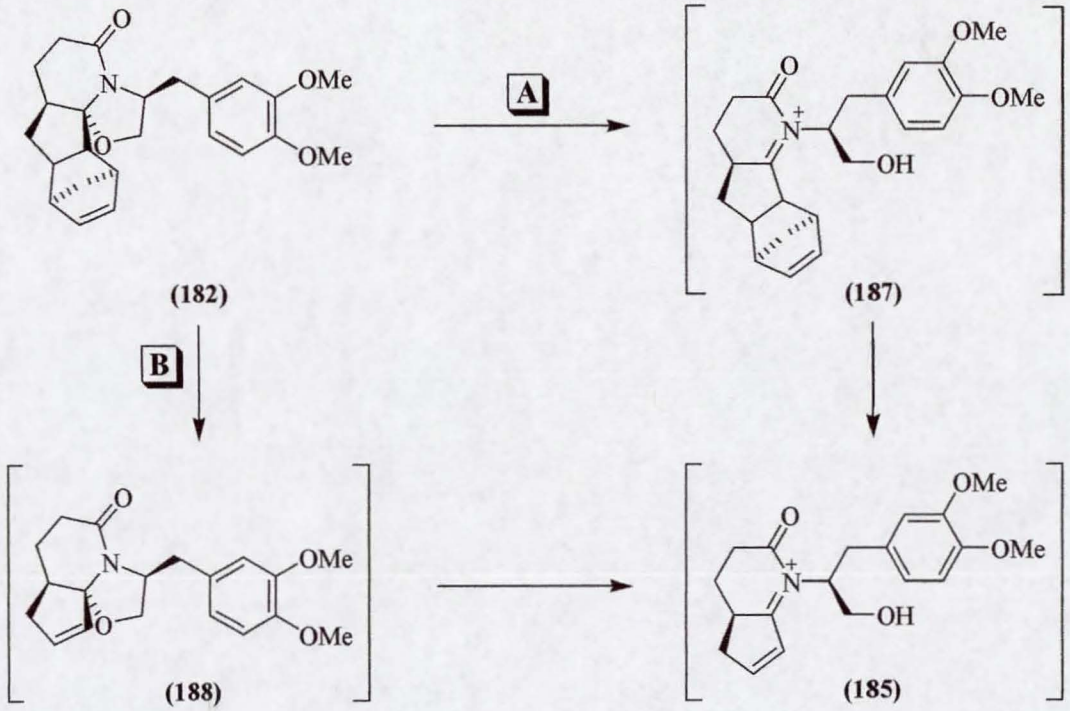


(186)



We propose that in the presence of excess Lewis acid and at moderately elevated temperatures, this unexpected tandem reaction is likely to occur *via* the stabilised *N*-acyliminium intermediate **(185)** shown in **Scheme 68**. The formation of **(185)** is possible by two mechanistic pathways, however to date, the intermediate alkene **(188)** generated in route B has not been observed at any point in the reaction **(Scheme 69)**.

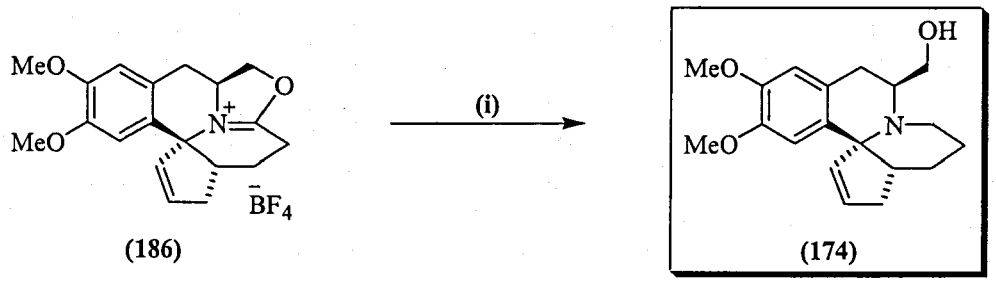
Scheme 69:



We believe that an initial ring opening of the bicyclic lactam occurs *via* route A to generate *N*-acyliminium ion **(187)**, which in turn triggers a *retro* Diels-Alder reaction under the Lewis acid catalysed conditions, to form the conjugated *N*-acyliminium ion intermediate **(185)**. Subsequent nucleophilic attack of the aromatic moiety at the *N*-acyliminium species would lead to the expected tetracyclic alkene **(184)**, however it appears that in the presence of excess boron trifluoride diethyl etherate, the free hydroxyl group undergoes a further 1,2-addition at the lactam carbonyl to generated the isolated oxazolidine-iminium salt **(186)** **(Scheme 68)**.

The final step outlined in **Scheme 70**, involved the reduction of the iminium species **(186)**, which was achieved in the presence of two equivalents of diisobutylaluminium hydride (DIBAL) to furnish the target chiral amine **(174)** in 65 % yield.

Scheme 70:



(186) (174)

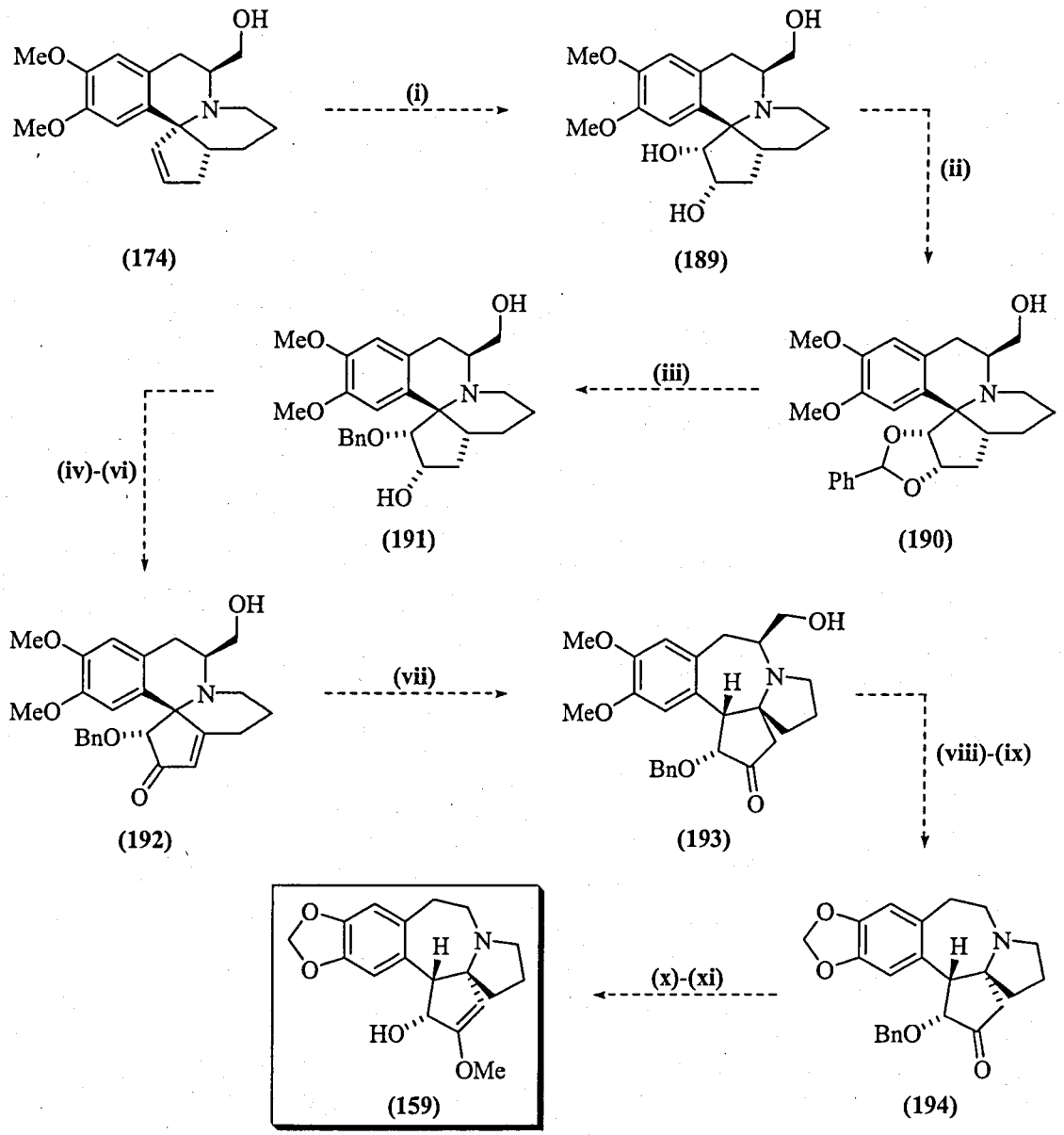
Reagents: **(i)** DIBAL, DCM, Δ, 5 h (65 %).

2.4.7. Future Work

We are confident that the alkene building block **(174)**, which is accessible in excellent yields over 6 steps and in a highly stereoselective fashion, can act as a key intermediate towards the target product (+)-cephalotaxine **(159)**. As demonstrated in **Scheme 71**, we envisage that the olefin moiety displayed by **(174)** can be converted to the enone **(192)** through the application of standard literature methodology, and would act as a suitable intermediate for the transannular rearrangement reported by Li and Wang.[38]

Dihydroxylation of the alkene function **(174)**, under the conditions reported by Sharpless,[42] would generate the diol **(189)** in an asymmetric fashion and allow a stereocontrolled introduction of the hydroxyl group present in (+)-cephalotaxine **(159)**.

Scheme 71:



Reagents: **(i)** AD-mix, *t*-BuOH/H_2O; **(ii)** Benzaldehyde dimethyl acetal, *p*-TsOH, DMF; **(iii)** DIBAL, DCM; **(iv)** Dess-Martin periodinane, DCM; **(v)** LDA, THF, PhSeBr, −78 °C to rt; **(vi)** $NaIO_4$, $NaHCO_3$; **(vii)** Zn/AcOH, 100 °C; **(viii)** BBr_3, CH_2Br_2; **(ix)** Raney-nickel, PhMe, Δ; **(x)** Pd/C, H_2 EtOH; **(xi)** Trimethyl orthoformate, PhMe, Δ.

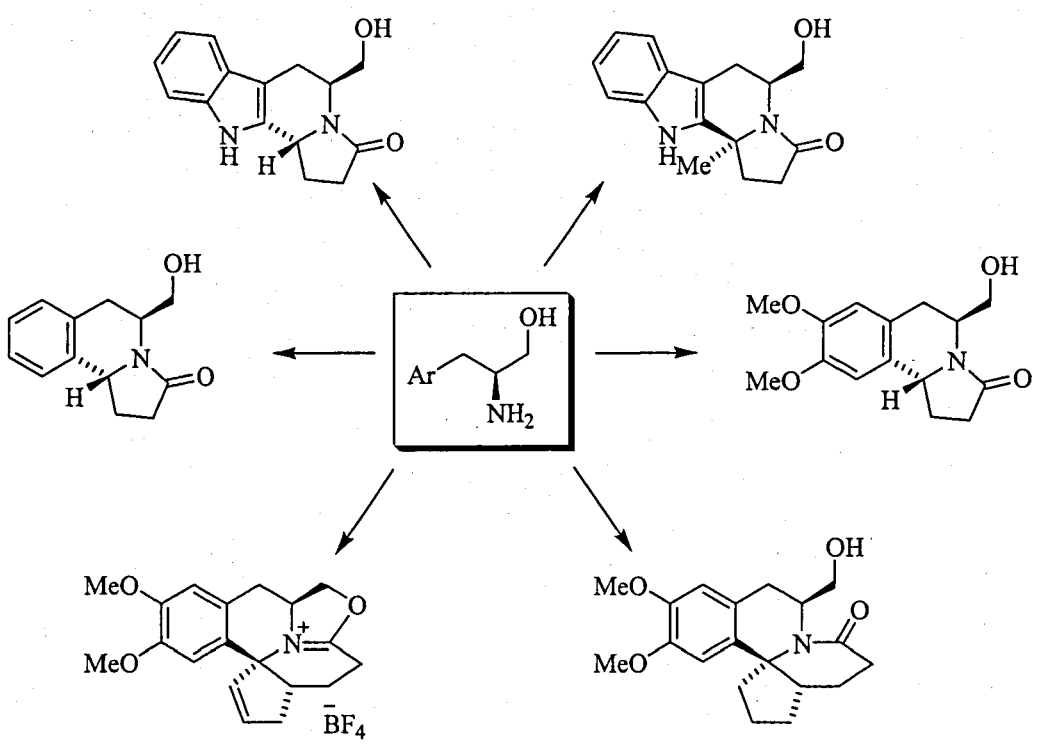
Protection of the diol **(189)** as the benylidene ketal **(190)** in the presence of benzaldehyde dimethyl acetal and *p*-tosic acid under reflux followed by selective cleavage with DIBAL,[50] which we believe would occur at the least hindered position, forms the mono-benyl ether **(191)**. Oxidation of the secondary hydroxyl group followed by α-selenylation and *syn* elimination, a conversion examined extensively by Reich *et al.*[51] and employed by Allin,[52] would then afford the target enone intermediate **(192)**.

A transannular reductive skeletal rearrangement of **(192)**, as reported by Li and Wang for a structurally related enone upon exposure to zinc dust in hot acetic acid, would allow transformation to the pyrrolobenzazepine **(193)**. We envisage the presence of the hydroxymethyl auxiliary may act as a chiral handle during this rearrangement and could contribute some degree of stereocontrol. With **(193)** in hand, removal of the hydroxymethyl group with Raney nickel and construction of the methylenedioxy group in the usual manner would then generate **(194)**,[53] which followed by hydrogenolysis and formation of the vinyl ether with methyl orthoformate would complete a highly stereocontrolled novel synthesis of the target (+)-cephalotaxine **(159)** in a total of 16 steps. This synthesis could also be easily transferred to the construction of naturally occurring enantiomer, (–)-cephalotaxine **(123)**, through the use of *D*-phenylalaninol as the starting amino alcohol and the appropriate asymmetric dihydroxylation reactants.

2.5. Conclusions

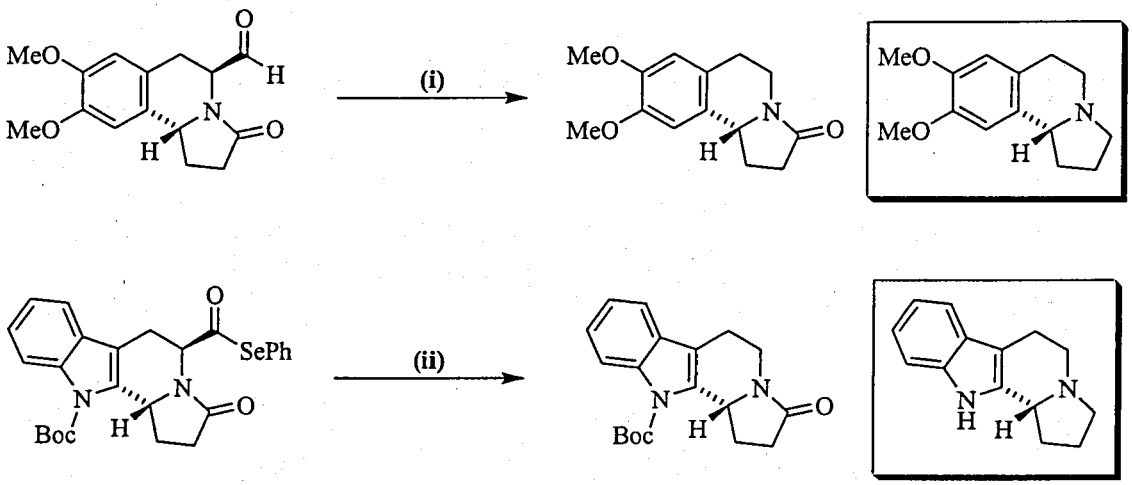
In summary, we have developed a highly stereoselective approach to a variety of enantiomerically pure heterocyclic templates from readily available non-racemic substrates *via* the application of novel *N*-acyliminium ion methodology **(Scheme 72)**.

Scheme 72:



The potential application of this novel methodology in target synthesis and the diverse nature of these key building blocks has been demonstrated by the removal of functionality using complementary procedures to access the biologically active natural alkaloids (+)-crispine A and (+)-harmicine **(Scheme 73).**[29]

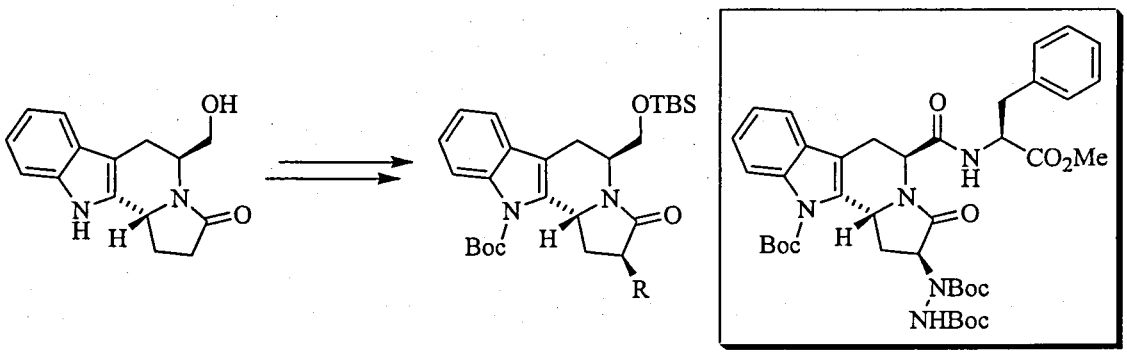
Scheme 73:



Reagents: **(i)** $Rh(PPh_3)_2(CO)Cl$, dppp, *p*-xylene, Δ, 10 d (46 %); **(ii)** *n*-Bu_3SnH, AIBN, PhMe, 80 °C (90 %).

We have also demonstrated the manipulation of existing functionality associated with these heterocyclic building blocks through the application of enolate addition chemistry, which was achieved with excellent levels of stereocontrol and allows access to a new range of potential CCK receptors antagonists **(Scheme 74).**

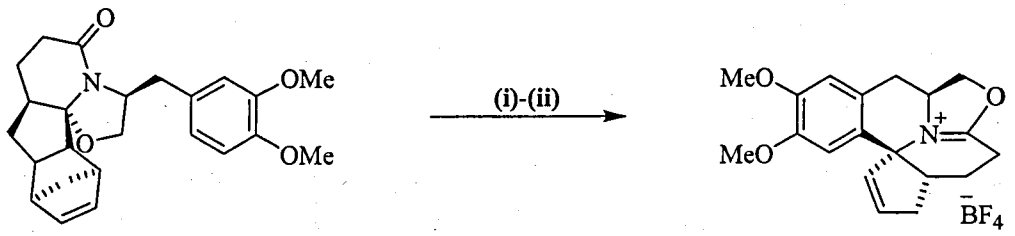
Scheme 74:



Finally, we have taken this methodology forward through the development of a novel *N*-acyliminium cyclisation/*retro* Diels-Alder tandem reaction to generate a highly functionalised pentacyclic template, which we envisage as the key intermediate toward

a novel stereoselective synthesis of the interesting target compound cephalotaxine **(Scheme 75).**

Scheme 75:



Reagents: **(i)** $BF_3.OEt_2$, DCM, Δ, 15 h (91 %); **(ii)** DIBAL, DCM, Δ, 5 h (65 %).

CHAPTER THREE:
EXPERIMENTAL

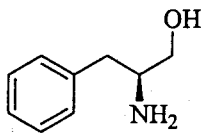
3.1. General Information.

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate, which was distilled from $CaCl_2$ and dichloromethane, which was distilled over phosphorus pentoxide. Light petroleum refers to the bp 40-60 °C fractions. Sodium hydride was obtained as 60 % dispersion in oil, and was washed with light petroleum, and a 2.5 M solution of *n*-butyl lithium in hexane was used in all stated cases. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 spectrometer as solutions of $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H NMR spectra and $CDCl_3$ the standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). Mass spectra were recorded on a Jeol JMS-SX102 quadrupole high-resolution mass spectrometer or carried out by the EPSRC MS service at the University of Wales, Swansea. TLC using silica gel as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F_{254}). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography unless otherwise specified.

3.2. Asymmetric Cyclisations of Chiral *N*-Acyliminium Ion Precursors

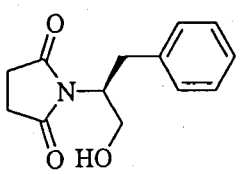
3.2.1. Stereoselective Synthesis of Pyrroloisoquinolines

(*S*)-2-Amino-3-phenyl-1-propanol (6).[3]



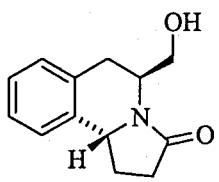
Trimethylsilylchloride (13.2 g, 15.4 ml, 121.1 mmol) was added to lithium borohydride (1.32 g, 60.5 mmol) in tetrahydrofuran (80 ml) over a 5 min period under nitrogen. *L*-Phenylalanine (5.0 g, 30.3 mmol) was added to the resultant mixture and the mixture stirred at room temperature for 24 h. Methanol (50 ml) was cautiously added and the volatiles were removed by evaporation. The residue was treated with 20 % potassium hydroxide solution and extracted with dichloromethane (3 × 50 ml). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and solvent was evaporated under reduced pressure to yield the target compound as a colourless crystalline solid (4.35 g, 95 %), Mp 92-94 °C, Lit: Mp 92-94 °C; $[\alpha]_D$ – 18.5 [*c* = 1.08 in CH_2Cl_2], Lit $[\alpha]_D$ – 22.8 [*c* = 1.20 in 1 N HCl]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 3356 (NH) and 3659 (OH); δ_H (400 MHz, $CDCl_3$) 2.50 (1 H, dd, *J* 8.8, 13.6 Hz, ArCH*(H)*$CHNH_2$), 2.79 (1 H, dd, *J* 5.2, 13.6 Hz, ArCH*(H)*$CHNH_2$), 3.10 (1 H, m, $ArCH_2CHNH_2$), 3.39 (1 H, dd, *J* 7.2, 10.8 Hz, CH*(H)*OH), 3.62 (1 H, dd, *J* 4.0, 10.8 Hz, CH*(H)*OH) and 7.18-7.32 (5 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 41.1 (CH_2), 54.6 (*C*H), 66.5 (CH_2), 126.8 (*C*H), 129.0 (*C*H), 129.0 (*C*H), 126.6 (*C*H), 126.6 (*C*H) and 139.1 (*C*); MS (FAB) *m/z* 152 [MH^+, 100 %] (MH^+, 152.1075. $C_9H_{13}NO$ requires 152.1075).

1-(2*S*)-(1-Hydroxymethyl-2-phenyl-ethyl)-pyrrolidine-2,5-dione (8).[1b]



Succinic anhydride (5.29 g, 52.9 mmol) and (*S*)-2-amino-3-phenyl-1-propanol **(6)** (8.0 g, 52.9 mmol) was stirred in toluene (100 ml) under a nitrogen atmosphere. Triethylamine (8 ml) was added to the resultant solution and the mixture heated under reflux for 18 h after which, the reaction was cooled to room temperature and solvent removed by evaporation to yield a yellow oil. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and 3:1 ethyl acetate/light petroleum as eluent to produce a colourless solid (7.65 g, 62 %), Mp 130-131 °C, Lit: Mp 130-131 °C; $[\alpha]_D$ – 89.2 [*c* = 0.50 in CH_2Cl_2], Lit $[\alpha]_D$ – 89.8 [*c* = 0.48 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1682 (NCO), 2972 (aliphatic CH) and 3419 (OH); δ_H (400 MHz, $CDCl_3$) 2.50-2.63 (4 H, m, $COCH_2CH_2CO$), 3.05-3.20 (2 H, m, $ArCH_2CHN$), 3.82 (1 H, dd, *J* 3.5, 11.9 Hz, CH*(H)*OH), 4.01 (1 H, dd, *J* 7.6, 11.9 Hz, CH*(H)*OH), 4.47-4.54 (1 H, m, $ArCH_2CHN$) and 7.16-7.28 (5 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_2), 27.8 (CH_2), 33.7 (CH_2), 55.7 (*C*H), 62.1 (CH_2), 126.8 (*C*H), 128.5 (*C*H), 128.5 (*C*H), 129.0 (*C*H), 129.0 (*C*H), 137.2 (*C*), 178.2 (*C*O) and 178.2 (*C*O); MS (EI) *m/z* 233 [M^+, 2.5 %] (M^+, 233.1055. $C_{13}H_{15}NO_3$ requires 233.1052).

(5*S*,10b*R*)-5-(Hydroxymethyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (10).[1b]

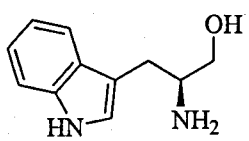


1-(2*S*)-3-Hydroxy-2-(phenylmethyl)ethyl-tetrahydro-1*H*-pyrrole-2,5-dione **(8)** (5.0 g, 21.4 mmol) was dissolved in absolute ethanol (100 ml) and cooled to 0 °C. Sodium borohydride (8.11 g, 214.4 mmol) was then added with stirring. HCl (2 M solution in absolute ethanol, 10.7 ml, 21.4 mmol) was then slowly added *via* syringe over a 3 h period. The resultant solution was acidified to pH 1-3 with HCl (2 M solution in absolute ethanol) over a 15 min period. This afforded a white suspension, which was stirred for a further 20 h. The reaction was quenched with sodium hydrogen carbonate and extracted with dichloromethane (3 × 75 ml). The dichloromethane layers were then combined and dried over anhydrous magnesium sulfate and solvent removed by rotary evaporation to yield the ethoxy lactam intermediate as a colourless oil (4.34 g). The

intermediate ethoxy lactam (4.34 g, 16.5 mmol) was dissolved in dry dichloromethane (100 ml) under nitrogen. The solution was cooled to –78 °C and titanium tetrachloride (4.69 g, 2.71 ml, 24.7 mmol) was added dropwise. After stirring at –78 °C for 10 min, the reaction was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (75 ml), extracted with dichloromethane (3 × 75 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by evaporation to yield the target compound as a single diastereoisomer, which was purified by column chromatography using silica gel absorbent and 10 % methanol/dichloromethane as eluent to yield a green solid (2.04 g, 44 %), Mp 110-111 °C, Lit: Mp 110-111 °C; $[\alpha]_D$ + 13.7 [*c* = 0.54 in CH_2Cl_2], Lit $[\alpha]_D$ + 13.3 [*c* = 0.08 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1643 (NCO), 2985 (aliphatic CH) and 3374 (OH); δ_H (400 MHz, $CDCl_3$) 1.92-2.07 (1 H, m, CH*(H)*CH_2CO), 2.41-2.51 (1 H, m, CH_2CH*(H)*CO), 2.59-2.70 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.74 (1 H, dd, *J* 3.6, 16.4 Hz, ArCH*(H)*CHN), 3.04 (1 H, dd, *J* 6.4, 16.4 Hz, ArCH*(H)*CHN), 3.59-3.73 (2 H, m, C*H*$_2$OH), 4.14 (1 H, br, s, O*H*), 4.43-4.49 (1 H, m, ArCH_2C*H*N), 4.83 (1 H, t, *J* 7.6 Hz, NC*H*Ar) and 7.09-7.31 (4 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 26.6 (*C*H_2), 29.6 (*C*H_2), 31.7 (*C*H_2), 49.5 (*C*H), 54.5 (*C*H), 62.8 (*C*H_2), 124.3 (*C*H), 126.9 (*C*H), 127.2 (*C*H), 128.7 (*C*H), 132.3 (*C*), 136.7 (*C*) and 175.2 (*C*O); MS (EI) *m/z* 217 [M^+, 8.3 %] (M^+, 217.1105. $C_{13}H_{15}NO_2$ requires 217.1103).

3.2.2. Stereoselective Synthesis of Indolizino[8,7-*b*]indoles

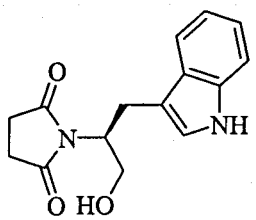
(2*S*)-2-Amino-3-(1*H*-indol-3-yl) propan-1-ol (22).



Trimethylsilylchloride (12.4 ml, 97.9 mmol) was added to lithium borohydride (1.07 g, 49.0 mmol) in tetrahydrofuran (80 ml) over a 5 min period under nitrogen. *L*-tryptophan (5.0 g, 24.5 mmol) was cautiously added to the resultant mixture and the reaction stirred at room temperature for 24 h. Methanol (50 ml) was cautiously added and the volatiles were removed by rotary evaporation. The red residue was treated with 20 % potassium hydroxide solution and extracted with ethyl acetate (3 × 50 ml). The organic extracts

were combined, dried over anhydrous magnesium sulfate, filtered and solvent was evaporated under reduced pressure resulting in a crude yellow solid (4.6 g, 99 %), Mp 72-76 °C, Lit: Mp 73-77 °C; $[\alpha]_D$ – 19.9 [*c* = 1.01 in MeOH], Lit $[\alpha]_D$ – 20.5 [*c* = 1.00 in MeOH]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 3282 (NH) and 3350 (OH); δ_H (400 MHz, DMSO) 2.57 (1 H, dd, *J* 7.3, 14.5 Hz, ArCH*(H)*$CHNH_2$), 2.81 (1 H, dd, *J* 6.0, 14.1 Hz, ArCH*(H)*$CHNH_2$), 2.95-3.02 (1 H, m, $ArCH_2CHNH_2$), 3.24 (1 H, dd, *J* 5.3, 15.9 Hz, CH*(H)*OH), 3.40 (1 H, dd, *J* 4.5, 10.1 Hz, CH*(H)*OH), 6.99 (1 H, t, *J* 6.8 Hz, Ar*H*), 7.08 (1 H, t, *J* 7.3 Hz, Ar*H*), 7.14 (1 H, s, C*H*NH), 7.35 (1 H, d, *J* 7.2 Hz, Ar*H*) and 7.55 (1 H, d, *J* 7.7 Hz, Ar*H*); δ_C (100 MHz, DMSO) 29.6 (CH_2), 53.6 (*C*H), 66.0 (CH_2), 111.3 (*C*H), 111.7 (*C*), 118.1 (*C*H), 118.5 (*C*H), 120.8 (*C*H), 123.3 (*C*H), 127.6 (*C*) and 136.2 (*C*); MS (EI) *m/z* 190 [M^+, 3.0 %] (M^+, 190.1102. $C_{11}H_{14}N_2O$ requires 190.1106).

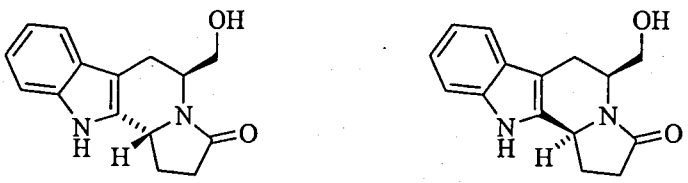
1-[(1*S*)-1-Hydroxymethyl-2-(1*H*-indol-3-yl)-ethyl]-pyrrolidine-2,5-dione (18).[2]



(2*S*)-2-Amino-3-(1*H*-indol-3-yl)propan-1-ol **(22)** (4.90 g, 26.0 mmol) and succinic anhydride (2.60 g, 26.0 mmol) were stirred in toluene (100 ml) under a nitrogen atmosphere. Triethylamine (4 ml) was added to the resultant solution and the mixture heated at reflux for 18 h after which, the reaction was cooled to room temperature and solvent removed by rotary evaporator to yield a dark brown oil. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and 3:1 ethyl acetate/hexane as eluent to produce a colourless solid (3.54 g, 72 %), Mp 144-148 °C; $[\alpha]_D$ – 74.0 [*c* = 1.00 in CH_2Cl_2] (Found: C, 66.27; H, 5.82; N, 10.32. $C_{15}H_{16}N_2O_3$ requires C, 66.16; H, 5.92; N, 10.29 %); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1674 (NCO), 2946 (aliphatic CH), 3408 (OH) and 3426 (NH); δ_H (400 MHz, $CDCl_3$) 2.39-2.56 (4 H, m, $COCH_2CH_2CO$), 3.18 (1 H, ddd, *J* 0.6, 8.7, 14.6 Hz, ArCH*(H)*CHN), 3.28 (1 H, ddd, *J* 0.6, 8.7, 14.6 Hz, ArCH*(H)*CHN), 3.66 (1 H, br, s, O*H*), 3.79 (1 H, dd, *J* 4.0, 11.7 Hz, CH*(H)*OH), 4.11 (1 H, dd, *J* 8.5, 11.7 Hz, CH*(H)*OH), 4.55-4.61 (1 H, m, $ArCH_2CHN$), 7.01 (1 H, d, C=C*H*), 7.04-7.08 (1 H, m, Ar*H*), 7.10-7.13 (1 H, m, Ar*H*), 7.31-7.34

(1 H, m, Ar*H*), 7.57-7.58 (1 H, m, Ar*H*) and 9.24 (1 H, br, s, N*H*); δ_C (100 MHz, $CDCl_3$) 23.7 (*C*H_2), 28.0 (*C*H_2), 28.0 (*C*H_2), 55.6 (*C*H), 61.5 (*C*H_2), 111.0 (*C*), 111.3 (*C*H), 118.4 (*C*H), 119.0 (*C*H), 121.6 (*C*H), 122.9 (*C*H), 127.3 (*C*), 136.2 (*C*), 178.3 (*C*O) and 178.3 (*C*O); MS (EI) *m/z* 272 [M^+, 13.9 %] (M^+, 272.1162. $C_{15}H_{16}N_2O_3$ requires 272.1161). The product was recrystallised from dichloromethane/hexane *via* vapour diffusion to produce a colourless crystalline solid.

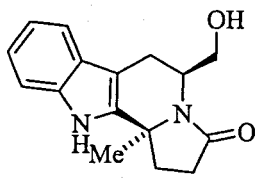
(5*S*,11b*R*)-5-Hydroxymethyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (21).[2]



1-[(1*S*)-1-Hydroxymethyl-2-(1*H*-indol-3-yl)-ethyl]-pyrrolidine-2,5-dione **(18)** (500 mg, 1.84 mmol) was dissolved in absolute ethanol (25 ml) at room temperature under a nitrogen atmosphere. The solution was then cooled to 0 °C and sodium borohydride (700 mg, 18.4 mmol) was added with stirring. The reaction mixture was warmed to room temperature and HCl (2 M solution in absolute ethanol, 0.92 ml, 1.84 mmol) was added with stirring over a 3 h period. The resultant solution was acidified (pH 1-3) with HCl (2 M solution in absolute ethanol) over a 15 min period. This afforded a white suspension, which was stirred for a further 20 h. The reaction was quenched with saturated sodium hydrogen carbonate (30 ml) and extracted with dichloromethane (3 × 30 ml). The dichloromethane layers were then combined and dried over anhydrous magnesium sulfate. The organic phase was then filtered and volatiles removed on the rotary evaporator to yield the target compound as a crude 9:1 mixture of diastereoisomers (400 mg, 85 %). The crude mixture was recrystallised from absolute ethanol, which precipitated the major isomer only as clear colourless needles (202 mg, 43 %), Mp 266-267 °C; $[\alpha]_D$ + 144.8 [*c* = 0.48 in EtOH] (Found: C, 70.57; H, 6.31; N, 10.74. $C_{15}H_{16}N_2O_2$ requires C, 70.29; H, 6.29; N, 10.93 %); ν_{max} (KBr disc)/cm^{-1} 1666 (NCO), 2968 (aliphatic CH) and 3269 (NH); δ_H (400 MHz, DMSO) 1.77-1.85 (1 H, m, CH*(H)*CH_2CO), 2.25-2.31 (1 H, m, CH_2CH*(H)*CO), 2.50-2.58 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.73 (1 H, dd, *J* 2.1, 6.6 Hz, ArCH*(H)*CHN), 2.82 (1 H, d,

J 15.8 Hz, ArCH*(H)*CHN), 3.38 (2 H, t, *J* 7.96, C*H*$_2$OH), 4.47-4.52 (1 H, m, ArCH$_2$C*H*N), 4.84-4.88 (2 H, m, NC*H*Ar and O*H*), 6.95-6.99 (1 H, m, Ar*H*), 7.04-7.07 (1 H, m, Ar*H*), 7.31-7.34 (1 H, m, Ar*H*), 7.38-7.40 (1 H, m, Ar*H*) and 11.02 (1 H, s, N*H*); δ_C (100 MHz, DMSO) 21.1 (*C*H$_2$), 25.5 (*C*H$_2$), 31.1 (*C*H$_2$), 48.0 (*C*H), 50.7 (*C*H), 60.1 (*C*H$_2$), 104.1 (*C*), 111.1 (*C*H), 117.7 (*C*H), 118.4 (*C*H), 120.9 (*C*H), 126.9 (*C*), 133.4 (*C*), 136.1 (*C*) and 172.6 (*C*O); MS (EI) *m/z* 256 [M$^+$, 86.8 %] (M$^+$, 256.1215. $C_{15}H_{16}N_2O_2$ requires 256.1212). The relative stereochemistry at C-5 and C-11b was determined by single crystal X-ray analysis.

(5*S*,11b*S*)-5-Hydroxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino [8,7-*b*]indol-3-one (25).[2]

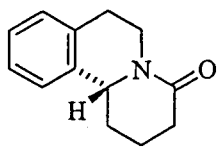


(2*S*)-2-Amino-3-(1*H*-indol-3-yl)propan-1-ol **(22)** (4.80 g, 25.2 mmol) and levulinic acid (2.93 g, 25.2 mmol) were added to toluene (150 ml) and refluxed under Dean-Stark conditions for 48 h. The reaction was cooled to room temperature and solvent removed by rotary evaporation. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 4:1 ethyl acetate/light petroleum as eluent to produce a colourless solid (3.75 g, 55 %), Mp 212-214 °C; $[\alpha]_D$ – 229.8 [*c* = 1.24 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1651 (NCO), 2970 (aliphatic CH), 3057 (aromatic CH), 3265 (OH) and 3269 (NH); δ_H (400 MHz, $CDCl_3$) 1.65 (3 H, s, C*H*$_3$), 2.25-2.32 (2 H, m, C*H*$_2$CH$_2$CO), 2.49 (1 H, ddd, *J* 3.1, 9.3, 17.0, Hz, CH$_2$CH*(H)*CO), 2.70-2.78 (2 H, m, CH$_2$CH*(H)*CO and ArCH*(H)*CHN), 3.05 (1 H, dd, *J* 11.7, 15.4 Hz, ArCH*(H)*CHN), 3.66-3.70 (1 H, m, ArCH$_2$C*H*N), 4.17-4.19 (2 H, m, C*H*$_2$OH), 5.29 (1 H, br, s, O*H*), 7.11-7.15 (1 H, m, Ar*H*), 7.17-7.21 (1 H, m, Ar*H*), 7.33-7.35 (1 H, m, Ar*H*), 7.46-7.48 (1 H, m, Ar*H*) and 8.37 (1 H, br, s, N*H*); δ_C (100 MHz, $CDCl_3$) 24.3 (*C*H$_2$), 25.4 (*C*H$_3$), 31.3 (*C*H$_2$), 32.7 (*C*H$_2$), 55.5 (*C*H), 62.3 (*C*), 62.7 (*C*H$_2$), 107.1 (*C*), 111.1 (*C*H), 118.5 (*C*H), 120.0 (*C*H), 122.3 (*C*H), 126.5 (*C*), 136.3 (*C*), 137.2 (*C*) and 174.6 (*C*O); MS (EI) *m/z* 270 [M$^+$, 3.4 %] (M$^+$, 270.1364. $C_{16}H_{18}N_2O_2$ requires 270.1368). The product was recrystallised from dichloromethane to produce clear, colourless needles.

3.3. Application in the Synthesis Of Naturally Occurring Alkaloids

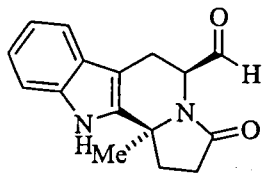
3.3.1. Removal of the Hydroxymethyl Auxiliary

(11b*R*)-1,2,3,6,7,11b-Hexahydro-pyrido[2,1-*a*]isoquinolin-4-one (48).



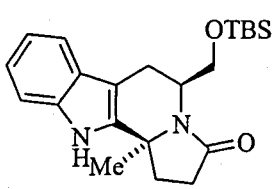
Raney nickel (W-2) (2.50 g) was washed with water (3 × 10 ml) followed by 2-propanol (2 × 10 ml). 2-Propanol was decanted and the Raney nickel was taken up in toluene (20 ml) and the residual water and 2-propanol were azeotropically removed using a Dean-Stark trap. A solution of (6*S*,11b*R*)-6-hydroxymethyl-1,2,3,6,7,11b-hexahydro-pyrido[2,1-*a*]isoquinolin-4-one **(45)** (500 mg, 2.16 mmol) in toluene (10 ml) was added and the reaction was refluxed under Dean-Stark conditions for 4.5 h. The resulting solution was filtered through a celite pad, washed with methanol and evaporated under reduced pressure to yield the target compound as a colourless oil (186 mg, 44 %), ν_{max} (thin film, $CHCl_3$)/cm^{-1} 1619 (NCO) and 2930 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.65-1.76 (1 H, m, CH*(H)*CH_2CH_2CO), 1.80-2.00 (2 H, m, $CH_2CH_2CH_2CO$), 2.30-2.45 (1 H, m, CH_2CH_2CH*(H)*CO), 2.49-2.63 (2 H, m, CH*(H)*CH_2CH_2CO and CH_2CH_2CH*(H)*CO), 2.70-2.79 (1 H, m, ArCH*(H)*CH_2N), 2.83-2.89 (1 H, m, ArCH*(H)*CH_2N), 2.91-3.03 (1 H, m, $ArCH_2CH$*(H)*N), 4.61-4.69 (1 H, m, NC*H*Ar), 4.76-4.85 (1 H, m, $ArCH_2CH$*(H)*N) and 7.08-7.30 (4 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 20.0 (*C*H_2), 29.3 (*C*H_2), 31.1 (*C*H_2), 32.6 (*C*H_2), 40.0 (*C*H_2), 57.3 (*C*H), 125.3 (*C*H), 126.9 (*C*H), 127.0 (*C*H), 129.4 (*C*H), 135.5 (*C*), 137.7 (*C*) and 169.7 (*C*O); MS (EI) *m/z* 201 [M^+, 100 %] (M^+, 201.1156. $C_{13}H_{15}NO$ requires 201.1136).

(5*S*,11b*S*)-11b-Methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-5-carbaldehyde (32).



