Application of $N$-acyliminium ions in the asymmetric synthesis of indole alkaloids

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Application of $N$-Acyliminium Ions in the Asymmetric Synthesis of Indole Alkaloids

by

Christopher Ian Thomas
BSc (Hons) DIS

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of

Doctor of Philosophy

at Loughborough University

August 2004
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MS = mass spectrum
NMM = N-methylmorpholine
NMO = N-methylmorpholine N-oxide
NMR = nuclear magnetic resonance
NOE = nuclear overhauser effect
Nu = nucleophile
PCC = pyridinium chlorochromate
PDC = pyridinium dichromate
q = quartet
Red-Al® = sodium bis(methoxyethoxy)aluminium hydride
RT = room temperature
s = singlet
t = triplet
TBAF = tetra-n-butylammonium fluoride
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TMS = trimethylsilyl or tetramethylsilane (internal standard for NMR spectroscopy)
TPAP = tetrapropylammonium perruthenate
UV = ultraviolet
Abstract

We have developed a new and highly stereoselective approach to indolizino[8,7-b]indole derivatives such as (A) and indolizino[2,3-a]quinolizidines (B). Our protocol involves the cyclisation of pendent aromatic substituents onto N-acyliminium intermediates as a key ring-forming step. The indolizino[2,3-a]quinolizidines are of great interest and significance since this heterocyclic template is found within a plethora of indole alkaloids.

In order to demonstrate the synthetic potential of this methodology we have established conditions for removal of the pendent hydroxymethyl substituent from cyclisation products such as (A) and (B). Furthermore, we have demonstrated the functionalisation of our cyclisation products via conjugate addition chemistry.

We have utilised this methodology and herein describe the asymmetric synthesis of both enantiomers of deplancheine (C), furnishing the natural product and its enantiomer with >95% e.e. Our route relies on a highly stereoselective cyclisation reaction to access the indolizino[2,3-a]quinolizidine template from a readily available non-racemic chiral template.

Chapter 1

Introduction
1.1 *N*-Acyliminium Ions

1.1.1 Brief History

In the last few decades progress in the art of organic synthesis has been achieved through marked advances in classical and newly developed reagents in terms of their chemo-, regio- and stereoselectivity. With respect to the former, the Mannich reagent (1) and the amidoalkylating reagent (2) are well known. The latter of these two, also known as an *N*-acyliminium ion, had been primarily designed to allow Mannich type condensations with primary amines. It emerged, however, that the *N*-acyliminium ion has highly versatile reaction characteristics in a much broader sense, reflected in an impressive number of synthetic applications; the majority of these reactions are of the intermolecular type. The study of intramolecular processes has demonstrated the reactivity and selectivity pattern of amidoalkylative reagents in another dimension.

![Structural formulas](image)

1.1.2 *N*-Acyliminium Ions in Synthesis

The development of cyclisations that proceed via *N*-acyliminium species is relatively recent, in contrast to cyclisations involving iminium cations, such as the venerable Mannich reaction, the Bischler-Napieralski reaction and the Pictet-Spengler reaction. Both types of intermediate have been employed extensively in the synthesis of alkaloidal and related systems, including some early uses of *N*-acyliminium ions in amidoalkylation reactions.

*N*-Acyliminium ions (2) are an important class of electrophile, which participate in carbon-carbon bond forming reactions. Reactions between *N*-acyliminium ions and nucleophiles (also named amidoalkylation or Mannich-type condensations) have been utilised frequently to introduce substituents at the α-carbon of an amine. The
mechanistic scheme applicable to most amidoalkylation reactions is shown in Scheme 1. Through acid activation, precursor (3) can be induced to form the corresponding $N$-acyliminium ion (2). Subsequent reaction (irreversibly) of a nucleophile yields the substituted product (4). $^7$

![Scheme 1](image)

This scheme closely resembles that of an $S_N 1$ process. Although at present kinetic data pertinent to this type of amidoalkylation is unknown, a study by Zaugg and Martin $^8$ distinguished between two extreme kinetic situations:

(i) Formation of the $N$-acyliminium ion is rate-limiting.

(ii) Reaction of the nucleophile is rate-limiting.

The former case would imply that a more stable $N$-acyliminium ion leads to a faster reaction whereas in the latter case the opposite is true. Other factors which influence the rate of amidoalkylation are the nature of the leaving group and the solvent, as well as the structure of the acidic catalyst.

An important side reaction in $N$-acyliminium ion chemistry is enamide formation via the loss of a proton. In an acidic medium this reaction may be reversible but this is not always the case. Subsequent nucleophilic reaction of the enamide with the $N$-acyliminium ions still present can lead to dimeric structures. Such problems may arise if the $N$-acyliminium ion is not trapped fast enough by a nucleophile. Factors which may facilitate this are:

- The nucleophile is not very reactive.
- There is too much steric hindrance.
• Stereoelectronic factors are unfavourable (intramolecular case).

• A medium or large-sized ring is to be formed.7

1.1.3 Reactivity of N-Acyliminium Ions vs Mannich (Iminium) Ion

Intermediates

It has been established throughout the last two decades that substitution with electron-attracting groups at nitrogen renders the Mannich-intermediate (5) considerably more reactive by enhancing its cationic character. Of such modified cations the \( N \)-acyl derivative (6) and the carbamate (7) have been most widely exploited through the application of other electronegative substituents such as the amide (8) and \( N \)-tosyl (9) cations. Depending on the type of \( R^1, R^2 \) and \( R^3 \) numerous cyclic and linear forms can be distinguished and new variations such as the hydrazonium (10) can be utilised.9

\[
\begin{align*}
    & R^2 \quad R^1 \quad (5) R^4 = H, \text{ alkyl} \quad (8) R^4 = \text{CONR}_2 \\
    & R^3 \quad R^4 \quad (6) R^4 = \text{acyl} \quad (9) R^4 = \text{Tos} \\
    & (7) R^4 = \text{COOR} \quad (10) R^4 = \text{NR}_2
\end{align*}
\]

A study by Wurthwein10 et al. compared the \( ^{13} \text{C} \) NMR spectra of the iminium salts (11) and (12) and found that substitution of an \( N \)-methyl by an \( N \)-acetyl group leads to a downfield shift of the imino carbon absorption of approximately 5 ppm. Thus, one may predict that \( N \)-acyliminium ions are more electrophilic, i.e. more reactive than iminium ions.

\[
\begin{align*}
    \text{184.6 ppm} & \quad \begin{array}{c}
    \text{Ph} \\
    \text{Ph} \\
    \Theta
    \end{array} & \quad \begin{array}{c}
    \text{Ph} \\
    \text{Ph} \\
    \text{SbCl}_6
    \end{array} \\
    \text{(11)} \\

    \text{189.7 ppm} & \quad \begin{array}{c}
    \text{Ph} \\
    \text{Me} \\
    \Theta
    \end{array} & \quad \begin{array}{c}
    \text{Ph} \\
    \text{Me} \\
    \text{SbCl}_6
    \end{array} \\
    \text{(12)}
\end{align*}
\]

The difference in reactivity in intramolecular reactions is well illustrated through olefin cyclisations applied to Erythrina alkaloid synthesis in work carried out by Boekelheide and co-workers.11 Both \( N \)-acyliminium ions (13a, 13b) generated from
the keto amide precursors (14a, 14b) gave the expected cyclisation products (15a, 15b). Conversely, attempted ring closure of the iminium salt (16) led to unidentifiable products.

![Chemical Structures](image)

One should note that these olefin cyclisations are in fact reversible processes, the reverse reaction being a Grob fragmentation. The product of an iminium-olefin cyclisation being an amine is much more susceptible to fragmentation than the amide derived from an N-acyliminium-olefin cyclisation. Consequently, the greater usefulness of N-acyliminium ion cyclisations in organic synthesis may be primarily attributed to their irreversibility.7

1.1.4 N-Acyliminium Ion Formation and Synthesis of their Precursors

For application in elaborate organic syntheses, N-acyliminium ions are almost always generated in situ, in view of their limited stability and high reactivity. There are five principal mechanisms for the formation of N-acyliminium ions as illustrated in Scheme 2.
Route a) $N$-Acylation of Imines (Schiff Bases)

Condensation of aldehydes or ketones with primary amines produces imines in high yield. In 1914, James and Judd\(^2\) first reported the acylation of imines with reactive carboxylic acid derivatives such as acid chlorides or anhydrides. Benzalaniline (17) and benzoyl chloride (18) were reacted to give the precursor (19), which was readily hydrolysed in water to give benzaldehyde (21) and benzanilide (22) (Scheme 3). The lability of the carbon-chlorine bond illustrates the propensity to $N$-acyliminium ion (20) formation in this system.\(^7\)
Route b) *N*-Protonation of *N*-acylimines

Due to the relative instability of *N*-acylimines (tautomerize rapidly into the corresponding enamide), this method for the preparation of *N*-acyliminium ions is more of mechanistic than synthetic interest. Wurthwein and co-workers\textsuperscript{10} investigated the protonation of imine (23) and produced convincing evidence for the *N*-acyliminium ion structure of the product (24) (Scheme 4).

Route c) Electrophilic Addition to Enamides

Acylation of an imine (25) with an acid chloride, followed by elimination generates the enamide (26). *N*-Acyliminium ion formation is possible via protonation of the enamide (Scheme 5).
Route d) Oxidation of Amides

The removal of hydride from the α-carbon of an amide formally leads to an \( N \)-acyliminium ion. Several research groups have developed an electrochemical method to facilitate this transformation.\(^{13-15}\) The mechanism (Scheme 6) involves initial removal of an electron from the lone pair on nitrogen of (27) generating the species (28). Subsequent loss of a proton and another electron from (28) forms the corresponding \( N \)-acyliminium ion (29). These electrochemical oxidations are conducted in the presence of a nucleophile, normally methanol, in order that the \( N \)-acyliminium ion is trapped as soon as it is formed to give the α-methoxyalkyl amide (30). This reaction is effective for a wide variety of amides and carbamates and there are few other reports of \( N \)-acyliminium ion generation via hydride abstraction from amides.
The heterolysis of α-substituted amides is the most common method employed for the generation of synthetically useful N-acyliminium ions. In the vast majority of cases the leaving group is an oxygen substituent, but may also be a halogen, nitrogen, sulphur or phosphorous substituent. Generally, Brønsted or Lewis acids are used to generate the N-acyliminium ion (32) from the α-oxyalkyl amide precursor (31) if R is alkyl or hydrogen (Scheme 7). If R is acetyl or methanesulfonyl, no acidic catalyst is required.
1.1.5 N-Acyliminium Ion Formation - Synthesis of Bicyclic and Tricyclic Lactams

Bicyclic lactams have been employed in various ways in the asymmetric synthesis of tertiary and quaternary carbon centres. Two general methods have been developed for the construction of the bicyclic lactam system and involve condensation of an optically pure amino alcohol and a dicarbonyl compound.
In the first route a cyclodehydration process was utilised between an optically pure amino alcohol (33) and a \( \gamma \)-ketoacid (34) (Scheme 8).\(^{16}\) The second route developed to access these bicyclic lactams is related to the extensive work of Speckamp\(^{9,17}\) involving \( N \)-acyliminium species (Scheme 9).

Condensation of an optically pure amino alcohol (35) with a cyclic anhydride afforded the imide (36), which, on addition of hydride, afforded the ethoxy lactam (37). This intermediate was subjected to acidic conditions resulting in ring closure via the \( N \)-acyliminium ion species (38), furnishing the lactam (39).

Meyers has extensively studied the chemistry of such chiral lactams utilising and extending the scope of this methodology.\(^{18,19}\) This group accessed these templates by condensation of \( \beta \)-amino alcohol derivatives with \( \gamma \)-carboxylic acids.\(^{20}\) Applications of the Meyers bicyclic lactam substrates in synthesis are discussed in Section 1.3.

![Scheme 10](attachment:scheme10.png)

Tricyclic lactams as \( N \)-acyliminium ion precursors have been reported by Allin\(^{21-24}\) \( et al.\) for the synthesis of substituted isoindolinone derivatives. Diastereomerically pure \( N \)-acyliminium ion precursor (40) required for initial studies on isoindolinone targets
(41a, 41b) was prepared directly from the corresponding enantiomerically pure amino alcohol substrate, S-phenylalaninol, as outlined in Scheme 10.