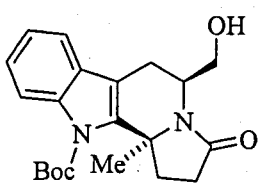
o-Iodoxybenzoic acid (2.78 g, 10.0 mmol) was added to a solution of (5*S*,11b*S*)-5-hydroxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one **(25)** (1.36 g, 5.00 mmol) in dimethyl sulfoxide (15 ml) and the reaction stirred for 24 h at room temperature. The resulting mixture was added to a solution of ethyl acetate/water and product extracted with ethyl acetate (3 × 50 ml). The organic layer was washed with water (5 × 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated to a crude yellow solid. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and ethyl acetate as eluent to isolate the target compound as a colourless solid (666 mg, 49 %), Mp 170-171 °C; $[\alpha]_D$ – 91.9 [*c* = 1.30 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1670 (NCO), 1670 (CHO), 2969 (aliphatic CH) and 3307 (NH); δ_H (400 MHz, $CDCl_3$) 1.68 (3 H, s, C*H*$_3$), 2.16-2.35 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.46-2.56 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.99 (1 H, dd, *J* 5.2, 15.6 Hz, ArCH*(H)*CHN), 3.11 (1 H, dd, *J* 11.2, 16.0 Hz, ArCH*(H)*CHN), 3.84 (1 H, dd, *J* 4.8, 10.8 Hz, ArCH_2C*H*N), 7.05-7.09 (1 H, m, Ar*H*), 7.12-7.16 (1 H, m, Ar*H*), 7.28-7.31 (1 H, m Ar*H*), 7.42-7.44 (1 H, m, Ar*H*), 9.29 (1 H, br, s, N*H*) and 10.08 (1 H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 21.3 (*C*H_2), 27.2 (*C*H_3), 29.5 (*C*H_2), 32.4 (*C*H_2), 58.8 (*C*H), 61.6 (*C*), 106.5 (*C*), 111.4 (*C*H), 118.4 (*C*H), 119.8 (*C*H), 122.4 (*C*H), 126.6 (*C*), 136.5 (*C*), 137.2 (*C*), 178.4 (*C*O) and 196.2 (*C*HO); MS (EI) *m/z* 268 [M^+, 0.60 %] (M^+, 268.1206. $C_{16}H_{16}N_2O_2$ requires 268.1212).

(5*S*,11b*S*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (49).



Imidazole (1.37 g, 20.2 mmol) and 4-dimethylaminopyridine (0.21 g, 1.68 mmol) followed by (5*S*,11b*S*)-5-hydroxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one **(25)** (4.54 g, 16.8 mmol) was dissolved in anhydrous dichloromethane (60 ml) under a nitrogen atmosphere. To this solution, *tert*-butyldimethylsilylchloride (2.78 g, 18.5 mmol) was added and the solution stirred at room temperature for 4 h. The resulting mixture was filtered to remove the solid phase and concentrated under reduced pressure. The crude product was chromatographed using silica gel as absorbent and 2:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (5.2 g, 81 %), Mp 221-223 °C; $[\alpha]_D$ – 172.8 [*c* = 1.00 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1669 (NCO), 2950 (aliphatic CH) and 3279 (NH); δ_H (400 MHz, $CDCl_3$) 0.11 (3 H, s, SiC*H*$_3$), 0.13 (3 H, s, SiC*H*$_3$), 0.93 (9 H, s, SiC(C*H*$_3$)$_3$), 1.65 (3 H, s, C*H*$_3$), 2.20-2.33 (3 H, m, C*H*$_2$CH$_2$CO and CH$_2$CH*(H)*CO), 2.48-2.59 (1 H, m, CH$_2$CH*(H)*CO), 2.81 (1 H, dd, *J* 11.0, 15.2 Hz, ArCH*(H)*CHN), 3.06 (1 H, dd, *J* 3.9, 15.2 Hz, ArCH*(H)*CHN), 3.57-3.64 (1 H, m, ArCH$_2$C*H*N), 4.46-4.54 (2 H, m, C*H*$_2$OSi), 7.10-7.20 (2 H, m, Ar*H*), 7.29-7.33 (1 H, m, Ar*H*), 7.49-7.51 (1 H, m, Ar*H*) and 8.01 (1 H, br, s, N*H*); δ_C (100 MHz, $CDCl_3$) –5.2 (SiCH$_3$), –5.2 (SiCH$_3$), 18.2 (*C*), 24.9 (*C*H$_2$), 25.7 (SiC(*C*H$_3$)$_3$), 26.6 (*C*H$_3$), 30.7 (*C*H$_2$), 32.6 (*C*H$_2$), 55.5 (*C*H), 62.0 (*C*), 64.0 (*C*H$_2$), 108.8 (*C*), 111.0 (*C*H), 118.5 (*C*H), 119.8 (*C*H), 122.2 (*C*H), 126.9 (*C*), 136.1 (*C*), 137.7 (*C*) and 175.8 (*C*O); MS (EI) *m/z* 385 [MH^+, 6.5 %] (MH^+, 385.2311. $C_{22}H_{32}N_2O_2Si$ requires 385.2318).

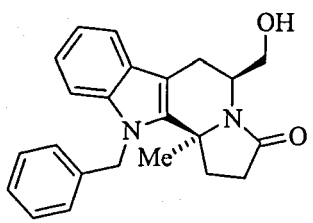
(5*S*,11b*S*)-5-Hydroxymethyl-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino [8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (50).



To a solution of the (5*S*,11b*S*)-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(99)** (1.05 g, 2.17 mmol) in tetrahydrofuran (15 ml) was added tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 2.17 ml, 2.17 mmol) and the reaction stirred for 5 min at room temperature. The resultant solution was concentrated and

chromatographed through a pad of silica gel using 2:1 light petroleum/ethyl acetate as eluent to yield the target compound as a colourless solid (769 mg, 97 %), Mp 96-99 °C; $[\alpha]_D$ – 215.8 [*c* = 1.01 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1665 (NCO), 2950 (aliphatic CH) and 3265 (OH); δ_H (400 MHz, $CDCl_3$) 1.71 (9 H, s, $CO_2C(CH_3)_3$), 1.84 (3 H, s, CH_3), 2.19-2.23 (1 H, m, CH*(H)*CH_2CO), 2.42-2.66 (3 H, m, CH*(H)*CH_2CO and CH_2CH_2CO), 2.75-2.79 (1 H, m, ArCH*(H)*CHN), 3.04 (1 H, dd, *J* 4.0, 15.4 Hz, ArCH*(H)*CHN), 3.59-3.66 (1 H, m, $ArCH_2CHN$), 4.45-4.50 (2 H, m, CH_2OH), 7.22-7.29 (2 H, m, Ar*H*), 7.41-7.45 (1 H, m, Ar*H*) and 7.94-7.99 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 25.1 (CH_3), 25.5 (CH_2), 28.3 ($CO_2C(CH_3)_3$), 30.5 (CH_2), 32.2 (CH_2), 53.6 (*C*H), 63.8 (CH_2), 65.0 (*C*), 84.1 (*C*), 116.0 (*C*H), 116.3 (*C*), 118.4 (*C*H), 122.7 (*C*H), 124.5 (*C*H), 128.6 (*C*), 135.7 (*C*), 139.3 (*C*), 149.9 (*C*O) and 173.8 (*C*O); MS (EI) *m/z* 371 [MH^+, 10.2 %] (MH^+, 371.1888. $C_{21}H_{26}N_2O_4$ requires 371.1893).

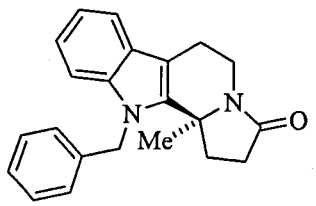
(5*S*,11b*S*)-11-Benzyl-5-hydroxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (51).



Anhydrous *N*,*N*-dimethylformamide (8 ml) was added to sodium hydride (14 mg, 3.70 mmol) in a dry three-necked round bottom flask under nitrogen and cooled to 0 °C with an ice bath. (5*S*,11b*S*)-5-Hydroxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one **(25)** (1.00 g, 3.70 mmol) in anhydrous *N*,*N*-dimethylformamide (8 ml) was added and stirred for 30 min at room temperature. Benzyl bromide (696 mg, 0.47 ml, 4.07 mmol) was added and the reaction stirred at room temperature for 3 h under nitrogen. Ice and water were added to quench and the product extracted with ethyl acetate (3 × 10 ml). Organic phases were combined and washed with saturated brine, dried over anhydrous magnesium sulfate, filtered and evaporated to a crude green solid. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 2 % methanol/ethyl acetate as eluent to isolate the target compound as a green solid (830 mg, 62 %), Mp 82-86 °C; $[\alpha]_D$

– 174.1 [c = 0.27 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1660 (NCO), 2927 (aliphatic CH) and 3389 (OH); δ_H (400 MHz, $CDCl_3$) 1.60 (3 H, s, CH_3), 2.18-2.33 (2 H, m, CH_2CH_2CO), 2.42 (1 H, ddd, J 2.0, 9.6, 16.8 Hz, $CH_2CH(H)CO$), 2.61-2.81 (2 H, m, $CH_2CH(H)CO$ and $ArCH(H)CHN$), 3.09 (1 H, dd, J 11.6, 15.2 Hz, $ArCH(H)CHN$), 3.65-3.71 (1 H, m, $ArCH_2CHN$), 4.18 (2 H, d, J 3.2 Hz, CH_2OH), 4.99 (1 H, br, s, OH), 5.39 (1 H, d, J 17.8 Hz, $NCH(H)Ph$), 5.44 (1 H, d, J 17.8 Hz, $NCH(H)Ph$), 6.75-6.81 (2 H, m, ArH), 7.05-7.08 (1 H, m, ArH), 7.12-7.19 (2 H, m, ArH), 7.22-7.28 (3 H, m, ArH) and 7.50-7.54 (1 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 24.5 (CH_2), 25.2 (CH_3), 31.2 (CH_2), 32.5 (CH_2), 47.7 (CH_2), 55.3 (CH), 62.3 (CH_2), 63.3 (C), 107.7 (C), 110.0 (CH), 118.6 (CH), 120.0 (CH), 122.4 (CH), 125.4 (CH), 125.4 (CH), 126.3 (C), 127.5 (CH), 128.9 (CH), 128.9 (CH), 137.2 (C), 137.2 (C), 138.0 (C) and 173.8 (CO); MS (FAB) m/z 361 [MH^+, 60.4 %] (MH^+, 361.1916. $C_{23}H_{24}N_2O_2$ requires 361.1916).

(11b*S*)-11-Benzyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (52).

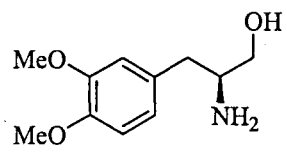


Raney nickel (W-2) (3.0 g) was washed with water (3 × 10 ml) followed by 2-propanol (2 × 10 ml). 2-Propanol was decanted and the Raney nickel was taken up in toluene and the residual water and 2-propanol were azeotropically removed using a Dean-Stark trap. A solution of (5*S*,11b*S*)-11-benzyl-5-hydroxymethyl-11b-methyl-1,2,5,6,11,11b-hexa hydro-indolizino[8,7-*b*]indol-3-one **(51)** (500 mg, 1.39 mmol) in toluene (30 ml) was added and the reaction was refluxed under Dean-Stark conditions for 4 h. The resulting solution was filtered through a celite pad, washed with methanol and evaporated under reduced pressure to yield the target compound as a colourless oil (353 mg, 77 %), Mp 130-131 °C; $[\alpha]_D$ – 134.2 [c = 0.28 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1682 (NCO) and 2970 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.54 (3 H, s, CH_3), 2.15 (1 H, dd, J 11.2, 21.6 Hz, $CH(H)CH_2CO$), 2.30 (1 H, ddd, J 1.6, 8.8, 12.0 Hz, $CH(H)CH_2CO$), 2.44 (1 H, ddd, J 1.6, 9.6, 12.0 Hz, $CH_2CH(H)CO$), 2.57-2.66 (1 H, m, $CH_2CH(H)CO$), 2.86-2.95 (2 H, m, $ArCH_2CH_2N$), 3.08-3.16 (1 H, m, $ArCH_2CH(H)N$),

4.50 (1 H, ddd, *J* 3.2, 4.4, 13.2 Hz, ArCH$_2$CH*(H)*N), 5.39 (1 H, d, *J* 17.4 Hz, NCH*(H)*Ph), 5.45 (1 H, d, *J* 17.4 Hz, NCH*(H)*Ph), 6.88-6.90 (2 H, m, Ar*H*), 7.05-7.08 (1 H, m, Ar*H*), 7.11-7.15 (2 H, m, Ar*H*), 7.21-7.29 (3 H, m, Ar*H*) and 7.51-7.55 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (*C*H$_2$), 25.2(*C*H$_3$), 30.5 (*C*H$_2$), 32.5 (*C*H$_2$), 34.5 (*C*H$_2$), 47.7 (*C*H$_2$), 60.0 (*C*), 107.3 (*C*), 110.0 (*C*H), 118.6 (*C*H), 119.8 (*C*H), 122.3 (*C*H), 125.5 (*C*H), 125.5 (*C*H), 126.6 (*C*), 127.4 (*C*H), 128.9 (*C*H), 128.9 (*C*H), 137.0 (*C*), 137.3 (*C*), 138.7 (*C*) and 171.9 (*C*O); MS (EI) *m/z* 330 [M$^+$, 26.6 %] (M$^+$, 330.1737. $C_{22}H_{22}N_2O$ requires 330.1732).

3.3.2. Total Synthesis of (*R*)-(+)-Crispine A

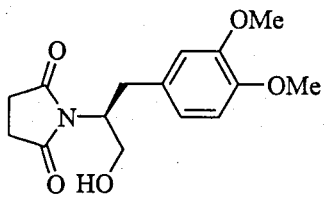
(2*S*)-2-Amino-3-(3,4-dimethyloxy)phenyl)propan-1-ol (62).



Trimethylsilylchloride (3.85 g, 4.50 ml, 35.5 mmol) was added under nitrogen to a solution of lithium borohydride (2.0 M solution in tetrahydrofuran, 8.88 ml, 17.8 mmol) in anhydrous tetrahydrofuran (10 ml) over a 2 min period. 3-(3,4-Dimethoxyphenyl)-*L*-alanine (2.00 g, 8.88 mmol) was cautiously added to the resultant mixture over a 5 min period and the reaction stirred at room temperature for 24 h. Methanol (20 ml) was cautiously added and volatiles were removed by rotary evaporation. The residue was treated with 20 % potassium hydroxide solution and extracted with dichloromethane (3 × 20 ml). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and solvent was evaporated under reduced pressure resulting in a colourless crystalline solid (1.70 g, 91 %), Mp 81-82 °C, Lit: Mp 78-79 °C; $[\alpha]_D$ – 21.6 [*c* = 1.00 in EtOH], Lit: $[\alpha]_D$ – 21.5 [*c* = 8.0 in EtOH]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 2933 (aliphatic CH) and 3348 (OH); δ_H (400 MHz, $CDCl_3$) 2.46 (1 H, dd, *J* 8.8, 13.6 Hz, CH*(H)*CHNH$_2$), 2.62 (3 H, br, s, O*H* and N*H*$_2$), 2.74 (1 H, dd, *J* 4.9, 13.5 Hz, CH*(H)*CHNH$_2$), 3.09-3.11 (1 H, m, C*H*NH$_2$), 3.41 (1 H, dd, *J* 7.1, 10.6 Hz, CH*(H)*OH), 3.63 (1 H, dd, *J* 3.6, 10.7 Hz, CH*(H)*OH), 3.85 (3 H, s, OC*H*$_3$), 3.86 (3 H, s, OC*H*$_3$), 6.72-6.74 (2 H, m, Ar*H*) and 6.79-6.81 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 40.0 (*C*H$_2$), 54.3 (*C*H), 55.8 (O*C*H$_3$), 55.9 (O*C*H$_3$), 65.9 (*C*H$_2$), 111.2 (*C*H), 112.2 (*C*H),

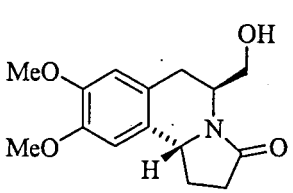
121.1 (*C*H), 131.2 (*C*), 147.5 (*C*) and 148.9 (*C*); MS (EI) *m/z* 211 [M^+, 6.5 %] (M^+, 211.1211. $C_{11}H_{17}NO_3$ requires 211.1208).

1-(2*S*)-[2-(3,4-Dimethoxy-phenyl)-1-hydroxymethyl-ethyl]-pyrrolidine-2,5-dione (63).[1b]



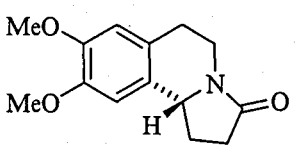
Succinic anhydride (2.56 g, 25.6 mmol) and (2*S*)-2-amino-3-(3,4-dimethyloxy)phenyl) propan-1-ol **(62)** (4.92, 23.3 mmol) was stirred in toluene (100 ml) under nitrogen. Triethylamine (4 ml) was added to the resultant solution and the mixture heated under reflux for 18 h. After 18 h, the reaction was cooled to room temperature and solvent removed by rotary evaporator to yield a yellow oil. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and ethyl acetate as eluent to produce a colourless solid (4.87 g, 71 %), Mp 124-125 °C, $[\alpha]_D$ – 73.2 [*c* = 1.01 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1700 (NCO), 2938 (aliphatic CH) and 3447 (OH); δ_H (400 MHz, $CDCl_3$) 2.51-2.61 (4 H, m, COC*H*$_2$C*H*$_2$CO), 3.04 (2 H, ddd, *J* 6.8, 14.0, 20.8 Hz, ArC*H*$_2$CHN), 3.79 (1 H, dd, *J* 3.6, 11.6 Hz, CH*(H)*OH), 3.83 (3 H, s, OC*H*$_3$), 3.84 (3 H, s, OC*H*$_3$), 4.03 (1 H, dd, *J* 8.0, 11.6 Hz, CH*(H)*OH), 4.47-4.52 (1 H, m, ArCH$_2$C*H*N) and 4.47-4.52 (3 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (*C*H$_2$), 27.8 (*C*H$_2$), 33.1 (*C*H$_2$), 55.6 (*C*H), 55.8 (O*C*H$_3$), 55.8 (O*C*H$_3$), 61.8 (*C*H$_2$), 111.0 (*C*H), 111.9 (*C*H), 121.0 (*C*H), 129.6 (*C*), 147.6 (*C*), 148.7 (*C*), 178.3 (*C*O) and 178.3 (*C*O); MS (FAB) *m/z* 294 [MH^+, 4.0 %] (MH^+, 294.1344. $C_{15}H_{19}NO_5$ requires 294.1342).

(5*S*,10b*R*)-5-Hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo [2,1-*a*]isoquinolin-3-one (64).[1b]



1-(2*S*)-[2-(3,4-Dimethoxy-phenyl)-1-hydroxymethyl-ethyl]-pyrrolidine-2,5-dione **(63)** (4.09 g, 13.9 mmol) was dissolved in absolute ethanol (100 ml) and cooled to 0 °C. Sodium borohydride (5.28 g, 139.4 mmol) was then added with stirring. HCl (2 M solution in absolute ethanol, 6.97 ml, 13.9 mmol) was then slowly added *via* syringe over a 3 h period. The resultant solution was acidified to pH 1-3 with HCl (2 M solution in absolute ethanol) over a 15 min period. This afforded a white suspension, which was stirred for a further 20 h. The reaction was quenched with sodium hydrogen carbonate and extracted with dichloromethane (3 × 40 ml). The dichloromethane layers were then combined and dried over anhydrous magnesium sulfate and solvent removed by rotary evaporation to yield the target cyclised compound as a single diastereoisomer, which was purified by column chromatography using silica gel as absorbent and 5 % methanol/dichloromethane as eluent to yield a colourless solid (3.01 g, 78 %), Mp 177-179 °C, $[\alpha]_D$ + 133.6 [*c* = 1.03 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1666 (NCO), 2939 (aliphatic CH) and 3369 (OH); δ_H (400 MHz, $CDCl_3$) 1.91-1.98 (1 H, m, CH*(H)*CH_2CO), 2.46-2.52 (1 H, m, CH_2CH*(H)*CO), 2.61-2.69 (3 H, m, CH*(H)*CH_2CO, CH_2CH*(H)*CO and ArCH*(H)*CHN), 3.00 (1 H, dd, *J* 6.8, 16.0 Hz, ArCH*(H)*CHN), 3.62-3.73 (2 H, m, CH_2OH), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.47-4.50 (1 H, m, $ArCH_2CHN$), 4.76 (1 H, t, *J* 7.6 Hz, NCHAr), 6.59 (1 H, s, Ar*H*) and 6.63 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.1 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 49.5 (CH), 54.2 (CH), 55.9 (OCH_3), 56.1 (OCH_3), 63.2 (CH_2), 107.3 (CH), 111.7 (CH), 124.1 (C), 128.4 (C), 148.0 (C), 148.2 (C) and 175.1 (CO); MS (FAB) *m/z* 278 [MH^+, 27.5 %] (MH^+, 278.1395. $C_{15}H_{19}NO_4$ requires 278.1392).

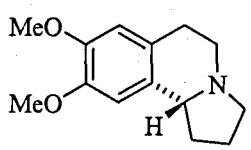
(10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (65).



Raney nickel (W-2) (7.08 g) was washed with water (3 × 20 ml) followed by 2-propanol (2 × 20 ml). 2-Propanol was decanted and the Raney nickel was taken up in toluene and the residual water and 2-propanol were azeotropically removed using a Dean-Stark trap. A solution of (5*S*,10b*R*)-5-hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-

pyrrolo[2,1-*a*]isoquinolin-3-one **(64)** (1.18 g, 6.49 mmol) in toluene (60 ml) was added and the reaction was refluxed under Dean-Stark conditions for 4 h. The resulting solution was filtered through a celite pad, washed with methanol and evaporated under reduced pressure to yield the target compound as a yellow oil (1.03 g, 98 %), $[\alpha]_D$ + 175.8 [*c* = 3.09 in $CHCl_3$]; ν_{max} (thin film, $CHCl_3$)/cm^{-1} 1681 (NCO) and 2934 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.82-1.90 (1 H, m, CH*(H)*CH_2CO), 2.45-2.71 (4 H, m, CH*(H)*CH_2CO, CH_2CH_2CO and ArCH*(H)*CH_2N), 2.85-2.93 (1 H, m, ArCH*(H)*CH_2N), 2.99-3.06 (1 H, m, $ArCH_2CH$*(H)*N), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.31 (1 H, ddd, *J* 2.4, 6.0, 12.8 Hz, $ArCH_2CH$*(H)*N), 4.74 (1 H, t, *J* 8.0 Hz, NC*H*Ar), 6.58 (1 H, s, Ar*H*) and 6.63 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_2), 28.1 (CH_2), 31.8 (CH_2), 37.1 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 56.6 (*C*H), 107.6 (*C*H), 111.6 (*C*H), 125.5 (*C*), 129.3 (*C*), 147.9 (*C*), 148.0 (*C*) and 173.4 (*C*O); MS (FAB) *m/z* 248 [MH^+, 31.3 %] (MH^+, 248.1287. $C_{14}H_{17}NO_3$ requires 248.1287).

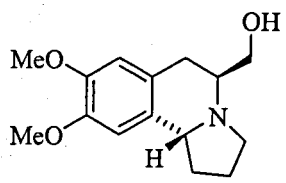
(*R*)-(+)-Crispine A (53).[22]



Lithium aluminium hydride (1 M solution in tetrahydrofuran, 4.5 ml, 4.49 mmol) was added to a pre-dried flask fitted with a reflux condenser under a nitrogen atmosphere. Anhydrous tetrahydrofuran (100 ml) was added and the solution cooled to 0 °C. (10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one **(65)** (1.05 g, 4.49 mmol) in anhydrous tetrahydrofuran (50 ml) was added dropwise to the hydride solution at 0 °C and the resulting solution heated under reflux for 3 h, then stirred for a further 12 h at room temperature. Diethyl ether (50 ml) was added and reaction was quenched by the careful addition of saturated sodium potassium tartate. The mixture was stirred for a further 1 h before the addition of anhydrous magnesium sulfate prior to filtrate through a celite pad. The filtrate was evaporated under reduced pressure and the resultant yellow solid was purified by column chromatography using silica gel as absorbent and 10:1 chloroform/methanol as eluent to yield a colourless solid (752 mg, 76 %), Mp 87-89 °C, Lit: Mp 87-89 °C; $[\alpha]_D$ + 43.9 [*c* = 1.14 in MeOH], Lit $[\alpha]_D$ + 91.0 [MeOH]; ν_{max} (thin film, $CHCl_3$)/cm^{-1} 2927 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.72-

1.79 (1 H, m, CH*(H)*CH_2CH_2N), 1.86-1.96 (2 H, m, $CH_2CH_2CH_2N$), 2.31-2.37 (1 H, m, CH*(H)*CH_2CH_2N), 2.60-2.79 (3 H, m, CH_2CH_2CH*(H)*N, ArCH*(H)*CH_2N and $ArCH_2CH$*(H)*N), 2.98-3.11 (2 H, m, CH_2CH_2CH*(H)*N and ArCH*(H)*CH_2N), 3.18 (1 H, ddd, *J* 2.8, 5.6, 10.8 Hz, $ArCH_2CH$*(H)*N), 3.50 (1 H, t, *J* 8.4 Hz, NC*H*Ar), 3.84 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 6.57 (1 H, s, Ar*H*) and 6.61 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_2), 27.9 (CH_2), 30.6 (CH_2), 48.3 (CH_2), 53.2 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 62.9 (*C*H), 108.8 (*C*H), 111.3 (*C*H), 126.1 (*C*), 130.5 (*C*), 147.3 (*C*) and 147.4 (*C*); MS (FAB) *m/z* 232 [M^+, 66.6 %] (M^+, 233.1419. $C_{14}H_{19}NO_2$ requires 233.1416).

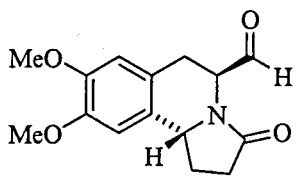
(5*S*,10b*R*)-(8,9-Dimethoxy-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolin-5-yl)-methanol (66).



Lithium aluminium hydride (1 M solution in tetrahydrofuran, 3.61 ml, 3.61 mmol) was added to a pre-dried flask fitted with a reflux condenser under nitrogen. Anhydrous tetrahydrofuran (50 ml) was added and the solution cooled to 0 °C. (5*S*,10b*R*)-5-Hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*] isoquinolin-3-one **(64)** (500 mg, 1.80 mmol) in anhydrous tetrahydrofuran (20 ml) was added dropwise to the hydride solution at 0 °C and the resulting solution heated under reflux for 3 h, then stirred for a further 12 h at room temperature. Diethyl ether (20 ml) was added and reaction was quenched by the careful addition of saturated sodium potassium tartate. The mixture was stirred for a further 1 h before the addition of anhydrous magnesium sulfate prior to filtrate through a celite pad. The filtrate was evaporated under reduced pressure and the resultant yellow solid was purified by column chromatography using silica gel as absorbent and 10:1 chloroform/methanol as eluent to yield a colourless solid (460 mg, 97 %), $[\alpha]_D$ + 79.1 [*c* = 1.83 in $CHCl_3$]; ν_{max} (thin film, neat)/cm^{-1} 2934 (aliphatic CH) and 3374 (OH); δ_H (400 MHz, $CDCl_3$) 1.78-1.89 (3 H, m, $CH_2CH_2CH_2N$ and CH_2CH*(H)*CH_2N), 2.41-2.46 (2 H, m, CH_2CH*(H)*CH_2N and ArCH*(H)*CHN), 2.76-2.81 (1 H, m, CH_2CH_2CH*(H)*N), 2.96 (1 H, dd, *J* 5.2, 16.0 Hz, ArCH*(H)*CHN), 3.05-3.09 (1 H, m, CH_2CH_2CH*(H)*N), 3.13-3.16 (1 H, m, $ArCH_2CH$N),

3.22 (1 H, br, s, O*H*), 3.42 (1 H, dd, *J* 8.0, 10.4 Hz, CH*(H)*OH), 3.52 (1 H, dd, *J* 5.2, 10.4 Hz, CH*(H)*OH), 3.85 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 4.22 (1 H, t, *J* 6.4 Hz, NC*H*Ar) and 6.56 (2 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 24.0 (*C*H_2), 26.3 (*C*H_2), 33.5 (*C*H_2), 51.9 (*C*H_2), 55.6 (*C*H), 55.8 (O*C*H_3), 56.0 (O*C*H_3), 56.4 (*C*H), 62.6 (*C*H_2), 109.0 (*C*H), 111.2 (*C*H), 124.9 (*C*), 130.9 (*C*), 147.3 (*C*) and 147.6 (*C*); MS (FAB) *m/z* 264 [MH^+, 14.2 %] (MH^+, 264.1596. $C_{15}H_{21}NO_3$ requires 264.1600).

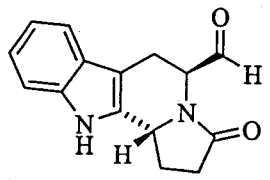
(5*S*,10b*R*)-8,9-Dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*] isoquinoline-5-carbaldehyde (67).



o-Iodoxybenzoic acid (4.48 g, 16.1 mmol) was added to a solution of (5*S*,10b*R*)-5-hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one **(64)** (1.49 g, 5.37 mmol) in ethyl acetate (75 ml) and the reaction was heated under reflux for 4 h. The resulting mixture was cooled to room temperature, filtered through a sinter funnel and evaporated to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3:1 light petroleum/ethyl acetate as eluent to isolate the target compound as a yellow foam (1.46 g, 99 %), $[\alpha]_D$ + 66.5 [*c* = 1.3 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1672 (NCO) and 2937 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.85-1.93 (1 H, m, CH*(H)*CH_2CO), 2.47-2.55 (1 H, m, CH_2CH*(H)*CO), 2.68-2.75 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 3.06 (1 H, dd, *J* 7.2, 16.0 Hz, ArCH*(H)*CHN), 3.22 (1 H, dd, *J* 2.4, 16.4 Hz, ArCH*(H)*CHN), 3.85 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.91 (1 H, t, *J* 6.8 Hz, NC*H*Ar), 5.01 (1 H, dd, *J* 2.4, 7.2 Hz, ArCH_2C*H*N), 6.53 (1 H, s, Ar*H*), 6.65 (1 H, s, Ar*H*) and 9.62 (1 H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 26.5 (*C*H_2), 28.2 (*C*H_2), 31.4 (*C*H_2), 54.7 (*C*H), 55.7 (*C*H), 56.0 (O*C*H_3), 56.1 (O*C*H_3), 107.5 (*C*H), 111.5 (*C*H), 122.3 (*C*), 128.1 (*C*), 148.2 (*C*), 148.5 (*C*), 174.4 (*C*O) and 198.9 (*C*HO); MS (FAB) *m/z* 276 [MH^+, 22.2 %] (MH^+, 276.1240. $C_{15}H_{17}NO_4$ requires 276.1236).

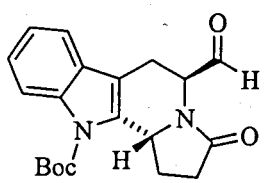
3.3.3. Total Synthesis of (*R*)-(+)-Harmicine

(5*S*,11b*R*)-3-Oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-5-carbaldehyde (69).



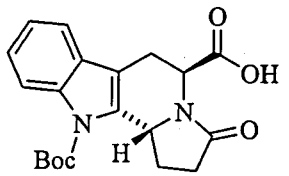
o-Iodoxybenzoic acid (148 mg, 0.531 mmol) was added to a solution of (5*S*,11b*R*)-5-hydroxymethyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one **(21)** (68 mg, 0.265 mmol) in dimethyl sulfoxide (3 ml) and the reaction stirred for 24 h at room temperature. The resulting mixture was added to a solution of ethyl acetate/water and the product extracted with ethyl acetate (3 × 8 ml). The organic layer was washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated to a crude yellow solid. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and ethyl acetate as eluent to isolate the target compound as a brown oil (49 mg, 72 %), $[\alpha]_D$ + 112.4 [*c* = 1.01 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/ cm^{-1} 1668 (NCO), 2915 (aliphatic CH) and 3271 (NH); δ_H (400 MHz, $CDCl_3$) 1.84-1.98 (1 H, m, CH*(H)*CH_2CO), 2.45-2.60 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.65-2.74 (1 H, m, CH_2CH*(H)*CO), 3.05 (1 H, ddd, *J* 2.4, 8.0, 16.0 Hz, ArCH*(H)*CHN), 3.39 (1 H, d, *J* 16.0 Hz, ArCH*(H)*CHN), 5.07-5.11 (1 H, m, NC*H*Ar), 5.20 (1 H, d, *J* 7.2 Hz, $ArCH_2CHN$), 7.06-7.16 (2 H, m, Ar*H*), 7.26 (1 H, d, *J* 8.0 Hz, Ar*H*), 7.45 (1 H, d, *J* 7.6 Hz, Ar*H*), 7.91 (1 H, s, N*H*) and 9.52 (1 H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 19.0 (CH_2), 25.4 (CH_2), 30.4 (CH_2), 51.2 (*C*H), 55.0 (*C*H), 104.3 (*C*), 110.1 (*C*H), 117.4 (*C*H), 119.1 (*C*H), 121.6 (*C*H), 125.4 (*C*), 131.5 (*C*), 135.3 (*C*), 173.1 (*C*O) and 197.6 (*C*HO); MS (EI) *m/z* 254 [M^+, 66.0 %] (M^+, 254.1055. $C_{15}H_{14}N_2O_2$ requires 254.1059).

(5*S*,11b*R*)-5-Formyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (70).



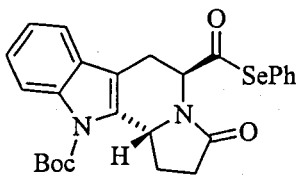
(5*S*,11b*R*)-3-Oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-5-carbaldehyde **(69)** (1.24 g, 4.88 mmol) was dissolved in anhydrous tetrahydrofuran (35 ml) under a nitrogen atmosphere. To this solution was added triethylamine (988 mg, 1.36 ml, 9.16 mmol), 4-dimethylaminopyridine (119 mg, 0.976 mmol) and di-*tert*-butyl dicarbonate (1.28 g, 5.86 mmol) successively and the resultant mixture was stirred overnight. The volatiles were removed by evaporation and the orange residue dissolved in ethyl acetate and washed successively with saturated ammonium chloride (2 × 50 ml), saturated sodium bicarbonate (2 × 30 ml) and saturated brine (30 ml). The organic phase was then dried over anhydrous magnesium sulfate and the solvent removed under pressure to yield a colourless solid, which was chromatographed using silica gel as absorbent and 3:1 light petroleum/ethyl acetate as eluent to isolate the target compound as an orange oil (1.73 g, 98 %), $[\alpha]_D$ + 248.2 [*c* = 1.02 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1691 (NCO), 1730 (CO) and 2977 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.69 (9 H, s, $CO_2C(CH_3)_3$), 1.81-1.92 (1 H, m, CH*(H)*CH_2CO), 2.51 (1 H, ddd, *J* 1.6, 9.6, 16.8 Hz, CH_2CH*(H)*CO), 2.70-2.77 (1 H, m, CH_2CH*(H)*CO), 2.95-3.01 (2 H, m, CH*(H)*CH_2CO and ArCH*(H)*CHN), 3.40 (1 H, d, *J* 16.4 Hz, ArCH*(H)*CHN), 5.27 (1 H, d, *J* 7.2 Hz, $ArCH_2CHN$), 5.42-5.46 (1 H, m, NC*H*Ar), 7.24-7.34 (2 H, m, Ar*H*), 7.45-7.47 (1 H, m, Ar*H*), 8.01 (1 H, d, *J* 8.0 Hz, Ar*H*) and 9.63 (1 H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_2), 27.6 (CH_2), 28.2 ($CO_2C(CH_3)_3$), 31.1 (CH_2), 54.6 (*C*H), 55.4 (*C*H), 84.7 (*C*), 112.6 (*C*), 115.6 (*C*H), 118.4 (*C*H), 123.1 (*C*H), 124.9 (*C*H), 128.4 (*C*), 134.2 (*C*), 135.7 (*C*), 149.7 (*C*O), 175.0 (*C*O) and 198.8 (*C*HO); MS (FAB) *m/z* 355 [MH^+, 21.9 %] (MH^+, 355.1651. $C_{20}H_{22}N_2O_4$ requires 355.1658).

(5*S*,11b*R*)-3-Oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-5,11-dicarboxylic acid 11-*tert*-butyl ester (71).



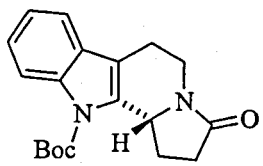
A solution of (5*S*,11b*R*)-5-formyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*] indole-11-carboxylic acid *tert*-butyl ester **(70)** (1.68 g, 4.74 mmol) in acetonitrile (22 ml), *tert*-butanol (87 ml) and cyclohexene (44 ml) was stirred rapidly as it cooled to 0 °C. A solution of sodium chlorite (4.13 g, 36.5 mmol) and sodium dihydrogen phosphate (3.98 g, 33.2 mmol) in water (87 ml) was added dropwise over a 10 min period and the reaction stirred at room temperature for 17 h. The reaction mixture was added to a solution of saturated brine/ethyl acetate (1:1) (70 ml) and product extracted with ethyl acetate (3 × 70 ml). Organics were combined and washed with a 1 M solution of sodium hydrosulfite, dried over anhydrous magnesium sulfate, filtered and evaporated to a crude green oil. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 2:1 ethyl acetate/light petroleum as eluent to produce a green solid (1.37 g, 79 %), Mp 111-112 °C; $[\alpha]_D$ + 194.0 [*c* = 1.00 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1668 (NCO), 1732 (CO), 2977 (aliphatic CH) and 3290 (OH); δ_H (400 MHz, $CDCl_3$) 1.68 (9 H, s, $CO_2C(CH_3)_3$), 1.74-1.85 (1 H, m, $CH(H)CH_2CO$), 2.46 (1 H, dd, *J* 8.4, 17.2 Hz, $CH_2CH(H)CO$), 2.62-2.71 (1 H, m, $CH_2CH(H)CO$), 2.90-3.03 (2 H, m, $CH(H)CH_2CO$ and $ArCH(H)CHN$), 3.38 (1 H, d, *J* 16.0 Hz, $ArCH(H)CHN$), 5.38 (1 H, d, *J* 6.8 Hz, $ArCH_2CHN$), 5.44-5.48 (1 H, m, NC*H*Ar), 7.21-7.31 (2 H, m, Ar*H*), 7.41-7.43 (1 H, m, Ar*H*) and 7.99 (1 H, d, *J* 8.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 23.8 (CH_2), 27.5 (CH_2), 28.2 ($CO_2C(CH_3)_3$), 31.2 (CH_2), 48.6 (*C*H), 54.7 (*C*H), 84.6 (*C*), 112.7 (*C*), 115.6 (*C*H), 118.5 (*C*H), 123.0 (*C*H), 124.7 (*C*H), 128.5 (*C*), 134.0 (*C*), 135.7 (*C*), 149.8 (*C*O), 174.2 (*C*O) and 178.8 (*C*O); MS (EI) *m/z* 370 [M^+, 23.3 %] (M^+, 370.1534. $C_{20}H_{22}N_2O_5$ requires 370.1529).

(5*S*,11b*R*)-3-Oxo-5-phenylselanylcarbonyl-1,2,3,5,6,11b-hexahydro-indolizino [8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (72).



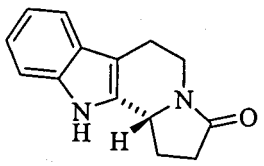
To a flask containing (5*S*,11b*R*)-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*] indole-5,11-dicarboxylic acid 11-*tert*-butyl ester **(71)** (481 mg, 1.30 mmol) under a nitrogen atmosphere was added anhydrous dichloromethane (3 ml) followed by dephenyldiselenide (609 mg, 1.95 mmol). The resulting mixture was cooled to 0 °C and tributylphospine (526 mg, 0.64 ml, 2.60 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirring continued for a further 24 h at room temperature. Dichloromethane (10 ml) and water (10 ml) were added and the aqueous layer was extracted further with dichloromethane (2 × 10 ml). The combined organic extracts were washed with brine (10 ml), dried over anhydrous magnesium sulfate and evaporated to a crude yellow oil. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 4:1 light petroleum/ethyl acetate as eluent to produce a colourless solid (438 g, 66 %), Mp 76-80 °C; $[\alpha]_D$ + 70.3 [*c* = 1.03 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1700 (NCO), 1729 (CO) and 2977 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.71 (9 H, s, $CO_2C(CH_3)_3$), 1.85-1.92 (1 H, m, CH*(H)*CH_2CO), 2.56 (1 H, ddd, *J* 0.8, 8.8, 16.8 Hz, CH_2CH*(H)*CO), 2.74-2.83 (1 H, m, CH_2CH*(H)*CO), 2.91 (1 H, ddd, *J* 2.4, 7.2, 16.4 Hz, ArCH*(H)*CHN), 3.02-3.07 (1 H, m, CH*(H)*CH_2CO), 3.53 (1 H, dd, *J* 0.8, 16.4 Hz, ArCH*(H)*CHN), 5.47 (1 H, d, *J* 6.8 Hz, $ArCH_2CHN$), 5.63-5.70 (1 H, m, NC*H*Ar), 7.22-7.36 (5 H, m, Ar*H*), 7.43-7.45 (3 H, m, Ar*H*) and 7.99 (1 H, d, *J* 8.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_2), 28.0 (CH_2), 28.2 ($CO_2C(CH_3)_3$), 31.2 (CH_2), 54.4 (*C*H), 58.9 (*C*H), 84.6 (*C*), 112.8 (*C*), 115.5 (*C*H), 118.5 (*C*H), 123.0 (*C*H), 124.8 (*C*H), 125.2 (*C*), 128.5 (*C*), 129.1 (*C*H), 129.3 (*C*H), 129.3 (*C*H), 133.5 (*C*), 135.6 (*C*), 136.0 (*C*H), 136.0 (*C*H), 149.9 (*C*O), 175.3 (*C*O) and 200.1 (*C*O); MS (FAB) *m/z* 511 [MH^+, 4.8 %] (MH^+, 511.1127. $C_{26}H_{26}N_2O_4Se$ requires 511.1136).

(11b*R*)-3-Oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (73).