1.1.6 Detection of N-Acyliminium Ion Intermediates by NMR Spectroscopy

It has been mentioned already, that N-acyliminium ions, in view of their limited stability and high reactivity, are almost always generated in situ. Consequently, the observation of a transient N-acyliminium ion intermediate in dynamic NMR is extremely rare (reported only twice). Yamamoto and co-workers conducted a specially designed experiment in which the alkoxy carbamate (42), in the presence of TfO at -55 ºC, produced a clean 13C NMR spectrum of the intermediate (43) upon treatment with a Lewis acid (Scheme 11).

In a more recent study, it was found that treatment of bis(homoallyl) hydroxylactam (44) with BF3·OEt2 at 25 ºC produced the 13C NMR spectrum of the N-acyliminium ion (45). This intermediate was slowly (1 h) converted to the fluoro compound (46). Although not entirely clear, the reason for this unexpected stability is thought to be related to the greater withdrawing ability of the amide carbonyl compared to the carbamate, as demonstrated by spectral data.
1.2 Carbon-carbon Bond Formation Using N-Acyliminium Intermediates

1.2.1 Intramolecular Amidoalkylations with Aromatic π-Nucleophiles

The reactions of N-acyliminium ions with tethered π-bonds are among the most important methods for preparing complex nitrogen containing heterocycles. Since the introduction of the N-acyliminium method as a versatile tool the γ-lactam derivatives have prominently figured in the field of intramolecular applications.

\[
\text{TMS} \quad & \quad \begin{array}{c}
\begin{array}{c}
\text{TMS} \\
\text{HCOOH}
\end{array}
\end{array}
\quad & \\
\begin{array}{c}
\begin{array}{c}
\text{TMS} \\
\text{HCOOH}
\end{array}
\end{array}
\end{array}
\]

\[
(47a) \quad X, Y = \text{COOEt} \\
(47b) \quad X = \text{COOMe}, Y = \text{SO}_2\text{Ph}
\]

Scheme 12

Many examples include the presence of chiral elements mostly in the starting alkoxy lactam. Speckamp\textsuperscript{27} et al. examined cyclisation reactions between the tethered π-nucleophile in (47a-b) and the iminium ion generated by acid induced loss of the isopropoxy group resulting in (48) (Scheme 12).

Although isolated examples were known, the major breakthrough in the synthetic application of the intramolecular amidoalkylation occurred in the early 1950s, when the reaction was applied in alkaloid syntheses.\textsuperscript{7} The pioneering work carried out by Belleau\textsuperscript{28} and Mondon\textsuperscript{29} on the synthesis of Erythrina alkaloids by ring closure of N-acyliminium ions (49a) (R\textsuperscript{1} = O, R\textsuperscript{2} = H\textsubscript{2}) and (49b) (R\textsuperscript{1} = H\textsubscript{2}, R\textsuperscript{2} = O), respectively, as well as the synthesis of yohimbine by van Tamelen\textsuperscript{30} et al. via a route in which the essential step is the acid-catalysed ring closure of the N-acyliminium ion (50) can be considered as initiating studies in this field. Particularly in the latter case, the reaction proceeded remarkably easily indicating the high reactivity of an electron-rich aromatic ring as a nucleophile in such cyclisations.
The genus *Erythrina* is widely distributed in tropical and subtropical regions of the world and has been occasionally used in indigenous folk medicine. In flowers, seeds and bark of the genus *Erythrina*, there have been found erythrinan alkaloids, some of which have curare-like and hypnotic actions. A variety of pharmacological effects, including sedative, hypotensive, neuromuscular blocking and CNS depressant properties are also associated with the erythrinane skeleton. The vast majority of naturally occurring *Erythrina* alkaloids possess the tetracyclic framework and substitution pattern of (51).

Allin and James report a novel, stereoselective approach to a fused tricyclic ring system found within the core of the erythrinane ring system, the key step involving an asymmetric, intramolecular N-acyliminium mediated cyclisation. Treatment of the bicyclic lactam (52) with the Lewis acid TiCl$_4$ at -10 °C produced the target pyrroloisoquinoline ring system (53) as a single diastereoisomer, with inversion of stereochemistry at the newly created chiral centre (Scheme 13). Presumably,
cyclisation to yield the product (53) proceeds via the N-acyliminium ion intermediate (54).

Benzenes or substituted benzenes are one of the most commonly used π-nucleophiles in reactions of this type. Numerous polycyclic structures, including natural product systems can be accessed by the use of this particular reactive functional group, for example, neuvamine (56).

A racemic total synthesis of neuvamine has been reported by Alonso\textsuperscript{34} (Scheme 14). The intramolecular cyclisation of an electron rich aromatic π-nucleophile onto the generated N-acyliminium ion (55) is the key step in the synthetic route.
The versatility of the $N$-acyliminium cyclisation in the total synthesis of various indole alkaloids is reflected in the work of many research groups. In the vast majority of cases the essential step is the coupling of an oxo carboxylic acid (57) with tryptamine (58) and acid catalysed ring closure of the so-formed oxo amide (59) into the desired skeleton (61) via the $N$-acyliminium ion (60) (Scheme 15).

![Scheme 15](image_url)

An interesting example is the synthesis of indole alkaloids by van Tamelen $^{35}$ et al. starting from indole-3-acetic acid (62) and an amine to form the amide precursor (63) which is cyclised by acid-catalysed formation of the $N$-acyliminium intermediate (64) and subsequent ring closure to (65). Unlike the general reaction Scheme 15, where bond formation is observed at C(2) of the indole ring, in this case the product of the cyclisation of (64) is the spiro structure (65) via bond formation at C(3) of the indole nucleus to form the more stable $\gamma$-lactam (Scheme 16). This result is most likely accounted for by assuming initial attack at C(2) followed by a rearrangement. This distinct difference in behaviour between the ions (60) and (64) is extremely useful for exerting regiocontrol in these indole-based cyclisations.

Introduction
The synthesis of pyrrolidine and piperidine ring fused derivatives (67) has been accomplished through the $N$-acyliminium ion cyclisation of hydroxy and alkoxylactams (66) (Scheme 17).\textsuperscript{36}
Vernon\textsuperscript{37} and co-workers have investigated spiro cyclisations of fused oxazolidines such as (68) in which the bridgehead substituent \(-\text{CH}_2\text{CH}_2\text{Ph}\) provides the \(\pi\)-nucleophile for intramolecular reactions with the \(N\)-acyliminium ion intermediate (69) (Scheme 18).

Decroix\textsuperscript{38} investigated intramolecular addition reactions of thiophene to an \(N\)-acyliminium ion (71) formed from an isoindolinone derived hydroxylactam (70).
Diisoindolo(thieno)diazenes such as (72) could be readily accessed by this method (Scheme 19).

The furan moiety has also been employed in reactions of this type, providing routes to a variety of systems such as (±)-epilupinine (73) and (±)-perhydrohistrionicotoxin (74).

In an extensive investigation of the intramolecular nucleophilic addition of terminal furan substituents onto N-acyliminium ions by Tanis,\textsuperscript{39} routes toward alkaloid synthesis were devised. A variety of linearly-fused (75), spirocyclic (76) and bridged aza-cycles (77) could be synthesised by simply altering the placement of the furan tether on the N-acyliminium ion precursor as shown in Scheme 20.
Park\textsuperscript{40} \textit{et al.} have investigated imidazoles as internal nucleophiles for the synthesis of (±)-glochidine (78) and (±)-glochidicine (79), and more recently, sulphur atoms as nucleophiles have been reported in the literature.\textsuperscript{41}

Decroix\textsuperscript{41} \textit{et al.} showed that hydroxy lactam (80) could generate the \textit{N}-acyliminium ion (81) in an acidic medium. The ring closure into (82) takes place through an intramolecular $\alpha$-heteroamidoalkylation cyclisation (Scheme 21).
1.2.2 Intermolecular Carbon-carbon Bond Formation

There has been much recent interest in the synthetic utility and stereocontrol of the intermolecular N-acyliminium variant. A large number of new studies have been published, both with respect to the type of precursors and activated nucleophiles, as well as the experimental conditions.

Allyl trimethylsilane in combination with titanium tetrachloride (TiCl₄) has been used frequently. For example, Weinreb et al. commented on the efficiency of using titanium tetrachloride in the alkylation of α-alkoxyamides such as (83) with allyl trimethylsilane (Scheme 22).

Koizumi et al. examined the alkylation of the ethoxy compound (84) with allyl trimethyl silane in the presence of various Lewis acids and found titanium tetrachloride to be the most effective.
Meyers\textsuperscript{44} and Allin\textsuperscript{21} have prepared bicyclic and tricyclic lactams (85) and (86) respectively as single diastereoisomers and subjected them to aminal ring opening reactions using titanium tetrachloride and allyl trimethylsilane as the nucleophile. The latter group have also studied the effect on the stereochemical outcome of allyl trimethyl\textsuperscript{21-22} and triethylsilane\textsuperscript{23} intermolecular nucleophilic additions when varying the Lewis acid activator. It was shown that much higher levels of diastereoselectivity could be achieved using the triethylsilane protocol than with the Lewis acid/allyl trimethylsilane system, however, titanium tetrachloride was still found to be the most effective activator.

Examples of intermolecular additions of trimethylsilylcyanide (87) and trimethylphosphite (88)\textsuperscript{45} to N-acyliminium ions in the presence of titanium tetrachloride have been discussed in recent literature and are shown in Scheme 23.
Highly diastereoselective additions of organocopper reagents to \(N\)-acyliminium ions have also been examined. Wistrand and Skrinjar\textsuperscript{46} report addition of alkylcopper reagents to the optically active \(N\)-acyliminium ion (89) in the presence of boron trifluoride etherate (BF\(_3\).OEt\(_2\)) affording pyrrolidines (90a-c) (Scheme 24).

\[
\begin{align*}
\text{MeO} & \quad \text{CO}_2\text{Me} \\
\text{N} & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\(\text{RCu} \quad \text{BF}_3\cdot\text{OEt}_2\)

\[
\begin{align*}
\text{MeO} & \quad \text{CO}_2\text{Me} \\
\text{N} & \quad \text{CO}_2\text{Me} \\
\text{MeO} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\(R = n-\text{Pr}\)

\(R = n-\text{Bu}\)

\(R = n-\text{Hept}\)

Scheme 24

1.3 Applications of the Meyers Bicyclic Lactams

1.3.1 Introduction

Bicyclic lactams are an extremely versatile tool in the preparation of a plethora of optically active products, and provide access to a variety of natural and unnatural compounds such as pyrrolidines (91) and (92)\textsuperscript{47,48} and pyrrolidinones (93)\textsuperscript{48,49} shown in Scheme 25.\textsuperscript{20}

Other examples of ring systems present in a number of naturally occurring carbocycles that can be synthesised from these chiral non racemic templates include piperidines (94) and (95),\textsuperscript{50} tetrahydroisoquinolines (96),\textsuperscript{51} pyrroloisoquinolines (97),\textsuperscript{52} cyclohexenones (98)\textsuperscript{53} and hexahydroindenones (99).\textsuperscript{16}
1.3.2 Synthesis of Substituted Pyrrolidines and Pyrrolidinones

Highly functionalised pyrrolidines are compounds of considerable importance. They occur in a variety of natural products and pharmaceutically active compounds, either as isolated ring systems or embedded in more complex structures, which often possess wide ranging biological activity. For example, physostigmine\textsuperscript{54} (100) is a representative of this class of compounds.
Meyers developed a facile asymmetric synthesis of substituted pyrrolidines (102) and pyrrolidinones (103) from keto acid (101) and phenylglycinol (Scheme 26).

Scheme 26

1.3.3 Synthesis of Piperidine

Scheme 27

The route to asymmetric pyrrolidines was extended to the piperidine series (Scheme 27). This methodology was utilised in the synthesis of the natural products (-)-pipecoline (104) and (+)-coniine (105).

1.3.4 Synthesis of Tetrahydroisoquinolines

Routes to naturally occurring tetrahydroisoquinolines such as salsolidine (109) have been developed from chiral bicyclic lactams of type (106) (Scheme 28). Treatment of (106) with sodium bis(methoxyethoxy)aluminium hydride (Red-Al) gave the ring-opened lactam (107) which upon additional reduction with lithium aluminium hydride
gave the $N$-benzyl substituted isoquinoline (108). Reductive removal of the $N$-benzyl group afforded the natural product (109).