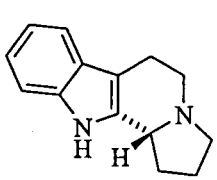
A three-necked round bottom flask fitted with a reflux condenser, glass stopper and suba seal was flushed with nitrogen. A solution of (5*S*,11b*R*)-3-oxo-5-phenylselanyl carbonyl-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(72)** (300 mg, 0.588 mmol) in dry toluene (4 ml) was added *via* cannula. The solution was then degassed with nitrogen for 15 min before adding tri-*n*-butyltin hydride (684 mg, 0.63 ml, 2.35 mmol). The resulting mixture was heated to 80 °C whereupon azobisisobutyronitrile (19 mg, 0.118 mmol) was added portionwise over a 2 h period. After an additional 2 h stirring at 80 °C, the mixture was cooled to room temperature and concentrated under reduced pressure. The resultant oily residue was adsorbed onto silica and chromatographed using silica gel as absorbent and 100 % light petroleum to 50 % light petroleum/ethyl acetate as eluent to produce a green solid (172 mg, 90 %), Mp 127-131 °C; $[\alpha]_D$ + 324.4 [*c* = 1.09 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1693 (NCO), 1731 (CO) and 2977 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.70 (9 H, s, $CO_2C(CH_3)_3$), 1.80-1.86 (1 H, m, CH*(H)*CH_2CO), 2.43 (1 H, ddd, *J* 1.6, 9.6, 16.4 Hz, CH_2CH*(H)*CO), 2.55-2.64 (1 H, m, CH_2CH*(H)*CO), 2.77-2.87 (3 H, m, CH*(H)*CH_2CO and $ArCH_2CH_2N$), 2.96-3.02 (1 H, m, $ArCH_2CH$*(H)*N), 4.54 (1 H, ddd, *J* 2.4, 4.4, 12.8 Hz, $ArCH_2CH$*(H)*N), 5.22-5.26 (1 H, m, NC*H*Ar), 7.24-7.33 (2 H, m, Ar*H*), 7.42-7.44 (1 H, m, Ar*H*) and 8.04 (1 H, d, *J* 8.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_2), 27.0 (CH_2), 28.2 ($CO_2C(CH_3)_3$), 31.3 (CH_2), 36.8 (CH_2), 56.4 (*C*H), 84.4 (*C*), 115.5 (*C*), 115.5 (*C*H), 118.4 (*C*H), 123.0 (*C*H), 124.5 (*C*H), 128.8 (*C*), 135.1 (*C*), 135.7 (*C*), 150.0 (*C*O) and 173.7 (*C*O); MS (FAB) *m/z* 327 [MH^+, 2.0 %] (MH^+, 327.1703. $C_{19}H_{22}N_2O_3$ requires 327.1709).

(11b*R*)-1,2,5,6,11,11b-Hexahydro-indolizino[8,7-*b*]indol-3-one (74).



(11b*R*)-3-Oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(73)** (100 mg, 0.306 mmol) was dissolved in tetrahydrofuran (10 ml) under an atmosphere of nitrogen. To this was added tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 3.06 ml, 3.06 mmol) and the reaction heated under reflux for 2 h. The resultant solution was cooled to room temperature and water added. The crude product was extracted with ethyl acetate (3 × 10 ml), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The compound was purified by chromatography using silica gel as absorbent and ethyl acetate as eluent to produce a green solid (51 mg, 69 %), Mp 250-252 °C; $[\alpha]_D$ + 188.4 [*c* = 0.55 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1668 (NCO), 2921 (aliphatic CH) and 3253 (NH); δ_H (400 MHz, $CDCl_3$) 1.90-2.02 (1 H, m, CH*(H)*CH_2CO), 2.44-2.68 (3 H, m, CH*(H)*CH_2CO and CH_2CH_2CO), 2.80-2.92 (2 H, m, $ArCH_2CH_2N$), 3.01-3.08 (1 H, m, $ArCH_2CH$*(H)*N), 4.54 (1 H, ddd, *J* 2.0, 5.0, 12.8 Hz, $ArCH_2CH$*(H)*N), 4.93-4.96 (1 H, m, NC*H*Ar), 7.13 (1 H, dt, *J* 1.2, 7.6 Hz, Ar*H*), 7.19 (1 H, dt, *J* 1.2, 7.6 Hz, Ar*H*), 7.35 (1 H, d, *J* 8.0 Hz, Ar*H*), 7.50 (1 H, d, *J* 8.0 Hz, Ar*H*) and 8.16 (1 H, br, s, N*H*); δ_C (100 MHz, $CDCl_3$) 21.0 (CH_2), 25.7 (CH_2), 31.7 (CH_2), 37.6 (CH_2), 54.3 (*C*H), 108.3 (*C*), 111.0 (*C*H), 118.5 (*C*H), 119.9 (*C*H), 122.3 (*C*H), 126.8 (*C*), 133.2 (*C*), 136.2 (*C*) and 173.3 (*C*O); MS (FAB) *m/z* 226 [MH^+, 11.5 %] (MH^+, 226.1106. $C_{14}H_{14}N_2O$ requires 226.1110).

(*R*)-(+)-Harmicine (68).[29]



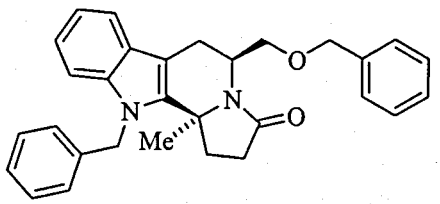
Lithium aluminium hydride (2 M solution in tetrahydrofuran, 0.12 ml, 0.230 mmol) was added to a pre-dried flask fitted with a reflux condenser under a nitrogen atmosphere.

Anhydrous tetrahydrofuran (3 ml) was added and the solution cooled to 0 °C. (11b*R*)-1,2,5,6,11,11b-Hexahydro-indolizino[8,7-*b*]indol-3-one **(74)** (37 mg, 0.153 mmol) in anhydrous tetrahydrofuran (2 ml) was added dropwise to the hydride solution at 0 °C and the resulting solution heated under reflux for 3 h, then stirred for a further 12 h at room temperature. Diethyl ether (10 ml) was added and reaction was quenched by the careful addition of saturated sodium potassium tartate. The mixture was stirred for a further 1 h before the addition of anhydrous magnesium sulfate prior to filtrate through a celite pad. The filtrate was evaporated under reduced pressure and the resultant yellow solid was purified by column chromatography using silica gel as absorbent and 10:1 dichloromethane/methanol as eluent to yield a yellow solid (28 mg, 80 %), Mp 161-164 °C; $[\alpha]_D$ + 118.2 [*c* = 1.6 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 2925 (aliphatic CH) and 3253 (NH); δ_H (400 MHz, $CDCl_3$) 1.77-2.05 (3 H, m, $CHCH(H)CH_2CH_2N$ and $CHCH_2CH_2CH_2N$), 2.35-2.44 (1 H, m, $CHCH(H)CH_2CH_2N$), 2.74-2.77 (1 H, m, $ArCH(H)CH_2N$), 2.88-2.96 (2 H, m, $CHCH_2CH_2CH(H)N$ and $ArCH(H)CH_2N$), 3.07-3.19 (2 H, m, $CHCH_2CH_2CH(H)N$ and $ArCH_2CH(H)N$), 3.31 (1 H, ddd, *J* 2.0, 5.2, 12.8 Hz, $ArCH_2CH(H)N$), 4.46-4.49 (1 H, m, NC*H*Ar), 7.06 (1 H, dt, *J* 1.2, 7.6 Hz, Ar*H*), 7.12 (1 H, dt, *J* 1.2, 7.6 Hz, Ar*H*), 7.36 (1 H, d, *J* 7.2 Hz, Ar*H*), 7.43 (1 H, d, *J* 7.2 Hz, Ar*H*) and 9.35 (1 H, br, s, N*H*); δ_C (100 MHz, $CDCl_3$) 17.4 (CH_2), 23.1 (CH_2), 29.7 (CH_2), 45.9 (CH_2), 49.5 (CH_2), 57.6 (*C*H), 106.6 (*C*), 111.3 (*C*H), 118.0 (*C*H), 119.3 (*C*H), 121.6 (*C*H), 126.7 (*C*), 133.1 (*C*) and 136.4 (*C*); MS (EI) *m/z* 212 [M^+, 75.0 %] (M^+, 212.1184. $C_{14}H_{16}N_2$ requires 212.1181).

3.4. Application as Potential Building Blocks for Peptide Mimics

3.4.1. Enolate Addition Studies

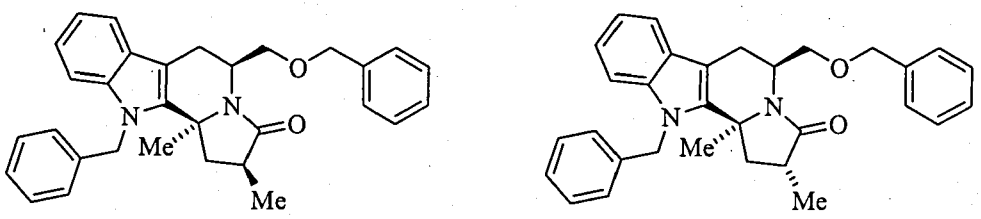
(5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (83).



Anhydrous *N,N*-dimethylformamide (30 ml) was added to sodium hydride (890 mg, 22.2 mmol) in a dry three-necked round bottom flask under nitrogen and cooled to 0 °C with an ice bath. (5*S*,11b*S*)-5-Hydroxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one **(25)** (2.0 g, 7.40 mmol) in *N,N*-dimethylformamide (20 ml) was added and stirred for 30 min at room temperature. Benzyl bromide (4.18 g, 2.79 ml, 24.4 mmol) was added and the reaction stirred at room temperature for 3 h under nitrogen. Ice and water were added and product extracted with diethyl ether (3 × 50 ml). Ether phases were combined and washed with saturated brine, dried over anhydrous magnesium sulfate, filtered and evaporated to a yellow oil. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3:2 hexane/ethyl acetate as eluent to isolate the target compound as a colourless solid (2.42 g, 72 %), Mp 139-140 °C; $[\alpha]_D$ – 163.2 [*c* = 1.01 in CH_2Cl_2] (Found: C, 79.76; H, 6.83; N, 6.36. $C_{30}H_{30}N_2O_2$ requires C, 79.97; H, 6.71; N, 6.22 %); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1684 (NCO), 2855 (aliphatic CH) and 2928 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 1.60 (3 H, s, C*H*$_3$), 2.16-2.30 (3 H, m, C*H*$_2$CH$_2$CO and CH$_2$CH*(H)*CO), 2.43-2.50 (1 H, m, CH$_2$CH*(H)*CO), 2.94 (1 H, dd, *J* 11.1, 15.2 Hz, ArCH*(H)*CHN), 3.13 (1 H, dd, *J* 4.0, 15.2 Hz, ArCH*(H)*CHN), 3.77-3.82 (1 H, m, ArCH$_2$C*H*N), 4.35 (1 H, dd, *J* 8.7, 9.4 Hz, CH*(H)*OBn), 4.50 (1 H, dd, *J* 4.6, 9.6 Hz, CH*(H)*OBn), 4.65 (1 H, d, *J* 11.9 Hz, OCH*(H)*Ph), 4.68 (1 H, d, *J* 11.9 Hz, OCH*(H)*Ph), 5.40 (2 H, s, NC*H*$_2$Ph), 6.82-6.84 (2 H, m, Ar*H*), 7.02-7.05 (1 H, m, Ar*H*), 7.10-7.12 (2 H, m, Ar*H*), 7.21-7.25 (3 H, m, Ar*H*), 7.26-7.31 (1 H, m, Ar*H*), 7.34-7.41 (4 H, m, Ar*H*) and 7.52-7.54 (1 H,

m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 25.8 (*C*H_2), 26.5 (*C*H_3), 30.8 (*C*H_2), 32.2 (*C*H_2), 47.7 (*C*H_2), 52.8 (*C*H), 62.6 (*C*), 71.1 (*C*H_2), 73.4 (*C*H_2), 108.9 (*C*), 110.0 (*C*H), 118.7 (*C*H), 119.9 (*C*H), 122.3 (*C*H), 125.4 (*C*H), 125.4 (*C*H), 126.6 (*C*), 127.4 (*C*H), 127.6 (*C*H), 127.8 (*C*H), 127.8 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.9 (*C*H), 128.9 (*C*H), 137.2 (*C*), 137.4 (*C*), 138.5 (*C*), 138.6 (*C*) and 174.7 (*C*O); MS (EI) *m/z* 450 [M^+, 50.1 %] (M^+, 450.2303. $C_{30}H_{30}N_2O_2$ requires 450.2307). The product was recrystallised from ethyl acetate/hexane to produce a colourless crystalline solid.

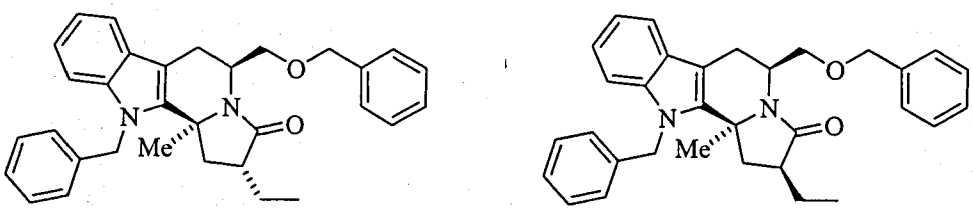
(2*S*,5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-2,11b-dimethyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (85a).



n-Butyl lithium (1.11 ml, 2.77 mmol) was added dropwise to a stirred solution of diisopropylamine (281 mg, 0.40 ml, 2.77 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 15 min then cooled to –78 °C. (5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro indolizino[8,7-*b*]indol-3-one **(83)** (500 mg, 1.11 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise and the reaction stirred for 15 min at –78 °C. Methyl iodide (315 mg, 0.14 ml, 2.22 mmol) was added dropwise at –78 °C and the reaction allowed to warm to room temperature overnight. The reaction mixture was then quenched with saturated ammonium chloride and product extracted with diethyl ether (3 × 50 ml). Ether phases were combined and washed with saturated brine (50 ml) and dried over anhydrous magnesium sulfate. Ether phase was then filtered and solvent removed on the rotary evaporator to yield the target compound as a 4:1 mixture of diastereoisomers, which were separated by column chromatography using silica gel as absorbent and 4:1 hexane/ethyl acetate as eluent to yield a colourless solid (345 mg, 67 %), Mp 117-118 °C; $[\alpha]_D$ – 176.0 [*c* = 1.02 in CH_2Cl_2] (Found: C, 79.90; H, 6.92; N, 5.94. $C_{31}H_{32}N_2O_2$ requires C, 80.14; H, 6.94; N, 6.03 %); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1688 (NCO) and 2928 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.05 (3 H, d, *J* 7.0 Hz, CH(C*H*$_3$)CO), 1.54 (3 H, s, C*H*$_3$), 1.83 (1 H, dd, *J* 10.6, 11.8 Hz, CH*(H)*CHCO), 2.53 (1 H, dd, *J* 8.6,

12.0 Hz, CH*(H)*CHCO), 2.58-2.68 (1 H, m, CH_2CHCO), 2.84 (1 H, dd, *J* 11.1, 15.2 Hz, ArCH*(H)*CHN), 3.16 (1 H, dd, *J* 3.8, 15.2 Hz, ArCH*(H)*CHN), 3.77-3.84 (1 H, m, $ArCH_2CHN$), 4.33 (1 H, dd, *J* 8.8, 9.4 Hz, CH*(H)*OBn), 4.54 (1 H, dd, *J* 4.7, 9.6 Hz, CH*(H)*OBn), 4.64 (1 H, d, *J* 11.9 Hz, OCH*(H)*Ph), 4.69 (1 H, d, *J* 11.9 Hz, OCH*(H)*Ph), 5.37 (2 H, s, NCH_2Ph), 6.86-6.88 (2 H, m, Ar*H*), 7.02-7.04 (1 H, m, Ar*H*), 7.10-7.12 (2 H, m, Ar*H*), 7.22-7.30 (4 H, m, Ar*H*), 7.33-7.41 (4 H, m, Ar*H*) and 7.51-7.55 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 15.8 (CH_3), 25.4 (CH_3), 26.2 (CH_2), 35.7 (*C*H), 41.6 (CH_2), 47.7 (CH_2), 52.8 (*C*H), 59.9 (*C*), 70.8 (CH_2), 73.3 (CH_2), 107.9 (*C*), 110.0 (*C*H), 118.7 (*C*H), 119.8 (*C*H), 122.1 (*C*H), 125.5 (*C*H), 125.5 (*C*H), 126.5 (*C*), 127.4 (*C*H), 127.6 (*C*H), 127.7 (*C*H), 127.7 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.8 (*C*H), 128.8 (*C*H), 137.1 (*C*), 137.3 (*C*), 138.5 (*C*), 139.3 (*C*) and 175.5 (*C*O); MS (EI) *m/z* 464 [M^+, 10.6 %] (M^+, 464.2472. $C_{31}H_{32}N_2O_2$ requires 464.2464). The product was recrystallised from ethyl acetate/hexane *via* vapour diffusion to produce clear, colourless crystals. Stereochemistry at C-2, C-5 and C-11b was determined by single crystal X-ray analysis.

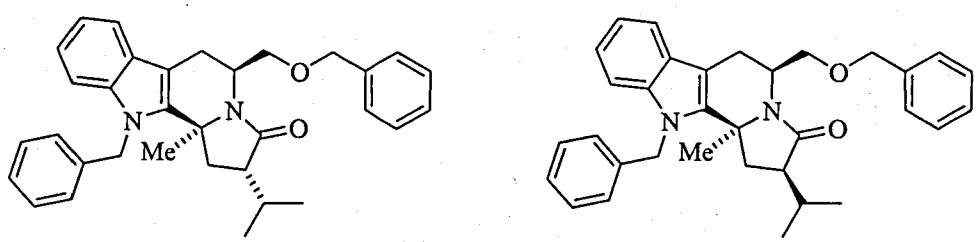
(2*R*,5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-2-ethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (86b).



n-Butyl lithium (0.55 ml, 1.37 mmol) was added dropwise to a stirred solution of diisopropylamine (139 mg, 0.19 ml, 1.37 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 15 min then cooled to –78 °C. (5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro indolizino[8,7-*b*]indol-3-one **(83)** (516 mg, 1.11 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise and the reaction stirred for 15 min at –78 °C. Iodoethane (268 mg, 0.14 ml, 1.72 mmol) was added dropwise at –78 °C and the reaction allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated ammonium chloride and product extracted with diethyl ether (3 × 50 ml). Ether phases were combined and washed with saturated brine (50 ml) and dried over anhydrous magnesium sulfate. Ether phase was then filtered and solvent removed on the

rotary evaporator to yield the target compound as an 8:1 mixture of diastereoisomers, which were separated by column chromatography using silica gel as absorbent and 7:1 hexane/ethyl acetate as eluent to yield a colourless solid (381 mg, 70 %), Mp 54-56 °C; $[\alpha]_D$ – 134.0 [*c* = 1.01 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1686 (NCO) and 2986 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 0.69 (3 H, t, *J* 7.4 Hz, CH(CH_2CH_3)CO), 1.26-1.33 (1 H, m, CH(CH*(H)*CH_3)CO), 1.64-1.69 (1 H, m, CH*(H)*CHCO), 1.66 (3 H, s, CH_3), 1.74-1.82 (1 H, m, CH(CH*(H)*CH_3)CO), 1.97-2.04 (1 H, m, CH_2CHCO), 2.56 (1 H, dd, *J* 9.0, 12.7 Hz, CH*(H)*CHCO), 3.05 (2 H, m, ArCH_2CHN), 3.74-3.81 (1 H, m, ArCH_2CHN), 4.40 (1 H, dd, *J* 4.3, 9.6 Hz, CH*(H)*OBn), 4.49 (1 H, dd, *J* 8.3, 9.6 Hz, CH*(H)*OBn), 4.66 (2 H, s, OCH_2Ph), 5.36 (1 H, d, *J* 17.6 Hz, NCH*(H)*Ph), 5.46 (1 H, d, *J* 17.6 Hz, NCH*(H)*Ph), 6.79-6.81 (2 H, m, Ar*H*), 7.03-7.05 (1 H, m, Ar*H*), 7.07-7.12 (2 H, m, Ar*H*), 7.20-7.31 (4 H, m, Ar*H*), 7.34-7.41 (4 H, m, Ar*H*) and 7.49-7.52 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 11.4 (CH_3), 24.1 (CH_2), 25.1 (CH_2), 28.5 (CH_3), 37.4 (CH_2), 43.1 (CH), 47.7 (CH_2), 52.9 (CH), 61.2 (C), 72.1 (CH_2), 73.4 (CH_2), 109.8 (CH), 110.2 (C), 118.6 (CH), 119.8 (CH), 122.3 (CH), 125.3 (CH), 125.3 (CH), 126.7 (C), 127.5 (CH), 127.6 (CH), 127.8 (CH), 127.8 (CH), 128.4 (CH), 128.4 (CH), 128.9 (CH), 128.9 (CH), 137.3 (C), 137.6 (C), 138.6 (C), 139.6 (C) and 179.9 (CO); MS (EI) *m/z* 478 [M^+, 24.8 %] (M^+, 478.2626. $C_{32}H_{34}N_2O_2$ requires 478.2620). The Stereochemistry at C-2, C-5 and C-11b was determined by nOe studies.

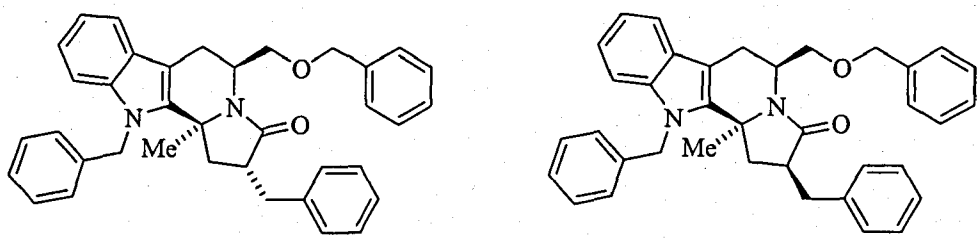
(2*S*,5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-2-isopropyl-11b-methyl-1,2,5,6,11, 11b-hexahydro-indolizino[8,7-*b*]indol-3-one (87b).



n-Butyl lithium (0.55 ml, 1.37 mmol) was added dropwise to a stirred solution of diisopropylamine (139 mg, 0.19 ml, 1.37 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 15 min then cooled to –78 °C. (5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro indolizino[8,7-*b*]indol-3-one **(83)** (516 mg, 1.11 mmol) in anhydrous tetrahydrofuran

(10 ml) was added dropwise and the reaction mixture stirred for 15 min at –78 °C. 2-Iodo-propane (268 mg, 0.14 ml, 1.72 mmol) was added dropwise at –78 °C and the reaction was allowed to warm to room temperature overnight. Saturated ammonium chloride was added to quench the reaction mixture and product extracted with diethyl ether (3 × 50 ml). Ether phases were combined and washed with saturated brine (50 ml) and dried over anhydrous magnesium sulfate. Ether phase was then filtered and solvent removed on the rotary evaporator to yield the target compound as an 10:1 mixture of diastereoisomers, which were separated by column chromatography using silica gel as absorbent and 7:1 hexane/ethyl acetate as eluent to yield a colourless solid (432 mg, 79 %), Mp 121-122 °C; $[\alpha]_D$ – 114.8 [c = 1.01 in CH_2Cl_2] (Found: C, 80.24; H, 7.44; N, 5.73. $C_{33}H_{36}N_2O_2$ requires C, 80.45; H, 7.37; N, 5.69 %); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1693 (NCO) and 2955 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 0.69 (3 H, d, J 6.7 Hz, CH(CHCH$_3$(C*H*$_3$))CO), 0.75 (3 H, d, J 6.7 Hz, CH(CHCH$_3$(C*H*$_3$))CO), 1.67 (3 H, s, C*H*$_3$), 1.74 (1 H, dd, J 10.3, 12.7 Hz, CH*(H)*CHCO), 2.02-2.09 (2 H, m, CH(C*H*(CH$_3$)$_2$)CO and CH$_2$C*H*CO), 2.36 (1 H, dd, J 8.8, 12.8 Hz, CH*(H)*CHCO), 3.00-3.12 (2 H, m, ArC*H*$_2$CHN), 3.73-3.79 (1 H, m ArCH$_2$C*H*N), 4.39 (1 H, dd, J 4.2, 9.6 Hz, CH*(H)*OBn), 4.50 (1 H, dd, J 8.2, 9.6 Hz, CH*(H)*OBn), 4.66 (2 H, s, OC*H*$_2$Ph), 5.36 (1 H, d, J 17.7 Hz, NCH*(H)*Ph), 5.48 (1 H, d, J 17.7 Hz, NCH*(H)*Ph), 6.78-6.80 (2 H, m, Ar*H*), 7.03-7.05 (1 H, m, Ar*H*), 7.08-7.11 (2 H, m, Ar*H*), 7.20-7.26 (3 H, m, Ar*H*), 7.28-7.30 (1 H, m, Ar*H*), 7.33-7.41 (4 H, m, Ar*H*) and 7.50-7.51 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 17.7 (*C*H$_3$), 20.3 (*C*H$_3$), 24.8 (*C*H$_2$), 27.3 (*C*H), 28.4 (*C*H$_3$), 32.8 (*C*H$_2$), 47.2 (*C*H), 47.7 (*C*H$_2$), 52.9 (*C*H), 60.9 (*C*), 72.3 (*C*H$_2$), 73.4 (*C*H$_2$), 109.8 (*C*H), 110.4 (*C*), 118.6 (*C*H), 119.8 (*C*H), 122.3 (*C*H), 125.3 (*C*H), 125.3 (*C*H), 126.7 (*C*), 127.5 (*C*H), 127.6 (*C*H), 127.8 (*C*H), 127.8 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.9 (*C*H), 128.9 (*C*H), 137.3 (*C*), 137.6 (*C*), 137.8 (*C*), 138.6 (*C*) and 179.8 (*C*O); MS (EI) *m/z* 492 [M$^+$, 24.4 %] (M$^+$, 492.2781. $C_{33}H_{36}N_2O_2$ requires 492.2777). The product was recrystallised from ethyl acetate/hexane *via* vapour diffusion to produce clear, colourless crystals. Stereochemistry at C-2, C-5 and C-11b was determined by single crystal X-ray analysis.

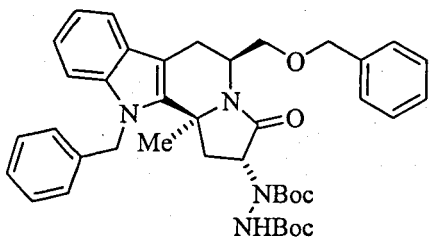
(2*R*,5*S*,11b*S*)-2,11-Dibenzyl-5-benzyloxymethyl-11b-methyl-1,2,5,6,11,11b-hexa hydro-indolizino[8,7-*b*]indol-3-one (88b).



n-Butyl lithium (0.62 ml, 1.55 mmol) was added dropwise to a stirred solution of diisopropylamine (157 mg, 0.22 ml, 1.55 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 15 min then cooled to –78 °C. (5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro indolizino[8,7-*b*]indol-3-one **(83)** (500 mg, 1.11 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise and the reaction stirred for 15 min at –78 °C. Benzyl bromide (247 mg, 0.16 ml, 1.44 mmol) was added dropwise at –78 °C and reaction allowed to warm to room temperature overnight. Saturated ammonium chloride was added to quench the reaction mixture and the product was extracted with diethyl ether (3 × 50 ml). Ether phases were combined and washed with saturated brine (50 ml) and dried over anhydrous magnesium sulfate. Ether phase was then filtered and solvent removed on the rotary evaporator to yield the target compound as an 2:1 mixture of diastereoisomers, which were separated by column chromatography using silica gel as absorbent and 7:1 hexane/ethyl acetate as eluent to yield a colourless solid (313 mg, 52 %), Mp 145-146 °C; $[\alpha]_D$ – 96.9 [*c* = 1.02 in CH_2Cl_2] (Found: C, 81.81; H, 6.67; N, 5.16. $C_{37}H_{36}N_2O_2$ requires C, 82.19; H, 6.71; N, 5.18 %); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1694 (NCO) and 2930 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.52 (3 H, s, C*H*$_3$), 1.74 (1 H, dd, *J* 8.3, 11.7 Hz, CH*(H)*CHCO), 2.43-2.52 (2 H, m, CH*(H)*CHCO and CH_2CHCO), 2.60-2.66 (1 H, m, CH(CH*(H)*Ph)CO), 3.05-3.08 (2 H, m, ArCH_2CHN), 3.14 (1 H, dd, *J* 3.6, 13.8 Hz, CH(CH*(H)*Ph)CO), 3.75-3.79 (1 H, m, ArCH_2CHN), 4.43-4.52 (2 H, m, CH_2OBn), 4.69 (2 H, s, OCH_2Ph), 5.28 (1 H, d, *J* 17.6 Hz, NCH*(H)*Ph), 5.36 (1 H, d, *J* 17.6 Hz, NCH*(H)*Ph), 6.70-6.72 (2 H, m, Ar*H*), 6.95-7.00 (3 H, m, Ar*H*), 7.07-7.18 (8 H, m, Ar*H*), 7.30-7.42 (5 H, m, Ar*H*) and 7.49-7.51 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 25.1 (CH_2), 28.4 (CH_3), 37.0 (CH_2), 37.1 (CH_2), 42.8 (CH), 47.6 (CH_2), 53.0 (CH), 61.3 (C), 71.9 (CH_2), 73.4 (CH_2), 109.9 (CH), 110.0 (C),

118.5 (*C*H), 119.8 (*C*H), 122.3 (*C*H), 125.2 (*C*H), 125.2 (*C*H), 126.2 (*C*H), 126.6 (*C*), 127.4 (*C*H), 127.6 (*C*H), 127.8 (*C*H), 127.9 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.7 (*C*H), 128.7 (*C*H), 128.8 (*C*H), 128.8 (*C*H), 137.2 (*C*), 137.2 (*C*), 137.8 (*C*), 138.5 (*C*), 138.9 (*C*) and 178.8 (*C*O); MS (EI) *m/z* 540 [M^+, 14.1 %] (M^+, 540.2777. $C_{37}H_{36}N_2O_2$ requires 540.2784). The product was recrystallised from dichloromethane/hexane *via* vapour diffusion to produce clear, colourless crystals. Stereochemistry at C-2, C-5 and C-11b was determined by single crystal X-ray analysis.

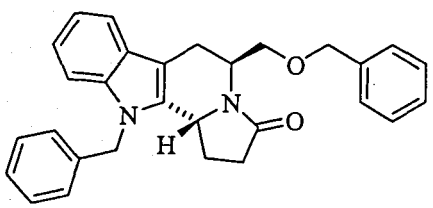
(2*R*,5*S*,11b*S*)-2-*N*,*N'*-Bis-(3,3-*tert*-butyl ester)-hydrazino-11-benzyl-5-benzyloxy methyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (89).



n-Butyl lithium (2.93 ml, 7.32 mmol) was added dropwise to a stirred solution of diisopropylamine (741 mg, 1.03 ml, 7.32 mmol) in anhydrous tetrahydrofuran (15 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 15 min then cooled to –78 °C. (5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-11b-methyl-1,2,5,6,11,11b-hexa hydro-indolizino[8,7-*b*]indol-3-one **(83)** (1.65 g, 3.66 mmol) in anhydrous tetrahydrofuran (20 ml) was added dropwise and the reaction stirred for 15 min at –78 °C. Di-*tert*-butyl azodicarboxylate (1.27 g, 5.49 mmol) in anhydrous tetrahydrofuran (15 ml) was added dropwise at –78 °C and the reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride and product was extracted with diethyl ether (3 × 75 ml). Ether phase was dried over magnesium sulfate and solvent removed on the rotary evaporator to yield the target compound as a single diastereoisomer, which was purified by column chromatography using silica gel as absorbent and 4:1 light petroleum/ethyl acetate as eluent to yield a colourless solid (2.04 g, 82 %), Mp 103-105 °C; $[\alpha]_D$ – 82.4 [*c* = 1.02 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1709 (NCO), 1709 (CO), 2976 (aliphatic CH) and 3284 (NH); δ_H (400 MHz, DMSO, 80 °C) 1.36 (9 H, s, $CO_2C(CH_3)_3$), 1.37 (9 H, s, $CO_2C(CH_3)_3$), 1.67 (3 H, s, CH_3), 2.30 (1 H, dd, *J* 9.2, 12.8 Hz, CH*(H)*CHCO), 2.78 (1 H, dd, *J* 9.6,

13.2 Hz, CH*(H)*CHCO), 2.85-3.00 (2 H, m, ArC*H*$_2$CHN), 3.79-3.84 (1 H, m, ArCH$_2$C*H*N), 4.29-4.35 (2 H, m, CH$_2$C*H*CO and CH*(H)*OBn), 4.47 (1 H, dd, *J* 5.2, 10.0 Hz, CH*(H)*OBn), 4.63 (1 H, d, *J* 12.0 Hz, OCH*(H)*Ph), 4.67 (1 H, d, *J* 12.0 Hz, OCH*(H)*Ph), 5.48 (1 H, d, *J* 17.6 Hz, NCH*(H)*Ph), 5.54 (1 H, d, *J* 17.6 Hz, NCH*(H)*Ph), 6.91 (2 H, d, *J* 7.2 Hz, Ar*H*), 7.02-7.09 (3 H, m, Ar*H*), 7.19-7.30 (4 H, m, Ar*H*), 7.34-7.41 (4 H, m, Ar*H*), 7.46-7.49 (1 H, m, Ar*H*) and 8.27 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 80 °C) 24.1 (*C*H$_2$), 27.1 (*C*H$_3$), 27.3 (CO$_2$C(*C*H$_3$)$_3$), 27.4 (CO$_2$C(*C*H$_3$)$_3$), 34.1 (*C*H$_2$), 46.8 (*C*H$_2$), 52.1 (*C*H), 58.8 (*C*), 58.9 (*C*H), 70.3 (*C*H$_2$), 71.9 (*C*H$_2$), 79.1 (*C*), 80.1 (*C*), 108.3 (*C*), 109.7 (*C*H), 117.6 (*C*H), 118.8 (*C*H), 121.2 (*C*H), 124.9 (*C*H), 124.9 (*C*H), 125.8 (*C*), 126.4 (*C*H), 126.6 (*C*H), 126.8 (*C*H), 126.8 (*C*H), 127.5 (*C*H), 127.5 (*C*H), 127.9 (*C*H), 127.9 (*C*H), 136.7 (*C*), 137.3 (*C*), 137.7 (*C*), 138.3 (*C*), 153.3 (*C*O), 154.8 (*C*O) and 171.6 (*C*O); MS (FAB) *m/z* 680 [M$^+$, 52.4 %] (M$^+$, 680.3580. $C_{40}H_{48}N_4O_6$ requires 680.3574). Stereochemistry at C-2, C-5 and C-11b was determined by nOe studies.

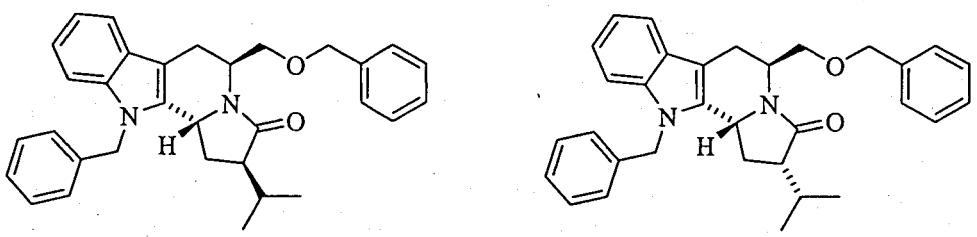
(5*S*,11b*R*)-11-Benzyl-5-benzyloxymethyl-1,2,5,6,11,11b-hexahydro-indolizino [8,7-*b*]indol-3-one (90).



Anhydrous *N*,*N*-dimethylformamide (50 ml) was added to sodium hydride (940 mg, 23.4 mmol) in a dry three-necked round bottom flask under nitrogen and cooled to 0 °C with an ice bath. (5*S*,11b*R*)-5-Hydroxymethyl-1,2,5,6,11,11b-hexahydro-indolizino [8,7-*b*]indol-3-one **(21)** (2.0 g, 7.80 mmol) in anhydrous *N*,*N*-dimethylformamide (65 ml) was added and stirred for 30 min at room temperature. Benzyl bromide (4.40 g, 2.94 ml, 25.8 mmol) was added and the reaction was stirred at room temperature for 3 h under nitrogen. Ice and water were added to quench and the product extracted with ethyl acetate (3 × 60 ml). The organic phases were combined and washed with saturated brine, dried over anhydrous magnesium sulfate, filtered and evaporated to a crude green oil. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3:2 ethyl acetate/hexane as eluent to isolate the target compound as a

yellow solid (3.30 g, 97 %), Mp 76-80 °C; $[\alpha]_D$ + 74.7 [*c* = 0.68 in $CHCl_3$]; ν_{max} (thin film, $CHCl_3$)/cm^{-1} 1690 (NCO) and 2855 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.76-1.86 (1 H, m, CH*(H)*CH_2CO), 2.36-2.57 (3 H, m, CH*(H)*CH_2CO and CH_2CH_2CO), 2.88 (1 H, d, *J* 16.0 Hz, ArCH*(H)*CHN), 3.04 (1 H, ddd, *J* 2.3, 6.7, 15.8 Hz, ArCH*(H)*CHN), 3.45 (2 H, d, *J* 7.5 Hz, CH_2OBn), 4.39 (1 H, d, *J* 12.0 Hz, OCH*(H)*Ph), 4.54 (1 H, d, *J* 12.0 Hz, OCH*(H)*Ph), 4.60 (1 H, br, t, *J* 7.9 Hz, NC*H*Ar), 5.02 (1 H, dd, *J* 7.2, 14.0 Hz, $ArCH_2CHN$), 5.23 (1 H, d, *J* 17.3 Hz, NCH*(H)*Ph), 5.32 (1 H, d, *J* 17.3 Hz, NCH*(H)*Ph), 6.85-6.89 (2 H, m, Ar*H*), 7.13-7.29 (11 H, m, Ar*H*) and 7.51-7.55 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_2), 26.9 (CH_2), 31.7 (CH_2), 45.7 (*C*H), 47.3 (CH_2), 51.6 (*C*H), 68.6 (CH_2), 72.7 (CH_2), 106.5 (*C*), 109.5 (*C*H), 118.6 (*C*H), 119.8 (*C*H), 122.2 (*C*H), 125.6 (*C*H), 125.6 (*C*H), 127.0 (*C*), 127.6 (*C*H), 127.7 (*C*H), 127.8 (*C*H), 127.8 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 129.0 (*C*H), 129.0 (*C*H), 133.4 (*C*), 137.2 (*C*), 137.4 (*C*), 138.0 (*C*) and 173.5 (*C*O); MS (FAB) *m/z* 436 [M^+, 7.7 %] (M^+, 436.2156. $C_{29}H_{28}N_2O_2$ requires 436.2151).

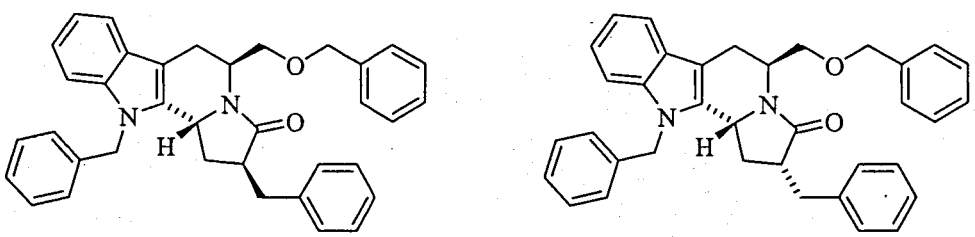
(2*R*,5*S*,11b*R*)-11-Benzyl-5-benzyloxymethyl-2-isopropyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (92a).



n-Butyl lithium (0.85 ml, 2.12 mmol) was added dropwise to a stirred solution of diisopropylamine (214 mg, 0.30 ml, 2.12 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 15 min then cooled to –78 °C. (5*S*,11b*R*)-11-Benzyl-5-benzyloxymethyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*] indol-3-one **(90)** (616 mg, 1.41 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise and the reaction stirred for 15 min at –78 °C. 2-Iodo-propane (312 mg, 0.18 ml, 1.70 mmol) was added dropwise at –78 °C and reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride and product was extracted with diethyl ether (3 × 50 ml). Ether phases were combined and washed with saturated brine (50 ml) and dried over anhydrous magnesium sulfate.

Ether phase was then filtered and solvent removed by evaporation to yield the target compound as an 3:1 mixture of diastereoisomers, which were separated by column chromatography using silica gel as absorbent and 5:1 light petroleum/ethyl acetate as eluent (448 mg, 66 %), Mp 68-72 °C; $[\alpha]_D$ + 21.6 [*c* = 1.10 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1704 (NCO) and 2959 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 0.83 (3 H, d, *J* 6.8 Hz, CH(CHCH$_3$(C*H*$_3$))CO), 0.95 (3 H, d, *J* 6.8 Hz, CH(CHCH$_3$(C*H*$_3$))CO), 1.95-2.03 (1 H, m, CH*(H)*CHCO), 2.12-2.18 (1 H, m, CH(C*H*(CH$_3$)$_2$)CO), 2.27 (1 H, ddd, *J* 1.8, 7.3, 12.6 Hz, CH*(H)*CHCO), 2.47 (1 H, ddd, *J* 1.9, 4.3, 10.1 Hz, CH$_2$C*H*CO), 2.81 (1 H, d, *J* 15.9, ArCH*(H)*CHN), 3.06 (1 H, ddd, *J* 2.3, 6.7, 15.9 Hz, ArCH*(H)*CHN), 3.45 (2 H, d, *J* 7.6 Hz, C*H*$_2$OBn), 4.40 (1 H, d, *J* 11.8 Hz, OCH*(H)*Ph), 4.50 (1 H, d, *J* 11.8 Hz, OCH*(H)*Ph), 4.58 (1 H, br, t, *J* 8.1 Hz, NC*H*Ar), 5.05 (1 H, dd, *J* 7.4, 14.4 Hz, ArCH$_2$C*H*N), 5.23 (1 H, d, *J* 17.0 Hz, NCH*(H)*Ph), 5.39 (1 H, d, *J* 17.0 Hz, NCH*(H)*Ph), 6.90-6.95 (2 H, m, Ar*H*), 7.13-7.30 (11 H, m, Ar*H*) and 7.50-7.55 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (*C*H$_3$), 20.7 (*C*H$_3$), 22.2 (*C*H$_2$), 28.2 (*C*H$_2$), 29.6 (*C*H), 45.5 (*C*H), 47.5 (*C*H$_2$), 48.9 (*C*H), 50.8 (*C*H), 68.5 (*C*H$_2$), 72.7 (*C*H$_2$), 106.5 (*C*), 109.5 (*C*H), 118.5 (*C*H), 119.7 (*C*H), 122.1 (*C*H), 125.8 (*C*H), 125.8 (*C*H), 127.0 (*C*), 127.6 (*C*H), 127.7 (*C*H), 127.8 (*C*H), 127.8 (*C*H), 128.3 (*C*H), 128.3 (*C*H), 128.9 (*C*H), 128.9 (*C*H), 134.1 (*C*), 137.2 (*C*), 137.4 (*C*), 137.9 (*C*) and 175.2 (*C*O); MS (EI) *m/z* 478 [M^+, 25.8 %] (M^+, 478.2614. $C_{32}H_{34}N_2O_2$ requires 478.2620).