![Scheme 28](image)

1.3.5 Synthesis of Substituted Pyrroloisoquinolines

Padwa et al. have recently described the preparation of pyrroloisoquinoline (112) by treatment of amido-substituted thioacetal (110) with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) giving five-membered thio-substituted lactams (111) (Scheme 29). Further reaction with DMTSF generates an $N$-acyliminium ion which undergoes cyclisation with the tethered aromatic ring to produce the pyrroloisoquinoline (112).
1.4 Functionalisation of Bicyclic Lactam Substrates

Their application to total synthesis has demonstrated that lactams can provide access to a wide variety of structural features. The versatility of the bicyclic lactam as a tool in the asymmetric synthesis of a variety of alkaloid ring systems is highlighted in the following section.
1.4.1 Unsaturated Bicyclic Lactams

The preparation of α,β-unsaturated carbonyl compounds is an important transformation, allowing further functionalisation of substrates. The most common preparation of such compounds involves the elimination of appropriate selenoxides as developed by Reich, who reported the conversion of ketones and esters to their α,β-unsaturated derivatives.

![Scheme 30](image)

Reaction of an appropriate lithium enolate with phenyl selenenyl bromide generates an α-phenylselenocarbonyl compound (113) which, under oxidative conditions, undergoes elimination to produce the α,β-unsaturated product and phenyl selenic acid by-product (Scheme 30).

![Scheme 31](image)
Meyers\textsuperscript{57} proposed an alternative route utilising methyl phenylsulfinate (114) for the elimination (Scheme 31). A variety of substituted $\alpha,\beta$-unsaturated bicyclic lactams were prepared in this way, precluding the use of toxic selenium.

Wagner\textsuperscript{58} \textit{et al.} utilised a ring-closing metathesis approach towards unsaturated fused bicyclic lactams, producing a range of different ring sizes (Table 1).

<table>
<thead>
<tr>
<th>Diene</th>
<th>Bicycle</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Diene 1" /></td>
<td><img src="image2" alt="Bicycle 1" /></td>
<td>94</td>
</tr>
<tr>
<td><img src="image3" alt="Diene 2" /></td>
<td><img src="image4" alt="Bicycle 2" /></td>
<td>81</td>
</tr>
<tr>
<td><img src="image5" alt="Diene 3" /></td>
<td><img src="image6" alt="Bicycle 3" /></td>
<td>35</td>
</tr>
</tbody>
</table>

\( ^a\)Conditions: \(\text{Cl}_2(\text{Pcy}_3)\text{Ru=CHPh} \) (10-15 mol\%), DCM, reflux, 16h

Table 1

1.4.2 Cyclopropanations

The first report on conjugate additions to bicyclic lactams included cyclopropanations \textit{via} the addition of sulfoxonium ylides\textsuperscript{59a-b} (Scheme 32).
1.4.3 Amine Conjugate Addition

The addition of amines to α,β-unsaturated bicyclic lactams has been applied in the synthesis of several 3-aminopyrrolidines as shown in Scheme 33. This has been utilised in the construction of benzamide derivatives such as (115), neuroleptic drugs useful in schizophrenia treatment.  

1.4.4 Aziridination by Conjugate Addition

An extension of the amine conjugate addition reactions involved construction of the aziridine moiety with high efficiency. Indeed, through modification of the α,β-unsaturated bicyclic lactam to include a leaving group at the α-carbon, i.e. iodide, an intramolecular pathway was available for formation of the aziridine (Scheme 34).
1.4.5 Organocuprate Conjugate Addition

The conjugate addition of cyanocuprates to α,β-unsaturated bicyclic lactams has been studied extensively in the literature.\cite{Meyers1,Meyers2} Meyers utilised such reactions in the synthesis of \textit{trans}-2,3-disubstituted pyrrolidines (116) (Scheme 35).\cite{Meyers1}

More recently, Amat\cite{Amat} described the enantioselective preparation of diversely substituted piperidine alkaloids by similar methodology to that in Scheme 35, and demonstrated the usefulness of this chemistry in the total synthesis of Femoxetine (117); an antidepressant.
1.4.6 Diels-Alder Reactions

Moloney et al. have been interested in developing methodology to provide a convenient synthesis of functionalised pyrrolidinones. This group, and others have performed Diels-Alder cycloaddition reactions between \( \alpha,\beta \)-unsaturated bicyclic lactams and numerous dienes and 1,3-dipoles. Some examples of which are shown in Table 2.

<table>
<thead>
<tr>
<th>Lactam</th>
<th>Diene</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Lactam1" /></td>
<td><img src="image2.png" alt="Diene1" /></td>
<td><img src="image3.png" alt="Product1" /></td>
</tr>
<tr>
<td><img src="image4.png" alt="Lactam2" /></td>
<td><img src="image5.png" alt="Diene2" /></td>
<td><img src="image6.png" alt="Product2" /></td>
</tr>
<tr>
<td><img src="image7.png" alt="Lactam3" /></td>
<td><img src="image8.png" alt="Diene3" /></td>
<td><img src="image9.png" alt="Product3" /></td>
</tr>
</tbody>
</table>

Table 2

1.5 Application of \( N \)-Acyliminium Ions in Alkaloid Synthesis

1.5.1 Stereoselective Synthesis of the Isoindolinone Ring System
The synthetic potential of \(N\)-acyliminium species is well documented. The wide range of synthetic applications of such compounds demonstrates the versatility of such intermediates.\(^{20}\) Some recent applications involve the synthesis of ring-fused heterocyclic systems utilising \(N\)-acyliminium ion cyclisations as the key ring-forming step.\(^{67a-f}\) A number of research groups reported the synthesis of chiral ring-fused isoindolinone targets via \(N\)-acyliminium ion cyclisations. However, the question of stereocontrol during the cyclisation reaction was not addressed.\(^{67a-f}\)

The isoindolinone ring system is of interest due to the actual and potential biological activities of many derivatives.\(^{68a-d}\) Furthermore, several naturally occurring chiral alkaloids contain a ring-fused isoindolinone moiety, including nuevamine (56)\(^{34,69}\) and lennoxamine (118).\(^{69-70}\) Nuevamine (56) was isolated from the \(Berberis\) darwinii, found in Southern Chile, and was the first isoindoloisoquinoline to be isolated from natural sources.\(^{71}\)

\[
\text{MeO} \quad \text{MeO} \\
\text{OMe} \quad \text{OMe}
\]

Allin and Northfield\(^{24}\) developed a facile new procedure for the synthesis of chiral ring-fused isoindolinone products in only two synthetic steps with extremely high levels of diastereoselectivity, from readily available substrates. It was recognised that substrates such as (40), the preparation of which is detailed in Scheme 10, could serve as valuable intermediates in the synthesis of non-racemic isoindolinones through Lewis acid mediated formation of an \(N\)-acyliminium intermediate, followed by intramolecular nucleophilic addition of a proximate, electron-rich aromatic substituent.
Indeed, on treatment with various Lewis acid activators (1.5 equivalents, -10 °C, dichloromethane), substrate (40) cyclised to give the desired tetracyclic isoindolinone target as a mixture of two possible diastereoisomers (41a) and (41b), the results of which are summarised in Table 3. Presumably, cyclisation to yield (41a/b) proceeds through an N-acyliminium intermediate such as (119) (Scheme 36).

![Diagram of reaction]

**Scheme 36**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activator</th>
<th>Yield (41) (%)</th>
<th>(41a) : (41b)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>SnCl$_4$</td>
<td>98</td>
<td>2 : 1</td>
</tr>
<tr>
<td>b</td>
<td>TiCl$_4$</td>
<td>93</td>
<td>2 : 1</td>
</tr>
<tr>
<td>c</td>
<td>BF$_3$.OEt$_2$</td>
<td>99</td>
<td>3 : 1</td>
</tr>
<tr>
<td>d</td>
<td>H$_2$SO$_4$</td>
<td>80</td>
<td>6 : 1</td>
</tr>
<tr>
<td>e</td>
<td>TMSOTf</td>
<td>97</td>
<td>≥49 : 1</td>
</tr>
</tbody>
</table>

* Determined from crude 270 MHz 'H NMR spectroscopy

**Table 3**

In all cases the cyclisation reaction proceeded cleanly and in excellent yield, providing a novel and highly stereoselective route to the ring-fused chiral...
isoindolinone ring system, the skeleton of which is common to many naturally occurring and biologically active compounds.

1.5.2 Stereoselective Synthesis of Isoquinoline Derivatives

Derivatives of the isoquinoline ring system comprise the major structural motif in a wide range of natural products and biologically active compounds and therefore new synthetic routes to these targets are of general interest. Following on from investigations into the isoindolinone ring system, Allin and Vaidya utilised chiral bicyclic lactam substrates as precursors in a stereoselective approach towards the tetrahydroisoquinoline ring system, which forms a sub-unit (BCD rings) of the protoberberine alkaloids exemplified by xylopinine (120) and its derivatives.

\[
\begin{align*}
\text{MeO} & & \text{MeO} \\
\text{X} & & \\
\text{OMe} & & \\
\text{X = H}_2, (120), \text{ Xylopinine} \\
\text{X = O, Known precursor} \\
\end{align*}
\]

The berberine class of alkaloids are widely distributed in nature, occurring in at least eight botanical families. The berberine alkaloids possess diverse biological actions including antipsychotic, sedative, hypotensive, anti-bacterial, anti-protazoal and DNA intercalating activity.

The approach used by Allin allows the introduction of asymmetry during the key ring-forming step; the stereoselective cyclisation of a bicyclic lactam substrate (121) via an \( N \)-acyliminium intermediate (123) (Scheme 37).
The desired tricyclic tetrahydroisoquinoline ring system (122), representing the BCD sub-unit of the protoberberine alkaloids, was isolated as a single diastereoisomer in 68% yield. Whilst bicyclic lactams derived from β-amino alcohols containing fused 5,5- and 5,6- ring systems have been widely used in asymmetric synthesis, the application of the corresponding fused 5,6-system (121) as a precursor in an N-acyliminium mediated cyclisation reaction leading to tetrahydroisoquinoline targets represents a novel application of this chiral template.

1.5.3 Stereoselective Synthesis of the Tetracyclic Erythrinane Core

In an extension of their investigations into the pyrroloisoquinoline ring system\(^{33}\) (refer to Section 1.2.1), Allin and James\(^{78}\) devised a novel approach to construct the tetracyclic core of the erythrinane ring system in a highly diastereoselective manner. There has been much interest in the synthesis of *Erythrina* alkaloids and their derivatives (Figure 1) (including pyrroloisoquinolines) over recent years,\(^{32,67d}\) with many approaches involving N-acyliminium cyclisation as a key ring-forming step, several of which have attempted to address the issue of stereocontrol in the cyclisation.
The lactam (124), synthesised in one step from readily available precursors, was treated under standard conditions of Lewis acid at -78 °C, generating the target tetracyclic product (125) as a single diastereoisomer in 98% yield. The N-acyliminium ion (126) can be envisaged as an intermediate in the cyclisation reaction (Scheme 38).
This methodology provides a facile and highly stereoselective synthesis of the tetracyclic erythrinane skeleton, assembled in only two steps from readily available reagents (condensation to the bicyclic lactam and Lewis acid promoted cyclisation).

1.5.4 Stereoselective Synthesis of Indole Alkaloids

We recognised that a further extension of the methodology described for the construction of the isoindolinone, isoquinoline and erythrinane ring systems might be its application to the synthesis of indole alkaloids. Figure 2 highlights some interesting indole natural products that have emerged as viable targets during the development of the novel methodology described in this thesis.

Deplancheine (127) Geissochizine (128) Dihydrocorynantheol (129)

Dihydrogambirtannine (130) Ajmalicine \((R^1 = H, R^2 = Me)\) (131)
Epi-ajmalicine \((R^1 = Me, R^2 = H)\) (132)

Figure 2

We wish to explore the potential of the intramolecular \(N\)-acyliminium ion cyclisation reaction for the asymmetric synthesis of these important heterocyclic systems. The indole alkaloids represented in Figure 2 share the common structural feature of a substituted piperidine unit containing a chiral centre with an indole substituent. Using
model (133), shown below, Scheme 39 outlines our retrosynthesis of this class of compound. This methodology may provide a route to the tetracyclic core (133) found as the structural motif in all of the alkaloids shown in Figure 2.