(5*S*,11b*R*)-2,11-Dibenzyl-5-benzyloxymethyl-1,2,5,6,11,11b-hexahydro-indolizino [8,7-*b*]indol-3-one (93).



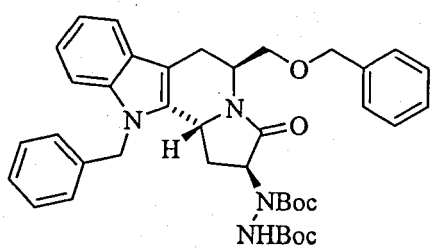
n-Butyl lithium (0.79 ml, 1.98 mmol) was added dropwise to a stirred solution of diisopropylamine (201 mg, 0.30 ml, 1.98 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 15 min then cooled to –78 °C. (5*S*,11b*R*)-11-Benzyl-5-benzyloxymethyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*] indol-3-one **(90)** (577 mg, 1.32 mmol) in anhydrous tetrahydrofuran (10 ml) was added

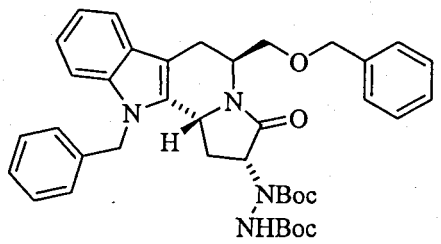
dropwise and the reaction stirred for 15 min at –78 °C. Benzyl bromide (294 mg, 0.20 ml, 1.50 mmol) was added dropwise at –78 °C and the reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride and the product extracted with diethyl ether (3 × 50 ml). Ether phases were combined and washed with saturated brine (50 ml) and dried over anhydrous magnesium sulfate. Ether phase was then filtered and solvent removed on the rotary evaporator to yield the target compound as an 1:1 mixture of diastereoisomers, which were separated by column chromatography using silica gel as absorbent and 5:1 light petroleum/ethyl acetate as eluent (404 mg, 58 %), Mp 83-85 °C; $[\alpha]_D$ + 35.6 [*c* = 1.05 in CH_2Cl_2] (Found: C, 82.27; H, 6.60; N, 5.60. $C_{36}H_{34}N_2O_2$ requires C, 82.10; H, 6.51; N, 5.32 %); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1699 (NCO) and 2930 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.42-1.51(1 H, m, CH(*H*)CHCO), 2.28-2.35 (1 H, m, CH(*H*)CHCO), 2.43 (1 H, dd, *J* 10.5, 13.7 Hz, CH(CH*(H)*Ph))CO, 2.78-2.89 (2 H, m, ArCH*(H)*CHN and CH_2CHCO), 3.04 (1 H, ddd, *J* 2.2, 6.7, 15.9 Hz, ArCH*(H)*CHN), 3.33 (1 H, dd, *J* 3.8, 13.7 Hz, CH(CH*(H)*Ph)CO), 3.45 (2 H, d, *J* 7.5 Hz, CH_2OBn), 4.39 (1 H, d, *J* 12.0 Hz, OCH*(H)*Ph), 4.53 (1 H, d, *J* 12.0 Hz, OCH*(H)*Ph), 4.48-4.52 (1 H, m, NC*H*Ar), 5.04 (1 H, dd, *J* 7.2, 14.1 Hz, $ArCH_2CHN$), 5.18 (2 H, s, NCH_2Ph), 6.73-6.79 (2 H, m, Ar*H*), 6.97-6.99 (2 H, m, Ar*H*), 7.14-7.24 (14 H, m, Ar*H*) and 7.52-7.54 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_2), 33.9 (CH_2), 36.9 (CH_2), 44.7 (*C*H), 45.9 (*C*H), 47.2 (CH_2), 49.9 (*C*H), 68.6 (CH_2), 72.7 (CH_2), 106.4 (*C*), 109.4 (*C*H), 118.6 (*C*H), 119.8 (*C*H), 122.3 (*C*H), 125.6 (*C*H), 125.6 (*C*H), 126.3 (*C*H), 127.0 (*C*), 127.5 (*C*H), 127.7 (*C*H), 127.7 (*C*H), 127.7 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.5 (*C*H), 128.5 (*C*H), 128.8 (*C*H), 128.8 (*C*H), 128.9 (*C*H), 128.9 (*C*H), 133.2 (*C*), 137.3 (*C*), 137.5 (*C*), 138.0 (*C*), 139.3 (*C*) and 174.4 (*C*O); MS (EI) *m/z* 526 [M^+, 11.3 %] (M^+, 526.2612. $C_{36}H_{34}N_2O_2$ requires 526.2619).

Mp 83-85 °C; $[\alpha]_D$ + 23.4 [*c* = 1.04 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1696 (NCO) and 2929 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.90 (1 H, dt, *J* 9.2, 18.4 Hz, CH(*H*)CHCO), 2.20 (1 H, ddd, *J* 1.3, 6.7, 12.4 Hz, CH(*H*)CHCO), 2.71 (1 H, dd, *J* 9.0, 13.4 Hz, CH(CH*(H)*Ph)CO), 2.80-2.85 (1 H, m, CH_2CHCO), 2.89 (1 H, d, *J* 15.9 Hz, ArCH*(H)*CHN), 2.98-3.06 (2 H, m, ArCH*(H)*CHN and CH(CH*(H)*Ph)CO), 3.29 (2 H, dd, *J* 3.4, 7.5 Hz, CH_2OBn), 4.12-4.17 (1 H, m, NC*H*Ar), 4.36 (1 H, d, *J* 11.9 Hz, OCH*(H)*Ph), 4.49 (1 H, d, *J* 11.9 Hz, OCH*(H)*Ph), 4.97 (1 H, dd, *J* 7.0, 13.8 Hz,

$ArCH_2CHN$), 5.06 (1 H, d, *J* 17.1 Hz, NCH*(H)*Ph), 5.24 (1 H, d, *J* 17.1 Hz, NCH*(H)*Ph), 6.75-6.82 (2 H, m, Ar*H*), 7.09-7.29 (16 H, m, Ar*H*) and 7.50-7.54 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_2), 30.7 (CH_2), 36.6 (CH_2), 44.4 (*C*H), 45.7 (*C*H), 47.3 (CH_2), 50.2 (*C*H), 68.5 (CH_2), 72.7 (CH_2), 106.6 (*C*), 109.3 (*C*H), 118.6 (*C*H), 119.7 (*C*H), 122.2 (*C*H), 125.8 (*C*H), 125.8 (*C*H), 126.6 (*C*H), 127.0 (*C*), 127.7 (*C*H), 127.7 (*C*H), 127.7 (*C*H), 127.7 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 128.5 (*C*H), 128.5 (*C*H), 128.9 (*C*H), 128.9 (*C*H), 129.2 (*C*H), 129.2 (*C*H), 133.3 (*C*), 137.2 (*C*), 137.5 (*C*), 138.0 (*C*), 138.6 (*C*) and 175.0 (*C*O); MS (EI) *m/z* 526 [M^+, 15.6 %] (M^+, 526.2615. $C_{36}H_{34}N_2O_2$ requires 526.2619).

(2*S*,5*S*,11b*R*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-11-Benzyl-5-benzyloxy methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (94a).



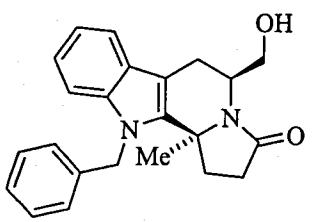


n-Butyl lithium (0.92 ml, 2.29 mmol) was added dropwise to a stirred solution of diisopropylamine (232 mg, 0.32 ml, 2.29 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 15 min then cooled to –78 °C. (5*S*,11b*R*)-11-Benzyl-5-benzyloxymethyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*] indol-3-one **(90)** (500 mg, 1.15 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise and the reaction stirred for 15 min at –78 °C. Di-*tert*-butyl azodicarboxylate (396 mg, 1.72 mmol) in anhydrous tetrahydrofuran (5 ml) was added dropwise at –78 °C and the reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride and product was extracted with diethyl ether (3 × 40 ml). Ether phases were combined and washed with saturated brine (50 ml) and dried over anhydrous magnesium sulfate. Ether phase was then filtered and solvent removed on the rotary evaporator to yield the target compound as an 6:1 mixture of diastereoisomers, which were separated by column chromatography using silica gel as absorbent and 4:1 light petroleum/ethyl acetate as eluent (439 mg, 57 %), Mp 93-96 °C; $[\alpha]_D$ + 63.5 [*c* = 1.01 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1701

(NCO), 1701 (CO), 2980 (aliphatic CH) and 3286 (NH); δ_H (400 MHz, DMSO, 100 °C) 1.34 (9 H, s, $CO_2C(CH_3)_3$), 1.42 (9 H, s, $CO_2C(CH_3)_3$), 2.16-2.25 (1 H, m, CH*(H)*CHCO), 2.71-2.76 (1 H, m, CH*(H)*CHCO), 2.89(1 H, ddd, *J* 2.1, 6.3, 15.8 Hz, ArCH*(H)*CHN), 2.95-3.00 (1 H, m, ArCH*(H)*CHN), 3.39-3.51 (2 H, m, CH_2OBn), 4.43 (1 H, d, *J* 12.4 Hz, OCH*(H)*Ph), 4.48 (1 H, d, *J* 12.4 Hz, OCH*(H)*Ph), 4.61 (1 H, d, *J* 7.7 Hz, CH_2CHCO), 4.80 (1 H, dd, *J* 6.5, 13.0 Hz, $ArCH_2CHN$), 4.87 (1 H, t, *J* 7.3 Hz, NC*H*Ar), 5.27 (1 H, d, *J* 17.2 Hz, NCH*(H)*Ph), 5.43 (1 H, d, *J* 17.2 Hz, NCH*(H)*Ph), 6.92-6.94 (1 H, m, Ar*H*), 7.06-7.11 (2 H, m, Ar*H*), 7.21-7.28 (10 H, m, Ar*H*), 7.49-7.53 (1 H, m, Ar*H*) and 8.47 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 100 °C) 22.6 (CH_2), 28.4 ($OC(CH_3)_3$), 28.4 ($OC(CH_3)_3$), 31.4 (CH_2), 46.9 (*C*H), 47.4 (CH_2), 50.7 (*C*H), 60.1 (*C*H), 69.3 (CH_2), 72.8 (CH_2), 80.2 (*C*), 81.1 (*C*), 106.2 (*C*), 110.4 (*C*H), 118.7 (*C*H), 119.7 (*C*H), 122.1 (*C*H), 126.3 (*C*H), 126.3 (*C*H), 127.5 (*C*), 127.6 (*C*H), 127.7 (*C*H), 127.7 (*C*H), 127.7 (*C*H), 128.5 (*C*H), 128.5 (*C*H), 129.0 (*C*H), 129.0 (*C*H), 134.0 (*C*), 134.6 (*C*), 137.8 (*C*), 138.3 (*C*), 154.5 (*C*O), 156.0 (*C*O) and 168.9 (*C*O) ; MS (EI) *m/z* 666 [M^+, 6.4 %] (M^+, 666.3414. $C_{39}H_{46}N_4O_6$ requires 666.3417).

3.4.2. Manipulation of the Hydroxymethyl Auxiliary

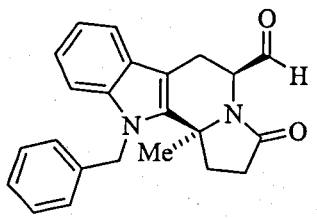
(5*S*,11b*S*)-11-Benzyl-5-hydroxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (51).



(5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one **(83)** (1.82 g, 2.67 mmol) was dissolved in ethanol (150 ml) under nitrogen at room temperature. To this was added 10 % Pd/C (200 mg) and reaction hydrogenated at room temperature under pressure (50 psi) for 4 days. The reaction mixture was then filtered through a celite pad and evaporated down to a crude colourless solid, which was adsorbed onto silica and chromatographed using silica gel

as absorbent and 3:1 light petroleum/ethyl acetate as eluent to produce a colourless solid (1.14 g, 78 %), which had identical spectral properties to the compound prepared as previous discussed.

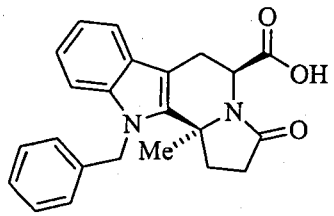
(5*S*,11b*S*)-11-Benzyl-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino [8,7-*b*]indole-5-carbaldehyde (95).



o-Iodoxybenzoic acid (2.43 g, 8.74 mmol) was added to a solution of (5*S*,11b*S*)-11-benzyl-5-hydroxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one **(51)** (2.10 g, 5.83 mmol) in dimethyl sulfoxide (40 ml) and the reaction stirred for 24 h at room temperature. The resulting mixture was added to a solution of ethyl acetate/water and product extracted with ethyl acetate (3 × 50 ml). The organic layer was washed with water (3 × 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated to a crude yellow solid. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 2:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (1.36 g, 65 %), Mp 81-85 °C; $[\alpha]_D$ – 184.3 [*c* = 1.02 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1682 (NCO), 1732 (CHO), 2928 (aliphatic CH) and 3057 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 1.71 (3 H, s, C*H*$_3$), 2.23-2.33 (2 H, m, CH*(H)*CH_2CO and CH*(H)*CO), 2.40-2.55 (2 H, m, CH*(H)*CH_2CO and CH*(H)*CO), 3.12 (1 H, dd, *J* 5.2, 15.8 Hz, ArCH*(H)*CHN), 3.21 (1 H, dd, *J* 10.8, 15.8 Hz, ArCH*(H)*CHN), 3.93 (1 H, dd, *J* 5.2, 10.8 Hz, ArCH_2C*H*N), 5.41 (1 H, d, *J* 17.4 Hz, NCH*(H)*Ph), 5.47 (1 H, d, *J* 17.4 Hz, NCH*(H)*Ph), 6.84-6.86 (2 H, m, Ar*H*), 7.05-7.07 (1 H, m, Ar*H*), 7.13-7.16 (2 H, m, Ar*H*), 7.24-7.29 (3 H, m, Ar*H*), 7.54-7.57 (1 H, m, Ar*H*) and 10.11 (1 H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 21.0 (*C*H_2), 27.3 (*C*H_3), 29.1 (*C*H_2), 32.2 (*C*H_2), 47.7 (*C*H_2), 58.3 (*C*H), 61.4 (*C*), 107.6 (*C*), 110.0 (*C*H), 118.7 (*C*H), 120.2 (*C*H), 122.7 (*C*H), 125.3 (*C*H), 125.3 (*C*H), 126.4 (*C*), 127.6 (*C*H), 129.0 (*C*H), 129.0 (*C*H), 137.1 (*C*), 137.3 (*C*), 137.4 (*C*), 176.2 (*C*O) and

195.8 (*C*HO); MS (EI) *m/z* 358 [M^+, 33.4 %] (M^+, 358.1681. $C_{23}H_{22}N_2O_2$ requires 358.1681).

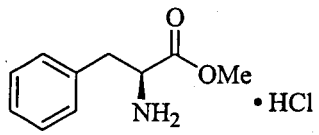
(5*S*,11b*S*)-11-Benzyl-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino [8,7-*b*]indole-5-carboxylic acid (96).



A solution of (5*S*,11b*S*)-11-benzyl-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-5-carbaldehyde **(95)** (1.79 g, 4.99 mmol) in acetonitrile (70 ml), *tert*-butanol (220 ml) and 1-methyl-1-cyclohexene (70 ml) was stirred rapidly as it cooled to 0 °C. A solution of sodium chlorite (4.35 g, 38.5 mmol) and sodium dihydrogen phosphate (4.19 g, 35.0 mmol) in water (150 ml) was added dropwise over a 10 min period and the reaction stirred at room temperature for 17 h. The resulting mixture was added to a solution of saturated brine/ethyl acetate (1:1) (50 ml) and the product extracted with ethyl acetate (3 × 50 ml). The organics were combined and washed with a 1 M solution of sodium hydrosulfite, dried over anhydrous magnesium sulfate, filtered and evaporated to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 1:1 ethyl acetate/light petroleum as eluent to produce a yellow solid (1.41 g, 75 %), Mp 98-101 °C; $[\alpha]_D$ – 136.7 [*c* = 1.20 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1681 (NCO), 1731 (CO) and 3440 (OH); δ_H (400 MHz, $CDCl_3$) 1.69 (3 H, s, C*H*$_3$), 2.21-2.31 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.37-2.56 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 3.10 (1 H, dd, *J* 4.7, 15.7 Hz, ArCH*(H)*CHN), 3.41 (1 H, dd, *J* 11.0, 15.7 Hz, ArCH*(H)*CHN), 4.22 (1 H, dd, *J* 4.7, 11.0 Hz, ArCH_2C*H*N), 5.39 (1 H, d, *J* 17.7 Hz, NCH*(H)*Ph), 5.45 (1 H, d, *J* 17.7 Hz, NCH*(H)*Ph), 6.83-6.85 (2 H, m, Ar*H*), 7.04-7.06 (1 H, m, Ar*H*), 7.10-7.14 (2 H, m, Ar*H*), 7.22-7.28 (3 H, m, Ar*H*) and 7.53-7.56 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 23.2 (*C*H_2), 27.3 (*C*H_3), 29.8 (*C*H_2), 31.8 (*C*H_2), 47.7 (*C*H_2), 52.7 (*C*H), 62.8 (*C*), 108.2 (*C*), 110.0 (*C*H), 118.7 (*C*H), 120.1 (*C*H), 122.6 (*C*H), 125.4 (*C*H), 125.4 (*C*H), 126.4 (*C*), 127.6 (*C*H), 129.0 (*C*H), 129.0 (*C*H),

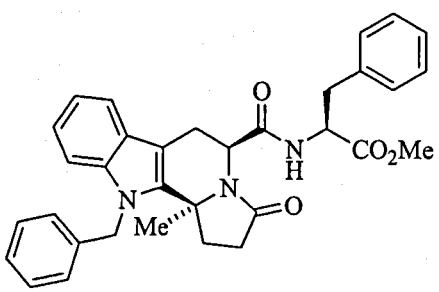
137.2 (*C*), 137.3 (*C*), 137.6 (*C*), 172.5 (*C*O) and 176.4 (*C*O); MS (EI) *m/z* 374 [M^+, 9.2 %] (M^+, 374.1637. $C_{23}H_{22}N_2O_3$ requires 374.1630).

_L_-Phenylalanine methyl ester hydrochloride (97).



Methanol (70 ml) was cooled to 0 °C with an ice bath and acetyl chloride (3.2 ml) was added dropwise whilst maintaining the temperature below 5 °C. *L*-Phenylalanine (2.0 g, 12.11 mmol) was added in one portion and the solution heated under reflux for 3 h. The solvent was removed under reduced pressure to yield the target compound as a colourless solid (2.97 g, 72 %), Mp 160-162 °C; $[\alpha]_D$ + 38.2 [*c* = 1.05 in EtOH]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1732 (CO) and 3410 (NH); δ_H (400 MHz, DMSO) 3.11 (1 H, dd, *J* 7.6, 14.0 Hz, ArCH*(H)*CHNH$_2$), 3.23 (1 H, dd, *J* 5.6, 13.6 Hz, ArCH*(H)*CHNH$_2$), 3.65 (3 H, s, OC*H*$_3$), 4.23 (1 H, dd, *J* 5.6, 7.2 Hz, ArCH$_2$C*H*NH$_2$), 7.24-7.36 (5 H, m, Ar*H*) and 8.81 (2 H, br, s, N*H*$_2$); δ_C (100 MHz, DMSO) 35.8 (*C*H$_2$), 52.5 (*C*H$_3$), 53.2 (*C*H), 127.2 (*C*H), 128.6 (*C*H), 128.6 (*C*H), 129.4 (*C*H), 129.4 (*C*H), 134.7 (*C*) and 169.3 (*C*O); MS (FAB) *m/z* 180 [MH^+, 100 %] (MH^+, 180.1026. $C_{10}H_{13}NO_2$ requires 180.1025).

(5*S*,11b*S*,3'*S*)-2-[(11-Benzyl-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-5-carbonyl)-amino]-3'-phenyl-propionic acid methyl ester (98).

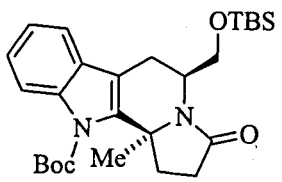


(5*S*,11b*S*)-11-Benzyl-11b-methyl-3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*] indole-5-carboxylic acid **(96)** (250 mg, 0.668 mmol) was dissolved in anhydrous

dichloromethane (10 ml) and cooled to −15 °C. 1-Hydroxyazabenzotriazole (100 mg, 0.734 mmol) and 1-ethyl-3-[(dimethylamino)propyl]carbodiimide hydrochoride (141 mg, 0.734 mmol) were added and the reaction stirred for 20 min at −15 °C. *N*-methyl morpholine (74 mg, 0.08 ml, 0.734 mmol) and *L*-phenylalanine methyl ester hydrochloride (**97**) (155 mg, 0.734 mmol) were added and the reaction stirred for a further 3 h at −15 °C. An ice cold 1 M solution of HCl (2 ml) was added and the reaction extracted with dichloromethane (3 × 10 ml). The organic phase was washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and solvent removed by rotary evaporation to yield a crude yellow residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 2:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (275 mg, 77 %), Mp 84-86 °C; $[\alpha]_D$ − 76.8 [*c* = 1.11 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1682 (NCO), 1738 (CO), 3418 (NH); δ_H (400 MHz, $CDCl_3$) 1.65 (3 H, s, C*H*$_3$), 2.05-2.20 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.33-2.46 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 3.06-3.16 (2 H, m, ArCH*(H)*CHN and CHCH*(H)*Ph), 3.22 (1 H, dd, *J* 5.3, 13.6 Hz, ArCH*(H)*CHN), 3.43 (1 H, dd, *J* 10.0, 15.9 Hz, CHCH*(H)*Ph), 3.68 (3 H, s, OC*H*$_3$), 4.17 (1 H, dd, *J* 5.2, 9.9 Hz, C*H*CO_2CH_3), 4.93-4.97 (1 H, m, $ArCH_2CHN$), 5.39 (1 H, d, *J* 17.6 Hz, NCH*(H)*Ph), 5.47 (1 H, d, *J* 17.6 Hz, NCH*(H)*Ph), 6.44 (1 H, br, d, *J* 7.6 Hz, N*H*), 6.78-6.81 (2 H, m, Ar*H*), 7.06-7.23 (11 H, m, Ar*H*), and 7.55-7.59 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (*C*H_2), 27.6 (*C*H_3), 29.6 (*C*H_2), 31.7 (*C*H_2), 38.1 (*C*H_2), 47.7 (*C*H_2), 52.2 (O*C*H_3), 53.3 (*C*H), 53.7 (*C*H), 62.5 (*C*), 109.3 (*C*), 109.9 (*C*H), 118.8 (*C*H), 120.2 (*C*H), 122.7 (*C*H), 125.2 (*C*H), 125.2 (*C*H), 126.5 (*C*), 127.0 (*C*H), 127.5 (*C*H), 128.4 (*C*H), 128.4 (*C*H), 129.0 (*C*H), 129.0 (*C*H), 129.5 (*C*H), 129.5 (*C*H), 136.0 (*C*), 137.0 (*C*), 137.2 (*C*), 137.4 (*C*), 169.4 (*C*O), 172.2 (*C*O) and 177.4 (*C*O); MS (EI) *m/z* 535 [M^+, 46.7 %] (M^+, 535.2465. $C_{33}H_{33}N_3O_4$ requires 535.2471).

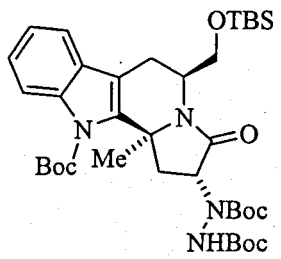
3.4.3. The *Anti*-Indolizino[8,7-*b*]indole Polypeptide

(5*S*,11b*S*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-11b-methyl-3-oxo-1,2,3,5,6,11b hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (99).



(5*S*,11b*S*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one **(49)** (5.2 g, 13.5 mmol) was dissolved in anhydrous tetrahydrofuran (50 ml) under a nitrogen atmosphere. Triethylamine (2.74 g, 3.77 ml, 27.0 mmol), 4-dimethylaminopyridine (0.33 g, 2.70 mmol) and di-*tert*-butyl dicarbonate (3.54 g, 16.2 mmol) were added successively and the resultant solution was stirred overnight. The volatiles were removed by evaporation and the orange residue dissolved in ethyl acetate and washed successively with saturated ammonium chloride (2 × 50 ml), saturated sodium bicarbonate (2 × 50 ml) and saturated brine (50 ml). The organic phase was then dried over anhydrous magnesium sulfate and the solvent removed under pressure to yield a colourless solid, which was chromatographed using silica gel as absorbent and 4:1 light petroleum/ethyl acetate as eluent to isolate the target compound as a colourless solid (6.0 g, 92 %), Mp 49-51 °C; $[\alpha]_D$ – 194.2 [*c* = 1.04 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1697 (NCO), 1736 (CO) and 2951 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 0.12 (3 H, s, $SiCH_3$), 0.13 (3 H, s, $SiCH_3$), 0.93 (9 H, s, $SiC(CH_3)_3$), 1.71 (9 H, s, $CO_2C(CH_3)_3$), 1.86 (3 H, s, CH_3), 2.19-2.25 (1 H, m, $CH(H)CH_2CO$), 2.41-2.64 (3 H, m, $CH(H)CH_2CO$ and CH_2CH_2CO), 2.77 (1 H, dd, *J* 11.1, 15.7 Hz, $ArCH(H)CHN$), 3.02 (1 H, dd, *J* 4.0, 15.7 Hz, $ArCH(H)CHN$), 3.59-3.66 (1 H, m, $ArCH_2CHN$), 4.45-4.56 (2 H, m, CH_2OSi), 7.22-7.32 (2 H, m, Ar*H*), 7.42-7.45 (1 H, m, Ar*H*) and 7.97-8.00 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) –5.2 ($SiCH_3$), –5.2 ($SiCH_3$), 18.3 (*C*), 25.3 (CH_3), 25.5 (CH_2), 26.0 ($SiC(CH_3)_3$), 28.3 ($CO_2C(CH_3)_3$), 30.5 (CH_2), 32.2 (CH_2), 53.9 (*C*H), 64.0 (CH_2), 65.0 (*C*), 84.3 (*C*), 116.0 (*C*H), 116.4 (*C*), 118.4 (*C*H), 122.8 (*C*H), 124.6 (*C*H), 128.7 (*C*), 135.7 (*C*), 139.3 (*C*), 149.8 (*C*O) and 175.1 (*C*O); MS (EI) *m/z* 485 [MH^+, 42.8 %] (MH^+, 485.2842. $C_{27}H_{40}N_2O_4Si$ requires 485.2836).

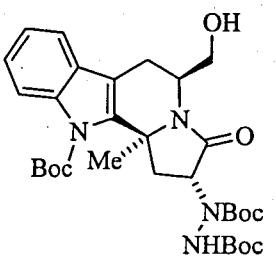
(2*R*,5*S*,10b*S*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-(5-(*tert*-butyl-dimethyl-silanyloxymethyl)-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*] indole-11-carboxylic acid tert-butyl ester (100).



n-Butyl lithium (0.65 ml, 1.64 mmol) was added dropwise to a stirred solution of diisopropylamine (166 mg, 0.23 ml, 1.64 mmol) in anhydrous tetrahydrofuran (5 ml) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 20 min then cooled to –78 °C. (5*S*,11b*S*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(99)** (563 mg, 1.17 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise and reaction stirred for 20 min at –78 °C. Di-*tert*-butyl azodicarboxylate (350 mg, 1.52 mmol) in anhydrous tetrahydrofuran (5 ml) was added dropwise at –78 °C and reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride and product was extracted with ethyl acetate (3 × 30 ml). Organic phase was then dried over anhydrous magnesium sulfate and solvent removed on the rotary evaporator to yield the target compound as a single diastereoisomer, which was purified by column chromatography using silica gel as absorbent and 2:1 light petroleum/ethyl acetate as eluent (742 mg, 89 %), Mp 99-110 °C; $[\alpha]_D$ – 97.5 [*c* = 1.12 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1697 (NCO), 1732 (CO), 2855 (aliphatic CH) and 3277 (NH); δ_H (400 MHz, DMSO, 80 °C) 0.11 (3 H, s, SiC*H*$_3$), 0.11 (3 H, s, SiC*H*$_3$), 0.95 (9 H, s, SiC(C*H*$_3$)$_3$), 1.41 (9 H, s, CO_2C(C*H*$_3$)$_3$), 1.45 (9 H, s, CO_2C(C*H*$_3$)$_3$), 1.71 (9 H, s, CO_2C(C*H*$_3$)$_3$), 1.88 (3 H, s, C*H*$_3$), 2.43 (1 H, dd, *J* 8.8, 14.0 Hz, CH*(H)*CHCO), 2.75 (1 H, dd, *J* 11.6, 16.0 Hz, ArCH*(H)*CHN), 2.89-2.94 (1 H, m, ArCH*(H)*CHN), 3.04 (1 H, dd, *J* 10.0, 14.4 Hz, CH*(H)*CHCO), 3.62-3.69 (1 H, m, ArCH$_2$C*H*N), 4.29-4.31 (1 H, m, CH$_2$C*H*CO), 4.50 (2 H, d, *J* 7.2 Hz, C*H*$_2$OSi), 7.22-7.26 (1 H, m, Ar*H*), 7.30-7.34 (1 H, m, Ar*H*), 7.45 (1 H, d, *J* 7.6 Hz, Ar*H*), 8.02 (1 H, d, *J* 8.4 Hz, Ar*H*) and 8.25 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 80 °C) –4.8 (SiCH$_3$), –4.8 (SiCH$_3$), 18.4 (*C*), 25.0 (*C*H$_2$), 26.3 (SiC(*C*H$_3$)$_3$), 27.4 (*C*H$_3$), 28.3 (CO_2C(*C*H$_3$)$_3$),

28.4 ($CO_2C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 36.0 (CH_2), 54.3 (*C*H), 61.7 (*C*H), 61.7 (*C*), 64.3 (CH_2), 80.1 (*C*), 81.0 (*C*), 85.3 (*C*), 116.1 (*C*H), 116.8 (*C*), 118.8 (*C*H), 123.3 (*C*H), 125.1 (*C*H), 128.6 (*C*), 136.2 (*C*), 139.2 (*C*), 150.0 (*C*O), 154.5 (*C*O), 156.0 (*C*O) and 172.1 (*C*O); MS (ES) *m/z* 715 [MH^+, 50.0 %] (MH^+, 715.4099. $C_{37}H_{58}N_4O_8Si$ requires 715.4102).

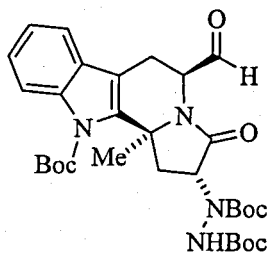
(2*R*,5*S*,10b*S*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-5-hydroxymethyl-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (101).



To a solution of the (2*R*,5*S*,10b*S*)-2-*N*,*N*'-bis-(3,3-*tert*-butyl ester)-hydrazino-(5-(*tert*-butyl-dimethyl-silanyloxymethyl)-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid tert-butyl ester **(100)** (435 mg, 0.608 mmol) in tetrahydrofuran (10 ml) was added tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 0.61 ml, 0.608 mmol) and the reaction stirred for 5 min at room temperature. The resultant solution was concentrated and chromatographed through a pad of silica gel using 2:1 light petroleum/ethyl acetate as eluent to yield the target compound as a colourless solid (358 mg, 98 %), Mp 95-97 °C; $[\alpha]_D$ – 112.0 [*c* = 1.10 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1697 (NCO), 1734 (CO), 2977 (aliphatic CH), 3289 (NH) and 3401 (OH); δ_H (400 MHz, DMSO, 80 °C) 1.42 (9 H, s, $CO_2C(CH_3)_3$), 1.46 (9 H, s, $CO_2C(CH_3)_3$), 1.72 (9 H, s, $CO_2C(CH_3)_3$), 1.87 (3 H, s, CH_3), 2.47-2.51 (1 H, m, CH*(H)*CHCO), 2.80 (2 H, d, *J* 8.0 Hz, ArCH_2CHN), 2.95 (1 H, t, *J* 13.6 Hz, CH*(H)*CHCO), 3.74-3.77 (1 H, m, ArCH_2CHN), 4.12-4.19 (2 H, m, CH_2OH), 4.43-4.53 (1 H, br, m, CH_2CHCO), 4.69 (1 H, br, s, O*H*), 7.25 (1 H, t, *J* 7.4 Hz, Ar*H*), 7.32 (1 H, t, *J* 7.4 Hz, Ar*H*), 7.48 (1 H, d, *J* 7.6 Hz Ar*H*), 8.01 (1 H, d, *J* 8.4 Hz, Ar*H*) and 8.66 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 80 °C) 24.4 (CH_2), 27.5 (CH_3), 28.3 ($CO_2C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 28.5 ($CO_2C(CH_3)_3$), 35.9 (CH_2), 54.1 (*C*H), 62.1 (*C*H), 62.4 (CH_2), 62.4 (*C*), 79.4 (*C*), 80.1 (*C*), 81.0 (*C*), 116.2 (*C*H), 116.4 (*C*), 118.8

(*C*H), 123.3 (*C*H), 125.1 (*C*H), 128.6 (*C*), 136.1 (*C*), 139.1 (*C*), 149.9 (*C*O), 153.8 (*C*O), 156.1 (*C*O) and 171.5 (*C*O); MS (ES) *m/z* 601 [MH^+, 100 %] (MH^+, 601.3233. $C_{31}H_{44}N_4O_8$ requires 601.3237).

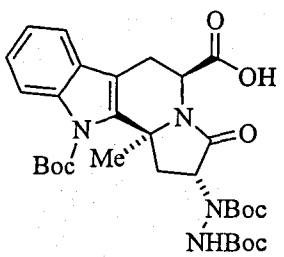
(2*R*,5*S*,10b*S*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-5-formyl-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (102).



o-Iodoxybenzoic acid (700 mg, 2.50 mmol) was added to a solution of (2*R*,5*S*,10b*S*)-2-*N*,*N*'-bis-(3,3-*tert*-butyl ester)-hydrazino-5-hydroxymethyl-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(101)** (1.00 g, 1.66 mmol) in dimethyl sulfoxide (30 ml) and the reaction stirred for 20 h at room temperature. The reaction mixture was added to a solution of ethyl acetate/water and product extracted with ethyl acetate (3 × 40 ml). The organic layer was washed with water (3 × 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated to a crude yellow solid. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 1:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (964 mg, 97 %), Mp 112-114 °C; $[\alpha]_D$ – 121.2 [*c* = 1.00 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1697 (NCO), 1736 (CO), 2977 (aliphatic CH) and 3299 (NH); δ_H (400 MHz, DMSO, 80 °C) 1.41 (9 H, s, $CO_2C(CH_3)_3$), 1.45 (9 H, s, $CO_2C(CH_3)_3$), 1.74 (9 H, s, $CO_2C(CH_3)_3$), 1.98 (3 H, s, CH_3), 2.50-2.58 (1 H, m, CH*(H)*CHCO), 2.83-2.95 (2 H, m, ArCH_2CHN), 3.06-3.14 (1 H, m, CH*(H)*CHCO), 4.31 (1 H, dd, *J* 5.6, 10.8 Hz, ArCH_2C*H*N), 4.39-4.49 (1 H, br, m, CH_2C*H*CO), 7.23-7.35 (2 H, m, Ar*H*), 7.53 (1 H, d, *J* 7.6 Hz Ar*H*), 8.02 (1 H, d, *J* 8.4 Hz, Ar*H*), 8.79 (1 H, br, s, N*H*) and 9.96 (1 H, s, C*H*O); δ_C (100 MHz, DMSO, 80 °C) 20.0 (CH_2), 26.5 (CH_3), 27.4 ($CO_2C(CH_3)_3$), 27.5 ($CO_2C(CH_3)_3$), 27.6 ($CO_2C(CH_3)_3$), 35.8 (CH_2), 56.3 (*C*H), 59.2 (*C*H), 60.0 (*C*), 78.5 (*C*), 79.3 (*C*), 80.3 (*C*), 114.3 (*C*), 115.3 (*C*H), 118.1 (*C*H), 122.4 (*C*H), 124.3 (*C*H), 127.7 (*C*), 135.2 (*C*),

137.8 (*C*), 149.0 (*CO*), 153.5 (*CO*), 155.2 (*CO*), 171.6 (*CO*) and 195.2 (*CHO*); MS (EI) *m/z* 598 [M^+, 1.6 %] (M^+, 598.3013. $C_{31}H_{42}N_4O_8$ requires 598.3003).

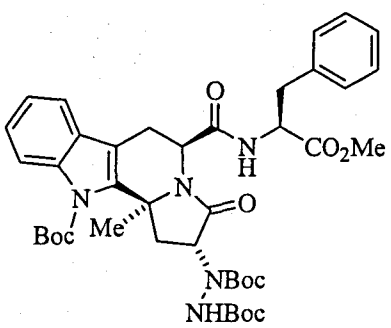
(2*R*,5*S*,10b*S*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-5,11-dicarboxylic acid 11-*tert*-butyl ester (103).



A solution of (2*R*,5*S*,10b*S*)-2-*N*,*N*'-bis-(3,3-*tert*-butyl ester)-hydrazino-5-formyl-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(102)** (6.80 g, 11.3 mmol) in acetonitrile (150 ml), *tert*-butanol (400 ml) and 1-methyl-1-cyclohexene (100 ml) was stirred rapidly as it cooled to 0 °C. A solution of sodium chlorite (9.89 g, 87.5 mmol) and sodium dihydrogen phosphate (9.54 g, 79.5 mmol) in water (300 ml) was added dropwise over a 10 min period and the reaction stirred at room temperature for 17 h. The reaction mixture was added to a solution of saturated brine/ethyl acetate (1:1) (200 ml) and product extracted with ethyl acetate (3 × 150 ml). Organics were combined and washed with a 1 M solution of sodium hydrosulfite, dried over anhydrous magnesium sulfate, filtered and evaporated to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3:1 ethyl acetate/light petroleum as eluent to produce an orange solid (5.79 g, 83 %), Mp 147-149 °C; $[\alpha]_D$ – 86.7 [*c* = 1.02 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1699 (NCO), 1733 (CO), (aliphatic CH), 3283 (NH) and 3401 (OH); δ_H (400 MHz, DMSO, 80 °C) 1.39 (9 H, s, $CO_2C(CH_3)_3$), 1.41 (9 H, s, $CO_2C(CH_3)_3$), 1.69 (9 H, s, $CO_2C(CH_3)_3$), 1.89 (3 H, s, CH_3), 2.34-2.43 (1 H, m, CH*(H)*CHCO), 2.83 (1 H, dd, *J* 8.0, 16.0 Hz, ArCH*(H)*CHN), 3.04 (1 H, dd, *J* 12.0, 16.0 Hz, ArCH*(H)*CHN), 3.13 (1 H, dd, *J* 8.0, 12.0 Hz, CH*(H)*CHCO), 4.18-4.30 (2 H, m, $ArCH_2CHN$ and CH_2CHCO), 7.21-7.32 (2 H, m, Ar*H*), 7.49 (1 H, d, *J* 8.0 Hz Ar*H*), 7.99 (1 H, d, *J* 8.0 Hz, Ar*H*) and 8.47 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 80 °C) 23.0 (CH_2), 27.3 (CH_3), 28.3 ($CO_2C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 28.5 ($CO_2C(CH_3)_3$),

36.0 (*C*H_2), 51.2 (*C*H), 61.3 (*C*H), 61.3 (*C*), 80.2 (*C*), 81.2 (*C*), 85.4 (*C*), 116.2 (*C*H), 116.6 (*C*), 118.9 (*C*H), 123.3 (*C*H), 125.2 (*C*H), 128.6 (*C*), 136.3 (*C*), 138.4 (*C*), 150.0 (*C*O), 154.5 (*C*O), 155.9 (*C*O), 170.4 (*C*O) and 171.7 (*C*O); MS (ES) *m/z* 615 [MH^+, 100 %] (MH^+, 615.3058. $C_{31}H_{42}N_4O_9$ requires 615.3030).

(2*R*,5*S*,11b*S*,1'*S*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-5-(1-methoxycarbonyl -2-phenyl-ethylcarbamoyl)-11b-methyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino [8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (104).