![Chemical Structures](image)

The fused tetracyclic core (133) is available from (134) via removal of the hydroxymethyl "auxiliary" and lactam reduction. Precursor (134) is formed through intramolecular cyclisation of the indole nucleus onto the N-acyliminium ion intermediate (135), which is generated by Lewis acid mediated activation of the bicyclic lactam (136). The chiral bicyclic lactam (136) is synthesised by condensation of the amino alcohol derivative of S-tryptophan (137) with the ester (138). Both enantiomers of the ring system would be available simply by using the antipodes of

Introduction
tryptophan as the original substrate. Others have shown that indoles can be used as an internal nucleophile in $N$-acyliminium cyclisation reactions with the same regioselectivity as planned in our syntheses.$^{67a,67b,79-81}$

Heaney and Shuhaibar$^{67b}$ carried out some preliminary investigations into the formation of imines such as (141) derived from the condensation of methyl 2-formylbenzoate (139) with primary amines, for example veratrylamine (140). The imines were afforded in high yield and undergo base catalysed rearrangement to methoxyisoindolones, such as (142), quantitatively in dry methanol containing a catalytic amount of sodium methoxide (Scheme 40).

Heaney and co-workers concluded that if the $\beta$-aryl residue on the amine was sufficiently nucleophilic, compounds such as (142) could act as $N$-acyliminium precursors. Indeed, treatment of these precursors with a Lewis acid such as titanium tetrachloride effected cyclisation to derivatives of isoindoloisoquinoline such as (143).
As a consequence of their primary findings, Heaney and Simcox\textsuperscript{79} postulated that acetals derived from esters of 2-acylbenzoic acids should undergo cascade sequences with suitable primary amines in the presence of mild Lewis acids. In a typical experiment, a solution of tryptamine (58) and acetal (144) were heated in toluene for 16 h in the presence of 10 mol\% of scandium triflate and 4Å molecular sieves. The
desired β-carboline derivative (145) was isolated in 91% yield. The reaction was thought to proceed via the sequence shown in Scheme 41.

Utilising the same cascade sequence β-carboline derivatives analogous to (145) were synthesised. For example, addition of acetal (122) to the ethyl ester of tryptophan (146) produced the cyclised product (148) as a single diastereoisomer. Presumably the reaction proceeds via the N-acyliminium ion (147).

Grigg and co-workers\textsuperscript{80} report a facile route to novel and complex heterocycles via sequential Pictet-Spengler/palladium catalysed carbonylation sequences. In the presence of catalytic $p$-toluene sulphonie acid in refluxing toluene the imine (149) undergoes Pictet-Spengler cyclisation to yield (150). The cyclisation product was converted to the β-carboline derivative (151) through a palladium catalysed carbonylation (Scheme 42). The catalyst system for the carbonylation reaction comprised 10 mol% Pd(OAc)$_2$, 20 mol% PPh$_3$ and Et$_3$N (1.2 mol equiv.).
Wawzonek and Maynard\textsuperscript{31} utilised the indole nucleus as a π-nucleophile in their synthesis of tetrahydro-[12H]-pyrroloazapinoindoles. They reacted an indole derivative (152) with an unsaturated lactone (153) to produce the amide (154). The amide, under the influence of magnesium metal in methanol, cyclised to give the hydroxylactam (155). Subsequent acid activation, using methanolic hydrochloric acid, generated the \textit{N}-acyliminium ion intermediate (156) which cyclised to form the tetracyclic product (157) (Scheme 43).
1.6 **Biosynthesis of Indole Alkaloids**

1.6.1 **Introduction**

The alkaloids are structurally the most diverse class of secondary metabolites. Over 5000 compounds are known with varying degrees of complexity. Whilst they are most commonly encountered in the plant kingdom, examples have been isolated from most other orders of organisms ranging from fungi to mammals. Interest in this family of
compounds stems mostly from the broad range of pharmacological activities associated with them. Indeed, since early times selected plant products, many containing alkaloids, have been used as poisons for hunting and murder, euphorians, psychedelics, stimulants as well as medicines. It is not surprising, therefore, that many of our modern drugs contain the same compounds or synthetic analogues, and the pharmacological and toxicological properties of these compounds are thus of immense interest and importance.82

1.6.2 Simple β-Carboline Alkaloids

Alkaloids based on a β-carboline system (161) exemplify the formation of a new six-membered heterocyclic ring using the ethylamine side-chain of tryptamine (58); derived from L-tryptophan via decarboxylation. Reaction of tryptamine with an aldehyde (158) (or keto acid) generates a Schiff base (159) which undergoes nucleophilic attack via the indole C(2) position in a Mannich/Pictet-Spengler type reaction. Subsequent loss of the C(2) proton restores aromaticity generating the β-carboline (161) as shown in Scheme 44. It should be noted that the analogous chemical reaction actually involves nucleophilic attack from C(3), followed by a rearrangement to give bonding at C(2); there is no evidence yet for this type of process in biosynthetic pathways.

![Scheme 44](image-url)
1.6.3 Terpenoid Indole Alkaloids

The terpenoid indole alkaloids constitute one of the major groups of alkaloids in plants, with in excess of three thousand different compounds. Found largely within eight plant families, it is the Apocynaceae, the Loganiaceae and the Rubiaceae which provide the best sources. Rationalising the biochemical origins of these often complicated structures is possible due to the wide interest shown in these interesting natural products.

In most structures, a tryptamine portion is clearly recognisable, and the remaining fragment is usually a C9 or C10 residue, with three main structural types discernable. These are termed the Corynanthe type, as in ajmalicine (131), the Aspidosperma type, as in tabersonine (162), and the Iboga type, exemplified by catharanthine (163). The C9 or C10 fragment has been shown to be of terpenoid origin, and the secoiridoid secologanin (164) was identified as the terpenoid derivative which initially combines with the tryptamine portion of the molecule.

The three types of terpenoids described above can be rationalised by rearrangements occurring in the terpenoid part of the structure (Scheme 45). Indeed, secologanin contains the ten carbon framework found in the Corynanthe type which can be rearranged as shown to produce the other varieties. This rearrangement involves detachment of a three carbon unit which is re-attached to the remaining C7 fragment producing the required carbon skeleton. In some instances C9 terpenoid units are observed; where loss of the carboxylate function of secologanin has occurred through hydrolysis/decarboxylation processes.
carbon atom lost by hydrolysis/decarboxylation
denotes detachment

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Chapter 2

Results and Discussion
2.1 Stereoselective Synthesis of the Indolizino[8,7-b]Indole Ring System

2.1.1 Introduction

The bicyclic lactams of Meyers have proven to be exceptional chiral templates for the construction of a wide variety of optically enriched carbocycles and heterocycles. A vast number of papers have appeared addressing their application in the preparation of such systems, and notable advances continue to be made.

Over the past decade or so, Meyers has demonstrated the synthetic utility of chiral, non-racemic, bicyclic lactams. Following the general methodology adopted by Meyers for the synthesis of such compounds, the Allin group has developed new and stereoselective routes for the synthesis of a wide range of non-racemic heterocyclic targets including the isoindolinone, isoquinoline, and pyrroloisoquinoline ring systems.

Based on the investigations leading to the construction of the aforementioned ring systems (detailed in Section 1.5), we recognised that a suitably substituted bicyclic lactam could act as a precursor for a stereoselective approach to the indole alkaloids, some examples of which are represented in Section 1.5.4; and which share the common indolizino[2,3-a]quinolizidine structural motif (1).

![Chemical Structure](Image)

Our initial investigations focus on the development of the cyclisation methodology in model substrate systems, namely the indolizino[8,7-b]indole ring system (2).
These model systems provide the understanding from which more interesting targets containing the tetracyclic core (1) can be synthesised.

2.1.2 Potential Applications of the Indolizino[8,7-b]indole Ring System

Indolizino[8,7-b]indoles of general structure (2) are themselves of biological importance and have attracted interest from the pharmaceutical industry. Indeed, such compounds have been used as intermediates in the preparation of diuretic compounds. Furthermore, they are known to exhibit analgesic and anti-inflammatory activity in their own right. Other, more functionalised templates such as (3), have been shown to act as β-turn mimics and display high binding affinity and selectivity for CCK₁ receptors.

Cholecystokinin (CCK) is a peptide hormone and neurotransmitter involved in modulating gastrointestinal and behavioural activities by interacting with specific receptors. Changes in the levels of CCK found in tissues and sera of patients with various disease states, including schizophrenia and eating disorders, as well as the effects of CCK derivatives in neuroprotection, models of Parkinson’s disease, cancer, anxiety and pain indicate the potential utility of CCK receptor ligands as therapeutic agents.
Gonzalez-Muniz et al. demonstrated the ability of templates such as (3) to behave as CCK₁ receptor antagonists and propose that the presence of a β-turn-like conformation within the peptide backbone of dipeptoids could contribute to their bioactive conformation at the CCK₁ receptor subtype. An important feature of peptide and protein secondary structure is when the amino acid chain reverses direction. Due to their frequent appearance on the external surface of the molecule, the reverse turns are postulated as loci for receptor binding, antibody recognition and posttranslational modifications. However, most of the biologically active peptides are highly flexible molecules and the number of their possible conformations complicates attempts to relate structural parameters and activities. For all these reasons, in recent years, major efforts have been devoted to the development of templates or scaffolds that mimic or stabilise these secondary structural features, especially β-turns. Several non-peptide systems, including heterocyclic, aromatic and lactam derivatives, have been designed to mimic the different types of β-turns. Although the incorporation of some of these scaffolds into bioactive peptides has led to peptidomimetics with enhanced activity or metabolic stability, most of them lack an appendage for the corner residue side chains and can only be obtained by a lengthy synthesis.

As a result of the factors discussed above, structures based on (3) were designed as potential β-turn dipeptide mimics. The potential of templates such as (3) is based on the fact that certain bicyclic lactams structurally related to (3) are known to mimic the central dipeptide core of β-turns and the presence of the indole ring could represent an additional advantage in the case of β-turns having aromatic or hydrophobic amino acids in the residue.

Consequently, the usefulness of the indolizino[8,7-b]indole ring system is demonstrated by the wide range of biological applications of such systems. As is common in medicinal chemistry, the absolute stereochemistry of many of these chiral heterocycles can have a profound effect on their biological activity and toxicity. Therefore, new synthetic methods that provide good levels of stereocontrol are particularly interesting.
2.1.3 Approaches to the Indolizino[8,7-b]indole Ring System

Indolizino[8,7-b]indole derivatives (general formula (2)) have been used as synthetic intermediates for the preparation of more complex alkaloids. Molecules of general structure (2) are usually prepared by reacting a tryptamine or tryptophan derivative with species carrying an aldehyde (or ketone) and a second functional group (usually an ester) separated by three carbon atoms. Pictet-Spengler condensation with the aldehyde first gives rise to an intermediate tetrahydro-β-carboline derivative. The resulting secondary amine then reacts intramolecularly with the second functional group effecting ring closure. Alternatively, tryptamine or tryptophan can be converted to their succinimide derivatives and cyclisation to a β-carboline compound accomplished under Bischler-Napieralski conditions.

Lete et al. described the preparation of fused β-carboline systems analogous to templates (1) and (2) through an alkyllithium addition-N-acyliminium ion cyclisation sequence on readily available imides (Scheme 1).

Scheme 1

The imide intermediates (6) were prepared by reacting tryptamine (4) with a cyclic anhydride (5) under classical conditions. The imides undergo nucleophilic addition with an organolithium reagent affording an oxo amide (8) or the cyclic tautomeric...
hydroxylactam (7). Subsequent treatment with TFA effects cyclisation to the fused β-carboline system (9) via an N-acyliminium ion intermediate.

As mentioned already, based on our investigations into various heterocyclic ring systems,¹³ we recognised that a suitably substituted bicyclic lactam could act as a precursor for a stereoselective approach to the indolizino[8,7-b]indole ring system. Our approach to the synthesis of the required bicyclic lactam substrate (13) followed the general method previously used in our group.¹⁻³ The starting material is the commercially available (2S)-2-amino-3-(1H-indol-3-yl)propan-1-ol (11). However, reduction of the more readily available L-tryptophan (10) using lithium borohydride and chlorotrimethylsilane in anhydrous tetrahydrofuran via a method developed by Giannis and Sandhoff,¹¹ gave the enantiomERICALLY pure ‘β-amino alcohol’ (11) in 70% yield. The β-amino alcohol was heated under Dean-Stark conditions with the appropriate keto-acid (levulinic acid) (12) for 48 hours (Scheme 2). Under these reaction conditions we were able to isolate the expected bicyclic lactam (13) in only 3% yield. The major product of the reaction, isolated in 55% yield, was found to be the target indolizino[8,7-b]indole derivative (14).¹²

\[ \text{Scheme 2} \]
Examination of the crude reaction mixture by 250 MHz $^1$H NMR spectroscopy revealed the formation of (14) as a single diastereoisomer. The relative stereochemistry of product (14) was determined by single crystal X-ray analysis (Figure 1) and was found to be as expected based on our experience of cyclisation reactions involving similar $N$-acyliminium precursors. Effectively, retention of configuration at the methyl-bearing chiral centre is observed if one considers bicyclic lactam (13) to be an intermediate.  

Interestingly, compound (14) was observed to form two crystallographically unique hydrogen bonds; one intramolecular $O(2)$-$H(2A)$"$'$-$O(1)$ \{O(1)$'$-$O(2) = 2.597(2) Å, $O(2)$-$H(2A)$"$'$-$O(1) = 154°\} and one intermolecular $N(2)$-$H(2)$"$'$-$O(2A)$ \{$N(2)$"$'$-$O(2A) = 2.788(3) Å, $N(2)$-$H(2)$"$'$-$O(2A) = 168°\} forming chains along the crystallographic $c$-direction.

One could, of course, envisage an alternative mechanism to explain the formation of (14) that avoids the intermediacy of bicyclic lactam (13); a stereoselective Pictet-Spengler reaction in which condensation of the $\beta$-amino alcohol and keto-acid substrate results in formation of a tetrahydro-$\beta$-carboline derivative which then

Figure 1. Crystal structure of (14)
undergoes lactam formation to yield (14) in the final step. To date, no intermediates have been observed by us that would support this hypothesis with our substrates.

An alternative approach to the indolizino[8,7-b]indole ring system was also investigated through formation and subsequent borohydride reduction of the imide intermediate (16), accessed in 54% yield from the required β-amino alcohol (11) and succinic anhydride (15). In this approach, summarised in Scheme 3, the intermediate ethoxy lactam derivative (17) was not isolated since, under the reaction conditions, direct cyclisation via an N-acyliminium intermediate was observed to yield the target heterocycle (18) in 45% yield and as a 9:1 mixture of diastereoisomers. The major diastereoisomer was isolated by crystallisation and the relative stereochemistry of this product was determined to be as shown in Scheme 3 by 1D NOE studies; the absence of an NOE between the protons situated at positions 5 and 11b is consistent with the proposed structure. As we were unable to isolate the minor diastereoisomer we could not carry out a comparative NOE study. Again, the relative stereochemistry observed on cyclisation of the attacking aromatic nucleus was as expected based on previous results from our group.
2.1.4 Rationalisation of the Stereochemical Outcome of the Cyclisation Reactions

In order to rationalise the stereochemical outcome of the cyclisation reactions leading to products (18) and (14), we have invoked the conformational models highlighted in Figures 2 and 3 respectively, whereby activation of the bicyclic lactam leads to a formal $N$-acyliminium species as an intermediate.

In reactive conformation (A), leading to the favoured diastereoisomer of (18), as represented in Scheme 3, the carbonyl moiety is “eclipsed” in a 1,3-fashion by the small hydrogen atom at the $\beta$-amino alcohol chiral centre. The angular H-atom at the iminium carbon provides no significant steric bulk to interfere with the steric positioning of the indole or hydroxymethyl groups. In this model the hydroxymethyl group is viewed as the larger substituent.

The alternative reactive conformation (B), which would lead to the minor diastereoisomer of (18), has the indole group positioned as the larger substituent. In this scenario an unfavourable 1,3-interaction appears to exist between the carbonyl group and the more bulky hydroxymethyl group.

Results and Discussion
With respect to product (14), the steric influence exercised by the angular methyl substituent at the iminium carbon overrides the conformational effect noted in Figure 2 and this leads to the exclusive formation of a diastereoisomer of opposite relative stereochemistry. Indeed, one can envisage interactions between this angular methyl group and the indole substituent as shown in conformation (C) (Figure 3).

Bond rotation about the extra-annular C-N bond leads to an alternative reactive conformation (D) with minimised steric interference from the iminium carbon substituent, which furnishes the observed product diastereoisomer (14) with retention of stereochemistry.

The slight reduction in the level of diastereoselectivity observed in the cyclisation reaction to produce (18) (9:1) in comparison to (14) (exclusive), may be explained by the greater importance attached to the influence of the angular substituent at the iminium carbon in the conformational models described above.
2.2 Manipulation of the Indolizino[8,7-b]indole Ring System

2.2.1 Introduction

Having established the potential of the *N*-acyliminium cyclisation methodology in the construction of indolizino[8,7-b]indole derivatives, a procedure to remove the pendent hydroxymethyl auxiliary was sought. This would demonstrate the potential synthetic utility of this new methodology in target synthesis. Furthermore, we decided to investigate conditions for reduction of the lactam functionality. This section outlines the methodology adopted by us to perform these transformations.

2.2.2 Decarbonylation studies

The decarbonylation of aldehydes is a useful and important reaction in organic synthesis, providing the reaction proceeds smoothly under mild conditions. The most efficient compounds so far discovered to facilitate this reaction are complexes of rhodium. Tsuji and Ohno\textsuperscript{15} studied the decarbonylation of aldehydes and acyl halides using the complex chlorotris(triphenylphosphine)rhodium (19), more commonly known as Wilkinson’s catalyst.

\[
\begin{align*}
\text{PPh}_3 & \quad \text{Cl-Rh}\text{-PPh}_3 \\
\text{Cl-Rh-CO} & \quad \text{PPh}_3
\end{align*}
\]

The decarbonylation reactions were typically carried out using stoichiometric rhodium, refluxing in benzene, toluene or *p*-xylene. The same workers utilised the complex chlorocarbonylbis(triphenylphosphine)rhodium (20) and discovered that if the decarbonylation was performed at temperatures in excess of 200 °C, catalytic amounts of the rhodium complex (20) could be used.\textsuperscript{16} This is of course extremely advantageous considering the high cost of the rhodium complexes involved. These rhodium complexes have the additional advantage of being stable and easy to handle.
A further modification of the procedure utilised by Tsuji and Ohno was investigated by Kruse on the decarbonylation of indole-2-carboxaldehydes (21), whereby chlorobis[1,2-bis(diphenylphosphino)propane]rhodium was prepared in situ from (20) and 1,3-bis(diphenylphosphino)propane (dppp) (Scheme 4). This system was used in catalytic quantities without the usual requirement for high temperatures, the decarbonylation reactions proceeding at 140 °C.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{NH} & \quad \text{CHO}
\end{align*}
\]

\[
\begin{align*}
\text{RhCl(CO)}(\text{PPh}_3)_2 & \\
\text{Ph}_2\text{P}(&\text{CH}_2)_3\text{PPh}_2 & \\
p-\text{xylene, } \Delta, 24 \text{ h}
\end{align*}
\]

Scheme 4

The usefulness of the decarbonylation procedure described in Scheme 4 was demonstrated by Moody, who used this reaction as the final step in the total synthesis of the alkaloid lennoxamine (22).

We decided to investigate the potential of the conditions used by Moody for the removal of the hydroxymethyl auxiliary group from our indolizino[8,7-b]indole substrate (14). The first requirement was oxidation of (14) to the corresponding aldehyde (23), the substrate for our decarbonylation reaction. Numerous oxidation methods were attempted for the synthesis of (23) including Dess-Martin periodinane, Swern oxidation, PDC and TPAP/NMO. None of these methods proved successful, probably due to the presence of an indole moiety with an unsubstituted NH group, known to be unstable in the presence of oxidising reagents. Therefore, we turned our attention to an alternative, milder oxidising reagent known as IBX. This reagent has been reported to selectively oxidise primary alcohols in the

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presence of indole, without the need for protection of the indole NH. Oxidation of (14) with IBX gave an excellent 90% yield of aldehyde (23) using the conditions detailed in scheme 5.

With (23) in hand, we next attempted the decarbonylation applying the same conditions as Moody, which had previously been used in our group in the decarbonylation of pyrroloisoquinoline substrates. However, after refluxing (23) with 10 mol% of the rhodium complex (20) in the presence of the dppp ligand for 5 days in p-xylene (Scheme 6), no formation of product (24) was observed and the aldehyde starting material remained.

The reaction was repeated under these same conditions on numerous occasions using different batches of the rhodium catalyst, ensuring all equipment and solvents were thoroughly dry before use, but each attempt was met without success. As a result of our initial failed attempts at the catalytic decarbonylation, we decided to examine the use of stoichiometric equivalents of (20), which should allow us to determine the feasibility of the rhodium decarbonylation reaction on our indole substrates (Scheme 7).

Results and Discussion
We were pleased to observe complete disappearance of the aldehyde signals from the crude $^1\text{H}$ NMR after 5 days refluxing in $p$-xylene in the presence of (20). After purification we obtained a 38% yield of the desired product (24) in addition to 12% of the enamide (25). The enamide was subjected to catalytic hydrogenation to produce the desired target lactam (24) in a yield of 85%. It is worth noting that the purification of enamide (25) and target lactam (24) was not straightforward due to a co-eluting phosphorous by-product, which is thought to be triphenylphosphine oxide. Thus we decided to investigate removal of the lactam functionality from (24) to reveal the tertiary amine derivative (28), which would hopefully allow removal of any remaining phosphorous impurities through acid/base extraction.

2.2.3 Lactam reduction

Lee$^{25}$ et al. have used LiAlH$_4$ in the presence of AlCl$_3$ to cleanly reduce lactams. Igarashi and co-workers$^{26}$ have reported a transition metal catalysed transformation of amides to amines using monohydrosilanes as the reducing agent.

Lenz$^{27}$ used two methods to reduce racemic 8-oxoberbines; reduction with lithium aluminium hydride in tetrahydrofuran and sodium bis(methoxyethoxy)aluminium...
hydride (Red-\textsuperscript{Al\textregistered}) in benzene. In general, he obtained inferior yields and less clean products with lithium aluminium hydride than with the alternative hydride reagent. Comins\textsuperscript{28} \textit{et al.} have also used Red-\textsuperscript{Al\textregistered} for their reduction of chiral 8-oxoberbine (26) as shown in Scheme 8.

![Scheme 8](image)

To test the suitability of Red-\textsuperscript{Al\textregistered} on our substrates compound (14) was reacted under the conditions outlined in Scheme 9 to produce the clean reduction product (27) in 68\% yield.

![Scheme 9](image)

The same protocol was used to reduce the decarbonylated product (24) to generate the tertiary amine (28) in 67\% yield (Scheme 10). We were able to remove any unwanted phosphorous impurities by acid/base extraction during the work-up procedure.

![Scheme 10](image)
2.3 Stereoselective Synthesis of the Indolizino[2,3-a]quinolizidine Ring System

2.3.1 Introduction

As noted in Section 2.1.1, access to the indolizino[2,3-a]quinolizidine template (1) through application of our cyclisation methodology would be highly attractive as it would allow access to a wide range of desirable indole targets. Indeed, this heterocyclic template is found within a plethora of highly bioactive indole alkaloids, including geissoschizine (29), vellosimine (30) and ajmalicine (31).

Vellosimine (30), was first isolated from the tree Geissospermum vellosit in 1958 by Rapoport et al. Extracts of this bark, known as pao pereira, have been used in Brazilian folk medicine and have been reported to have curare-like activity. Ajmalicine (31) is isolated from the roots of the commercially grown Catharanthus roseus and is a member of the general family of the heteroyohimbine alkaloids. This alkaloid is a potent peripheral and central vasodilator which has been demonstrated clinically to prevent platelet aggregation. Ajmalicine has been prescribed widely for the treatment of cardiovascular diseases.
2.3.2 Approaches to the Indolizino[2,3-a]quinolizidine Template

Numerous strategies for the construction of the target heterocyclic system (1) have been investigated, reflecting the interest in alkaloids bearing this structural motif. Together with the important physiological properties they possess, the structural diversity and complexity of the various indole alkaloid subgroups provides a significant challenge in natural product synthesis.