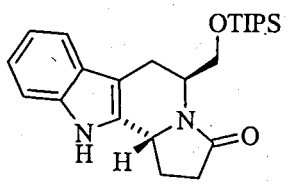


(2*R*,5*S*,10b*S*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-11b-methyl-3-oxo-1,2,3,5,6, 11b-hexahydro-indolizino[8,7-*b*]indole-5,11-dicarboxylic acid 11-*tert*-butyl ester **(103)** (1.00 g, 1.64 mmol) was dissolved in anhydrous dichloromethane (35 ml) and cooled to –15 °C under nitrogen. 1-Hydroxyazabenzotriazole (245 mg, 1.80 mmol) and 1-ethyl-3-[(dimethylamino)propyl]carbodiimide hydrochoride (345 mg, 1.80 mmol) were added and the reaction stirred for 20 min at –15 °C. *N*-methyl morpholine (82 mg, 0.20 ml, 1.80 mmol) and *L*-phenylalanine methyl ester hydrochloride **(97)** (388 mg, 1.80 mmol) were added and the reaction stirred for a further 3 h at –15 °C. An ice cold 1 M solution of HCl (6 ml) was added and the reaction extracted with dichloromethane (3 × 30 ml). The organic phase was washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and solvent removed by rotary evaporation to yield a crude orange residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 1:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (584 mg, 46 %), Mp 135-137 °C; $[\alpha]_D$ – 70.4 [*c* = 1.04 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1693 (NCO), 1745 (CO), (aliphatic CH) and 3345 (NH); δ_H (400 MHz, DMSO, 80 °C) 1.42 (9 H, s, $CO_2C(CH_3)_3$), 1.47 (9 H, s, $CO_2C(CH_3)_3$), 1.72 (9 H, s, $CO_2C(CH_3)_3$), 1.93 (3 H, s, CH_3), 2.50-2.52 (1 H, m,

CH*(H)*CHCO), 2.89 (1 H, dd, *J* 4.8, 16.4 Hz, CHCH*(H)*Ph), 3.00-3.18 (4 H, m, CH*(H)*CHCO, CHCH*(H)*Ph and ArCH_2CHN), 3.58 (3 H, s, OCH_3), 4.29 (2 H, m, C*H*CO_2CH_3 and CH_2C*H*CO), 4.68-4.69 (1 H, m, ArCH_2C*H*N), 7.22-7.35 (7 H, m, Ar*H*), 7.51 (1 H, d, *J* 7.8 Hz Ar*H*), 7.99 (1 H, d, *J* 7.8 Hz, Ar*H*) and 8.52 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 80 °C) 22.5 (CH_2), 27.1 (CH_3), 28.3 ($CO_2C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 28.5 ($CO_2C(CH_3)_3$), 36.0 (CH_2), 38.0 (CH_2), 51.9 (OCH_3), 52.2 (*C*H), 54.4 (*C*H), 59.8 (*C*H), 61.8 (*C*), 80.4 (*C*), 81.7 (*C*), 85.4 (*C*), 116.2 (*C*H), 116.5 (*C*), 118.9 (*C*H), 123.3 (*C*H), 125.2 (*C*H), 126.9 (*C*H), 128.6 (*C*), 128.7 (*C*H), 128.7 (*C*H), 129.5 (*C*H), 129.5 (*C*H), 136.2 (*C*), 137.6 (*C*), 138.8 (*C*), 150.0 (*C*O), 154.5 (*C*O), 154.5 (*C*O), 168.6 (*C*O), 172.0 (*C*O) and 172.1 (*C*O); MS (ES) *m/z* 776 [MH^+, 100 %] (MH^+, 776.3909. $C_{41}H_{53}N_5O_{10}$ requires 776.3871).

3.4.4. The *Syn*-Indolizino[8,7-*b*]indole Polypeptide

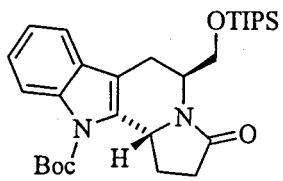
(5*S*,11b*R*)-5-Triisopropylsilanyloxymethyl-1,2,5,6,11,11b-hexahydro-indolizino [8,7-*b*]indol-3-one (107).



Imidazole (529 mg, 7.76 mmol) followed by (5*S*,11b*R*)-5-hydroxymethyl-1,2,5,6,11, 11b-hexahydro-indolizino[8,7-*b*]indol-3-one **(21)** (995 mg, 3.88 mmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (30 ml) under nitrogen. To this solution, triisopropylsilylchloride (1.12 g, 1.25 ml, 5.82 mmol) was added and the solution was stirred at room temperature for 6.5 h. The resulting mixture was filtered to remove the solid phase and concentrated under reduced pressure. The green residue was then dissolved in dichloromethane (20 ml) and washed with water (3 × 30 ml), dried over anhydrous magnesium sulfate and evaporated to a blue oil. The crude product was chromatographed using silica gel as absorbent and 2:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a blue oil (1.57 g, 98 %), $[\alpha]_D$ + 80.4 [*c* = 1.06 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1674 (NCO), 2941 (aliphatic CH) and 3262 (NH); δ_H (400 MHz, $CDCl_3$) 0.94-1.03 (18 H, m, Si(CH(CH_3)$_2$)$_3$), 1.05 (3 H, s,

Si(C*H*$(CH_3)_2)_3$), 1.90-1.98 (1 H, m, CH*(H)*CH_2CO), 2.48-2.65 (3 H, m, CH*(H)*CH_2CO and CH_2CH_2CO), 2.87 (1 H, d, *J* 15.6 Hz, ArCH*(H)*CHN), 2.96 (1 H, ddd, *J* 2.4, 6.8, 16.0 Hz, ArCH*(H)*CHN), 3.74 (2 H, d, *J* 7.6 Hz, CH_2OSi), 4.83 (1 H, dd, *J* 6.8, 14.0 Hz, $ArCH_2CHN$), 4.89-4.93 (1 H, m, NC*H*Ar), 7.12 (1 H, dt, *J* 1.2, 7.8 Hz, Ar*H*), 7.18 (1 H, dt, *J* 1.2, 7.8 Hz, Ar*H*), 7.34 (1 H, d, *J* 7.8 Hz, Ar*H*), 7.49 (1 H, d, *J* 7.8 Hz, Ar*H*) and 8.23 (1 H, br, s, N*H*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*H$(CH_3)_2)_3$), 17.9 (Si(CH(*C*$H_3)_2)_3$), 21.5 (*C*H_2), 25.9 (*C*H_2), 31.8 (*C*H_2), 48.3 (*C*H), 51.6 (*C*H), 62.6 (*C*H_2), 106.7 (*C*), 111.0 (*C*H), 118.5 (*C*H), 119.8 (*C*H), 122.1 (*C*H), 127.2 (*C*), 132.2 (*C*), 136.4 (*C*) and 173.5 (*C*O); MS (EI) *m/z* 412 [M^+, 32.6 %] (M^+, 412.2544. $C_{24}H_{36}N_2O_2Si$ requires 412.2546).

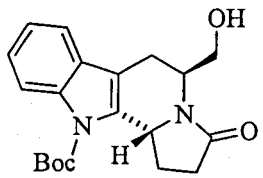
(5*S*,11b*R*)-3-Oxo-5-triisopropylsilanyloxymethyl-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (108).



(5*S*,11b*R*)-5-Triisopropylsilanyloxymethyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*] indol-3-one **(107)** (1.76 g, 4.27 mmol) was dissolved in anhydrous tetrahydrofuran (50 ml) under nitrogen. Triethylamine (863 mg, 1.19 ml, 8.53 mmol), 4-dimethylaminopyridine (104 mg, 0.853 mmol) and di-*tert*-butyl dicarbonate (1.12 g, 5.13 mmol) were added successively and the resultant solution was stirring overnight. The volatiles were removed by evaporation and the orange residue was dissolved in ethyl acetate, which was washed successively with saturated ammonium chloride (2 × 20 ml), saturated sodium bicarbonate (2 × 20 ml) and saturated brine (20 ml). The organic phase was then dried over anhydrous magnesium sulfate and the solvent removed under pressure to yield a green residue, which was chromatographed using silica gel as absorbent and 3:1 light petroleum/ethyl acetate as eluent to isolate the target compound as a green oil (1.60 g, 73 %), $[\alpha]_D$ + 91.2 [*c* = 1.11 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1698 (NCO), 1731 (CO), 2938 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 0.92-0.99 (21 H, m, Si(CH(C$H_3)_2)_3$ and Si(C*H*$(CH_3)_2)_3$), 1.70 (9 H, s, $CO_2C(CH_3)_3$), 1.79-1.85 (1 H, m, CH*(H)*CH_2CO), 2.43 (1 H, ddd, *J* 1.6, 9.6, 16.8 Hz,

$CH_2CH(H)CO$), 2.54-2.64 (1 H, m, $CH_2CH(H)CO$), 2.85-2.92 (3 H, m, $CH(H)CH_2CO$ and $ArCH_2CHN$), 3.77 (2 H, d, *J* 6.8 Hz, CH_2OSi), 4.82-4.85 (1 H, m, $ArCH_2CHN$), 5.17-5.21 (1 H, m, NC*H*Ar), 7.25 (1 H, dt, *J* 1.2, 7.4 Hz, Ar*H*), 7.31 (1 H, dt, *J* 1.2, 7.4 Hz, Ar*H*), 7.43 (1 H, d, *J* 8.0 Hz, Ar*H*) and 8.04 (1 H, d, *J* 8.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 11.9 ($Si(CH(CH_3)_2)_3$), 17.9 ($Si(CH(CH_3)_2)_3$), 21.9 (CH_2), 27.3 (CH_2), 28.2 ($CO_2C(CH_3)_3$), 31.4 (CH_2), 47.3 (*C*H), 54.1 (*C*H), 62.6 (CH_2), 84.3 (*C*), 113.6 (*C*), 115.5 (*C*H), 118.4 (*C*H), 122.9 (*C*H), 124.5 (*C*H), 129.2 (*C*), 134.0 (*C*), 135.8 (*C*), 150.0 (*C*O) and 174.0 (*C*O); MS (EI) *m/z* 512 [M^+, 6.1 %] (M^+, 512.3078. $C_{29}H_{44}N_2O_4Si$ requires 512.3070).

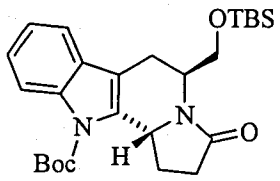
(5*S*,11b*R*)-5-Hydroxymethyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*] indole-11-carboxylic acid *tert*-butyl ester (110).



To a solution of the (5*S*,11b*R*)-3-oxo-5-triisopropylsilanyloxymethyl-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(108)** (1.0 g, 1.95 mmol) in tetrahydrofuran (30 ml) was added tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 1.95 ml, 1.95 mmol) and the reaction stirred for 10 min at room temperature. The resultant solution was concentrated and chromatographed through a pad of silica gel using ethyl acetate as eluent to yield the target compound as a green solid (502 mg, 72 %), Mp 77-78 °C; $[\alpha]_D$ + 264.0 [*c* = 1.05 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1673 (NCO), 1732 (CO), 2976 (aliphatic CH) and 3368 (OH); δ_H (400 MHz, $CDCl_3$) 1.70 (9 H, s, $CO_2C(CH_3)_3$), 1.79-1.88 (1 H, m, $CH(H)CH_2CO$), 2.47 (1 H, ddd, *J* 1.6, 9.6, 16.8 Hz, $CH_2CH(H)CO$), 2.62-2.72 (1 H, m, $CH_2CH(H)CO$), 2.77 (1 H, dd, *J* 1.6, 16.8 Hz, $ArCH(H)CHN$), 2.89-2.97 (2 H, m, $CH(H)CH_2CO$ and $ArCH(H)CHN$), 3.67-3.70 (2 H, m, CH_2OH), 4.85 (1 H, dd, *J* 7.2, 15.6 Hz, $ArCH_2CHN$), 5.23-5.27 (1 H, m, NC*H*Ar), 7.23-7.27 (1 H, m, Ar*H*), 7.30-7.34 (1 H, m, Ar*H*), 7.41-7.43 (1 H, m, Ar*H*) and 8.03 (1 H, d, *J* 8.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.1 (CH_2), 27.1 (CH_2), 28.2 ($CO_2C(CH_3)_3$), 31.4 (CH_2), 48.0 (*C*H), 53.7 (*C*H), 61.6 (CH_2), 84.5 (*C*), 113.2 (*C*), 115.5 (*C*H), 118.4 (*C*H), 123.0 (*C*H), 124.7 (*C*H), 128.9 (*C*),

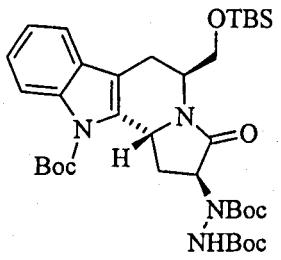
133.6 (*C*), 135.8 (*C*), 149.9 (*C*O) and 175.3 (*C*O); MS (EI) *m/z* 356 [M^+, 1.1 %] (M^+, 356.1729. $C_{20}H_{24}N_2O_4$ requires 356.1736).

(5*S*,11b*R*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (111).



Imidazole (472 mg, 6.94 mmol) and 4-dimethylaminopyridine (65 mg, 0.534 mmol) followed by (5*S*,11b*R*)-5-hydroxymethyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino [8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(110)** (1.90 g, 5.34 mmol) was dissolved in anhydrous dichloromethane (20 ml) under a nitrogen atmosphere. To this solution, *tert*-butyldimethylsilylchloride (1.01 g, 6.67 mmol) was added and the solution stirred at room temperature for 4 h. The resulting mixture was filtered to remove the solid phase and concentrated under reduced pressure. The crude product was chromatographed using silica gel as absorbent and 3:1 light petroleum/ethyl acetate as eluent to isolate the target compound as a green solid (2.14 g, 85 %), Mp 75-76 °C; $[\alpha]_D$ + 102.3 [*c* = 1.00 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1697 (NCO), 1731 (CO) and 2951 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) –0.03 (3 H, s, SiC*H*$_3$), –0.02 (3 H, s, SiC*H*$_3$), 0.80 (9 H, s, SiC(C*H*$_3$)$_3$), 1.70 (9 H, s, $CO_2C(CH_3)_3$), 1.79-1.84 (1 H, m, CH*(H)*CH_2CO), 2.38-2.43 (1 H, m, CH_2CH*(H)*CO), 2.52-2.62 (1 H, m, CH_2CH*(H)*CO), 2.80-2.92 (3 H, m, ArC*H*$_2$CHN and CH*(H)*CH_2CO), 3.67 (2 H, d, *J* 6.8 Hz, C*H*$_2$OSi), 4.76-4.83 (1 H, m, $ArCH_2CHN$), 5.14-5.20 (1 H, m, NC*H*Ar), 7.23-7.33 (2 H, m, Ar*H*), 7.42-7.44 (1 H, m, Ar*H*) and 8.03 (1 H, d, *J* 8.0 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) –5.5 (SiCH$_3$), –5.5 (SiCH$_3$), 18.0 (*C*), 22.0 (*C*H$_2$), 25.7 (SiC(*C*H$_3$)$_3$), 27.2 (*C*H$_2$), 28.2 ($CO_2C(CH_3)_3$), 31.4 (*C*H$_2$), 47.1 (*C*H), 54.1 (*C*H), 62.2 (*C*H$_2$), 84.3 (*C*), 113.6 (*C*), 115.4 (*C*H), 118.3 (*C*H), 122.9 (*C*H), 124.5 (*C*H), 129.2 (*C*), 134.0 (*C*), 135.8 (*C*), 150.0 (*C*O) and 173.9 (*C*O); MS (EI) *m/z* 470 [M^+, 7.3 %] (M^+, 470.2609. $C_{26}H_{38}N_2O_4Si$ requires 470.2601).

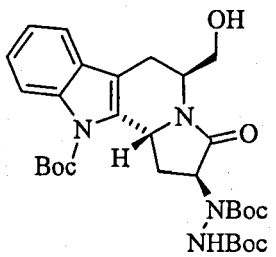
(2*S*,5*S*,11b*R*)-2-*N*,*N'*-Bis-(3,3-*tert*-butyl ester)-hydrazino-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (112).



n-Butyl lithium (1.67 ml, 4.17 mmol) was added dropwise to a stirred solution of diisopropylamine (0.42 mg, 0.58 ml, 4.17 mmol) in anhydrous tetrahydrofuran (15 ml) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 20 min then cooled to −78 °C. (5*S*,11b*R*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-3-oxo-1,2,3,5,6,11b-hexa hydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(111)** (1.40 g, 2.98 mmol) in anhydrous tetrahydrofuran (15 ml) was added dropwise and reaction stirred for 20 min at −78 °C. Di-*tert*-butyl azodicarboxylate (891 mg, 3.87 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise at −78 °C and reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride and product was extracted with ethyl acetate (3 × 40 ml). Organic phase was then dried over anhydrous magnesium sulfate and solvent removed on the rotary evaporator to yield the target compound as a 6:1 mixture of diastereoisomers, which were purified by column chromatography using silica gel as absorbent and 7:2 light petroleum/ethyl acetate as eluent (1.79 g, 86 %), Mp 74-75 °C; $[\alpha]_D$ + 78.1 [*c* = 1.05 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1708 (NCO), 1732 (CO), 2929 (aliphatic CH) and 3261 (NH); δ_H (400 MHz, DMSO, 100 °C) –0.07 (3 H, s, SiC*H*$_3$), –0.04 (3 H, s, SiC*H*$_3$), 0.58 (9 H, s, SiC(C*H*$_3$)$_3$), 1.44 (9 H, s, $CO_2C(CH_3)_3$), 1.46 (9 H, s, $CO_2C(CH_3)_3$), 1.67 (9 H, s, $CO_2C(CH_3)_3$), 2.14-2.28 (1 H, m, CH*(H)*CHCO), 2.80-2.86 (2 H, m, ArC*H*$_2$CHN), 2.90-3.00 (1 H, m, CH*(H)*CHCO), 3.72-3.80 (2 H, m, C*H*$_2$OSi), 4.46-4.56 (1 H, m, CH_2CHCO), 4.57-4.65 (1 H, m, $ArCH_2CHN$), 5.21 (1 H, t, *J* 6.8 Hz, NC*H*Ar), 7.23 (1 H, t, *J* 7.6 Hz, Ar*H*), 7.30 (1 H, t, *J* 7.2 Hz, Ar*H*), 7.45 (1 H, d, *J* 7.2 Hz, Ar*H*), 8.01 (1 H, d, *J* 8.0 Hz, Ar*H*) and 8.39 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 100 °C) –5.27 (SiCH$_3$), –5.25 (SiCH$_3$), 18.0 (*C*), 22.2 (CH_2), 26.0 (SiC(CH$_3$)$_3$), 28.2 ($CO_2C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 28.5 ($CO_2C(CH_3)_3$), 31.0 (CH_2), 48.0 (CH), 52.7 (CH), 60.1 (CH),

63.6 (CH_2), 80.3 (*C*), 81.1 (*C*), 84.9 (*C*), 113.9 (*C*), 115.5 (*C*H), 118.6 (*C*H), 123.2 (*C*H), 124.7 (*C*H), 129.3 (*C*), 134.8 (*C*), 136.2 (*C*), 149.8 (*C*O), 154.5 (*C*O), 156.0 (*C*O) and 169.6 (*C*O); MS (FAB) *m/z* 701 [MH^+, 7.8 %] (MH^+, 701.3936. $C_{36}H_{56}N_4O_8Si$ requires 701.3946).

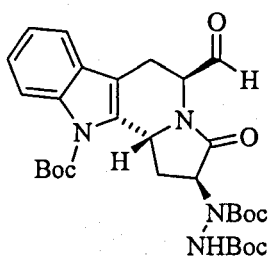
(2*S*,5*S*,11b*R*)-2-*N*,*N'*-Bis-(3,3-*tert*-butyl ester)-hydrazino-5-hydroxymethyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (113).



To a solution of the (2*S*,5*S*,11b*R*)-2-*N*,*N'*-bis-(3,3-*tert*-butyl ester)-hydrazino-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*] indole-11-carboxylic acid *tert*-butyl ester **(112)** (1.65 g, 2.35 mmol) in tetrahydrofuran (40 ml) was added tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 2.53 ml, 2.59 mmol) and the reaction stirred for 20 min at room temperature. The resultant solution was concentrated and chromatographed through a pad of silica gel using 3:1 ethyl acetate/light petroleum as eluent to yield the target compound as a yellow solid (994 mg, 72 %), Mp 129-131 °C; $[\alpha]_D$ + 117.6 [*c* = 1.01 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1704 (NCO), 1732 (CO), 2931 (aliphatic CH), 3261 (NH) and 3404 (OH); δ_H (400 MHz, DMSO, 80 °C) 1.44 (9 H, s, $CO_2C(CH_3)_3$), 1.47 (9 H, s, $CO_2C(CH_3)_3$), 1.68 (9 H, s, $CO_2C(CH_3)_3$), 2.14-2.29 (1 H, m, CH*(H)*CHCO), 2.70-2.78 (1 H, m, ArCH*(H)*CHN), 2.86-2.95 (2 H, m, CH*(H)*CHCO and ArCH*(H)*CHN), 3.46-3.58 (2 H, m, CH_2OH), 4.45-4.60 (3 H, m, $ArCH_2CHN$, CH_2CHCO and O*H*), 5.15 (1 H, t, *J* 6.8 Hz, NC*H*Ar), 7.23-7.27 (1 H, m, Ar*H*), 7.30-7.34 (1 H, m, Ar*H*), 7.48 (1 H, d, *J* 8.0 Hz, Ar*H*), 8.02 (1 H, d, *J* 8.0 Hz, Ar*H*) and 8.66 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 80 °C) 21.9 (CH_2), 28.2 ($CO_2C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 28.5 ($CO_2C(CH_3)_3$), 30.9 (CH_2), 48.6 (*C*H), 51.9 (*C*H), 60.4 (*C*H), 60.4 (CH_2), 80.2 (*C*), 80.9 (*C*), 85.0 (*C*), 113.7 (*C*), 115.5 (*C*H), 118.9 (*C*H), 123.2 (*C*H), 124.8 (*C*H), 129.3 (*C*),

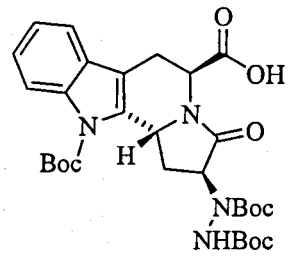
134.6 (*C*), 136.1 (*C*), 149.8 (*CO*), 154.5 (*CO*), 156.0 (*CO*) and 169.7 (*CO*); MS (FAB) *m/z* 587 [MH^+, 20.1 %] (MH^+, 587.3087. $C_{30}H_{42}N_4O_8$ requires 587.3081).

(2*S*,5*S*,11b*R*)-3-*N*,*N'*-Bis-(3,3-*tert*-butyl ester)-hydrazino-5-formyl-3-oxo-1,2,3,5,6, 11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (114).



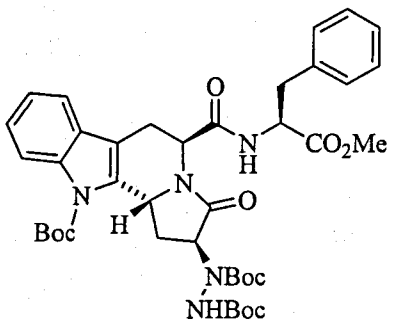
o-Iodoxybenzoic acid (964 mg, 3.47 mmol) was added to a solution of (2*S*,5*S*,11b*R*)-2-*N*,*N'*-bis-(3,3-*tert*-butyl ester)-hydrazino-5-hydroxymethyl-3-oxo-1,2,3,5,6,11b-hexa hydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(113)** (678 mg, 1.16 mmol) in ethyl acetate (30 ml) and the reaction was heated under reflux for 5 h. The resulting mixture was cooled to room temperature, filtered through a sinter funnel and evaporated to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3:1 light petroleum/ethyl acetate as eluent to isolate the target compound as a yellow solid (633 mg, 94 %), Mp 127-129 °C; $[\alpha]_D$ + 663.3 [*c* = 1.20 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1700 (NCO), 1731 (CO), 2931 (aliphatic CH) and 3279 (NH); δ_H (400 MHz, DMSO, 80 °C) 1.46 (9 H, s, $CO_2C(CH_3)_3$), 1.48 (9 H, s, $CO_2C(CH_3)_3$), 1.68 (9 H, s, $CO_2C(CH_3)_3$), 2.23-2.31 (1 H, m, CH*(H)*CHCO), 2.87 (1 H, ddd, *J* 2.4, 7.2, 16.4 Hz, ArCH*(H)*CHN), 2.95-3.02 (1 H, m, CH*(H)*CHCO), 3.33 (1 H, d, *J* 16.4 Hz, ArCH*(H)*CHN), 4.44-4.63 (1 H, m, CH_2CHCO), 5.22 (1 H, d, *J* 6.8 Hz, $ArCH_2CHN$), 5.35 (1 H, t, *J* 8.0 Hz, NC*H*Ar), 7.27 (1 H, dt, *J* 0.8, 7.6 Hz, Ar*H*), 7.33 (1 H, dt, *J* 1.2, 7.2 Hz, Ar*H*), 7.54 (1 H, d, *J* 7.6 Hz, Ar*H*), 8.01 (1 H, d, *J* 8.4 Hz, Ar*H*), 8.74 (1 H, br, s, N*H*) and 9.64 (1 H, s, C*H*O); δ_C (100 MHz, DMSO, 80 °C) 20.3 (CH_2), 28.2 ($CO_2C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 28.5 ($CO_2C(CH_3)_3$), 31.1 (CH_2), 52.7 (*C*H), 56.0 (*C*H), 72.5 (*C*H), 80.3 (*C*), 81.1 (*C*), 85.2 (*C*), 113.4 (*C*), 115.5 (*C*H), 119.0 (*C*H), 123.3 (*C*H), 125.1 (*C*H), 128.7 (*C*), 128.7 (*C*), 134.6 (*C*), 149.7 (*CO*), 149.7 (*CO*), 149.7 (*CO*), 170.6 (*CO*) and 200.1 (*C*HO); MS (FAB) *m/z* 585 [MH^+, 4.2 %] (MH^+, 585.2911. $C_{30}H_{40}N_4O_8$ requires 585.2924).

(2*S*,5*S*,11b*R*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazide-3-oxo-1,2,3,5,6,11b-hexa hydro-indolizino[8,7-*b*]indole-5,11-dicarboxylic acid 11-*tert*-butyl ester (115).



A solution of (2*S*,5*S*,11b*R*)-3-*N*,*N*'-bis-(3,3-*tert*-butyl ester)-hydrazino-5-formyl-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester **(114)** (594 mg, 1.02 mmol) in acetonitrile (13 ml), *tert*-butanol (42 ml) and 1-methyl-1-cyclohexene (13 ml) was stirred rapidly as it cooled to 0 °C. A solution of sodium chlorite (884 g, 7.82 mmol) and sodium dihydrogen phosphate (853 g, 7.11 mmol) in water (26 ml) was added dropwise over a 10 min period and the reaction stirred at room temperature for 17 h. The reaction mixture was added to a solution of saturated brine/ethyl acetate (1:1) (50 ml) and product extracted with ethyl acetate (3 × 40 ml). Organics were combined and washed with a 1 M solution of sodium hydrosulfite, dried over anhydrous magnesium sulfate, filtered and evaporated to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 2:1 light petroleum/ethyl acetate as eluent to produce a yellow solid (517 mg, 85 %), Mp 125-126 °C; $[\alpha]_D$ + 62.1 [*c* = 1.03 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1698 (NCO), 1737 (CO), 2980 (aliphatic CH), 3288 (NH) and 3409 (OH); δ_H (400 MHz, DMSO, 80 °C) 1.44 (9 H, s, $CO_2C(CH_3)_3$), 1.47 (9 H, s, $CO_2C(CH_3)_3$), 1.69 (9 H, s, $CO_2C(CH_3)_3$), 2.18-2.32 (1 H, m, CH*(H)*CHCO), 2.84-2.99 (2 H, m, CH*(H)*CHCO and ArCH*(H)*CHN), 3.25 (1 H, d, *J* 16.4 Hz, ArCH*(H)*CHN), 4.58 (1 H, br, s, CH_2CHCO), 5.12 (1 H, br, s, $ArCH_2CHN$), 5.49 (1 H, br, s, NC*H*Ar), 7.25 (1 H, t, *J* 7.2 Hz, Ar*H*), 7.32 (1 H, t, *J* 7.2 Hz, Ar*H*), 7.49 (1 H, d, *J* 7.2 Hz, Ar*H*), 8.01 (1 H, d, *J* 7.2 Hz, Ar*H*) and 8.64 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 80 °C) 24.1 (CH_2), 28.2 ($CO_2C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 28.5 ($CO_2C(CH_3)_3$), 30.5 (CH_2), 50.2 (*C*H), 52.5 (*C*H), 60.0 (*C*H), 80.2 (*C*), 81.0 (*C*), 85.0 (*C*), 113.6 (*C*), 115.5 (*C*H), 118.8 (*C*H), 123.3 (*C*H), 124.9 (*C*H), 128.9 (*C*), 135.0 (*C*), 135.9 (*C*), 149.7 (*C*O), 154.5 (*C*O), 156.1 (*C*O), 170.0 (*C*O) and 172.0 (*C*O); MS (FAB) *m/z* 601 [MH^+, 2.0 %] (MH^+, 601.2863. $C_{30}H_{42}N_4O_9$ requires 601.2874).

(2*S*,5*S*,11b*R*,1'*S*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazide-5-(1-methoxycarbonyl -2-phenyl-ethylcarbamoyl)-3-oxo-1,2,3,5,6,11b-hexahydro-indolizino[8,7-*b*]indole-11-carboxylic acid *tert*-butyl ester (116).

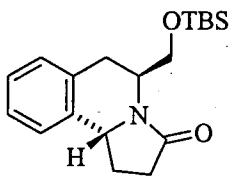


(2*S*,5*S*,11b*R*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazide-3-oxo-1,2,3,5,6,11b-hexa hydro-indolizino[8,7-*b*]indole-5,11-dicarboxylic acid 11-*tert*-butyl ester **(115)** (429 mg, 0.714 mmol) was dissolved in anhydrous dichloromethane (5 ml) and cooled to –15 °C under a nitrogen atmosphere. 1-Hydroxyazabenzotriazole (107 mg, 0.786 mmol) and 1-ethyl-3-[(dimethylamino)propyl]carbodiimide hydrochoride (151 mg, 0.786 mmol) were added and reaction stirred for 20 min at –15 °C. *N*-methyl morpholine (80 mg, 0.09 ml, 0.786 mmol) and *L*-phenylalanine methyl ester hydrochloride **(97)** (170 mg, 0.786 mmol) were added and reaction stirred for a further 3 h at –15 °C. An ice cold 1 M solution of HCl (3 ml) was added and reaction extracted with dichloromethane (3 × 10 ml). The organic phase was washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and solvent removed by rotary evaporation to yield a crude orange residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 1:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (350 mg, 64 %), Mp 130-133 °C; $[\alpha]_D$ + 50.0 [*c* = 1.44 in $CHCl_3$]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1686 (NCO), 1736 (CO), 2931 (aliphatic CH) and 3343 (NH); δ_H (400 MHz, DMSO, 80 °C) 1.47 (9 H, s, $CO_2C(CH_3)_3$), 1.48 (9 H, s, $CO_2C(CH_3)_3$), 1.69 (9 H, s, $CO_2C(CH_3)_3$), 2.18-2.26 (1 H, m, CH*(H)*CHCO), 2.75-2.79 (1 H, m, ArCH*(H)*CHN), 2.96-3.05 (2 H, m, CH*(H)*CHCO and CHCH*(H)*Ph), 3.17 (1 H, dd, *J* 5.6, 14.0 Hz, CHCH*(H)*Ph), 3.37 (1 H, d, *J* 15.6 Hz, ArCH*(H)*CHN), 3.56 (3 H, s, OCH_3), 4.42-4.55 (2 H, m, CH_2CHCO and $CHCO_2CH_3$), 5.13 (1 H, d, *J* 6.8 Hz, $ArCH_2CHN$), 5.31-5.37 (1 H, br, m, NC*H*Ar), 7.08-7.16 (5 H, m, Ar*H*), 7.25 (1 H, t, *J* 6.8 Hz, Ar*H*), 7.32 (1 H, t, *J* 7.2 Hz, Ar*H*), 7.48 (1 H, d, *J* 7.6 Hz,

Ar*H*), 7.92 (1 H, br, s, N*H*), 8.01 (1 H, d, *J* 8.0 Hz, Ar*H*) and 9.05 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 80 °C) 22.3 (*C*H_2), 28.2 ($CO_2C(CH_3)_3$), 28.4 ($CO_2C(CH_3)_3$), 28.5 ($CO_2C(CH_3)_3$), 31.4 (*C*H_2), 37.4 (*C*H_2), 49.9 (*C*H), 52.2 (OCH_3), 53.1 (*C*H), 54.6 (*C*H), 60.1 (*C*H), 80.3 (*C*), 81.4 (*C*), 85.1 (*C*), 113.5 (*C*), 115.5 (*C*H), 118.9 (*C*H), 123.3 (*C*H), 124.9 (*C*H), 126.7 (*C*H), 128.6 (*C*H), 128.6 (*C*H), 128.9 (*C*), 129.1 (*C*H), 129.1 (*C*H), 134.3 (*C*), 135.9 (*C*), 137.8 (*C*), 149.6 (*C*O), 154.8 (*C*O), 155.8 (*C*O), 169.1 (*C*O), 170.5 (*C*O) and 171.8 (*C*O); MS (FAB) *m/z* 762 [M^+, 3.7 %] (M^+, 762.3705. $C_{40}H_{51}N_5O_{10}$ requires 762.3714).

3.4.5. The *Syn*-Pyrrolo[2,1-*a*]isoquinoline Polypeptide

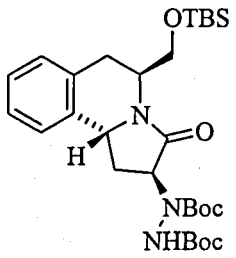
(5*S*,10b*R*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (117).



Imidazole (750 mg, 11.01 mmol), 4-dimethylaminopyridine (104 mg, 0.849 mmol) and (5*S*,10b*R*)-5-(hydroxymethyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*] isoquinolin-3-one (**10**) (1.84 g, 8.45 mmol) were dissolved in anhydrous dichloromethane (20 ml) under nitrogen. To this solution, *tert*-butyldimethylsilylchloride (1.60 g, 10.6 mmol) was added and the solution was stirred at room temperature for 4 h. The resulting mixture was filtered to remove the solid phase and concentrated under reduced pressure. The crude product was chromatographed using silica gel as absorbent and 10 % methanol/dichloromethane as eluent to isolate the target compound as a blue oil (2.88 g, 99 %), $[\alpha]_D$ + 33.0 [*c* = 1.12 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1702 (NCO); δ_H (400 MHz, $CDCl_3$) –0.02 (3 H, s, SiC*H*$_3$), 0.00 (3 H, s, SiC*H*$_3$), 0.82 (9 H, s, SiC(C*H*$_3$)$_3$), 1.90-2.00 (1 H, m, CH*(H)*CH_2CO), 2.42-2.49 (1 H, m, CH_2CH*(H)*CO), 2.54-2.70 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.89 (1 H, dd, *J* 3.2, 16.4 Hz, ArCH*(H)*CHN), 3.02 (1 H, dd, *J* 6.8, 16.4 Hz, ArCH*(H)*CHN), 3.65 (1 H, dd, *J* 5.8, 10.4 Hz, CH*(H)*OSi), 3.74 (1 H, dd, *J* 6.2, 10.4 Hz, CH*(H)*OSi), 4.46-4.51 (1 H, m, ArCH_2C*H*N), 4.79 (1 H, t, *J* 8.0 Hz, NC*H*Ar) and 7.10-7.28 (4 H, m, Ar*H*); δ_C (100

MHz, $CDCl_3$) –5.57 ($SiCH_3$), –5.50 ($SiCH_3$), 18.0 (*C*), 25.7 ($SiC(CH_3)_3$), 26.9 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 48.0 (*C*H), 54.8 (*C*H), 62.7 (CH_2), 124.2 (*C*H), 126.5 (*C*H), 127.0 (*C*H), 129.2 (*C*H), 132.8 (*C*), 137.1 (*C*) and 173.7 (*C*O); MS (EI) *m/z* 331 [M^+, 22.1 %] (M^+, 331.1963. $C_{19}H_{29}NO_2Si$ requires 331.1968).

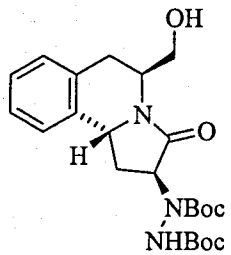
(2*S*,5*S*,10b*R*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (118).



n-Butyl lithium (4.3 ml, 10.6 mmol) was added dropwise to a stirred solution of diisopropylamine (1.09 g, 1.51 ml, 10.6 mmol) in anhydrous tetrahydofuran (15 ml) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 15 min then cooled to –78 °C. (5*S*,10b*R*)-5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-1,5,6,10b-tetrahydro-2*H*-pyrrolo [2,1-*a*]isoquinolin-3-one **(117)** (2.55 g, 7.68 mmol) in anhydrous tetrahydofuran (20 ml) was added dropwise and the reaction stirred for 15 min at –78 °C. Di-*tert*-butyl azodicarboxylate (2.30 g, 9.98 mmol) in anhydrous tetrahydofuran (15 ml) was then added dropwise at –78 °C and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated ammonium chloride and the product was extracted with ethyl acetate (3 × 60 ml). The organic phase was then dried over anhydrous magnesium sulfate and the solvent removed on the rotary evaporator to yield the target compound as a 15:1 mixture of diastereoisomers, which were separated by column chromatography using silica gel as absorbent and 2:1 light petroleum/ethyl acetate as eluent (3.80 g, 88 %), Mp 70-72 °C; $[\alpha]_D$ – 16.3 [*c* = 1.08 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1682 (NCO), 1715 (CO) and 3271 (NH); δ_H (400 MHz, DMSO, 100 °C) 0.01 (3 H, s, $SiCH_3$), 0.02 (3 H, s, $SiCH_3$), 0.85 (9 H, s, $SiC(CH_3)_3$), 1.42 (9 H, s, $CO_2C(CH_3)_3$), 1.45 (9 H, s, $CO_2C(CH_3)_3$), 2.30-2.37 (1 H, m, CH*(H)*CHCO), 2.70-2.76 (1 H, m, CH*(H)*CHCO), 2.85-3.01 (2 H, m, $ArCH_2CHN$), 3.69 (2 H, dd, *J* 6.8, 10.0 Hz, CH*(H)*OSi), 3.79 (2 H, dd, *J* 4.4, 10.0 Hz, CH*(H)*OSi), 4.17-4.20 (1 H, m, $ArCH_2CHN$), 4.55 (1 H, dd, *J* 6.0, 8.4 Hz, CH_2CHCO), 4.76 (1 H, t,

J 7.2 Hz, NC*H*Ar), 7.18-7.25 (4 H, m, Ar*H*) and 8.34 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 100 °C) –6.19 (Si*C*H$_3$), –6.19 (Si*C*H$_3$), 17.1 (*C*), 25.1 (SiC(*C*H$_3$)$_3$), 27.4 (CO$_2$C(*C*H$_3$)$_3$), 27.5 (CO$_2$C(*C*H$_3$)$_3$), 28.4 (*C*H$_2$), 28.9 (*C*H$_2$), 48.2 (*C*H), 51.9 (*C*H), 59.0 (*C*H), 62.8 (*C*H$_2$), 79.1 (*C*), 80.0 (*C*), 123.2 (*C*H), 125.7 (*C*H), 126.2 (*C*H), 128.1 (*C*H), 132.7 (*C*), 136.7 (*C*), 153.5 (*C*O), 155.0 (*C*O) and 168.1 (*C*O); MS (FAB) *m/z* 562 [MH$^+$, 19.5 %] (MH$^+$, 562.3304. $C_{29}H_{47}N_3O_6Si$ requires 562.3312). The Stereochemistry at C-2, C-5 and C-11b was determined by nOe studies.

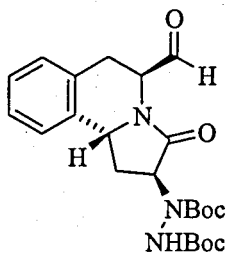
(2*S*,5*S*,10b*R*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-5-hydroxymethyl-1,5,6, 10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (119).



To a solution of (2*S*,5*S*,10b*R*)-2-*N*,*N*'-bis-(3,3-*tert*-butyl ester)-hydrazino-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one **(118)** (1.0 g, 1.78 mmol) in tetrahydrofuran (30 ml) was added tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 1.78 ml, 1.78 mmol) and the reaction stirred for 5 min at room temperature. The resultant solution was concentrated and chromatographed through a pad of silica using 2:1 light petroleum/ethyl acetate as eluent to yield the target compound as a yellow solid (319 mg, 40 %), Mp 92-95 °C; $[\alpha]_D$ + 16.8 [*c* = 1.00 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1697 (CO), 1715 (CO), 2977 (aliphatic CH), 3273 (NH) and 3409 (OH); δ_H (400 MHz, DMSO, 100 °C) 1.45 (9 H, s, CO$_2$C(C*H*$_3$)$_3$), 1.46 (9 H, s, CO$_2$C(C*H*$_3$)$_3$), 2.31-2.35 (1 H, m, CH*(H)*CHCO), 2.72-2.78 (1 H, m, CH*(H)*CHCO), 2.85-3.02 (2 H, m, ArC*H*$_2$CHN), 3.50-3.59 (2 H, m, C*H*$_2$OH), 4.15-4.18 (1 H, m, ArCH$_2$C*H*N), 4.41 (1 H, t, *J* 6.0 Hz, O*H*), 4.53 (1 H, dd, *J* 4.4, 8.4 Hz, CH$_2$C*H*CO), 4.79 (1 H, t, *J* 6.8 Hz, NC*H*Ar), 7.18-7.26 (4 H, m, Ar*H*) and 8.40 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 100 °C) 28.4 (CO$_2$C(*C*H$_3$)$_3$), 28.5 (CO$_2$C(*C*H$_3$)$_3$), 29.4 (*C*H$_2$), 30.3 (*C*H$_2$), 49.9 (*C*H), 52.7 (*C*H), 60.4 (*C*H), 61.7 (*C*H$_2$), 80.3 (*C*), 81.2 (*C*), 124.3 (*C*H), 126.8 (*C*H), 127.3 (*C*H), 129.4 (*C*H), 133.8 (*C*), 137.8

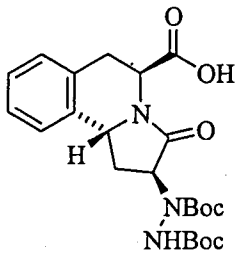
(*C*), 154.6 (*C*O), 156.0 (*C*O) and 164.9 (*C*O); MS (EI) *m/z* 448 [MH^+, 4.3 %] (MH^+, 448.2441. $C_{23}H_{33}N_3O_6$ requires 448.2449).