Martin\textsuperscript{34} et al. utilised the vinylogous Mannich reaction in the synthesis of Geissochizine (29). The vinyl ketene acetal (33) was reacted with the dihydrocarboline iminium species (32) to produce (34) (Scheme 11). Nucleophilic attack of (33) onto (34) proceeded from the face opposite to the carboxyl group at C(5), establishing the correct absolute stereochemistry at C(3) for the natural product.

![Scheme 11](image)

An alternative approach was applied by Martin\textsuperscript{35} in the synthesis of the corynantheine alkaloid dihydrocorynantheol (35), which was first isolated from the bark of \textit{Aspidosperma marcggravianum} Woodson in 1962.\textsuperscript{36}
The key step in the assembly of the indoloquinolizidine skeleton was a Bischler-Napieralski cyclisation of the intermediate (36) followed by stereoselective hydride reduction to furnish (37) (Scheme 12). Regioselective hydroboration of the pendant vinyl group of (37) delivered dihydrocorynantheol (35).

Montgomery et al. described an entry to the isogeissoschizoid (±)-deformyl-isogeissoschizine (40) through the application of a late stage Fischer indole synthesis between ketone (38) and phenyl hydrazine (39) as shown in Scheme 13.

Cook demonstrated the utility of the asymmetric Pictet-Spengler reaction in the synthesis of the sarpagine alkaloid vellosimine (30). The N-benzyl derivative of D-tryptophan methyl ester (40) was reacted with the acetal (41) producing the key intermediate (42) with the necessary chirality at C(3) and C(5) (Scheme 14).
Based on our novel approach to the indolizino[8,7-b]indole ring system (2),\textsuperscript{12} we recognised that a suitably substituted bicyclic lactam could act as a precursor in a stereoselective approach to the indolizino[2,3-a]quinolizidine template (1).

Our approach to the synthesis of the required bicyclic lactam substrate (46) followed the general method previously used in our group.\textsuperscript{1-3} The β-amino alcohol derivative of L-tryptophan (11) was heated under Dean-Stark conditions in toluene with an appropriate keto-acid (45) derivative for 48 hours (Scheme 15). Substrate (45) was synthesised by acid-catalysed ring opening of δ-valerolactone (43) giving (44) in 98% yield followed by oxidation with PCC\textsuperscript{38} to produce (45) in 68% yield. Under these reaction conditions we were able to isolate the expected bicyclic lactam in 69% yield as a 5:1 mixture of separable diastereoisomers, (46a) and (46b).
The relative stereochemistry of the major diastereoisomer (46a) was determined by single crystal X-ray analysis (Figure 4). This indole-containing bicyclic lactam is a novel example of the fused 5,6-ring system favoured by Amat and Bosch, and the relative stereochemistry observed for the major diastereoisomer (46a) is consistent with results obtained by both these researchers and previous work in our group on isoquinoline substrates.

Indeed, under the neutral reaction conditions utilised in Scheme 15, the cis lactam (46a) is formed as the major product, which is thought to be the kinetic product (formed fastest), whilst the trans lactam (46b), formed as the minor product under these conditions is thought to be the thermodynamic product. Indeed, Amat and Bosch found that the cis lactam formed from R-phenylglycinol and (45) under similar neutral conditions as those employed in Scheme 15, could be converted to the more stable trans lactam by equilibration under acidic (TFA) conditions of the initially formed reaction mixture.
Based on the investigations carried out on the synthesis of the isoquinoline ring system, the bicyclic lactam diastereoisomers (46a/b) were not separated, but were treated with TiCl₄ to promote the stereoselective cyclisation reaction (Scheme 16).

We were pleased to isolate the cyclised product (47) in 54% yield and ¹H NMR analysis of the crude reaction mixture revealed formation of the product as a 5:2 mixture of separable diastereoisomers. A comparative 1D NOE study was undertaken on the isolated diastereoisomers to confirm that the relative stereochemistry of the major diastereoisomer is as shown in Scheme 16. Indeed, in the case of the minor diastereoisomer a positive NOE interaction was observed between the protons at positions 6 and 12b. In the case of the major diastereoisomer, (47), no NOE was observed. This assignment of the relative stereochemistry was confirmed by a single crystal X-ray analysis of the major diastereoisomer (47) (Figure 5).
Due to the poor level of product diastereoselectivity (5:2) obtained from the TiCl$_4$ mediated synthesis of (47), we decided to investigate the effect of the activator on the cyclisation reaction in an attempt to improve the stereoselectivity. In Section 2.1.3 we detailed the synthesis of the indolizino[8,7-b]indole derivative (18), whereby under the acidic reaction conditions, direct cyclisation of the imide (16) via an N-acyliminium intermediate was observed to yield the target heterocycle (18) as a 9:1 mixture of diastereoisomers. Therefore, we subjected the mixture of bicyclic lactam substrate diastereoisomers, (46a/b), to the same conditions to observe the effect on the stereoselectivity of the cyclisation reaction (Scheme 17).

We were extremely pleased to find that by simply treating the mixture of bicyclic lactams (46a/b) with 2M HCl in ethanol at room temperature for 20 hours gives an excellent yield of 97% for the cyclisation reaction and leads to the formation of the desired indolizino[2,3-a]quinolizidine product (47) as a single diastereoisomer. The relative stereochemistry of the single isomer formed was found to be as favoured in

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the TiCl₄ mediated cyclisation reaction that had previously given only a 5:2 ratio of product diastereoisomers.

An alternative approach to access the tetracyclic product (47) was also investigated based on our synthesis of the indolizino[8,7-b]indole derivative (18), through the formation and subsequent reductive cyclisation of an imide intermediate. This would constitute a more direct approach to the desired tetracyclic core, but unfortunately we were unable to synthesise the imide precursor from amino alcohol (11) and glutaric anhydride.

2.3.3 Rationalisation of the Stereochemical Outcome of the Cyclisation Reactions

We have invoked the same conformational models as described in Section 2.1.4 in order to rationalise the stereochemistry of the cyclisation reactions producing (47). In the first scenario, Figure 6, the bicyclic lactam substrate (46a/b) was activated by the Lewis acid TiCl₄ leading to a formal N-acyliminium species as an intermediate.

![Figure 6](image-url)
In reactive conformation (E), leading to the favoured diastereoisomer of (47), as represented in Scheme 16, the carbonyl moiety is “eclipsed” in a 1,3-fashion by the small hydrogen atom at the β-amino alcohol chiral centre. The angular H-atom at the iminium carbon provides no significant steric bulk to interfere with the steric positioning of the indole or Lewis acid-complexed oxymethyl groups. In this model, the Lewis acid-complexed oxymethyl group is viewed as the larger substituent.

The alternative reactive conformation (F), which would lead to the minor diastereoisomer of (47), has the indole group positioned as the larger substituent. In this scenario an unfavourable 1,3-interaction appears to exist between the carbonyl group and the more bulky Lewis acid-complexed oxymethyl group.

In the second scenario, the bicyclic lactam substrate (46a/b) was activated by treatment with 2M HCl to produce (47) as a single diastereoisomer. One might expect that the Lewis acid-complexed oxymethyl group (from TiCl₄ activation), being bulkier than a hydroxymethyl group as in the case of activation with HCl, would perhaps increase the level of diastereoselectivity, with conformation (F) becoming even less favourable. However, one cannot rule out the possibility of chelation control with a Lewis-acid such as TiCl₄ whereby conformation (F) could be stabilised somewhat by chelation between the Lewis acid-complexed oxymethyl group and the carbonyl moiety. This may explain the occurrence of the minor diastereoisomer of (47) under TiCl₄ activating conditions.

2.3.4 Epimerisation of the Indolizino[2,3-α]quinolizidine Template

Access to both enantiomers of the indolizino[2,3-α]quinolizidine template (1) is highly desirable, and is possible with our methodology by simply starting with the opposite antipodes of tryptophan as the original substrate. Indeed, the amino alcohol derivative of D-tryptophan (48) was condensed with ester (45) under standard Dean-Stark conditions to produce the expected bicyclic lactam (49) in 68% yield as a 5:1 mixture of separable diastereoisomers. The relative stereochemistry of the major diastereoisomer, shown in Scheme 18, was determined by 1D NOE and was as expected based on the synthesis of (46a/b). The 5:1 mixture of bicyclic lactam diastereoisomers (49) were treated as before with 2M HCl in ethanol to produce the
desired indolizino[2,3-α]quinolizidine product (50) as a single diastereoisomer in 97% yield. The relative stereochemistry of the single diastereoisomer (50) was determined by a single crystal X-ray analysis (Figure 7) and was found to be as expected from our investigations in the synthesis of (47).

Scheme 18

![Scheme 18](image)

Figure 7. Crystal structure of (50)

Whilst the synthesis of templates (47) and (50), starting from the antipodes of tryptophan, provides access to both enantiomers of the indolizino[2,3-α]quinolizidine template (1), the use of the more costly D-tryptophan is perhaps less attractive.
Indeed, unnatural $D$-tryptophan is approximately four times more expensive than the corresponding naturally occurring $L$-tryptophan.

However, we recognised the potential for the epimerisation of our indolizino[2,3-$a$]quinolizidine templates, since there are numerous literature reports on epimerisation reactions in closely related systems. Indeed, in some early investigations on the structure of the pharmacologically important alkaloid reserpine (51), it was found to be chemically labile under acid catalysis and was found to equilibrate to a mixture with its epimer isoreserpine (52) (Scheme 19).

The heteroyohimbine Akuammigine (53) was epimerised with hot acetic acid by Sakai$^{41}$ and co-workers to give tetrahydroalstonine (54) (Scheme 20).

Furthermore, by replacing acetic acid with its stronger derivative, trifluoroacetic acid, the acid-catalysed epimerisation of indolizino[2,3-$a$]quinolizidines has been made.
faster and consequently more useful for compounds which do not contain methoxy groups on the indole ring.

Indeed, in their investigations toward the synthesis of the pharmacologically valuable indole alkaloid vincamine, Rapoport et al. utilised the acid-catalysed epimerisation to prepare a key intermediate (56) for the stereoselective construction of this compound. They showed that by refluxing (55) in trifluoroacetic acid for 18 hours, key intermediate (56) could be isolated in 71% yield (Scheme 21).

Based on these observations, we decided to attempt the epimerisation of our key building block (47), which was synthesised starting from readily available L-tryptophan (10), utilising the conditions described in Scheme 21 by Rapoport. If successful, this may provide a route to both enantiomers of the parent indolizino[2,3-a]quinolizidine template (1), found as the core ring system of many indole alkaloids currently of interest in our group.

Therefore, the tetracyclic product (47) was heated at reflux in toluene for 24 hours in the presence of trifluoroacetic acid (Scheme 22).
Examination of the crude 250 MHz $^1$H NMR revealed the complete conversion of cis (47) into trans (57), which was isolated in a 90% yield. The relative stereochemistry of the epimerisation product (57) was determined by a positive 1D NOE interaction between the protons at positions 6 and 12b. This assignment of the relative stereochemistry was confirmed by a single crystal X-ray analysis of product (57) (Figure 8).

![Figure 8. Crystal structure of (57)](image)

The conversion of (47) to (57) as demonstrated in Scheme 22 suggests that (47) is the kinetic product formed fastest under the cyclisation conditions employed in Scheme 17, which can be converted to the more stable thermodynamic product (57) when subjected to equilibrating reaction conditions. The reason for the increased stability of (57) compared to (47) may be explained by examination of the X-ray crystal structures whereby in the thermodynamic product (57) (Figure 8), the hydroxymethyl auxiliary group adopts an orientation which alleviates some of the ring strain caused by the planar lactam moiety.

As stated previously, the success of this reaction should enable us to synthesise both enantiomers of the core ring system (1) starting from the same cheap, readily available chiral building block.
2.4 Functionalisation of the Indolizino[2,3-a]quinolizidine Ring System

2.4.1 Introduction

Having developed a stereoselective route to the indolizino[2,3-a]quinolizidine core, which forms the tetracyclic skeleton of numerous interesting indole alkaloids, we decided to examine the potential for functionalisation of our cyclisation products. It is our intention that these investigations may have applicability in future work en route to some of those indole alkaloids identified by us as potential targets for total synthesis. Figure 9 highlights some possible avenues for further functionalisation of cyclisation products.

![Figure 9](image)

The presence of a carbonyl group on ring D in the key precursor (47) provides a handle for further derivatisation through exploitation of the carbonyl group reactivity, e.g. enolate derivatisation, potential conjugate addition on to ring D. The presence of asymmetry in the molecule, set up by the acyliminium cyclisation reaction, could be expected to provide some stereocontrol in these functionalisation reactions. We decided to investigate the potential for functionalisation of our substrates through conjugate addition. However, \(\alpha,\beta\)-unsaturated lactams are known to be poor Michael acceptors\(^{43}\) and only a few examples of conjugate addition reactions to unsaturated piperidinones are available.\(^{35,44}\) Furthermore, the presence of an additional electron withdrawing group on the nitrogen atom and/or in conjugation with the double bond appears to be necessary. Nevertheless, we decided to explore this possibility and so
we initially required a suitable method for the introduction of $\alpha,\beta$-unsaturation into our substrates.

### 2.4.2 Introduction of $\alpha,\beta$-unsaturation

The issue of the preparation of $\alpha,\beta$-unsaturated carbonyl compounds has received much attention due to the variety of synthetic transformations they undergo. The dehydrogenation of carbonyl compounds is the most straightforward method and there are numerous methods for performing this conversion; the most important of which is the $\alpha$-bromination-dehydrobromination method.\(^{45}\) However, in the direct bromination of ketones orientational control is difficult to achieve. Nevertheless, Stotter and Hill\(^{45\text{a}}\) demonstrated that bromination of cyclohexanone enolates can be carried out in high yield and that dehydrobromination can be performed without loss of regiospecificity. However, under the conditions of the debrominations, isomerisation of $\alpha$-bromo ketones has been frequently reported,\(^{45\text{b}}\) most notably for bromides of $\beta$-dicarbonyl compounds.\(^{45\text{c}}\) In addition, this method is incompatible with sensitive enones because of the vigorous reaction conditions, employing temperatures frequently in excess of 120 °C.

The discovery by Jones, Mundy and Whitehouse\(^{46}\) that selenoxides undergo clean syn elimination to form olefins at or below room temperature offered a solution to the problem discussed above. Reich\(^{47}\) et al. explored the scope and limitation of the transformation of ketones to enones by selenenylation followed by selenoxide elimination.

We decided, therefore, to examine the utility of the selenoxide elimination protocol as described by Reich\(^{47}\) for the introduction of the required $\alpha,\beta$-unsaturation into our substrates (Scheme 23), which may allow further functionalisation via conjugate addition of suitable species.

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The indolizino[2,3-a]quinolizidine derivative (47) was initially bis-protected by treatment with sodium hydride (2 equivalents) followed by benzyl bromide (2.2 equivalents) to give (58) in 90% yield. Protection of the indole nitrogen and the primary alcohol group proved necessary to avoid unwanted side-reactions at either position during the selenenylation step to make (59). The enolate of (58), generated from lithium diisopropylamide (LDA), was reacted with phenyl selenenyl bromide at -78 °C to produce the selenide (59). The selenide was not purified and on treatment with sodium periodate undergoes selenoxide elimination to give the desired \( \alpha,\beta \)-unsaturated compound (60) in 85% yield from (58) (Scheme 23). Interestingly, we found that the indole nitrogen of (47) can be mono-protected producing (61) in 83% yield by use of one equivalent of sodium hydride followed by benzyl bromide (Scheme 24).
2.4.3 Conjugate Addition Reactions

With the α,β-unsaturated compound (60) in hand, we turned our attention to the proposed functionalisation of our substrates through possible conjugate addition reactions of various nucleophiles. We investigated the ability of three nucleophilic species to undergo conjugate addition with (60) (Scheme 25). The conditions and results for each of the attempted reactions are summarised in Table 1.

![Scheme 25]

**Table 1**

<table>
<thead>
<tr>
<th>Product</th>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Yield</th>
<th>d.r.*</th>
</tr>
</thead>
</table>
| (62a)   | S-S         | 1,3-dithiane (1.2 eq.)
          |             | n-BuLi (1.2 eq.)
          |       | -78 °C to RT | 52% exclusive |
| (62b)   | EtO₂C-CO₂Et | Malonate (3 eq.)
          |             | NaOEt (3.1 eq.)
          |       | 0 °C to RT  | 20% exclusive |
| (62c)   | BrMg≡       | Vinyl MgBr (10 eq.)
          |             | CuCN (5 eq.)
          |       | -78 °C to RT | 65% exclusive |

* Determined by 250 MHz ¹H NMR spectroscopy of crude reaction mixture

From the results in Table 1 it is evident that the conjugate addition products were isolated with varying yields but we were pleased to observe in each case the formation of the product as a single diastereoisomer with the relative stereochemistry, supported
by 1D NOE studies to be as shown in (62) (no NOE was observed between the protons at positions 2 and 12b) (Scheme 25). Due to the formation of (62a-c) as a single diastereoisomer we were unable to perform a set of comparative NOE studies. We were, however, able to obtain more conclusive support for the relative stereochemistry of products (62a-c) through the observation of the positive 1D NOE interactions as indicated in Figures 10-12 respectively.

In each of the products (62a-c), you would not expect to observe the positive 1D NOE interactions shown in Figures 10-12, if the nucleophilic species was located on the opposite face. The stereochemical outcome of the conjugate addition reactions could
be explained by a preference for the nucleophilic species to adopt a pseudo-equatorial position on the lactam ring.

2.4.4 Conjugate Addition Reactions of Epimerised Key Building Block

Following our initial investigations into the conjugate addition reactions of our key precursor (47), we thought it would be interesting to observe the effect, if any, of the epimerisation of (47) on the diastereoselectivity of the conjugate addition reactions. Therefore, we utilised the same approach as described above (Section 2.4.2) to introduce the required α,β-unsaturation into our epimerised building block (57) (Scheme 26).

The indolizino[2,3-a]quinolizidine derivative (57) was initially bis-protected by treatment with sodium hydride followed by benzyl bromide to give (63) in 70% yield. The enolate of (63), generated from LDA, was treated with phenyl selenenyl bromide at -78 °C to produce the selenide (64). The selenide was not purified and on treatment with sodium periodate undergoes selenoxide elimination to give the desired α,β-unsaturated compound (65) in 70% yield from (63).

Results and Discussion
With the α,β-unsaturated compound (65) in hand, we turned our attention to the Michael-addition chemistry. We investigated the conjugate addition reaction of two nucleophilic species with (65) (Scheme 27). The conditions and results for each of the attempted reactions are summarised in Table 2.

![Scheme 27](image)

<table>
<thead>
<tr>
<th>Product</th>
<th>Nucleophile</th>
<th>Conditions</th>
<th>Yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(66a)</td>
<td>BrMgBr</td>
<td>Vinyl MgBr (10 eq.) CuCN (5 eq.) TMSCl (5 eq.) -78 °C to RT</td>
<td>53%</td>
<td>exclusive</td>
</tr>
<tr>
<td>(66b)</td>
<td>CO₂Et</td>
<td>Dithiolane (2 eq.) LDA (2 eq.) -78 °C to RT</td>
<td>55%</td>
<td>exclusive</td>
</tr>
</tbody>
</table>

Table 2

The results of the conjugate addition reactions detailed in Table 2 were pleasing as the products were isolated in respectable yields and as single diastereoisomers. The relative stereochemistry of the single diastereoisomers were rationalised by 1D NOE studies and are as shown in structure (66) (Scheme 27).

The important 1D NOE interactions for (66a) are highlighted in Figure 13, which support the relative stereochemistry of (66a) to be as shown in Scheme 27. Due to the complexity of the ¹H NMR spectrum of (66a) in chloroform, it was necessary to
perform the 1D NOE studies with benzene as solvent, as this gave superior separation of the signals in the $^1$H NMR spectrum.

The positive NOE interactions observed between H12b and H1$_{ax}$, H1$_{eq}$ and H3$_{ax}$ suggest the lactam ring of (66a) adopts a boat-like conformation (Figure 13). A strong positive NOE was observed between H1$_{ax}$ and the CH of the vinyl moiety which supports the relative stereochemistry of (66a) to be as shown in Figure 13; with the vinyl group at C2 orientated in a pseudo-equatorial position. Indeed, you would not expect to observe such an interaction if the vinyl group was occupying a pseudo-axial position. Furthermore, no NOE was observed between H1$_{ax}$ and the proton at C2, which you might expect if the vinyl moiety was in the pseudo-axial position. More evidence to support the proposed pseudo-equatorial vinyl moiety was the observation of positive NOE interactions between the vinyl CH and H3$_{ax}$ and H3$_{eq}$. Indeed, you would only expect to observe a positive NOE between the vinyl CH and H3$_{eq}$ given a pseudo-axial disposition of the vinyl moiety.

The observation of a boat-like conformation for the lactam ring of (66a) is not surprising considering the preferred structure of the corynantheoid alkaloid geissochizine (29) is thought to be one in which the D-ring occupies a twist-boat conformation.\(^{48}\)
With respect to the "dithiolane" product (66b), the important 1D NOE interactions are highlighted in Figure 14, which support the relative stereochemistry of (66b) to be as shown in Scheme 27.

The positive NOE interactions between H12b and H1eq as well as H12b and H3ax suggest the lactam ring of (66b) adopts a boat-like conformation (Figure 14), similar to (66a). A strong positive interaction was observed between H1ax and H2ax and a weaker positive interaction was found between H1eq and H2ax, which leads to a pseudo-equatorial orientation of the "dithiolane" group. Indeed, if the dithiolane moiety was occupying the pseudo-axial position at C(2), you would not expect to observe the strong correlation seen between H1ax and H2ax as well as H1eq and H2ax. Furthermore, the absence of an NOE between H2ax and H3ax suggests the pseudo-equatorial disposition of the bulky dithiolane, as you would expect two similar NOE interactions between H3ax/eq and the proton at position 2 if the dithiolane group was in
a pseudo-axial orientation. The stereochemical outcome of the conjugate addition reactions to (65) could be explained by a preference for the nucleophilic species to adopt a pseudo-equatorial position on the lactam ring, which is in agreement with the results obtained for products (62a-c).

2.4.5 Conjugation Addition Reactions on Key Building Block (50)

Our final investigations into conjugate addition reactions of our indolizino[2,3-a]quinolizidine substrates involved the 1,4-addition of the vinyl cuprate derived from vinyl magnesium bromide and copper cyanide following our adopted standard conditions\(^\text{35}\) with key building block (50) (Scheme 28).
The indolizino[2,3-α]quinolizidine derivative (50) was initially bis-protected by treatment with sodium hydride followed by benzyl bromide to give (67) in 90% yield. The enolate of (67), generated from LDA, was reacted with phenyl seleneny1 bromide at -78 °C to produce the selenide (68). The selenide was not purified and on treatment with sodium periodate undergoes selenoxide elimination to give the desired α,β-unsaturated compound (69) in 85% yield from (67). The 1,4-addition product (70) was isolated in 70% yield as a single diastereoisomer as determined by examination of the crude 250 MHz ¹H NMR. The relative stereochemistry of (70) was determined by the observation of a strong positive 1D NOE interaction between the proton at position 12b and the Vinyl CH as shown in Scheme 28.

2.4.6 Future Applications of Conjugate Addition Chemistry

We have successfully demonstrated the introduction of a variety of nucleophilic species to the β-position of the lactam ring of our indolizino[2,3-α]quinolizidine derivatives. We envisage that this methodology may have potential future application in the total synthesis of natural products exemplified by geissochizine (29) and dihydrocorynantheol (35).