(2*S*,5*S*,10b*R*)-2-*N*,*N'*-Bis-(3,3-*tert*-butyl ester)-hydrazino-3-oxo-1,2,3,5,6,10b-hexa hydro-pyrrolo[2,1-*a*]isoquinoline-5-carbaldehyde (120)



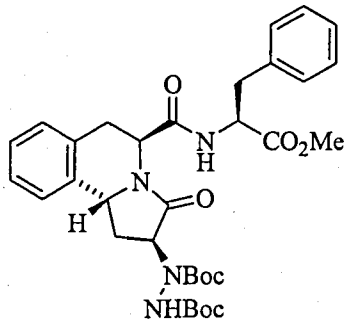
o-Iodoxybenzoic acid (221 mg, 0.794 mmol) was added to a solution of (2*S*,5*S*,10b*R*)-2-*N*,*N'*-bis-(3,3-*tert*-butyl ester)-hydrazino-5-hydroxymethyl-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one **(119)** (237 mg, 0.530 mmol) in dimethyl sulfoxide (20 ml) and the reaction stirred for 24 h at room temperature. The reaction mixture was added to a solution of ethyl acetate/water and product extracted with ethyl acetate (3 × 30 ml). The organic layer was washed with water (3 × 30 ml), dried over anhydrous magnesium sulfate, filtered and evaporated to a crude yellow solid. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 1:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (144 mg, 61 %), Mp 84-87 °C; $[\alpha]_D$ – 8.80 [*c* = 1.00 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1700 (CO), 1700 (CO), 2977 (aliphatic CH) and 3281 (NH); δ_H (400 MHz, DMSO, 100 °C) 1.46 (18 H, s, 2 × $CO_2C(CH_3)_3$), 2.31-2.38 (1 H, m, CH*(H)*CHCO), 2.83-3.07 (2 H, m, CH*(H)*CHCO and ArCH*(H)*CHN), 3.17 (1 H, dd, *J* 4.8, 16.4 Hz, ArCH*(H)*CHN), 4.65 (1 H, dd, *J* 3.2, 9.2 Hz, CH_2CHCO), 4.72 (1 H, dd, *J* 5.2, 7.6 Hz, $ArCH_2CHN$), 4.89 (1 H, t, *J* 7.2 Hz, NC*H*Ar), 7.17-7.36 (4 H, m, Ar*H*), 8.57 (1 H, br, s, N*H*) and 9.64 (1 H, s, C*H*O); δ_C (100 MHz, DMSO, 100 °C) 26.9 (CH_2), 28.4 ($CO_2C(CH_3)_3$), 28.5 ($CO_2C(CH_3)_3$), 31.2 (CH_2), 53.3 (*C*H), 56.7 (*C*H), 60.0 (*C*H), 80.4 (*C*), 81.3 (*C*), 124.7 (*C*H), 127.4 (*C*H), 127.5 (*C*H), 129.1 (*C*H), 132.3 (*C*), 137.4 (*C*), 154.5 (*C*O), 156.0 (*C*O), 170.0 (*C*O) and 200.0 (*C*HO); MS (ES) *m/z* 446 [MH^+, 100 %] (MH^+, 446.2364. $C_{23}H_{31}N_3O_6$ requires 446.2291).

(2*S*,5*S*,10b*R*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-3-oxo-1,2,3,5,6,10b-hexa hydro-pyrrolo[2,1-*a*]isoquinoline-5-carboxylic acid (121).



A solution of (2*S*,5*S*,10b*R*)-2-*N*,*N*'-bis-(3,3-*tert*-butyl ester)-hydrazino-3-oxo-1,2,3,5,6, 10b-hexahydro-pyrrolo[2,1-*a*]isoquinoline-5-carbaldehyde **(120)** (862 mg, 1.94 mmol) in acetonitrile (28 ml), *tert*-butanol (80 ml) and 1-methyl-1-cyclohexene (28 ml) was stirred rapidly as it cooled to 0 °C. A solution of sodium chlorite (1.68 g, 14.9 mmol) and sodium dihydrogen phosphate (1.63 g, 13.5 mmol) in water (55 ml) was added dropwise over a 10 min period and the reaction stirred at room temperature for 17 h. The reaction mixture was added to a solution of saturated brine/ethyl acetate (1:1) (50 ml) and product extracted with ethyl acetate (3 × 50 ml). Organics were combined and washed with a 1 M solution of sodium hydrosulfite, dried over anhydrous magnesium sulfate, filtered and evaporated to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 2:1 light petroleum/ethyl acetate as eluent to produce a yellow solid (713 mg, 80 %). Product still contained impurities which we were unable to remove by chromatography. For this reason, the intermediate carboxylic acid was reacted crude and purified at a later stage.

(2*S*,5*S*,10b*R*,3'*S*)-2-*N*,*N*'-Bis-(3,3-*tert*-butyl ester)-hydrazino-2-[(3-oxo-1,2,3,5,6, 10b-hexahydro-pyrrolo[2,1-*a*]isoquinoline-5-carbonyl)-amino]-3-phenyl-propionic acid methyl ester (122).

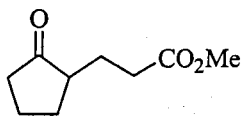


(2*S*,5*S*,10b*R*)-2-*N*,*N'*-Bis-(3,3-*tert*-butyl ester)-hydrazino-3-oxo-1,2,3,5,6,10b-hexa hydro-pyrrolo[2,1-*a*]isoquinoline-5-carboxylic acid **(121)** (713 mg, 1.55 mmol) was dissolved in anhydrous dichloromethane (30 ml) and cooled to –15 °C under nitrogen. 1-Hydroxyazabenzotriazole (231 mg, 1.70 mmol) and 1-ethyl-3-[(dimethylamino) propyl]carbodiimide hydrochoride (326 mg, 1.70 mmol) were added and reaction stirred for 20 min at –15 °C. *N*-methyl morpholine (172 mg, 0.19 ml, 1.70 mmol) and *L*-phenylalanine methyl ester hydrochloride **(97)** (366 mg, 1.70 mmol) were added and reaction stirred for a further 3 h at –15 °C. An ice cold solution of 1 M HCl (6 ml) was added and reaction extracted with dichloromethane (3 × 30 ml). The organic phase was washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and solvent removed by rotary evaporation to yield a crude orange residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 1:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (549 mg, 57 %), Mp 89-92 °C; $[\alpha]_D$ – 28.0 [*c* = 1.10 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1699 (NCO), 1738 (CO), 2977 (aliphatic CH) and 3342 (NH); δ_H (400 MHz, DMSO, 100 °C) 1.48 (18 H, s, 2 × $CO_2C(CH_3)_3$), 2.34 (1 H, ddd, *J* 6.0, 10.0, 13.6 Hz, CH*(H)*CHCO), 2.76-2.82 (1 H, m, CH*(H)*CHCO), 2.91-3.05 (2 H, m, ArCH*(H)*CHN and CHCH*(H)*Ph), 3.07-3.23 (2 H, m, ArCH*(H)*CHN and CHCH*(H)*Ph), 3.60 (3 H, s, OCH_3), 4.48 (1 H, dd, *J* 4.4, 9.6 Hz, CH_2CHCO), 4.59-4.64 (1 H, m, $CHCO_2CH_3$), 4.67-4.72 (1 H, m, NC*H*Ar), 4.76 (1 H, dd, *J* 3.6, 7.2 Hz, $ArCH_2CHN$), 7.05-7.26 (9 H, m, Ar*H*), 7.75 (1 H, d, *J* 8.0 Hz, N*H*) and 8.62 (1 H, br, s, N*H*); δ_C (100 MHz, DMSO, 100 °C) 28.4 ($CO_2C(CH_3)_3$), 28.6 ($CO_2C(CH_3)_3$), 29.8 (CH_2), 30.5 (CH_2), 37.4 (CH_2), 50.8 (CH), 52.1 (OCH_3), 52.9 (CH), 54.1 (CH), 60.9 (CH), 80.4 (C), 81.5 (C), 124.7 (CH), 126.9 (CH), 126.9 (CH), 127.2 (CH), 128.5 (CH), 128.5 (CH), 129.0 (CH), 129.3 (CH), 129.3 (CH), 132.7 (C), 137.4 (C), 137.6 (C), 154.8 (CO), 155.9 (CO), 169.6 (CO), 169.8 (CO) and 171.9 (CO); MS (ES) *m/z* 623 [MH^+, 100 %] (MH^+, 623.3077. $C_{33}H_{42}N_4O_8$ requires 623.3081).

3.5. Application Toward the Synthesis of Cephalotaxine

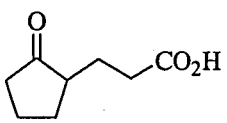
3.5.1. Stereoselective Synthesis of a Tetracyclic Model System

Methyl-3-(2-oxocyclopentyl)-propionate (132).[39]



A solution of cyclopentanone pyrrolidine enamine **(131)** (4.55 g, 33.2 mmol) and methyl acrylate (5.50 g, 63.9 mmol) in dioxane (13 ml) was heated under reflux for 3.5 h. The addition of water (5 ml) and reflux for a further 30 min was followed by the removal of most of the solvent under pressure. The product was extracted with ethyl acetate and washed with a 5 % solution of HCl. The organic phase was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The crude product was purified by distillation to yield a clear yellow oil (4.50 g, 79 %), Bp 130-132 °C, Lit: Bp 127-130 °C; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1739 (CO) and 2954 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.51-2.45 (11 H, m, 5 × C*H*$_2$ and C*H*) and 3.67 (3 H, s, OC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 20.5 (*C*H$_2$), 24.7 (*C*H$_2$), 29.4 (*C*H$_2$), 31.6 (*C*H$_2$), 37.7 (*C*H$_2$), 48.1 (*C*H), 51.4 (O*C*H$_3$), 173.5 (*C*O) and 173.8 (*C*O); MS (EI) *m/z* 170 [M^+, 21.5 %] (M^+, 170.0940. $C_9H_{14}O_3$ requires 170.0943).

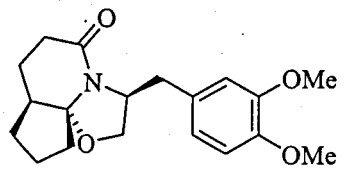
3-(2-Oxo-cyclopentyl)-propionic acid (133).



Methyl 3-(2-oxocyclopentyl)-propionate **(132)** (3.63 g, 21.3 mmol) was dissolved in a mixture of tetrahydrofuran (140 ml) and water (62 ml). Lithium hydroxide (770 mg, 32.0 mmol) was added and mixture stirred for 20 h at room temperature. The reaction mixture was concentrated, re-suspended in water (200 ml) and acidified with a 1 M solution of HCl. The aqueous layer was extracted with ethyl acetate (3 × 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated to a yellow oil (3.29 g,

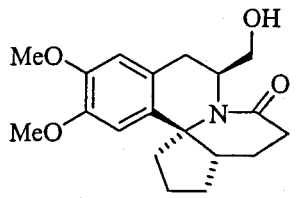
99 %); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1734 (CO), 2959 (aliphatic CH) and 3255 (OH); δ_H (400 MHz, $CDCl_3$) 1.36-2.40 (11 H, m, 5 × C*H*$_2$ and C*H*) and 10.10 (1 H, br, s, O*H*); δ_C (100 MHz, $CDCl_3$) 25.2 (*C*H_2), 25.2 (*C*H_2), 27.3 (*C*H_2), 27.3 (*C*H_2), 31.8 (*C*H_2), 48.4 (*C*H), 175.4 (*C*O) and 221.1 (*C*O); MS (EI) *m/z* 156 [M^+, 30.9 %] (M^+, 156.0785. $C_8H_{12}O_3$ requires 156.0787).

(3*S*,6a*S*,10a*R*)-3-(3,4-Dimethoxy-benzyl)-hexahydro-1-oxa-3a-aza-cyclopenta[*d*] inden-5-one (134).



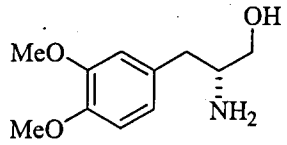
(2*S*)-2-Amino-3-(3,4-dimethyloxy)phenyl)propan-1-ol **(62)** (900 mg, 4.26 mmol) and 3-(2-oxo-cyclopentyl)-propionic acid **(133)** (798 mg, 5.11 mmol) were dissolved in toluene (60 ml) and refluxed under Dean-Stark conditions for 48 h. The reaction was allowed to cool to room temperature and solvent removed by rotary evaporation. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3 % methanol/dichloromethane as eluent to produce the target compound as a yellow oil (1.07 g, 76 %), $[\alpha]_D$ + 80.8 [*c* = 1.00 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1648 (NCO) and 2950 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.37-1.46 (2 H, m, NCCH_2CH*(H)*CH_2 and NCCH_2CH_2CH*(H)*), 1.59-1.66 (2 H, m, NCCH*(H)*CH_2CH_2 and CHCH*(H)*CH_2CO), 1.74-1.81 (2 H, m, NCCH*(H)*CH_2CH_2 and CHCH*(H)*CH_2CO), 1.87-1.90 (1 H, m, NCCH_2CH*(H)*CH_2), 2.01-2.15 (2 H, m, NCCH_2CH_2CH*(H)* and C*H*CH_2CH_2CO), 2.34-2.37 (2 H, m, CHCH_2C*H*$_2$CO), 2.66 (1 H, dd, *J* 10.0, 13.4 Hz, ArCH*(H)*CHN), 3.32 (1 H, dd, *J* 3.6, 13.3 Hz, ArCH*(H)*CHN), 3.69 (1 H, dd, *J* 8.0, 9.1 Hz, ArCH_2CHCH*(H)*O), 3.86 (3 H, s, OC*H*$_3$), 3.88 (3 H, s, OC*H*$_3$), 3.96 (1 H, dd, *J* 7.8, 9.2 Hz, ArCH_2CHCH*(H)*O), 4.39-4.47 (1 H, m, ArCH_2C*H*N) and 6.73-6.80 (3 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (*C*H_2), 24.9 (*C*H_2), 29.3 (*C*H_2), 30.6 (*C*H_2), 36.0 (*C*H_2), 38.8 (*C*H_2), 42.1 (*C*H), 55.9 (O*C*H_3), 55.9 (O*C*H_3), 56.1 (*C*H), 67.2 (*C*H_2), 102.0 (*C*), 111.1 (*C*H), 112.4 (*C*H), 121.3 (*C*H), 129.7 (*C*), 147.7 (*C*), 148.9 (*C*) and 169.6 (*C*O); MS (EI) *m/z* 331 [M^+, 28.5 %] (M^+, 331.1782. $C_{19}H_{25}NO_4$ requires 331.1784).

(5*S*,10b*S*,13a*S*)-5-Hydroxymethyl-8,9-dimethoxy-1,2,5,6,11,12,13,13a-octahydro-cyclopenta[2,3]pyrido[2,1-*a*]isoquinolin-3-one (130).



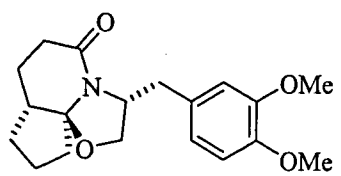
(3*S*,7a*S*,10a*R*)-3-(3,4-Dimethoxy-benzyl)-hexahydro-1-oxa-3a-aza-cyclopenta[*d*]inden-5-one **(134)** (438 mg, 1.32 mmol) was dissolved in anhydrous dichloromethane (25 ml) under nitrogen. The mixture was cooled to –78 °C and titanium tetrachloride (752 mg, 0.43 ml, 3.97 mmol) was added dropwise. After stirring at –78 °C for 10 min, reaction was allowing to warm to room temperature and stirred for 48 h. The reaction mixture was quenched with saturated ammonium chloride (50 ml), extracted with dichloromethane (3 × 50 ml) and dried over anhydrous magnesium sulfate. The product was filtered and the solvent removed by rotary evaporation to yield the target compound as a single diastereoisomer, which were purified by column chromatography using silica gel as absorbent and ethyl acetate as eluent to yield a colourless solid (300 mg, 68 %); Mp 138-141 °C; $[\alpha]_D$ – 136.8 [*c* = 5.00 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1620 (NCO), 2947 (aliphatic CH) and 3376 (OH); δ_H (400 MHz, $CDCl_3$) 1.70-1.82 (5 H, m, $NCCH_2CH_2CH$*(H)*, $NCCH_2CH_2CH_2$ and $CHCH_2CH_2CO$), 1.95-2.02 (1 H, m, $NCCH$*(H)*CH_2CH_2), 2.14-2.25 (2 H, m, $NCCH$*(H)*CH_2CH_2 and $NCCH_2CH_2CH$*(H)*), 2.29-2.36 (1 H, m, $CHCH_2CH$*(H)*CO), 2.52-2.57 (1 H, m, $CHCH_2CH$*(H)*CO), 2.69-2.80 (2 H, m, $CHCH_2CH_2CO$ and $ArCH$*(H)*CHN), 3.24 (1 H, dd, *J* 9.4, 16.2 Hz $ArCH$*(H)*CHN), 3.71-3.75 (2 H, m, CH_2OH), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.07-4.13 (1 H, m, $ArCH_2CHN$), 4.72 (1 H, br, s, O*H*), 6.64 (1 H, s, Ar*H*) and 6.69 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.7 (CH_2), 23.9 (CH_2), 30.1 (CH_2), 30.2 (CH_2), 30.4 (CH_2), 43.1 (CH), 43.9 (CH_2), 55.9 (OCH_3), 56.3 (OCH_3), 56.5 (CH), 63.7 (CH_2), 72.0 (C), 108.5 (CH), 112.0 (CH), 127.9 (C), 134.0 (C), 147.2 (C), 147.9 (C) and 173.1 (CO); MS (EI) *m/z* 331 [M^+, 46.5 %] (M^+, 331.1782. $C_{19}H_{25}NO_4$ requires 331.1784). The product was recrystallised from dichloromethane/hexane *via* vapour diffusion to produce clear, colourless crystals. Relative stereochemistry was confirmed by single crystal X-ray analysis.

(2*R*)-2-Amino-3-(3,4-dimethyloxy)phenyl)propan-1-ol (136).[3]



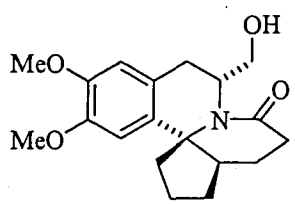
Trimethylsilylchloride (1.54 g, 1.80 ml, 14.2 mmol) was added under nitrogen to a solution of lithium borohydride (2.0 M solution in tetrahydrofuran, 3.55 ml, 7.10 mmol) over a 2 min period. 3-(3,4-Dimethoxyphenyl)-*D*-alanine (800 mg, 3.55 mmol) was cautiously added to the resultant mixture over a 5 min period and the reaction stirred at room temperature for 24 h. Methanol (20 ml) was cautiously added and volatiles were removed by rotary evaporation. The residue was treated with 20 % potassium hydroxide solution and extracted with dichloromethane (3 × 20 ml). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and solvent was evaporated under reduced pressure resulting in a colourless crystalline solid (615 mg, 82 %), Mp 82-83 °C; $[\alpha]_D$ + 21.7 [*c* = 1.27 in EtOH]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 2838 (OCH_3), 2938 (aliphatic CH) and 3385 (OH); δ_H (400 MHz, $CDCl_3$) 2.44 (1 H, dd, *J* 8.8, 13.6 Hz, CH*(H)*$CHNH_2$), 2.62 (3 H, br, s, O*H* and NH_2), 2.73 (1 H, dd, *J* 4.9, 13.5 Hz, CH*(H)*$CHNH_2$), 3.09-3.13 (1 H, m, C*H*NH_2), 3.42 (1 H, dd, *J* 7.1, 10.6 Hz, CH*(H)*OH), 3.63 (1 H, dd, *J* 3.6, 10.7 Hz, CH*(H)*OH), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 6.72-6.75 (2 H, m, Ar*H*) and 6.79-6.81 (1 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 40.5 (CH_2), 54.2 (*C*H), 55.8 (OCH_3), 55.9 (OCH_3), 65.9 (CH_2), 111.3 (*C*H), 112.3 (*C*H), 121.2 (*C*H), 131.2 (*C*), 147.6 (*C*) and 149.0 (*C*); MS (EI) *m/z* 211 [M^+, 1.2 %] (M^+, 211.1134. $C_{11}H_{17}NO_3$ requires 211.1130).

(3*R*,6a*R*,10a*S*)-3-(3,4-Dimethoxy-benzyl)-hexahydro-1-oxa-3a-aza-cyclopenta[*d*] inden-5-one (137).



(2*R*)-2-Amino-3-(3,4-dimethyloxy)phenyl)propan-1-ol **(136)** (584 mg, 2.77 mmol) and 3-(2-oxo-cyclopentyl)-propionic acid **(133)** (518 mg, 3.32 mmol) were dissolved in toluene (60 ml) and refluxed under Dean-Stark conditions for 48 h. The reaction was allowed to cool to room temperature and solvent removed by rotary evaporation. Crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3 % methanol in dichloromethane as eluent to produce a yellow oil (652 mg, 71 %), $[\alpha]_D$ – 86.3 [*c* = 1.05 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1651 (NCO) and 2950 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.37-1.46 (2 H, m, $NCCH_2CH(H)CH_2$ and $NCCH_2CH_2CH(H)$), 1.60-1.66 (2 H, m, $NCCH(H)CH_2CH_2$ and $CHCH(H)CH_2CO$), 1.73-1.80 (2 H, m, $NCCH(H)CH_2CH_2$ and $CHCH(H)CH_2CO$), 1.87-1.91 (1 H, m, $NCCH_2CH(H)CH_2$), 2.01-2.16 (2 H, m, $NCCH_2CH_2CH(H)$ and $CHCH_2CH_2CO$), 2.34-2.37 (2 H, m, $CHCH_2CH_2CO$), 2.67 (1 H, dd, *J* 10.0, 13.4 Hz, $ArCH(H)CHN$), 3.31 (1 H, dd, *J* 3.6, 13.3 Hz, $ArCH(H)CHN$), 3.70 (1 H, dd, *J* 8.0, 9.1 Hz, $ArCH_2CHCH(H)O$), 3.86 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 3.96 (1 H, dd, *J* 7.8, 9.2 Hz, $ArCH_2CHCH(H)O$), 4.39-4.48 (1 H, m, $ArCH_2CHN$) and 6.74-6.81 (3 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.9 (CH_2), 25.0 (CH_2), 29.4 (CH_2), 30.6 (CH_2), 36.1 (CH_2), 38.8 (CH_2), 42.1 (*C*H), 56.0 (OCH_3), 55.9 (OCH_3), 56.2 (*C*H), 67.3 (CH_2), 102.1 (*C*), 111.2 (*C*H), 112.5 (*C*H), 121.3 (*C*H), 129.7 (*C*), 147.7 (*C*), 148.9 (*C*) and 169.8 (*C*O); MS (EI) *m/z* 331 [M^+, 28.5 %] (M^+, 331.1782. $C_{19}H_{25}NO_4$ requires 331.1784).

(5*R*,10b*R*,13a*R*)-5-Hydroxymethyl-8,9-dimethoxy-1,2,5,6,11,12,13,13a-octahydro cyclopenta[2,3]pyrido[2,1-*a*]isoquinolin-3-one (138).

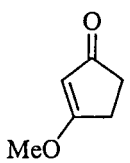


(3*R*,7a*R*,10a*S*)-3-(3,4-Dimethoxy-benzyl)-hexahydro-1-oxa-3a-aza-cyclopenta[*d*]inden-5-one **(137)** (426 mg, 1.29 mmol) was dissolved in dry dichloromethane (25 ml) under nitrogen. The mixture was cooled to –78 °C and titanium tetrachloride (732 mg, 0.43 ml, 3.86 mmol) was dropwise. After stirring at –78 °C for 10 min, reaction was allowing to warm to room temperature and stirred for 48 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 ml), extracted with

dichloromethane (3 × 50 ml) and dried over anhydrous magnesium sulfate. The product was filtered and the solvent removed by rotary evaporation to yield the target compound as a single diastereoisomer, which were purified by column chromatography using silica gel as absorbent and ethyl acetate as eluent to yield a colourless solid (310 mg, 73 %), Mp 138-141 °C; $[\alpha]_D$ + 141.2 [*c* = 1.01 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1621 (NCO), 2947 (aliphatic CH) and 3379 (OH); δ_H (400 MHz, $CDCl_3$) 1.70-1.82 (5 H, m, $NCCH_2CH_2CH(H)$, $NCCH_2CH_2CH_2$ and $CHCH_2CH_2CO$), 1.95-2.02 (1 H, m, $NCCH(H)CH_2CH_2$), 2.14-2.25 (2 H, m, $NCCH(H)CH_2CH_2$ and $NCCH_2CH_2CH(H)$), 2.29-2.36 (1 H, m, $CHCH_2CH(H)CO$), 2.52-2.57 (1 H, m, $CHCH_2CH(H)CO$), 2.69-2.80 (2 H, m, $CHCH_2CH_2CO$ and $ArCH(H)CHN$), 3.24 (1 H, dd, *J* 9.4, 16.2 Hz $ArCH(H)CHN$), 3.71-3.75 (2 H, m, CH_2OH), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.07-4.13 (1 H, m, $ArCH_2CHN$), 4.72 (1 H, br, s, OH), 6.64 (1 H, s, ArH) and 6.69 (1 H, s, ArH); δ_C (100 MHz, $CDCl_3$) 22.7 (CH_2), 23.9 (CH_2), 30.1 (CH_2), 30.2 (CH_2), 30.4 (CH_2), 43.1 (CH), 43.9 (CH_2), 55.9 (OCH_3), 56.3 (OCH_3), 56.5 (CH), 63.7 (CH_2), 72.0 (C), 108.5 (CH), 112.0 (CH), 127.9 (C), 134.0 (C), 147.2 (C), 147.9 (C) and 173.1 (CO); MS (EI) *m/z* 331 [M^+, 46.5 %] (M^+, 331.1784. $C_{19}H_{25}NO_4$ requires 331.1784). The product was recrystallised from dichloromethane/hexane *via* vapour diffusion to produce clear, colourless crystals. The relative stereochemistry was confirmed by single crystal X-ray analysis.

3.5.2. Synthesis of an Appropriate Keto-Acid Substrate

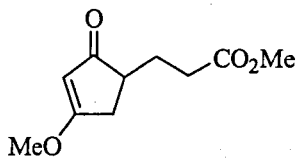
3-Methoxy-cyclopent-2-enone (148).



A mixture of 1,3-cyclopentanedione **(147)** (1.0 g, 10.2 mmol), *p*-toluenesulfonic acid (48 mg, 0.255 mmol), methanol (5 ml) and trimethyl orthoformate (1.08 g, 1.12 ml, 10.2 mmol) was heated under reflux in toluene (30 ml) for 80 min. Solvent was removed under pressure and the resultant residue was dissolved in ethyl acetate. The organic phase was washed with 10 % sodium hydroxide solution (2 × 30 ml) and

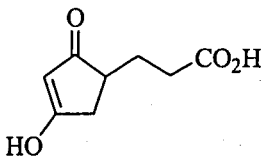
saturated brine (30 ml), dried over magnesium sulfate and evaporated to a brown oil (822 mg, 72 %); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1692 (CO); δ_H (400 MHz, $CDCl_3$) 2.45-2.48 (2 H, m, CH_2CH_2CO), 2.61-2.64 (2 H, m, CH_2CH_2CO), 3.86 (3 H, s, OCH_3) and 5.33 (1 H, t, *J* 1.2 Hz, C=C*H*CO); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_2), 34.3 (CH_2), 58.8 (OCH_3), 104.5 (*C*H), 191.2 (*C*) and 205.9 (*C*O).

3-(4-Methoxy-2-oxo-cyclopent-3-enyl)-propionic acid methyl ester (149).



n-Butyl lithium (5.90 ml, 14.8 mmol) was added dropwise to a stirred solution of diisopropylamine (1.50 g, 2.10 ml, 14.8 mmol) in anhydrous tetrahydrofuran (10 ml) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 15 min then cooled to –78 °C. 3-Methoxy-cyclopent-2-enone **(148)** (663 mg, 5.91 mmol) in dry tetrahydrofuran (10 ml) was added dropwise and reaction stirred for 15 min at –78 °C. Methyl-3-bromopropionate (1.98 g, 1.30 ml, 11.8 mmol) was added dropwise at –78 °C and the reaction allowed to warm to room temperature overnight. The resulting mixture was quenched with saturated ammonium chloride and product was extracted with ethyl acetate (3 × 40 ml). Organic phases were combined and washed with saturated brine (40 ml) and dried over anhydrous magnesium sulfate. Organic phase was then filtered and solvent removed on the rotary evaporator to give the target compound, which was purified by column chromatography using silica gel as absorbent and 1:1 ethyl acetate/light petroleum as eluent to yield a colourless oil (257 mg, 22 %), ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1731 (CO); δ_H (400 MHz, $CDCl_3$) 1.73-1.81 (1 H, m, CH*(H)*$CH_2CO_2CH_3$), 2.05-2.15 (1 H, m, CH*(H)*$CH_2CO_2CH_3$), 2.29 (1 H, ddd, *J* 1.2, 3.2, 17.6 Hz, C=CHCH*(H)*), 2.45 (2 H, t, *J* 7.6 Hz, $CH_2CH_2CO_2CH_3$), 2.50-2.55 (1 H, m, $CHCH_2CH_2CO_2CH_3$), 2.80 (1 H, ddd, *J* 1.2, 7.6, 17.6 Hz, C=CHCH*(H)*), 3.67 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3) and 5.28 (1 H, t, *J* 1.2 Hz, *H*C=$COCH_3$); δ_C (100 MHz, $CDCl_3$) 25.6 (CH_2), 30.5 (CH_2), 33.8 (CH_2), 43.4 (*C*H), 50.7 (OCH_3), 57.8 (OCH_3), 102.6 (H*C*=C), 172.5 ($COCH_3$), 188.7 (*C*O) and 205.9 (*C*O); MS (EI) *m/z* 198 [M^+, 2.0 %] (M^+, 198.0891. $C_{10}H_{14}O_4$ requires 198.0892).

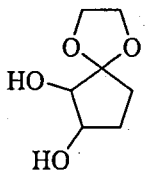
3-(4-Hydroxy-2-oxo-cyclopent-3-enyl)-propionic acid (150).



Methyl 3-(2-oxocyclopentyl)-propionate **(149)** (608 mg, 3.07 mmol) was dissolved in a mixture of tetrahydrofuran (4 ml) and water (2 ml). Lithium hydroxide (322 mg, 7.67 mmol) was added and mixture stirred for 20 h. The mixture was concentrated, re-suspended in water (10 ml) and acidified with a 1 M solution of HCl. The aqueous layer was extracted with ethyl acetate (3 × 10 ml), dried over anhydrous magnesium sulfate, filtered and evaporated to a yellow oil (288 mg, 55 %); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1732 (CO), 2959 (aliphatic CH) and 3281 (OH); δ_H (400 MHz, $CDCl_3$) 1.36-2.40 (7 H, m, 3 × C*H*$_2$ and C*H*), 6.11 (1 H, t, *J* 1.4 Hz, *H*C=COH) and 10.23 (1 H, br, s, O*H*); δ_C (100 MHz, $CDCl_3$) 25.4 (*C*H_2), 31.3 (*C*H_2), 33.8 (*C*H_2), 44.9 (*C*H), 104.0 (H*C*=C), 173.0 (*C*OH), 189.2 (*C*O_2H) and 205.9 (*C*O); MS (FAB) *m/z* 171 [M^+, 19.5 %] (M^+, 171.0653. $C_8H_{10}O_4$ requires 171.0657).

3.5.3. An Alternate Approach Towards a Tetracyclic Diol

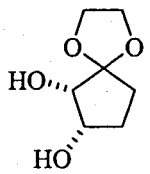
1,4-Dioxa-spiro[4.4]nonane-6,7-diol (162).[44]



2-Cyclopenten-1-one ethylene ketal **(161)** (1.0 g, 0.94 ml, 7.93 mmol) was dissolved in ethanol (48 ml) and cooled to –78 °C. A solution of potassium permanganate (1.25 g, 7.93 mmol) and magnesium sulfate (1.5 g) in water (48 ml) was added rapidly while maintaining the temperature below 0 °C. The reaction was stirred overnight at room temperature then filtered through charcoal. Filtrate was evaporated to a colourless solid, which was dissolved in water (3 ml) and extracted with dichloromethane (3 × 50 ml). Organic phase was dried over magnesium sulfate, filtered and evaporated to a colourless

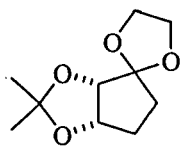
oil (523 mg, 41 %), ν_{max} (thin film, neat)/cm^{-1} 2947 (aliphatic CH) and 3363 (OH); δ_H (400 MHz, $CDCl_3$) 1.73-1.85 (2 H, m, $CH_2CH(H)COO$) and $CH(H)CH_2COO$), 1.91-2.10 (2 H, m, $CH_2CH(H)COO$) and $CH(H)CH_2COO$), 2.46 (1 H, br, s, O*H*), 2.77 (1 H, br, s, O*H*), 3.78 (1 H, d, *J* 4.8 Hz, C*H*(OH)COO), 3.91-4.07 (4 H, m, OCH_2CH_2O) and 4.10-4.14 (1 H, m, C*H*(OH)CH(OH)COO); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_2), 31.6 (CH_2), 64.9 (CH_2), 65.5 (CH_2), 71.4 (*C*H), 75.9 (*C*H) and 114.4 (*C*); MS (FAB) *m/z* 161 [MH^+, 10.9 %] (MH^+, 161.0812. $C_7H_{12}O_4$ requires 161.0814).

(6*S*,7*S*)-1,4-Dioxa-spiro[4.4]nonane-6,7-diol (162).



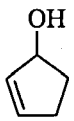
A 500 ml round bottom flask was charged with *tert*-butyl alcohol (150 ml), water (150 ml) and AD-mix-*β* (60.9 g). Stirring at room temperature produced two clear phases; the lower aqueous phase appears bright yellow. Methanesulfonamide (5.79 g, 60.90 mmol) was added and the mixture cooled to 0 °C. 2-Cyclopenten-1-one ethylene ketal **(161)** (5.0 g, 5.10 ml, 60.9 mmol) was added at once and the heterogeneous slurry was stirred vigorously at 0 °C for 25 h. Solid sodium sulfite (36.0 g) was added and the mixture warmed to room temperature for 60 min. The reaction was extracted with ethyl acetate (3 × 80 ml) and organics washed with 2 M potassium hydroxide. The organic layers were combined and dried over magnesium sulfate and concentrated to give the crude diol, which was purified by column chromatography using silica gel as absorbent and ethyl acetate as eluent to yield a colourless oil (6.62 g, 94 %), $[\alpha]_D$ + 6.8 [*c* = 1.12 in CH_2Cl_2]; ν_{max} (thin film, neat)/cm^{-1} 2947 (aliphatic CH) and 3363 (OH); δ_H (400 MHz, $CDCl_3$) 1.70-1.82 (2 H, m, $CH_2CH(H)COO$) and $CH(H)CH_2COO$), 1.88-1.95 (1 H, m, $CH(H)CH_2COO$), 2.04-2.12 (1 H, m, $CH_2CH(H)COO$), 3.38 (2 H, br, s, O*H*), 3.74 (1 H, d, *J* 5.2 Hz, C*H*(OH)COO), 3.93-4.04 (4 H, m, OCH_2CH_2O) and 4.09-4.13 (1 H, m, C*H*(OH)CH(OH)COO); δ_C (100 MHz, $CDCl_3$) 28.5 (CH_2), 31.8 (CH_2), 64.9 (CH_2), 65.6 (CH_2), 71.4 (*C*H), 76.1 (*C*H) and 114.7 (*C*); MS (FAB) *m/z* 161 [MH^+, 22.3 %] (MH^+, 161.0812. $C_7H_{12}O_4$ requires 161.0814).

6,7-Isopropylidene-1,4-dioxa-spiro[4.4]nonane-6,7-diol (164).



1,4-Dioxa-spiro[4.4]nonane-6,7-diol **(162)** (1.16 g, 7.23 mmol) was dissolved in neat dimethoxypropane (7.53 g, 9.0 ml, 72.3 mmol) and boron trifluoride diethyl etherate (103 mg, 0.09 ml, 0.723 mmol) was added. The reaction was stirred for 30 min at room temperature then purified by column chromatography using silica gel as absorbent and 2:1 ethyl acetate/light petroleum as eluent to yield a colourless oil (1.14 g, 79 %), ν_{max} (thin film, neat)/cm^{-1} 2950 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.31 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 1.60-1.64 (1 H, m, CH*(H)*CH_2COO), 1.70-1.82 (2 H, m, CH_2CH_2COO), 2.07-2.18 (1 H, m, CH*(H)*CH_2COO), 3.91-4.08 (5 H, m, OCH_2CH_2O and C*H*(O)COO) and 4.68-4.70 (1 H, m, C*H*(O)CH(O)COO); δ_C (100 MHz, $CDCl_3$) 24.0 (*C*H_3), 26.2 (*C*H_3), 28.2 (*C*H_2), 30.4 (*C*H_2), 64.2 (*C*H_2), 65.6 (*C*H_2), 79.2 (*C*H), 80.9 (*C*H), 110.8 (*C*) and 115.0 (*C*); MS (EI) *m/z* 200 [M^+, 10.7 %] (M^+, 200.1046. $C_{10}H_{16}O_4$ requires 200.1045).

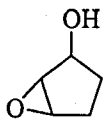
Cyclopent-2-enol (166).[45]



At –78 °C, pre-cooled tetrahydrofuran (48 ml), diisopropylamine (4.81 g, 6.66 ml, 47.6 mmol) and potassium *tert*-butoxide (5.34 g, 47.6 mmol) was consecutively added to *n*-Butyl lithium (19.02 ml, 47.6 mmol). After 15 min of vigorous stirring a homogeneous solution was obtained, to which cyclopentane oxide **(167)** (4.0 g, 4.12 ml, 47.6 mmol) was added. The mixture was allowed to warm to 0 °C and stirred for 90 min. The volatiles were removed by evaporation and the residue treated with water and extracted with hexane (3 × 50 ml). The organics were dried over magnesium sulfate and evaporated to an orange oil (3.54 g, 88 %), ν_{max} (thin film, neat)/cm^{-1} 2952 (aliphatic CH) and 3388 (OH); δ_H (400 MHz, $CDCl_3$) 1.56 (1 H, br, s, OH), 1.66-1.73

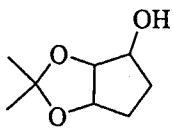
(1 H, m, $CH_2CH(H)CHOH$), 2.21-2.32 (2 H, m, $CH_2CH(H)CHOH$ and $CH(H)CH_2CHOH$), 2.47-2.55 (1 H, m, $CH(H)CH_2CHOH$), 4.88 (1 H, br, d, *J* 4.8 Hz $CHOH$) and 5.83-5.86 (1 H, m, HC=CHCHOH), 5.98-6.01 (1 H, m, HC=CHCH(OH)); δ_C (100 MHz, $CDCl_3$) 31.0 (CH_2), 31.2 (CH), 33.3 (CH_2), 133.3 (CH) and 135.2 (CH).

6-Oxa-bicyclo[3.1.0]hexan-2-ol (167).



Cyclopent-2-enol **(168)** (1.0 g, 11.9 mmol) was dissolved in anhydrous dichloromethane (15 ml). *m*-Chloroperbenzoic acid (77 %) (3.08 g, 17.8 mmol) was dissolved in anhydrous dichloromethane (40 ml) and dried over anhydrous magnesium sulfate. The *m*-chloroperbenzoic acid solution was then added in one portion to the reaction mixture and stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using silica gel treated with triethylamine as absorbent and 2:1 light petroleum/ethyl acetate as eluent to produce a yellow oil (807 mg, 68 %), ν_{max} (thin film, neat)/cm^{-1} 1067 (CO), 2952 (aliphatic CH) and 3388 (OH); δ_H (400 MHz, $CDCl_3$) 1.22-1.32 (1 H, m, $CH_2CH(H)CHOH$), 1.59-1.70 (1 H, m, $CH(H)CH_2CHOH$), 1.94 (1 H, dt, *J* 6.4, 16.4 Hz, $CH_2CH(H)CHOH$), 2.11 (1 H, dd, *J* 8.0, 14.0 Hz, $CH(H)CH_2CHOH$), 2.30 (1 H, d, *J* 7.6 Hz OH), 3.47-3.50 (2 H, m, $(CH)_2O$) and 4.28 (1 H, dd, *J* 7.6, 14.8 Hz $CHOH$); δ_C (100 MHz, $CDCl_3$) 25.9 (CH_2), 27.0 (CH_2), 56.2 (CH), 58.9 (CH) and 73.6 ($CHOH$).

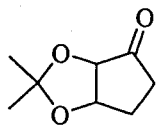
2,2-Dimethyl-tetrahydro-cyclopenta[1,3]dioxol-4-ol (168).



To a stirred solution of 6-oxa-bicyclo[3.1.0]hexan-2-ol **(167)** (3.40 g, 34.0 mmol) in acetone (70 ml), boron trifluoride diethyl etherate (963 mg, 0.83 ml, 6.78 mmol) was added at 0 °C. After 1 h of stirring, a saturated solution of sodium bicarbonate (40 ml)

was added and the product extracted with dichloromethane (3 × 40 ml). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to yield the crude product, which was purified by column chromatography using silica gel treated with triethylamine as absorbent and 3:1 light petroleum/ethyl acetate as eluent to produce a colourless oil (4.36 g, 81 %), ν_{max} (thin film, neat)/cm^{-1} 2936 (aliphatic CH) and 3419 (OH); δ_H (400 MHz, $CDCl_3$) 1.30 (3 H, s, C*H*$_3$), 1.42 (3 H, s, C*H*$_3$), 1.61-1.65 (1 H, m, CH*(H)*CH_2CHOH), 1.69 (1 H, br, s, O*H*), 1.80-1.89 (1 H, m, CH_2CH*(H)*CHOH), 1.91-2.00 (2 H, m, CH_2CH*(H)*CHOH and CH*(H)*CH_2CHOH), 4.18 (1 H, d, *J* 3.6 Hz, C*H*OH), 4.36 (1 H, dd, *J* 1.6, 5.6 Hz, C*H*(O)CHOH) and 4.76 (1 H, t, *J* 5.2 Hz, C*H*(O)CH(O)CHOH); δ_C (100 MHz, $CDCl_3$) 23.8 (*C*H_3), 26.2 (*C*H_3), 30.0 (*C*H_2), 30.8 (*C*H_2), 76.6 (*C*H), 80.4 (*C*H), 86.6 (*C*H) and 109.8 (*C*).

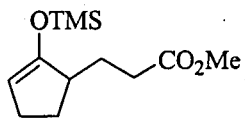
2,2-Dimethyl-tetrahydro-cyclopenta[1,3]dioxol-4-one (153).



At 0 °C, Dess-Martin periodinane (5.41 g, 12.8 mmol) was added to a solution of 2,2-dimethyl-tetrahydro-cyclopenta[1,3]dioxol-4-ol **(168)** (1.26 g, 7.97 mmol) in dichloromethane (20 ml). The mixture was stirred for 1 h at 0 °C then stirred for 3 h at room temperature. The resulting solution was evaporated to dryness to yield a colourless oil, which was purified by column chromatography using silica gel as absorbent and 3:1 light petroleum/ethyl acetate as eluent to produce a colourless oil (1.11 g, 90 %), ν_{max} (thin film, neat)/cm^{-1} 1751 (CO) and 2937 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.37 (3 H, s, C*H*$_3$), 1.43 (3 H, s, C*H*$_3$), 2.01-2.13 (1 H, m, CH*(H)*CH_2CO), 2.24-2.33 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.55-2.65 (1 H, m, CH_2CH*(H)*CO), 4.20 (1 H, d, *J* 5.2 Hz, C*H*(O)CO) and 4.84 (1 H, t, *J* 4.8 Hz, C*H*(O)CH(O)CO); δ_C (100 MHz, $CDCl_3$) 23.5 (*C*H_2), 25.0 (*C*H_3), 26.9 (*C*H_3), 33.1 (*C*H_2), 77.5 (*C*H), 79.1 (*C*H), 112.2 (*C*) and 215.1 (*C*O).

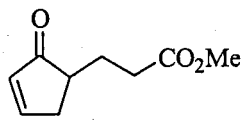
3.5.4. Manipulation of the Keto-ester Test Substrate

3-(2-Trimethylsilanyloxy-cyclopent-2-enyl)-propionic acid methyl ester (173).



n-Butyl lithium (2.47 ml, 6.17 mmol) was added dropwise to a stirred solution of diisopropylamine (624 mg, 0.87 ml, 6.17 mmol) in anhydrous tetrahydrofuran (10 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 15 min then cooled to –78 °C. Methyl-3-(2-oxocyclopentyl)-propionate **(132)** (1.0 g, 5.88 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise and the reaction stirred for 15 min at –78 °C. Trimethylsilylchloride (766 mg, 0.90 ml, 7.05 mmol) was added dropwise at –78 °C and the reaction allowed to warm to room temperature over 4 h. The volatiles were then removed by evaporation and the resultant residue dissolved in chloroform and filtered. Organics were then reduced to dryness to yield the desired product as a crude orange oil (1.43 g, 99 %), which was reacted without purification.

3-(2-Oxy-cyclopent-3-enyl)-propionic acid methyl ester (171).

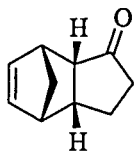


To a solution of palladium (II) acetate (662 mg, 2.95 mmol) and 1,4-benzoquinone (319 mg, 2.95 mmol) in acetonitrile (24 ml), 3-(2-trimethylsilanyloxy-cyclopent-2-enyl)-propionic acid methyl ester **(173)** (1.43 g, 5.90 mmol) was added with stirring under a nitrogen atmosphere at room temperature. The reaction was stirred for 4 h at room temperature and then filtered through a pad of celite and evaporated to yield a yellow oil, which was purified by column chromatography using silica gel as absorbent and 3:1 light petroleum/ethyl acetate as eluent to produce a yellow oil (386 mg, 39 %), ν_{max} (thin film, neat)/cm^{-1} 1737 (CO) and 2950 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.72-1.79 (1 H, m, CH*(H)*$CH_2CO_2CH_3$), 2.05-2.13 (1 H, m, CH*(H)*$CH_2CO_2CH_3$), 2.33-2.39 (2 H, m, C*H*$CH_2CH_2CO_2CH_3$ and HC=CHCH*(H)*), 2.47 (2 H, t, *J* 7.6 Hz

$CH_2CH_2CO_2CH_3$), 2.88-2.96 (1 H, m, HC=CHCH*(H)*), 3.68 (3 H, s, OCH_3), 6.19 (1 H, dt, *J* 2.0, 5.6 Hz, COCH=C*H*), 7.70 (1 H, dt, *J* 2.8, 5.6 Hz, COC*H*=CH); δ_C (100 MHz, $CDCl_3$) 24.1 (CH_2), 29.4 (CH_2), 33.3 (CH_2), 41.5 (*C*H), 49.4 (OCH_3), 131.5 (*C*H), 161.1 (*C*H), 171.3 (*C*O) and 209.3 (*C*O); MS (FAB) *m/z* 169 [MH^+, 19.8 %] (MH^+, 169.0868. $C_9H_{12}O_3$ requires 169.0864).

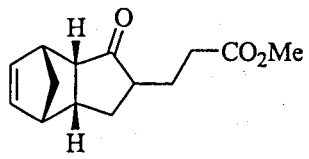
3.5.5. Synthesis of a Tetracyclic Olefin *via* a Diels-Alder Strategy

2,3,3a,4,7,7a-Hexahydro-4,7-methano-inden-1-one (179).[49]



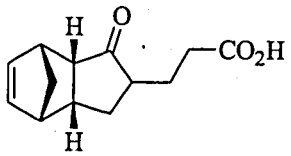
To a mixture of 2-cyclopenten-1-one **(152)** (5.0 g, 5.10 ml, 60.9 mmol) and cyclopentadiene (6.03 g, 6.10 ml, 91.4 mmol) in diethyl ether (61 ml) at 0 °C, was added a catalytic amount of boron trifluoride diethyl etherate (3.46 g, 3.00 ml, 24.4 mmol) over a 5 min period. The reaction mixture was stirred while the cooling bath warmed to room temperature then stirred for a further 24 h. Water (60 ml) was added and the product was extracted with diethyl ether (3 × 40 ml), washed with saturated brine and dried over anhydrous magnesium sulfate. The resulting yellow oil was purified by column chromatography using silica gel as absorbent and 2 % ethyl acetate/light petroleum as eluent to produce a yellow oil (9.02 g, 99 %), ν_{max} (thin film, neat)/cm^{-1} 1730 (CO) and 2960 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.41-1.44 (1 H, m, CHCH*(H)*CH), 1.48-1.57 (2 H, m, CHCH*(H)*CH and CH*(H)*CH_2CO), 1.94-2.06 (2 H, m, CH*(H)*CH_2CO and CH_2CH*(H)*CO), 2.08-2.21 (1 H, m, CH_2CH*(H)*CO), 2.86 (1 H, ddd, *J* 1.6, 4.8, 8.8 Hz, CH(CH_2)C*H*CO), 2.93-3.01 (2 H, m, CH(CH_2)C*H*CH_2 and C*H*(CH_2)$CHCH_2$), 3.19-3.22 (1 H, m, C*H*(CH_2)CHCO), 6.12 (1 H, dd, *J* 2.8, 5.6 Hz, C=C*H*CHCHCO) and 6.23 (1 H, dd, *J* 2.8, 5.6 Hz, C=C*H*CHCHCH_2); δ_C (100 MHz, $CDCl_3$) 22.7 (CH_2), 40.6 (CH_2), 41.2 (*C*H), 47.1 (*C*H), 47.5 (*C*H), 52.3 (CH_2), 54.4 (*C*H), 134.8 (*C*H), 136.2 (*C*H) and 222.5 (*C*O); MS (FAB) *m/z* 148 [M^+, 16.0 %] (M^+, 148.0886. $C_{10}H_{12}O$ requires 148.0888).

3-(1-Oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methano-inden-2-yl)-propionic acid methyl ester (180).



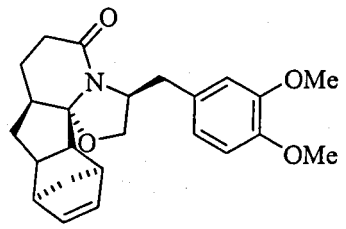
n-Butyl lithium (2.97 ml, 7.42 mmol) was added dropwise to a stirred solution of diisopropylamine (751 mg, 1.05 ml, 7.42 mmol) in anhydrous tetrahydrofuran (20 ml) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 15 min then cooled to –78 °C. 2,3,3a,4,7,7a-Hexahydro-4,7-methano-inden-1-one **(179)** (1.00 g, 6.75 mmol) in dry tetrahydrofuran (20 ml) was added dropwise and the reaction stirred for 15 min at –78 °C. Methyl-3-bromopropionate (1.35 g, 0.86 ml, 8.10 mmol) was added dropwise at –78 °C and the reaction allowed to warm to room temperature overnight. The resulting mixture was quenched with saturated ammonium chloride and product was extracted with ethyl acetate (3 × 40 ml). Organic phases were combined and washed with saturated brine (40 ml) and dried over anhydrous magnesium sulfate. Organic phase was then filtered and solvent removed on the rotary evaporator to give the target compound, which was purified by column chromatography using silica gel as absorbent and 6 % ethyl acetate/light petroleum as eluent to yield a colourless oil (1.03 g, 66 %), ν_{max} (thin film, neat)/cm^{-1} 1732 (CO) and 2950 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.38-1.41 (1 H, m, CHCH*(H)*CH), 1.42-1.53 (2 H, m, CHCH*(H)*CH and CH*(H)*$CH_2CO_2CH_3$), 1.58-1.67 (1 H, m, CHCH*(H)*CHCO), 1.79-1.85 (1 H, m, CHCH*(H)*CHCO), 1.89-1.97 (2 H, m, $CHCH_2CHCO$ and CH*(H)*$CH_2CO_2CH_3$), 2.28-2.32 (2 H, m, $CH_2CH_2CO_2CH_3$), 2.83-2.91 (2 H, m, $CH(CH_2)CHCH_2$ and $CH(CH_2)CHCO$), 2.99-3.03 (1 H, m, $CH(CH_2)CHCH_2$), 3.21-3.23 (1 H, m, $CH(CH_2)CHCO$), 3.65 (3 H, s, OCH_3), 6.06 (1 H, dd, *J* 3.2, 6.0 Hz, C=CHCHCHCO) and 6.26 (1 H, dd, *J* 3.2, 6.0 Hz, C=CHCHCHCH$_2$); δ_C (100 MHz, $CDCl_3$) 26.0 (CH_2), 29.9 (CH_2), 31.9 (CH_2), 38.9 (CH), 47.5 (CH), 47.8 (CH), 49.5 (CH), 51.6 (CH), 52.3 (CH_2), 54.6 (CH), 135.0 (CH), 136.3 (CH), 173.7 (CO) and 222.3 (CO); MS (FAB) *m/z* 235 [MH^+, 18.0 %] (MH^+, 235.1339. $C_{14}H_{18}O_3$ requires 235.1334).

3-(1-Oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methano-inden-2-yl)-propionic acid (181).



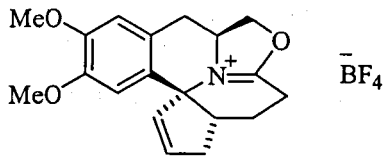
3-(1-Oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methano-inden-2-yl)-propionic acid methyl ester **(180)** (5.09 g, 21.7 mmol) was dissolved in a mixture of tetrahydrofuran (147 ml) and water (59 ml). Lithium hydroxide (1.37 g, 32.6 mmol) was added and mixture stirred for 90 min at room temperature. The reaction mixture was concentrated, re-suspended in water (200 ml) and acidified with a 1 M solution of HCl. The aqueous layer was extracted with ethyl acetate (3 × 50 ml), dried over anhydrous magnesium sulfate, filtered and evaporated to the target compound as a 1:1 mixture of inseperable diastereoisomers (4.74 g, 99 %), ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1718 (CO), 2961 (aliphatic CH) and 3369 (OH); Diastereoisomer 1; δ_H (400 MHz, $CDCl_3$) 1.39-1.52 (3 H, m, CHC*H*$_2$CH and CH*(H)*$CH_2CO_2CH_3$), 1.55-1.67 (1 H, m, CHCH*(H)*CHCO), 1.79-1.85 (1 H, m, CHCH*(H)*CHCO), 1.80-2.02 (1 H, m, CH*(H)*$CH_2CO_2CH_3$), 2.34-2.46 (3 H, m, $CH_2CH_2CO_2CH_3$ and $CHCH_2CHCO$), 2.82-2.92 (2 H, m, $CH(CH_2)CHCH_2$ and $CH(CH_2)CHCO$), 2.99-3.03 (1 H, m, C*H*$(CH_2)CHCH_2$), 3.20-3.24 (1 H, m, C*H*$(CH_2)CHCO$), 6.05-6.08 (1 H, m, C=C*H*CHCHCO) and 6.26 (1 H, dd, *J* 2.8, 5.6 Hz, C=C*H*CHCHCH_2); δ_C (100 MHz, $CDCl_3$) 25.7 (*C*H_2), 30.6 (*C*H_2), 32.0 (*C*H_2), 38.9 (*C*H), 47.5 (*C*H), 47.9 (*C*H), 51.2 (*C*H), 52.5 (*C*H_2), 54.6 (*C*H), 135.0 (*C*H), 135.2 (*C*H), 179.2 (*C*O) and 222.5 (*C*O); Diastereoisomer 2; δ_H (400 MHz, $CDCl_3$) 1.39-1.52 (3 H, m, CHC*H*$_2$CH and CH*(H)*$CH_2CO_2CH_3$), 1.55-1.67 (1 H, m, CHCH*(H)*CHCO), 1.79-1.85 (1 H, m, CHCH*(H)*CHCO), 1.80-2.02 (2 H, m, $CHCH_2CHCO$ and CH*(H)*$CH_2CO_2CH_3$), 2.35-2.46 (2 H, m, $CH_2CH_2CO_2CH_3$), 2.95-3.01 (3 H, m, $CH(CH_2)CHCH_2$, $CH(CH_2)CHCO$) and C*H*$(CH_2)CHCH_2$), 3.13-3.17 (1 H, m, C*H*$(CH_2)CHCO$), 6.05-6.08 (1 H, m, C=C*H*CHCHCO) and 6.17 (1 H, dd, *J* 2.8, 5.6 Hz, C=C*H*CHCHCH_2); δ_C (100 MHz, $CDCl_3$) 23.5 (*C*H_2), 29.9 (*C*H_2), 30.6 (*C*H_2), 38.6 (*C*H), 44.4 (*C*H), 46.0 (*C*H), 49.4 (*C*H), 52.2 (*C*H_2), 54.8 (*C*H), 136.3 (*C*H), 137.5 (*C*H), 179.0 (*C*O) and 219.0 (*C*O); MS (FAB) *m/z* 221 [MH^+, 17.9 %] (MH^+, 221.1182. $C_{13}H_{16}O_3$ requires 221.1178).

(3*S*,6a*R*,10a*S*)-3-(3,4-Dimethoxy-benzyl)-octahydro-1-oxa-3a-aza-cyclopenta[*d*] inden-4-one-8,9-bicyclo[2.2.1]hept-2-ene (182).



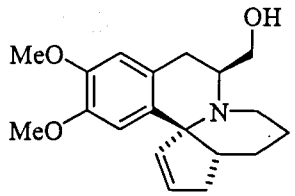
(2*S*)-2-Amino-3-(3,4-dimethyloxy)phenyl)propan-1-ol **(62)** (1.88 g, 8.91 mmol) and 3-(1-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methano-inden-2-yl)-propionic acid **(181)** (1.96 g, 8.91 mmol) were dissolved in toluene (50 ml) and refluxed under Dean-Stark conditions for 48 h. The reaction was allowed to cool to room temperature and solvent removed by rotary evaporation. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3:2 ethyl acetate/light petroleum as eluent to produce the single diastereoisomer as a yellow oil (1.59 g, 45 %), $[\alpha]_D$ – 34.1 [*c* = 1.08 in $CHCl_3$]; ν_{max} (thin film, neat)/cm^{-1} 1650 (NCO) and 2956 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.38-1.46 (2 H, m, CHCH*(H)*CH and CH*(H)*$CHCH_2CH_2CO$), 1.56-1.73 (3 H, m, CHCH*(H)*CH, CH*(H)*$CHCH_2CH_2CO$ and $CHCH(H)CH_2CO$), 1.77-1.85 (1 H, m, $CHCH(H)CH_2CO$), 2.05-2.09 (1 H, m, $CHCH_2CH_2CO$), 2.28-2.37 (1 H, m, $CHCH_2CH(H)CO$), 2.54 (1 H, dt, *J* 5.6, 18.0 Hz, $CHCH_2CH(H)CO$), 2.68-2.77 (3 H, m, $NCCHCH(CH_2)$, $NCCHCH(CH_2)$ and $ArCH(H)CHN$), 2.98-3.05 (2 H, m, $C{=}CHCH(CH_2)CHCH_2$ and $C{=}CHCH(CH_2)CHCH_2$), 3.41 (1 H, dd, *J* 4.0, 13.2 Hz, $ArCH(H)CHN$), 3.75 (1 H, dd, *J* 7.6, 8.8 Hz, $ArCH_2CHCH(H)O$), 3.83-3.88 (4 H, m, $ArCH_2CHCH(H)O$ and OCH_3), 3.90 (3 H, s, OCH_3), 4.56-4.60 (1 H, m, $ArCH_2CHN$), 6.12 (1 H, dd, *J* 3.2, 6.0 Hz, $C{=}CHCH(CH_2)CHCH_2$), 6.23 (1 H, dd, *J* 2.8, 5.6 Hz, $C{=}CHCH(CH_2)CHCN$), 6.81 (2 H, s, Ar*H*) and 6.84 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 24.1 (CH_2), 30.3 (CH_2), 31.8 (CH_2), 39.5 (CH_2), 44.8 (*C*H), 45.2 (*C*H), 46.7 (*C*H), 47.2 (*C*H), 53.8 (CH_2), 55.9 (OCH_3), 55.9 (OCH_3), 56.1 (*C*H), 57.1 (*C*H), 67.6 (CH_2), 101.3 (*C*), 111.2 (*C*H), 112.2 (*C*H), 121.1 (*C*H), 130.0 (*C*), 133.7 (*C*H), 137.0 (*C*H), 147.9 (*C*), 149.1 (*C*) and 170.1 (*C*O); MS (FAB) *m/z* 396 [MH^+, 0.4 %] (MH^+, 396.2181. $C_{24}H_{29}NO_4$ requires 396.2175).

(5*S*,10b*R*,13a*R*)-(8,9-dimethoxy-1,2,5,6,13,13a-hexahydro-cyclopenta[*e*]oxazolo [3,2-*a*]pyrido[2,1-*a*]isoquinolinylium; tetrafluoro borate (186).



To a stirred solution of (3*S*,6a*R*,10a*S*)-3-(3,4-dimethoxy-benzyl)-octahydro-1-oxa-3a-aza-cyclopenta[*d*]inden-4-one-8,9-bicyclo[2.2.1]hept-2-ene **(182)** (723 mg, 1.83 mmol) in anhydrous dichloromethane (15 ml), boron trifluoride diethyl etherate (778 mg, 0.68 ml, 5.48 mmol) was added dropwise at room temperature and the resultant solution was heated under reflux. After 15 h, the reaction was cooled to room temperature and quenched with a saturated solution of ammonium chloride (15 ml). The product was then extracted with dichloromethane (3 × 20 ml), dried over anhydrous magnesium sulfate and evaporated to yield the crude product, which was recrystallised from dichloromethane/hexane to yield a colourless crystalline solid (664 g, 91 %), Mp 206-207 °C; $[\alpha]_D$ – 286.3 [*c* = 1.01 in CH_2Cl_2]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1652 (NCO) and 2942 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 2.01-2.13 (2 H, m, CHC*H*$_2$CH$_2$CO), 2.55-2.62 (1 H, m, C=CCH*(H)*CH), 2.81-2.88 (2 H, m, CHCH$_2$C*H*$_2$CO), 2.98 (1 H, ddt, *J* 2.4, 9.2, 18.0 Hz, C=CHCH*(H)*CH), 3.17-3.23 (3 H, m, C*H*CH$_2$CH$_2$CO and ArC*H*$_2$CHN), 3.84 (3 H, s, OC*H*$_3$), 3.86 (3 H, s, OC*H*$_3$), 4.78-4.87 (1 H, m, ArCH$_2$C*H*N), 4.95 (1 H, dd, *J* 4.4, 9.6 Hz, CHCH*(H)*O$^+$), 5.30 (1 H, dd, *J* 6.0, 9.2 Hz, CHCH*(H)*O$^+$), 5.87-5.90 (1 H, m, C=C*H*CAr), 6.15-6.17 (1 H, m, C=C*H*CH$_2$CH), 6.53 (1 H, s, Ar*H*) and 6.61 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 20.1 (*C*H$_2$), 22.1 (*C*H$_2$), 33.8 (*C*H$_2$), 37.3 (*C*H$_2$), 42.9 (*C*H), 56.1 (*C*H), 56.1 (O*C*H$_3$), 56.2 (O*C*H$_3$), 74.1 (*C*), 77.7 (*C*H$_2$), 108.3 (*C*H), 111.6 (*C*H), 122.9 (*C*), 128.3 (*C*), 132.9 (*C*H), 135.2 (*C*H), 148.9 (*C*), 149.1 (*C*) and 175.2 (*C*O); MS (EI) *m/z* 312 [M^+, 3.4 %] (M^+, 312.1595. $C_{19}H_{22}NO_3$ requires 312.1600). The product was recrystallised from dichloromethane/ hexane *via* vapour diffusion to produce clear, colourless crystals. The relative stereochemistry was confirmed by single crystal X-ray analysis.

(5*S*,10b*R*,13a*R*)-(8,9-Dimethoxy-2,3,5,6,13,13a-hexahydro-1*H*-cyclopenta[2,3] pyrido[2,1-*a*]isoquinolin-5-yl)-methanol (174).



(5*S*,10b*R*,13a*R*)-(8,9-dimethoxy-1,2,5,6,13,13a-hexahydro-cyclopenta[*e*]oxazolo[3,2-*a*] pyrido[2,1-*a*]isoquinolinylium; tetrafluoro borate **(186)** (612 mg, 1.53 mmol) was dissolved in anhydrous dichloromethane (5 ml) under nitrogen and cooled to 0 °C in an ice bath. Diisobutylaluminium hydride (1 M solution in hexane, 3.83 ml, 3.83 mmol) was added dropwise at 0 °C and the reaction was heated under reflux for 5 h. The reaction was then cooled to 0 °C and methanol (5 ml) followed by saturated ammonium chloride (10 ml) was added carefully. Organics were washed with water (5 ml), dried over magnesium sulfate and concentrated to give an oily residue, which was purified by column chromatography using silica gel as absorbent and 3:2 ethyl acetate/light petroleum as eluent to yield a yellow oil (315 mg, 65 %), ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 2930 (aliphatic CH) and 3389 (OH); δ_H (400 MHz, $CDCl_3$) 1.42-1.54 (2 H, m, $CHCH(H)CH_2CH_2N$ and $CHCH_2CH(H)CH_2N$), 1.70-1.77 (2 H, m, $CHCH(H)CH_2CH_2N$ and $CHCH_2CH(H)CH_2N$), 2.14-2.20 (1 H, m, $CHCH_2CH_2CH(H)N$), 3.32-2.43 (2 H, m, $ArCH(H)CHN$ and $C{=}CCH(H)CH$), 2.64-2.71 (3 H, m, $CHCH_2CH_2CH(H)N$, $ArCH(H)CHN$ and $C{=}CCH(H)CH$), 2.75-2.82 (1 H, m, $CHCH_2CH_2CH_2N$), 3.40-3.46 (1 H, m, $ArCH_2CHN$), 3.52-3.63 (2 H, m, CH_2OH), 3.85 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.89-5.91 (1 H, m, $C{=}CHCAr$), 5.94-5.98 (1 H, m, $C{=}CHCH_2CH$), 6.58 (1 H, s, Ar*H*) and 6.76 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (CH_2), 24.0 (CH_2), 25.5 (CH_2), 35.7 (CH_2), 38.0 (CH_2), 44.0 (*C*H), 54.9 (*C*H), 55.8 (OCH_3), 56.0 (OCH_3), 60.8 (CH_2), 70.6 (*C*), 109.7 (*C*H), 111.7 (*C*H), 126.6 (*C*), 131.0 (*C*), 132.7 (*C*H), 139.9 (*C*H), 147.4 (*C*) and 147.7 (*C*); MS (FAB) *m/z* 316 (MH^+, 316.1920. $C_{19}H_{25}NO_3$ requires 316.1913).

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CHAPTER FOUR:

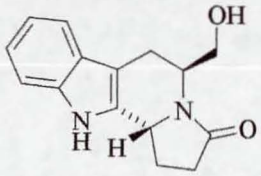
APPENDIX

4.1. X-Ray Crystallography Data

4.2. Publications

4.1. X-Ray Crystallography Data

(5*S*,11b*R*)-5-Hydroxymethyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (21).



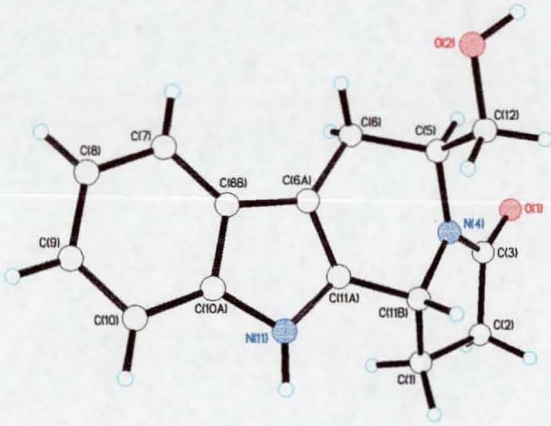


Table 1. Crystal data and structure refinement for **(21)**.

Identification code	sma39	
Chemical formula	$C_{15}H_{16}N_2O_2$	
Formula weight	256.30	
Temperature	120(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 9.5570(7) Å	α = 90°
	b = 11.0909(7) Å	β = 90°
	c = 11.5449(5) Å	γ = 90°
Cell volume	1223.71(13) $Å^3$	
Z	4	
Calculated density	1.391 g/cm^3	
Absorption coefficient μ	0.094 mm^{-1}	
F(000)	544	
Crystal colour and size	colourless, 0.10 × 0.07 × 0.07 mm^3	
Reflections for cell refinement	9900 (θ range 2.91 to 27.10°)	
Data collection method	Bruker-Nonius KappaCCD	
	Φ & ω scans	

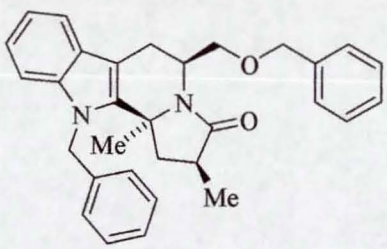
θ range for data collection	3.32 to 27.29°
Index ranges	h −11 to 12, k −12 to 14, l −14 to 13
Completeness to θ = 26.00°	99.8 %
Intensity decay	0%
Reflections collected	11883
Independent reflections	2685 (R_{int} = 0.1304)
Reflections with $F^2>2\sigma$	1866
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9907 and 0.9935
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0374, 0.5159
Data / restraints / parameters	2685 / 0 / 179
Final R indices [$F^2>2\sigma$]	R1 = 0.0602, wR2 = 0.1147
R indices (all data)	R1 = 0.1051, wR2 = 0.1299
Goodness-of-fit on F^2	1.039
Absolute structure parameter	−1(2)
Extinction coefficient	0.005(2)
Largest and mean shift/su	0.002 and 0.000
Largest diff. peak and hole	0.199 and −0.245 e $Å^{-3}$

Table 2. Hydrogen bonds for sma39 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(13)...O(1A)	0.94(4)	1.73(4)	2.649(3)	169(3)
N(11)–H(11)...O(2B)	0.94(4)	1.95(4)	2.842(3)	159(3)

Symmetry operations for equivalent atoms
A −x+2,y−1/2,−z+3/2 B −x+1,y+1/2,−z+3/2

(2*S*,5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-2,11b-dimethyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (85a).



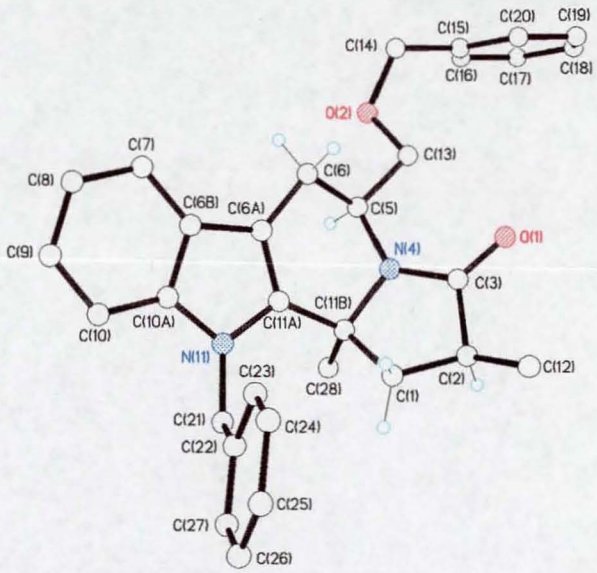


Table 1. Crystal data and structure refinement for **(85a)**.

Identification code	sma36	
Chemical formula	$C_{31}H_{32}N_2O_2$	
Formula weight	464.59	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 10.8211(5) Å	α = 90°
	b = 14.7247(7) Å	β = 92.979(2)°
	c = 15.8061(7) Å	γ = 90°
Cell volume	2515.1(2) $Å^3$	
Z	4	
Calculated density	1.227 g/cm^3	
Absorption coefficient μ	0.076 mm^{-1}	
F(000)	992	
Crystal colour and size	colourless, 0.81 × 0.60 × 0.40 mm^3	
Reflections for cell refinement	10772 (θ range 2.34 to 28.32°)	

Data collection method	Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames
θ range for data collection	1.88 to 29.03°
Index ranges	h −13 to 13, k −18 to 19, l −20 to 20
Completeness to θ = 26.00°	99.9 %
Intensity decay	0%
Reflections collected	22419
Independent reflections	11286 (R_{int} = 0.0155)
Reflections with $F^2>2\sigma$	9859
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.941 and 0.970
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0606, 0.3552
Data / restraints / parameters	11286 / 1 / 635
Final R indices [$F^2>2\sigma$]	R1 = 0.0422, wR2 = 0.1042
R indices (all data)	R1 = 0.0511, wR2 = 0.1111
Goodness-of-fit on F^2	1.050
Absolute structure parameter	0.3(8)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.505 and −0.216 e $Å^{-3}$

(2*S*,5*S*,11b*S*)-11-Benzyl-5-benzyloxymethyl-2-isopropyl-11b-methyl-1,2,5,6,11, 11b-hexahydro-indolizino[8,7-*b*]indol-3-one (87b).

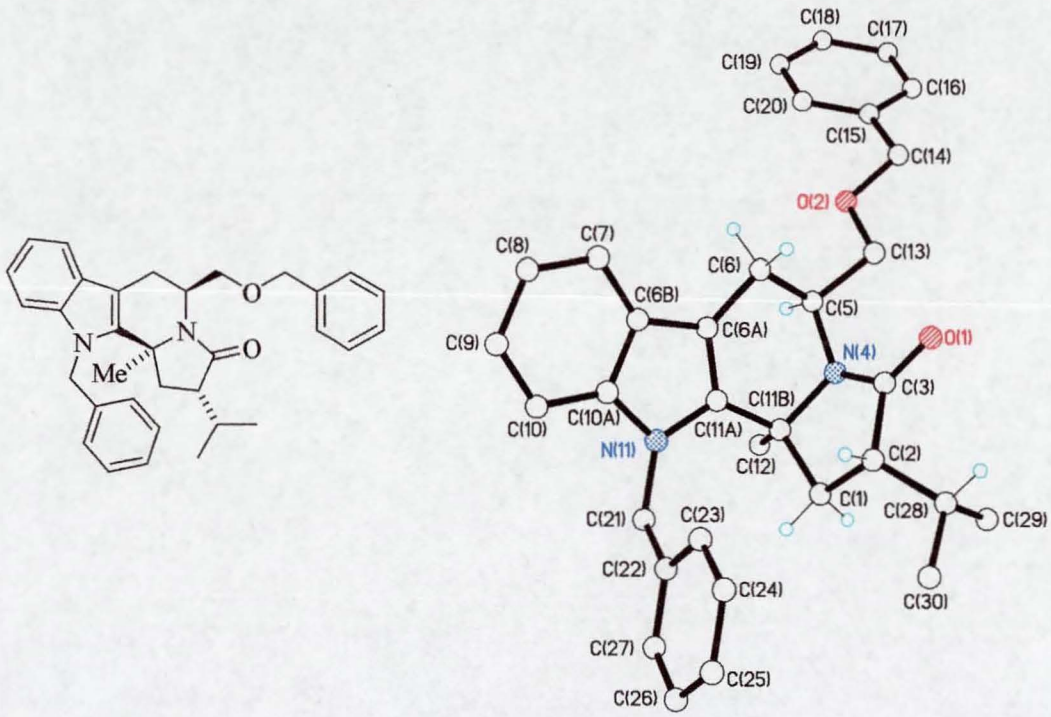
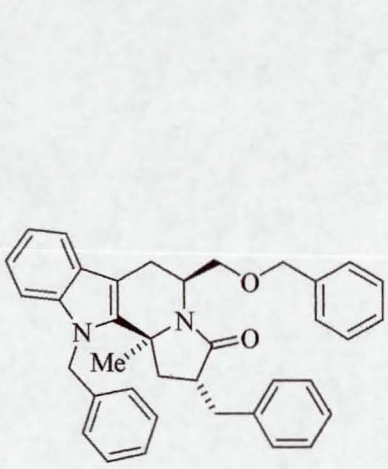


Table 1. Crystal data and structure refinement for **(87b)**.

Identification code	sma38	
Chemical formula	$C_{33}H_{36}N_2O_2$	
Formula weight	492.64	
Temperature	120(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 14.6043(4) Å	α = 90°
	b = 16.6815(3) Å	β = 90°
	c = 10.9921(3) Å	γ = 90°
Cell volume	2677.91(11) $Å^3$	
Z	4	
Calculated density	1.222 g/cm^3	
Absorption coefficient μ	0.076 mm^{-1}	
F(000)	1056	

Crystal colour and size	Colourless, 0.32 × 0.16 × 0.14 mm^3
Reflections for cell refinement	24590 (θ range 2.91 to 27.48°)
Data collection method	Enraf Nonius KappaCCD area detector phi and omega scans to fill Ewald sphere
θ range for data collection	3.05 to 27.48°
Index ranges	h –18 to 16, k –21 to 19, l –14 to 14
Completeness to θ = 26.50°	99.5 %
Intensity decay	0%
Reflections collected	29931
Independent reflections	6109 (R_{int} = 0.0825)
Reflections with $F^2>2\sigma$	5213
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9762 and 0.9895
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0235, 0.9331
Data / restraints / parameters	6109 / 0 / 338
Final R indices [$F^2>2\sigma$]	R1 = 0.0449, wR2 = 0.0922
R indices (all data)	R1 = 0.0573, wR2 = 0.0975
Goodness-of-fit on F^2	1.071
Absolute structure parameter	0.5(12)
Extinction coefficient	0.0049(7)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.182 and –0.165 e $Å^{-3}$

(2*R*,5*S*,11b*S*)-2,11-Dibenzyl-5-benzyloxymethyl-11b-methyl-1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (88b).



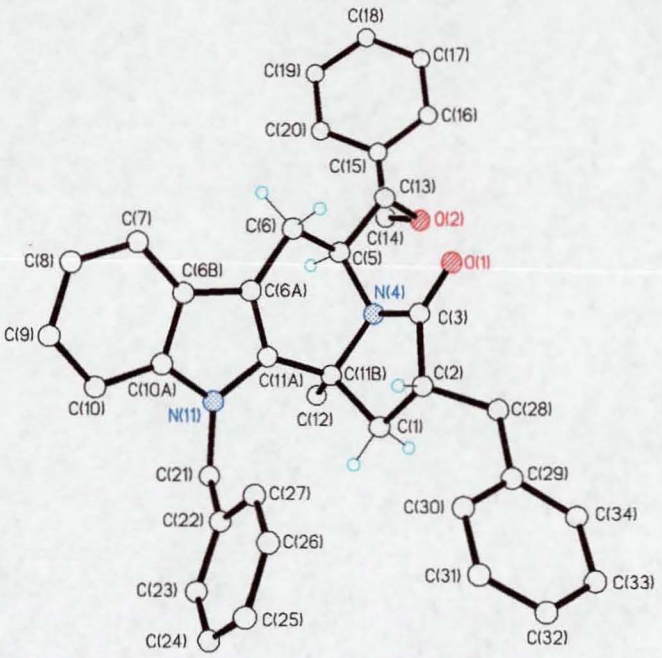
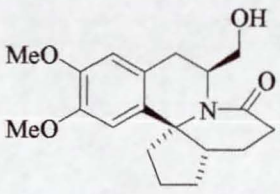


Table 1. Crystal data and structure refinement for **(88b)**.

Identification code	sma40	
Chemical formula	$C_{37}H_{36}N_2O_2$	
Formula weight	540.68	
Temperature	120(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 8.3134(17) Å	α = 90°
	b = 16.342(3) Å	β = 90°
	c = 21.244(4) Å	γ = 90°
Cell volume	2886.2(10) $Å^3$	
Z	4	
Calculated density	1.244 g/cm^3	
Absorption coefficient μ	0.077 mm^{-1}	
F(000)	1152	
Crystal colour and size	Colourless, 0.28 × 0.14 × 0.04 mm^3	

Reflections for cell refinement	36987 (θ range 2.91 to 27.48°)
Data collection method	Bruker-Nonius KappaCCD Φ & ω scans
θ range for data collection	3.11 to 27.53°
Index ranges	h –10 to 9, k –21 to 18, l –21 to 27
Completeness to θ = 26.00°	97.9 %
Intensity decay	0%
Reflections collected	23603
Independent reflections	6242 (R_{int} = 0.1235)
Reflections with $F^2>2\sigma$	3721
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9789 and 0.9969
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0397, 1.4907
Data / restraints / parameters	6242 / 0 / 372
Final R indices [$F^2>2\sigma$]	R1 = 0.0811, wR2 = 0.1343
R indices (all data)	R1 = 0.1533, wR2 = 0.1550
Goodness-of-fit on F^2	1.045
Absolute structure parameter	–1(2)
Extinction coefficient	0.0059(8)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.215 and –0.186 e $Å^{-3}$

(5*S*,10b*S*,13a*S*)-5-Hydroxymethyl-8,9-dimethoxy-1,2,5,6,11,12,13,13a-octahydro-cyclopenta[2,3]pyrido[2,1-*a*]isoquinolin-3-one (130).



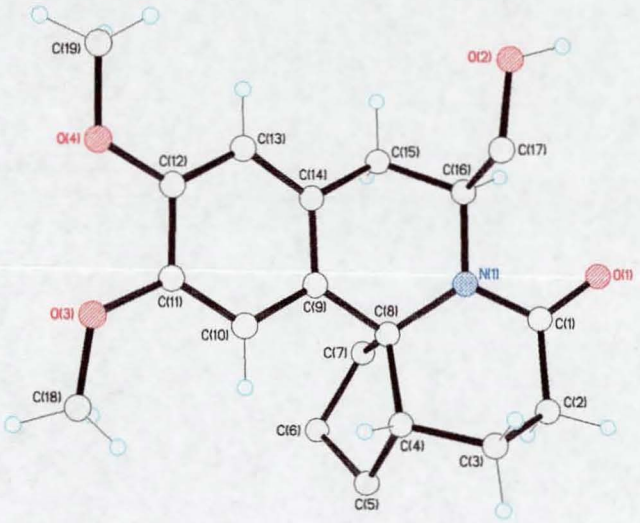


Table 1. Crystal data and structure refinement for **(130)**.

Identification code	sma51	
Chemical formula	$C_{20}H_{27}Cl_2NO_4$	
Formula weight	416.33	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $p2_1$	
Unit cell parameters	a = 7.5974(6) Å	α = 90°
	b = 8.9918(7) Å	β = 94.5680(10)°
	c = 14.6880(12) Å	γ = 90°
Cell volume	1000.21(14) $Å^3$	
Z	2	
Calculated density	1.382 g/cm^3	
Absorption coefficient μ	0.350 mm^{-1}	
F(000)	440	
Crystal colour and size	colourless, 1.51 × 0.30 × 0.11 mm^3	
Reflections for cell refinement	6175 (θ range 5.317 to 56.455°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	
	ω rotation with narrow frames	

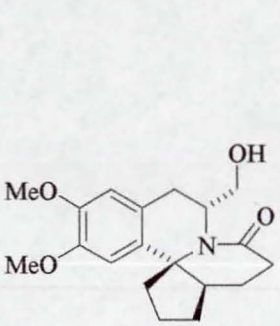
θ range for data collection	2.66 to 28.79°
Index ranges	h −9 to 9, k −11 to 11, l −19 to 19
Completeness to θ = 26.00°	100.0 %
Intensity decay	0%
Reflections collected	8843
Independent reflections	4570 (R_{int} = 0.0147)
Reflections with $F^2>2\sigma$	4298
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.620 and 0.963
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0507, 0.2973
Data / restraints / parameters	4570 / 1 / 249
Final R indices [$F^2>2\sigma$]	R1 = 0.0347, wR2 = 0.0884
R indices (all data)	R1 = 0.0375, wR2 = 0.0908
Goodness-of-fit on F^2	1.036
Absolute structure parameter	−0.03(5)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.255 and −0.275 e $Å^{-3}$

Table 2. Hydrogen bonds for sma51 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(1A)	0.82(3)	1.90(3)	2.7171(19)	172(3)

Symmetry operations for equivalent atoms
A −x,y−1/2,−z+1

(5*R*,10b*R*,13a*R*)-5-Hydroxymethyl-8,9-dimethoxy-1,2,5,6,11,12,13,13a-octahydro cyclopenta[2,3]pyrido[2,1-*a*]isoquinolin-3-one (138).



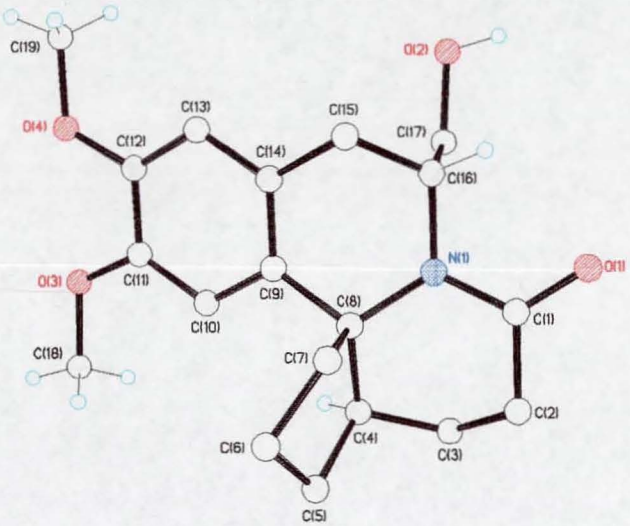


Table 1. Crystal data and structure refinement for **(138)**.

Identification code	sma52	
Chemical formula	$C_{19.33}H_{25.67}Cl_{0.67}NO_4$	
Formula weight	359.71	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 11.0731(9) Å	α = 90°
	b = 9.0461(7) Å	β = 96.247(2)°
	c = 27.116(2) Å	γ = 90°
Cell volume	2700.0(4) $Å^3$	
Z	6	
Calculated density	1.327 g/cm^3	
Absorption coefficient μ	0.187 mm^{-1}	
F(000)	1152	
Crystal colour and size	Colourless, 0.42 × 0.11 × 0.03 mm^3	
Reflections for cell refinement	3981 (θ range 4.516 to 52.827°)	
Data collection method	Bruker SMART 1000 CCD diffractometer	

	ω rotation with narrow frames
θ range for data collection	1.85 to 28.64°
Index ranges	h −14 to 14, k −12 to 11, l −34 to 33
Completeness to θ = 26.00°	100.0 %
Intensity decay	0%
Reflections collected	23177
Independent reflections	11816 (R_{int} = 0.0655)
Reflections with $F^2>2\sigma$	5847
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.9257 and 0.9944
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0479, 0.0299
Data / restraints / parameters	11816 / 1 / 687
Final R indices [$F^2>2\sigma$]	R1 = 0.0565, wR2 = 0.1022
R indices (all data)	R1 = 0.1595, wR2 = 0.1368
Goodness-of-fit on F^2	0.988
Absolute structure parameter	0.01(8)
Extinction coefficient	0.0040(5)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.282 and −0.350 e $Å^{-3}$

Table 2. Hydrogen bonds for sma52 [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(5)	0.84	1.88	2.716(4)	172.6
O(6)–H(6)...O(1A)	0.84	1.88	2.700(4)	165.9
O(10)–H(10A)...O(9B)	0.84	1.90	2.703(4)	159.5

Symmetry operations for equivalent atoms
A x,y−1,z B −x+2,y+1/2,−z+2

(5*S*,10b*R*,13a*R*)-(8,9-dimethoxy-1,2,5,6,13,13a-hexahydro-cyclopenta[*e*]oxazolo [3,2-*a*]pyrido[2,1-*a*]isoquinolinylium; tetrafluoro borate (186).

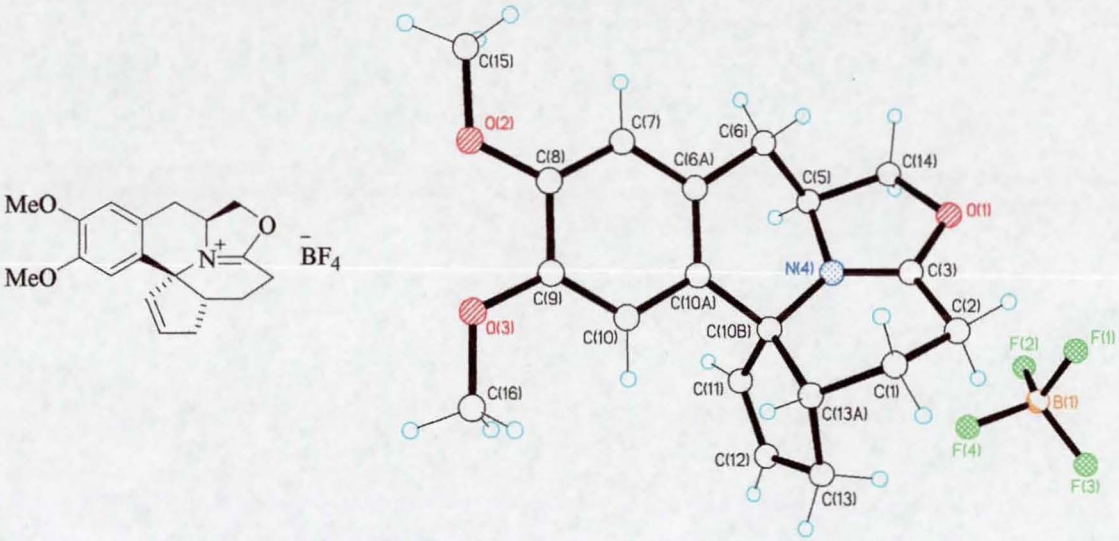


Table 1. Crystal data and structure refinement for **(186)**.

Identification code	smadl3	
Chemical formula	$C_{19}H_{22}BF_4NO_3$	
Formula weight	399.19	
Temperature	150(2) K	
Radiation, wavelength	synchrotron, 0.6904 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 7.3197(5) Å	α = 90°
	b = 9.0804(6) Å	β = 90°
	c = 28.5357(18) Å	γ = 90°
Cell volume	1896.6(2) $Å^3$	
Z	4	
Calculated density	1.398 g/cm^3	
Absorption coefficient μ	0.119 mm^{-1}	
F(000)	832	
Crystal colour and size	colourless, 0.19 × 0.05 × 0.05 mm^3	
Reflections for cell refinement	6221 (θ range 4.05 to 30.77°)	
Data collection method	Bruker APEX 2 CCD diffractometer	

	ω rotation with narrow frames
θ range for data collection	4.05 to 27.50°
Index ranges	h –7 to 9, k –12 to 11, l –33 to 38
Completeness to θ = 27.50°	97.6 %
Intensity decay	11%
Reflections collected	12211
Independent reflections	2672 (R_{int} = 0.0645)
Reflections with $F^2>2\sigma$	2489
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.978 and 0.994
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1086, 0.0340
Data / restraints / parameters	2672 / 0 / 255
Final R indices [$F^2>2\sigma$]	R1 = 0.0524, wR2 = 0.1483
R indices (all data)	R1 = 0.0549, wR2 = 0.1519
Goodness-of-fit on F^2	1.113
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.389 and –0.365 e $Å^{-3}$

4.2. Publications

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Tetrahedron Letters 48 (2007) 5669–5671

A new asymmetric synthesis of the natural enantiomer of the indolizidino[8,7-*b*]indole alkaloid (+)-harmicine

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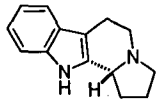
Abstract—We report a novel, facile and asymmetric approach for the synthesis of the indole alkaloid (+)-harmicine via a highly diastereoselective *N*-acyliminium cyclization reaction as a key synthetic step, and verify the relative stereochemistry of the key synthetic intermediate in this approach through X-ray crystallography.

Leishmaniasis, a disease spread by the bite of the sand fly, is found in tropical and sub-tropical regions, affecting some 12 million people in 88 countries. Symptoms of this disease vary from skin sores to fever, anaemia and damage to the spleen and liver. Common therapies have included the use of antimony-containing drugs, although less toxic treatments are currently in development.[1] Screening of the leaf extract of the Malaysian plant *Kopsia griffithii* by Kam and Sim showed strong *anti*-leishmania activity that was traced back to the fraction containing the indolizidino[8,7-*b*]indole alkaloid, (+)-harmicine, **1**.[2]



(+)-Harmicine, **1**

(+)-Harmicine has previously been prepared in racemic form by Knolker and Agarwal,[3] and asymmetric routes to (*S*)-*ent*-harmicine have been achieved by Ohsawa and co-workers, who were also able to establish that the absolute configuration of the naturally occurring compound was *R*.[4] Our research group has had considerable success in the development of asymmetric routes to several important heterocyclic templates over recent years, based around the development of a highly diastereoselective *N*-acyliminium cyclization strategy.[5] Our recent applications of this methodology in natural product synthesis has included targets from the *erythrina* group of alkaloids,[5f,i] and several indole alkaloids, including deplancheine.[5a,d,e,g] In this Letter we report the successful application of our *N*-acyliminium strategy in a new asymmetric synthesis of (*R*)-(+)-harmicine, **1**, the naturally occurring enantiomer.

Our approach to (+)-harmicine began with the synthesis of imide **2**, prepared from the β-amino alcohol derivative of (*S*)-tryptophan. Subjecting imide **2** to sodium borohydride reduction, as described in Scheme 1, resulted in a direct and highly diastereoselective cyclization to give the indolizidino[8,7-*b*]indole derivative **3** as a 9:1 mixture of diastereoisomers in 43% yield (Scheme 1). The major isomer was isolated by recrystallization from ethanol and its relative stereochemistry was confirmed by X-ray crystallographic analysis[6] (Scheme 1). Presumably, under the acidic reaction conditions, the electron-rich indole moiety is able to cyclize onto the *N*-acyliminium intermediate that is generated in situ.

The stereochemical outcome of the reaction can be rationalized based on models previously proposed by our group for similar types of substrates.[5k] The high degree of stereocontrol arises from a preferred conformation, shown in Scheme 1, having minimal $A^{(1,3)}$ strain between the H-atom at the stereogenic centre of the tryptophanol moiety and the lactam carbonyl group in the transition state.

To complete the synthesis of (+)-harmicine we were required to remove the hydroxymethyl auxiliary group

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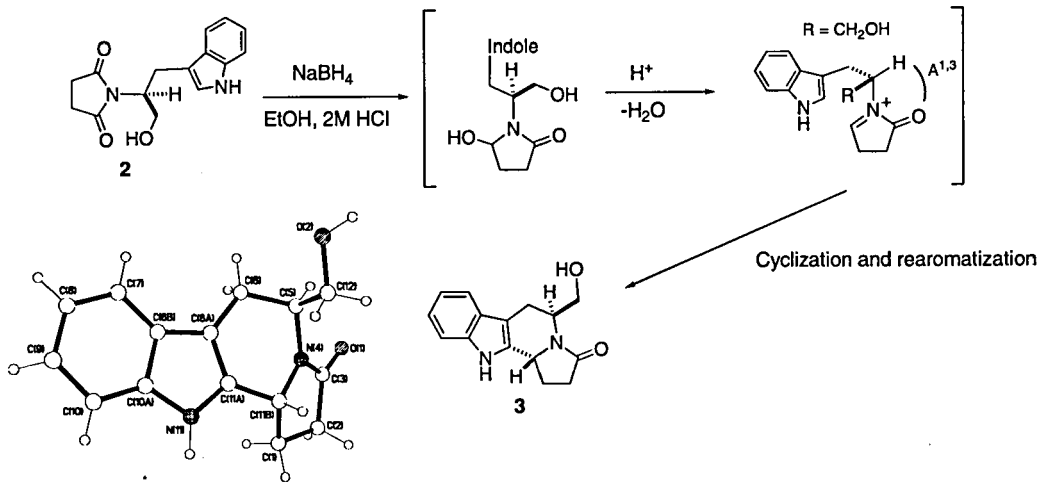
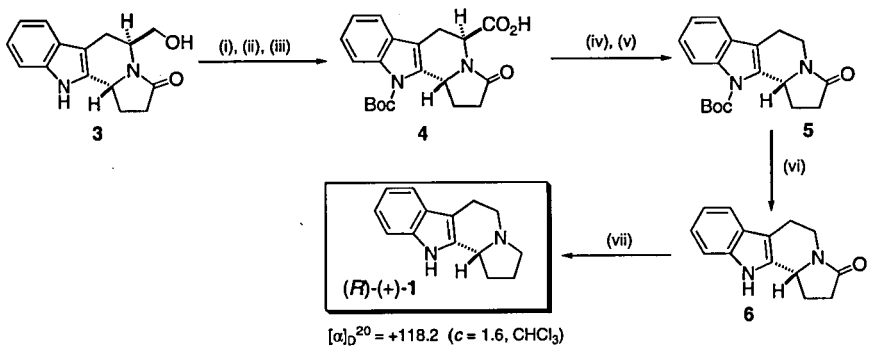
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.06.034



Scheme 1.



Scheme 2. Reagents and conditions: (i) IBX, DMSO, rt, 24 h (72%); (ii) Et_3N, $(Boc)_2O$, DMAP, THF, rt, 4 h (73%); (iii) $NaClO_2$, NaH_2PO_4, CH_3CN, *t*-BuOH, cyclohexene, 0 °C to rt, 18 h (79%); (iv) $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt, 18 h (66%); (v) *n*-Bu_3SnH, AIBN, toluene, Δ, 2 h (90%); (vi) TBAF, THF, Δ, 2 h then at rt, 9 h (69%); (vii) $LiAlH_4$, THF, Δ, 3 h (80%).

from compound **3**. Previous methods applied within our group to remove the hydroxymethyl 'auxiliary' substituent from other heterocyclic templates have involved a rhodium-induced decarbonylation sequence.[5f] Due to the rather long reaction times generally needed for substrates in this decarbonylation protocol we have now applied a more facile approach that relies upon a decarboxylation strategy (Scheme 2), used successfully by our group in recent natural product syntheses.[5a,d,e] Compound **3** was oxidized to the carboxylic acid derivative **4** through the corresponding aldehyde; from **4** we generated the acyl selenide derivative and subsequently performed a tin-mediated deacylation to yield the core indolizidino[8,7-*b*]indole ring system **5**. Deprotection of the indole nitrogen gave **6**, from which reductive removal of the lactam carbonyl group completed the synthesis of the natural product, **1**, (*R*)-(+)-harmicine, in 80% yield by LAH reduction in THF (Scheme 2). The optical rotation of our target compound, (*R*)-(+)-**1**, was determined to be +118.2 (*c* 1.6, $CHCl_3$) and was comparable to that reported by Kam and Sim for the isolated natural product [+119; (*c* 0.086, $CHCl_3$)].[2]

In summary we have reported a new and highly stereoselective synthesis of the indolizidino[8,7-*b*]indole alkaloid (*R*)-(+)-harmicine from a readily available, enantiomerically pure imide substrate.[7] Following acceptance of this Letter, our attention was brought to a recent asymmetric synthesis of (+)-harmicine by Czarnocki and Drabowicz that gave the natural product in 79% ee.[8]

Acknowledgements

The authors wish to thank Loughborough University and GSK Pharmaceuticals for the joint studentship support to S.N.G. We also wish to thank the EPSRC, UK, X-ray crystallography service in Southampton for collecting the data for the crystal structure of **3**.

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6. Crystallographic data (excluding structure factors) for structure **3** ($R = 0.0464$) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 641155. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
7. Data for selected compounds. Compound **3**: colourless needles, mp 266–267 °C; $[\alpha]_D$ 144.8 (*c* 0.48, EtOH); δ_H (400 MHz, DMSO) 1.77–1.85 (1H, m), 2.25–2.31 (1H, m), 2.50–2.58 (2H, m), 2.73 (1H, dd, *J* 2.1, 6.6), 2.82 (1H, d, *J* 15.8), 3.38 (2H, t, *J* 7.96), 4.47–4.52 (1H, m), 4.84–4.88 (2H, m), 6.95–6.99 (1H, m), 7.04–7.07 (1H, m), 7.31–7.34 (1H, m), 7.38–7.40 (1H) and 11.02 (1H, s); δ_C (100 MHz, DMSO) 21.1, 25.5, 31.1, 48.0, 50.7, 60.1, 104.1, 111.1, 117.7, 118.4, 120.9, 126.9, 133.4, 136.1, 172.6; MS (EI) *m/z* 256 [M^+, 87%] (M^+, 256.1215. $C_{15}H_{16}N_2O_2$ requires 256.1212). Compound *R*-(+)-**1**: yellow crystalline solid, mp 161–164 °C; $[\alpha]_D$ 118.2 (*c* 1.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.77–2.05 (3H, m), 2.35–2.44 (1H, m), 2.74–2.77 (1H, m), 2.88–2.96 (2H, m), 3.07–3.19 (2H, m), 3.31 (1H, ddd, *J* 2.0, 5.2, 12.8), 4.46–4.49 (1H, m), 7.06 (1H, dt, *J* 1.2, 7.6 Hz), 7.12 (1H, dt, *J* 1.2, 7.6 Hz), 7.36 (1H, d, *J* 7.2 Hz), 7.43 (1H, d, *J* 7.2 Hz) and 9.35 (1H, br s); δ_C (100 MHz, $CDCl_3$) 17.4, 23.1, 29.7, 45.9, 49.5, 57.6, 106.6, 111.3, 118.0, 119.3, 121.6, 126.7, 133.1, 136.4; MS (EI) *m/z* 212 [M^+, 75%] (M^+, 212.1184. $C_{14}H_{16}N_2$ requires 212.1181).
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JOC*Note*

A New Asymmetric Synthesis of the Anti-Tumor Alkaloid (*R*)-(+)-Crispine A

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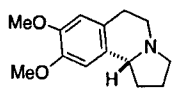
(*R*)-(+)-Crispine A

We report a novel, facile, and asymmetric approach for the synthesis of the anti-tumor alkaloid (+)-crispine A via a highly diastereoselective *N*-acyliminium cyclization reaction as a key synthetic step.

The pyrroloisoquinoline alkaloid (+)-crispine A, **1**, isolated in 2002 from *Clathrus crispus* by Zhao and co-workers, shows important biological activity against SKOV3, KB, and HeLa human cancer cell lines.[1] To date, syntheses of racemic crispine A have been achieved by Knolker and Agarwal,[2] Meyer and Opatz,[3] and more recently, by King.[4] The first enantioselective synthesis of this alkaloid was reported by Czarnocki and co-workers on the basis of the use of asymmetric transfer hydrogenation as a key synthetic step.[5]



Crispine A, **1**

Our own group has had considerable success in the development of asymmetric routes to several important heterocyclic templates, including the pyrroloisoquinoline system.[6] There has been considerable interest in the synthesis of the pyrroloisoquinoline core over recent years, with many approaches involving *N*-acyliminium chemistry in the key ring-forming step, of which several have also addressed the important question of stereocontrol in the cyclization.[7] In this current paper, we report the successful application of our own *N*-acyliminium strategy in an efficient new asymmetric synthesis of (+)-crispine A, **1**.

Our approach to crispine A began with the synthesis of imide **2**, prepared as previously reported from (2*S*)-2-amino-3-(3,4-dimethoxyphenyl)propan-1-ol and succinic anhydride.[6] Subjecting imide **2** to sodium borohydride reduction, as described in Scheme **1**, resulted in direct and highly diastereoselective cyclization to give tricyclic lactam **3** as a single diastereoisomer (as determined by 400 MHz ^{1}H NMR spectroscopy), in excellent yield (91%). Presumably, under the acidic reaction conditions, the electron-rich methoxy-substituted aryl ring is able to cyclize onto the *N*-acyliminium intermediate that is generated in situ. We have been able to confirm the relative stereochemistry of this advanced intermediate by single-crystal X-ray analysis.[6b] The relative stereochemistry observed in product **3** is as expected on the basis of the conformational models previously proposed by our group to rationalize such highly diastereoselective cyclization reactions onto *N*-acyliminium intermediates.[6]

Our completion of the total synthesis of crispine A required us to remove the hydroxymethyl auxiliary group, and to this end, we have investigated two alternative procedures. The most direct route to achieve this transformation would be the application of a method originally developed by Kraft,[8] and more recently applied by Martin,[9] involving a Raney nickel induced decarbonylative removal of the hydroxymethyl functionality. Martin has successfully applied this methodology in the synthesis of pumiliotoxin 251D from an advanced bicyclic lactam intermediate.[9] According to Kraft, primary alcohols undergo oxidation to aldehydes and are then subsequently decarbonylated when treated with Ra-Ni in refluxing toluene.[8] The quality of the Raney nickel used in this approach is known to be a critical factor in its success. In our hands, the Ra-Ni induced removal of the hydroxymethyl substituent from intermediate **3** proceeded smoothly as reported, and in an excellent yield of 98%, to give the corresponding lactam, **4**. Reductive

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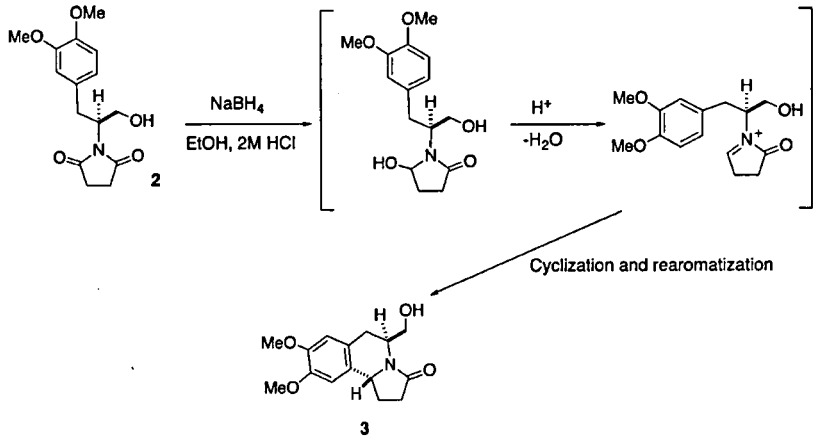
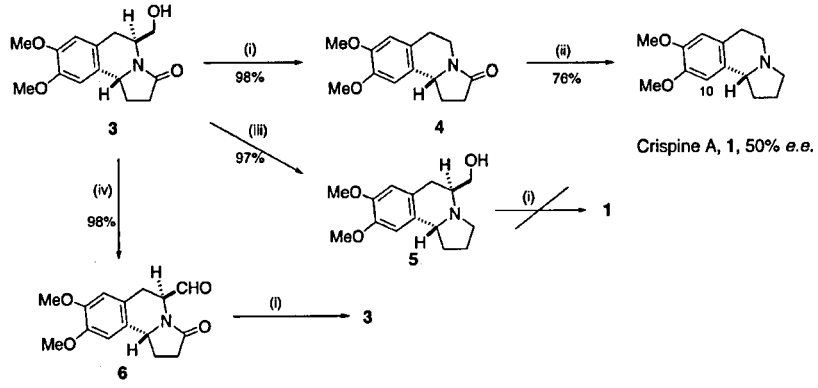
SCHEME 1



SCHEME 2[a]



[a] Key: (i) Ra-Ni (W2), toluene, Δ; (ii) LAH, THF, Δ, 3 h, then rt, 12 h; (iii) LAH, THF, Δ, 3 h, then rt, 12 h; (iv) IBX, EtOAc, Δ, 4 h.

removal of the lactam carbonyl group was achieved using LAH in THF, thus completing the synthesis of crispine A (Scheme 2). In the recent enantioselective synthesis of this alkaloid, reported by Czarnocki and Drabowicz,[5] the enantiomeric excess of the alkaloid was determined by NMR spectroscopic methods using (*R*)-(+)-*tert*-butylphenylphosphinothiolic acid as a chiral additive. This research team were kind enough to furnish us with an amount of this chiral reagent for use in our own studies, and the determinations of product ee described in this paper are thus based on an identical NMR spectroscopic procedure. Use of this thioacid as a chiral shift reagent allowed the determination of the ee of our product, which was shown to have a disappointingly low value of 50% ee. The diagnostic signal in the ^{1}H NMR spectrum used in the determination is the aromatic C(10) proton which, in the presence of the chiral shift reagent, shows distinct, well-separated singlet peaks for the enantiomers at 6.39 and 6.22 ppm. In our case, although the level of product ee was moderate, the major enantiomer was confirmed to be the desired (*R*)-crispine A, as expected. Although the use of Ra-Ni (W2) for removal of the hydroxymethyl group allows for rapid and relatively high-yielding access to crispine A, in only three synthetic steps from imide **2**, epimerization of the benzylic stereocentre was occurring at some point in the two-step sequence shown in Scheme 2 and thus compromising the enantiomeric purity of the final product.

As an alternative approach, we chose to reverse the order of synthetic transformations and first removed the lactam carbonyl using LAH to yield amine **5**, followed by the Ra-Ni reaction. Unfortunately we were unable to achieve the removal of the hydroxymethyl group by following this alternative scheme of events, observing only decomposition of amine **5**.

As noted above, the literature precedent for the use of Ra-Ni is suggestive of an initial oxidation of the hydroxymethyl group to an aldehyde intermediate before subsequent decarbonylation.[8] Based on this proposed mechanism, we decided to investigate the use of the aldehyde derivative **6** as a substrate for the Ra-Ni reaction, reasoning that the aldehyde may undergo direct decarbonylation. In our hands, however, compound **6** was simply reduced back to the hydroxymethylated substrate **3** under the usual reaction conditions. Since lactam removal to access **5** proceeded without affecting the diastereoisomer ratio (i.e., **5** was obtained as a single diastereoisomer), we propose that racemization of substrate **3** is taking place during the Ra-Ni procedure (step i, Scheme 2).

This issue was ultimately overcome through the application of a Rh-induced decarbonylation sequence previously applied by us in our work on the *Erythrina* alkaloid series.[10] Compound **3** was oxidized to aldehyde **6** in good yield using IBX in ethyl acetate, followed by Rh-induced decarbonylation using our previously developed procedure.[10] Amide **4** was again trans-

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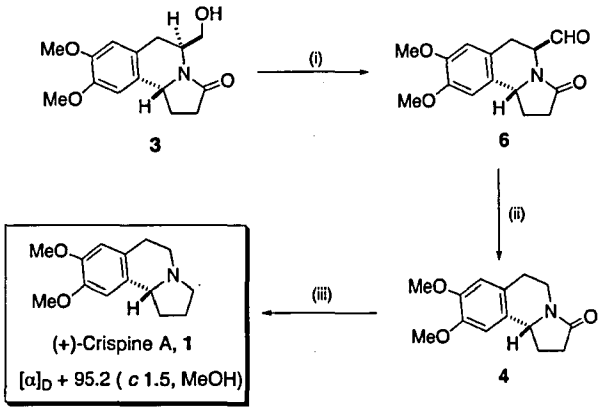
SCHEME 3[a]



[a] Key: (i) IBX, EtOAc, Δ, 4 h (98%); (ii) $Rh(PPh_3)_2(CO)Cl$, dppp, xylene, Δ, 240 h (46%); (iii) LAH, THF, 20 h (58%).

formed into the target, (*R*)-(+)-crispine A, **1**, in 58% yield by LAH reduction in THF (Scheme 3).

Compound **1**, obtained as detailed in Scheme 3, was shown to have an ee of 95% by using the ^1H NMR chiral shift experiment described above. The optical rotation of our product was determined to be +95.2 (*c* 1.5, MeOH) and was comparable to that reported by Zhao and co-workers for the natural product isolate [+91.0 (MeOH)].[1] Czarnocki and Drabowicz observed a rotation of + 100.4 (*c* 1) using chloroform as solvent, due to apparent problems of dissolution when using methanol.[5]

In summary, we report a new, efficient, and highly stereoselective synthesis of the anti-tumor alkaloid (+)-crispine A in four synthetic steps from a readily available enantiomerically pure imide substrate **2** in an overall yield of 24%.

Experimental Section

1-(2*S*)-[2-(3,4-Dimethoxyphenyl)-1-hydroxymethylethyl]pyrrolidine-2,5-dione, 2. Succinic anhydride (2.56 g, 25.60 mmol) and (2*S*)-2-amino-3-(3,4-dimethyloxy)phenyl)propan-1-ol (4.92, 23.27 mmol) were stirred in toluene (100 mL) under an atmosphere of nitrogen. Triethylamine (4 mL) was added to the resultant solution and the mixture heated at reflux for 18 h. After 18 h, the reaction was cooled to room temperature and solvent removed by rotary evaporator to yield a yellow oil. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and ethyl acetate as eluent to produce a colorless solid (4.87 g, 71%): mp 124−125 °C; $[\alpha]_D$ −73.2 (*c* = 1.01 in CH_2Cl_2); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1700 (CO), 2938 (aliphatic CH) and 3447 (OH); δ_H (400 MHz, $CDCl_3$) 2.51−2.61 (4 H, m, $COCH_2CH_2CO$), 2.95−3.10 (2 H, m, $ArCH_2CHN$), 3.79−3.85 (1 H, m, CH(*H*)OH), 3.83 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 4.03 (1 H, dd, J 8.0, 11.6 Hz, CH(*H*)OH), 4.47−4.52 (1 H, m, $ArCH_2CHN$) and 6.67−6.80 (4 H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_2), 27.8 (CH_2), 33.1 (CH_2), 55.6 (CH), 55.8 (OCH_3), 55.8 (OCH_3), 61.8 (CH_2), 111.0 (CH), 111.9 (CH), 121.0 (CH), 129.6 (C), 147.6 (C), 148.7 (C), 178.3 (CO) and 178.3 (CO); MS (FAB) *m/z* 294 [(M + H)$^+$, 4.0] ((M + H)$^+$, 294.1344, $C_{15}H_{19}NO_5$ requires 294.1342).

(5*S*,10b*R*)-5-Hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, 3. 1-(2*S*)-[2-(3,4-Dimethoxyphenyl)-1-hydroxymethylethyl]pyrrolidine-2,5-dione **2** (4.09 g, 13.94 mmol) was dissolved in absolute ethanol (100 mL) and cooled to 0 °C. Sodium borohydride (5.28 g, 139.4 mmol) was then added with stirring. A 2 M solution of HCl in absolute ethanol (6.97 mL, 13.94 mmol) was then slowly added via syringe over a 3 h period. The resultant solution was acidified to pH 1−3 by the addition of a 2 M solution of HCl in absolute ethanol over a 15 min period. This afforded a white suspension, which was stirred for a further 20 h. The reaction was quenched with sodium hydrogen carbonate and extracted with dichloromethane (3 × 40 mL). The dichloromethane layers were then combined and dried over anhydrous magnesium sulfate and solvent removed by rotary evaporation to yield the target cyclized compound as a single diastereoisomer, which was purified by column chromatography using silica gel as absorbent and 5% methanol/dichloromethane as eluent to yield a white solid (3.01 g, 78%): mp 177−179 °C; $[\alpha]_D$ +133.6 (*c* = 1.03 in CH_2Cl_2); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1666 (CO), 2939 (aliphatic CH) and 3369 (OH); δ_H (400 MHz, $CDCl_3$) 1.91−1.98 (1 H, m, CH(*H*)CH_2CO), 2.46−2.52 (1 H, m, CH_2CH(*H*)CO), 2.61−2.69 (3 H, m, CH(*H*)CH_2CO, CH_2CH(*H*)CO and ArCH(*H*)-CHN), 3.00 (1 H, dd, *J* 6.8, 16.0 Hz, ArCH(*H*)CHN), 3.62−3.73 (2 H, m, CH_2OH), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.47−4.50 (1 H, m, $ArCH_2CHN$), 4.76 (1 H, t, *J* 7.6 Hz, NCHAr), 6.59 (1 H, s, Ar*H*) and 6.63 (1 H, s, Ar*H*), (OH not visible); δ_C (100 MHz, $CDCl_3$) 27.1 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 49.5 (CH), 54.2 (CH), 55.9 (OCH_3), 56.1 (OCH_3), 63.2 (CH_2), 107.3 (CH), 111.7 (CH), 124.1 (C), 128.4 (C), 148.0 (C), 148.2 (C) and 175.1 (CO); MS (FAB) *m/z* 278 [(M + H)$^+$, 27.5] ((M + H)$^+$, 278.1395, $C_{15}H_{19}NO_4$ requires 278.1392).

(10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, 4, by Raney-Ni Route. Freshly prepared Raney nickel (W-2) (7.08 g) was washed with water (3 × 20 mL) followed by 2-propanol (2 × 20 mL). 2-Propanol was decanted, the Raney nickel was taken up in toluene, and the residual water and 2-propanol were azeotropically removed using a Dean−Stark trap. A solution of (5*S*,10b*R*)-5-hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one **3** (1.18 g, 6.49 mmol) in toluene (60 mL) was added, and the reaction was refluxed under Dean−Stark conditions for 4 h. The resulting solution was filtered through a Celite pad, washed with methanol, and evaporated under reduced pressure to yield the target compound as a yellow oil (1.03 g, 98%): $[\alpha]_D$ +175.8 (*c* = 3.09 in $CHCl_3$); ν_{max} (thin film, $CHCl_3$)/cm^{-1} 1681 (CO) and 2934 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.82−1.90 (1 H, m, CH(*H*)CH_2CO), 2.45−2.71 (4 H, m, CH(*H*)CH_2CO, CH_2CH_2CO and ArCH(*H*)CH_2N), 2.85−2.93 (1 H, m, ArCH(*H*)CH_2N), 2.99−3.06 (1 H, m, $ArCH_2$-CH(*H*)N), 3.87 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.31 (1 H, ddd, *J* 2.4, 6.0, 12.8 Hz, $ArCH_2$CH(*H*)N), 4.74 (1 H, t, *J* 8.0 Hz, NCHAr), 6.58 (1 H, s, Ar*H*) and 6.63 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_2), 28.1 (CH_2), 31.8 (CH_2), 37.1 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 56.6 (CH), 107.6 (CH), 111.6 (CH), 125.5 (C), 129.3 (C), 147.9 (C), 148.0 (C) and 173.4 (CO); MS (FAB) *m/z* 248 [(M + H)$^+$, 31.3] ((M + H)$^+$, 248.1287, $C_{14}H_{17}NO_3$ requires 248.1287).

(*R*)-(+)-Crispine A, 1, by Raney-Ni Route. Lithium aluminum hydride (1 M solution in tetrahydrofuran) (4.5 mL, 4.49 mmol) was added to a predried flask fitted with a reflux condenser under a nitrogen atmosphere. Anhydrous tetrahydrofuran (100 mL) was added and the solution cooled to 0 °C. (10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one **4** (1.05 g, 4.49 mmol) in anhydrous tetrahydrofuran (50 mL) was added dropwise to the hydride solution at 0 °C and the resulting solution heated under reflux for 3 h and then stirred for a further 12 h at room temperature. Diethyl ether (50 mL) was added, and reaction was quenched by the careful addition of saturated sodium potassium tartate. The mixture was stirred for a further 1 h before the addition of anhydrous magnesium sulfate prior to filtration through a Celite pad. The filtrate was evaporated under reduced pressure, and the resultant yellow solid was purified by column chromatography using silica gel as absorbent and 10:1 chloroform/methanol as eluent to yield a colorless solid (752 mg, 76%): mp 88−89 °C (lit.[1] mp 88−89 °C); $[\alpha]_D$ + 43.9 (*c* = 1.14 in CH_3OH) [lit.[1] $[\alpha]_D$ +91.0 (CH_3OH)]; ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 2934 (aliphatic CH); δ_H

(400 MHz, $CDCl_3$) 1.72−1.79 (1 H, m, CH(*H*)CH_2CH_2N), 1.86−1.96 (2 H, m, $CH_2CH_2CH_2N$), 2.31−2.37 (1 H, m, CH(*H*)CH_2-CH_2N), 2.60−2.79 (3 H, m, $CH_2CH_2CH(H)N$, ArCH(*H*)CH_2N and ArCH$_2$CH(*H*)N), 2.98−3.11 (2 H, m, $CH_2CH_2CH(H)N$ and ArCH-(*H*)CH_2N), 3.18 (1 H, ddd, *J* 2.8, 5.6, 10.8 Hz, ArCH$_2$CH(*H*)N), 3.50 (1 H, t, *J* 8.4 Hz, NC*H*Ar), 3.84 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 6.57 (1 H, s, Ar*H*) and 6.61 (1 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_2), 27.9 (CH_2), 30.6 (CH_2), 48.3 (CH_2), 53.2 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 62.9 (*C*H), 108.8 (*C*H), 111.3 (*C*H), 126.1 (*C*), 130.5 (*C*), 147.3 (*C*) and 147.4 (*C*); MS (FAB) *m/z* 232 [MI, 66.6] (MI, 233.1419, $C_{14}H_{19}NO_2$ requires 233.1416). The ee of crispine A obtained via this method was determined to be ca. 50% by the ^{1}H NMR chiral shift experiments described in the discussion.

(10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, 4, by Rh-Decarbonylation Route. Bis-(triphenylphosphine)rhodium(I) carbonyl chloride (0.012 g, 0.018 mmol) was added to anhydrous xylene (10 mL) under a nitrogen atmosphere. The mixture was then stirred at 80 °C for 15 min. 3-Bis(diphenylphosphino)propane (0.019 g, 0.046 mmol) was then added and the mixture stirred for a further 30 min at this temperature. To the stirred mixture was then added aldehyde **6** (0.102 g, 0.371 mmol) in anhydrous xylene (10 mL), and the resulting mixture was heated under reflux for a further 240 h. The solvent was removed under reduced pressure. The crude product was then adsorbed onto silica and purified by flash column chromatography over silica with 3:1 ethyl acetate/hexane as the eluent to produce the **4** as an oil (0.042 g, 46%). Spectral analysis of compound **4** obtained via this route was identical to that reported above.

(*R*)-(+)-Crispine A, 1, by Rh-Decarbonylation Route. Treatment of amide **4**, obtained via Rh-decarbonylation chemistry, as described above using LAH gave crispine A, **1**, in 58% yield and was shown to have an ee of >95% by ^{1}H NMR chiral shift experiments as described in the discussion. Spectral analysis of compound **1** obtained via this route was identical to that reported above. The optical rotation of this product was determined to be +95.2 (*c* 1.5, MeOH) and was comparable to that reported by Zhao and co-workers for the natural product isolate [+91.0 (MeOH)].[1]

(5*S*,10b*R*)-(8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-*a*]isoquinolin-5-yl)methanol, 5. Lithium aluminum hydride (1 M solution in tetrahydrofuran) (3.61 mL, 3.61 mmol) was added to a predried flask fitted with a reflux condenser under a nitrogen atmosphere. Anhydrous tetrahydrofuran (50 mL) was added and the solution cooled to 0 °C. (5*S*,10b*R*)-8,9-Dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, **3** (500 mg, 1.80 mmol), in anhydrous tetrahydrofuran (20 mL) was added dropwise to the hydride solution at 0 °C and the resulting solution heated under reflux for 3 h and then stirred for a further 12 h at room temperature. Diethyl ether (20 mL) was added, and the reaction was quenched by the careful addition of saturated sodium potassium tartrate. The mixture was stirred for a further 1 h before the addition of anhydrous magnesium sulfate prior to filtration through a Celite pad. The filtrate was evaporated under reduced pressure, and the resultant yellow solid was purified by column chromatography using silica gel as absorbent and 10:1 chloroform/methanol as eluent to yield a colorless solid (460 mg, 97%): $[\alpha]_D$ +79.1 (*c* = 1.83 in $CHCl_3$); ν_{max} (thin film, neat)/cm^{-1} 2934 (aliphatic CH) and 3374 (OH); δ_H (400 MHz, $CDCl_3$) 1.78−1.89 (3 H, m, C$H_2CH_2CH_2N$ and $CH_2CH(H)CH_2N$), 2.41−2.46 (2 H, m, $CH_2CH(H)CH_2N$ and ArCH(*H*)CHN), 2.76−2.81 (1 H, m, $CH_2CH_2CH(H)N$), 2.96 (1 H, dd, *J* 5.2, 16.0 Hz, ArCH(*H*)CHN), 3.05−3.09 (1 H, m, CH_2CH_2-CH(*H*)N), 3.13−3.16 (1 H, m, ArCH$_2$C*H*N), 3.22 (1 H, br, s, O*H*), 3.42 (1 H, dd, *J* 8.0, 10.4 Hz, CH(*H*)OH), 3.52 (1 H, dd, *J* 5.2, 10.4 Hz, CH(*H*)OH), 3.85 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 4.22 (1 H, t, *J* 6.4 Hz, NC*H*Ar) and 6.56 (2 H, s, Ar*H*); δ_C (100 MHz, $CDCl_3$) 24.0 (CH_2), 26.3 (CH_2), 33.5 (CH_2), 51.9 (CH_2), 55.6 (*C*H), 55.6 (OCH_3), 55.8 (OCH_3), 62.6 (CH_2), 109.0 (*C*H), 111.2 (*C*H), 112.3 (CH), 124.9 (*C*), 130.9 (*C*), 147.3 (*C*) and 147.6 (*C*); MS (FAB) *m/z* 264 [(M + H)$^+$, 14.2] ((M + H)$^+$, 264.1596, $C_{15}H_{21}$-NO_3 requires 264.1600).

(5*S*,10b*R*)-8,9-Dimethoxy-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbaldehyde, 6. *o*-Iodoxybenzoic acid (4.48 g, 16.12 mmol) was added to a solution of (5*S*,10b*R*)-5-hydroxymethyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, **3** (1.49 g, 5.37 mmol), in ethyl acetate (75 mL), and the reaction was heated under reflux for 4 h. The resulting mixture was cooled to room temperature, filtered through a sinter funnel, and evaporated to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 3:1 light petroleum/ethyl acetate as eluent to isolate the target compound as a yellow foam (1.46 g, 99%): $[\alpha]_D$ +66.5 (*c* = 1.3 in $CHCl_3$); ν_{max} (thin film, CH_2Cl_2)/cm^{-1} 1672 (CO) and 2937 (aliphatic CH); δ_H (400 MHz, $CDCl_3$) 1.85−1.93 (1 H, m, CH(*H*)CH_2CO), 2.47−2.55 (1 H, m, $CH_2CH(H)$CO), 2.68−2.75 (2 H, m, CH(*H*)CH_2CO and $CH_2CH(H)$CO), 3.06 (1 H, dd, *J* 7.2, 16.0 Hz, ArCH(*H*)CHN), 3.22 (1 H, dd, *J* 2.4, 16.4 Hz, ArCH-(*H*)CHN), 3.85 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.91 (1 H, t, *J* 6.8 Hz, NC*H*Ar), 5.01 (1 H, dd, *J* 2.4, 7.2 Hz, ArCH$_2$C*H*N), 6.53 (1 H, s, Ar*H*), 6.65 (1 H, s, Ar*H*) and 9.62 (1 H, s, C*H*O); δ_C (100 MHz, $CDCl_3$) 26.5 (CH_2), 28.2 (CH_2), 31.4 (CH_2), 54.7 (*C*H), 55.7 (*C*H), 56.0 (OCH_3), 56.1 (OCH_3), 107.5 (*C*H), 111.5 (*C*H), 122.3 (*C*), 128.1 (*C*), 148.2 (*C*), 148.5 (*C*), 174.4 (*C*O) and 198.9 (*C*HO); MS (FAB) *m/z* 276 [(M + H)$^+$, 22.2] ((M + H)$^+$, 276.1240, $C_{15}H_{17}NO_4$ requires 276.1236).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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