For example, one can imagine incorporation of the C(15) side chain of (35) via conjugate addition of a vinyl cuprate species to an α,β-unsaturated lactam ring followed by a regioselective hydroboration for which there is literature president. Furthermore, the ethyl group at C(20) could be introduced by an enolate reaction at the α-position of the lactam ring with an appropriate electrophile such as ethyl iodide. The group at C(15) could be expected to provide some stereocontrol over the enolate
reaction to give the desired *trans* relationship between the groups at C(15) and C(20) in (35).

The C(15) moiety of (29) could be incorporated in three stages, firstly by the conjugate addition of a dithiolane species, which can be desulphurised with nickel boride to leave an acetate side chain. Formylation of the acetate group has been achieved by Winterfeldt to give the desired functionality at C(15).

Thus the possible utility of our "Michael" chemistry in total synthesis is not without foundation and may be adopted in our future investigations.

2.5 Manipulation of the Indolizino[2,3-a]quinolizidine Ring System

2.5.1 Introduction

In order to demonstrate the potential synthetic utility of our novel N-acyliminium cyclisation methodology in target synthesis we decided to adopt the rhodium-induced decarbonylation sequence (Section 2.2.2) to remove the hydroxymethyl "auxiliary" from our indolizino[2,3-a]quinolizidine derivatives.

2.5.2 Rhodium Catalysed Decarbonylation Studies

In our investigations on the indolizino[8,7-b]indole ring system (2), we examined the utility of a rhodium induced decarbonylation sequence that involved generation of an aldehyde followed by a stoichiometric rhodium decarbonylation reaction. Following on from these initial studies, it was found that decarbonylation of the same aldehyde precursor (23) could be achieved without the need for stoichiometric quantities of the rhodium complex (20). Indeed, by simply changing the solvent for the decarbonylation reaction from p-xylene (b.p. = 137-138 °C) to mesitylene (b.p. = 163-165 °C), the decarbonylation of (23) proceeded with 10 mol% of the rhodium complex (20) again producing a mixture of the enamide (25) and the target lactam (24) (Refer to Section 2.2.2). Presumably, the higher reaction temperature overcomes
the energy barrier which prevents regeneration of the active rhodium species, thus allowing a catalytic decarbonylation sequence to operate.\textsuperscript{51}

Based on these observations, we utilised the chemistry detailed in Scheme 29 to facilitate removal of the hydroxymethyl group from our indolizino[2,3-a]quinolizidine substrate (47).

\begin{center}
\begin{tikzpicture}
    \node (a) at (0,0) {OH};
    \node (b) at (2,0) {CHO};
    \node (c) at (0,-2) {H};
    \node (d) at (2,-2) {N};
    \node (e) at (1,-1) {N};
    \node (f) at (1,-3) {N};
    \node (g) at (2,-3) {N};
    \node (h) at (0.5,-0.5) {IBX, DMSO};
    \node (i) at (2.5,0) {Rh\text{Cl}(CO)(PPh\text{3})\text{2}}
    \node (j) at (2.5,0) {10\text{mol\%}}
    \node (k) at (2.5,0) {Mesitylene, \Delta, 4 days}
    \node (l) at (0.5,-0.5) {RT, 24 h}
    \node (m) at (0,-4) {H};
    \node (n) at (2,-4) {H};
    \node (o) at (0,-5) {H};
    \node (p) at (2,-5) {H};
    \node (q) at (1,-6) {S};
    \node (r) at (2,-6) {S};
    \node (s) at (0,-8) {N};
    \node (t) at (2,-8) {N};
    \node (u) at (0,-10) {N};
    \node (v) at (2,-10) {N};
    \node (w) at (1,-11) {N};
    \node (x) at (2,-11) {N};
    \node (y) at (0,-13) {N};
    \node (z) at (2,-13) {N};
    \draw[->] (a) -- (b);
    \draw[->] (c) -- (d);
    \draw[->] (e) -- (f);
    \draw[->] (h) -- (i);
    \draw[->] (i) -- (j);
    \draw[->] (j) -- (k);
    \draw[->] (k) -- (l);
    \draw[->] (l) -- (m);
    \draw[->] (m) -- (n);
    \draw[->] (n) -- (o);
    \draw[->] (o) -- (p);
    \draw[->] (p) -- (q);
    \draw[->] (q) -- (r);
    \draw[->] (r) -- (s);
    \draw[->] (s) -- (t);
    \draw[->] (t) -- (u);
    \draw[->] (u) -- (v);
    \draw[->] (v) -- (w);
    \draw[->] (w) -- (x);
    \draw[->] (x) -- (y);
    \draw[->] (y) -- (z);
    \draw[->] (z) -- (a);
\end{tikzpicture}
\end{center}

Scheme 29

The cyclisation product (47) was converted to the aldehyde (71) through IBX oxidation in 70\% yield after purification. The aldehyde was subjected to the rhodium decarbonylation protocol employing mesitylene as the solvent with 10 mol\% of the rhodium species (20). After 4 days at reflux complete disappearance of the aldehyde was observed and the target lactam (72) was isolated in 60\% yield after purification. It is worth noting that examination of the crude 250 MHz \textsuperscript{1}H NMR revealed no formation of any enamide products in this reaction. Furthermore, the separation of any phosphorous impurities was made easier due to the reduced quantities present in the reaction mixture. However, perhaps the biggest advantage of these conditions is the reduction in the quantity of the expensive rhodium complex (£80/g) needed to facilitate the decarbonylation of (71). This has important implications should this

Results and Discussion

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methodology be adopted in total synthesis, where it may be necessary to perform this reaction on larger scales.

Having isolated lactam (72) we were able to grow crystals of this compound which were suitable for X-ray crystallography (Figure 15).

![Crystal structure of (72)](image)

**Figure 15. Crystal structure of (72)**

The X-ray structure of (72) confirmed the structure but revealed a problem had been encountered during the decarbonylation step. The X-ray data had determined the crystal was occupying a centrosymmetric space group. This means there is an inversion centre whereby each molecule in the unit cell has a “partner” related by a mirror reflection and a rotation. Thus in our crystal structure of (72) we have a 50:50 mixture of two inverted forms which can only arise given a racemic crystal.

Having made this discovery we were forced to examine the suitability of the rhodium decarbonylation step, which appears to have brought about racemisation of our substrate (72), perhaps a consequence of the rather long reaction time at high temperature. Therefore, we decided to monitor the decarbonylation reaction more closely for completion of the reaction with the intention of reducing the lengthy reaction time and hopefully the extent of the racemisation. Furthermore, we thought it would be useful to develop chiral HPLC conditions for (72), hopefully allowing us to measure the enantiomeric excess (e.e.) of the product (72) obtained from our decarbonylation reactions.
Initially, we were required to develop chiral HPLC conditions suitable for the separation of the enantiomers of (72), for which we utilised the crystal which had been shown conclusively by X-ray crystallography to be racemic. Figure 16 shows a chiral HPLC trace of racemic (72) with the enantiomers highlighted.

![Chiral HPLC trace of racemic (72)](image)

Chiral HPLC performed using a Chiracel OD-H column, 85:15 hexane:2-propanol, 0.6 ml/min

**Figure 16. Chiral HPLC trace of racemic (72)**

Having found suitable conditions for the separation of the enantiomers of (72) using chiral HPLC, a study was conducted on the decarbonylation reaction in which the reaction was monitored closely by $^1$H NMR for complete disappearance of the aldehyde proton signal in an attempt to minimise the reaction time and hopefully increase the e.e. of the product (72).

In our first attempt at monitoring the decarbonylation of (71) a $^1$H NMR sample after 36 hours at reflux in mesitylene showed complete conversion to (72) so the reaction was stopped and the e.e. determined by chiral HPLC (Figure 17). From the integration of the relevant peaks highlighted in Figure 17 the e.e. was found to be approximately 74%. Thus it appeared that the length of the reaction was a factor in the racemisation of (72) and perhaps an even higher e.e. could be obtained by further reductions in reaction time.
Chiral HPLC performed using a Chiracel OD-H column, 85:15 hexane:2-propanol, 0.6 ml/min

Figure 17. Chiral HPLC trace of (72) after 36 h decarbonylation

Following this significant improvement in the e.e. of (72) to around 74%, we were extremely pleased to find that through careful $^1$H NMR monitoring, the decarbonylation of (71) was complete after 21 hours. Furthermore, examination of the chiral HPLC trace from the 21 hour decarbonylation (Figure 18) provided an e.e. of around 94%.

Figure 18. Chiral HPLC trace of (72) after 21 h decarbonylation
Having obtained an e.e. of around 94% for the decarbonylation of (71) we were optimistic with respect to the potential application of the rhodium decarbonylation methodology in asymmetric synthesis. However, we decided to repeat the decarbonylation of (71) (Scheme 30) to ensure the high e.e. obtained for product (72) was reproducible, the results of which are summarised in Table 3.

![Scheme 30](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time for completion of reaction (h)</th>
<th>e.e. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>96</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

*Chiral HPLC performed using a Chiracel OD-H column, 85:15 hexane:2-propanol, 0.6 ml/min

Table 3

Unfortunately, as one can see from Table 3, we were unable to reproduce the high 94% e.e. initially obtained from the 21 hour decarbonylation (Entry 3, Table 3). Indeed, subsequent reactions (Entries 4-5, Table 3) gave poor e.e. values, even though the reaction was performed in an identical manner on each occasion.

Having spent a significant amount of time investigating the rhodium-induced decarbonylation we felt an alternative procedure for the removal of the hydroxymethyl auxiliary group was required; which would form the basis of our subsequent investigations on the indolizino[2,3-a]quinolizidine ring system.

Results and Discussion
2.5.3 Alternative Procedure for Removal of Hydroxymethyl "Auxiliary" Group

There are a number of radical chain decarbonylations reported in the literature,\textsuperscript{52} of which we became interested in the trialkylstannane-induced decarbonylation of phenyl seleno esters.\textsuperscript{53} Indeed, in their investigations towards the synthesis of Monensin, Ireland\textsuperscript{54} et al. found that phenyl seleno esters (74), derived from reaction of an acid (73) with phenyl dichlorophosphate followed by selenophenol, undergo radical decarbonylation to give the alkane (75) (Scheme 31).

![Scheme 31](image)

Martin employed similar methodology in the synthesis of geissochizine (29),\textsuperscript{29} which is detailed in Scheme 32.

![Scheme 32](image)

Martin discovered that the acyl selenide,\textsuperscript{55} prepared by sequential reaction of acid (76) with isobutyl chloroformate and then sodium phenyl selenide, underwent facile and efficient radical decarbonylation to give (77) in 79% yield from (76), which was converted in one step to the natural product (29).

The radical decarbonylation of phenyl seleno esters thus appeared to be an attractive alternative to the rhodium-induced decarbonylation reaction.
The application of this methodology on our substrates would initially require oxidation of (47) to the corresponding acid (78), either directly or in a stepwise fashion via aldehyde (71) (Scheme 33).

A variety of methods were employed for the attempted oxidation of aldehyde (71) to acid (78) including sodium chlorite in methanol, oxone in DMF, sodium chlorite in acetonitrile/water and potassium permanganate. However, none of these methods gave the desired acid (78) and so we turned to the possibility of direct oxidation from (47).

The direct oxidation of (47) to (78) was attempted using standard Jones oxidation conditions as well as pyridinium dichromate (PDC) in DMF/water but neither method delivered the acid.

The reason for the difficulties experienced in these oxidation reactions is probably the presence of the indole ring, which unprotected is known to be sensitive to oxidising conditions.

Results and Discussion
Therefore, a route was needed whereby the indole nitrogen of (47) could be selectively protected in the presence of the hydroxymethyl group prior to the attempted oxidation reactions. We exhausted numerous conditions for the selective protection of the indole nitrogen of (47) as the sulphonamide derivative. However, in all cases, mixtures of mono nitrogen, oxygen and bis-protected products were obtained. Eventually we found the protocol detailed in Scheme 34 to be the most practical for our purposes.

![Scheme 34](image)

The indole nitrogen of aldehyde (71) was protected as the t-butoxycarbonyl (BOC) derivative using triethylamine, N,N-dimethylaninopyridine (DMAP) and di-t-butyl dicarbonate ((Boc)₂O) producing (79) in 98% yield. Oxidation of the BOC-protected aldehyde (79) with sodium chlorite was now straightforward and the acid (80) was isolated in 83% yield.

The next stage would involve the radical decarbonylation of the phenyl seleno ester (81) under similar conditions to those employed by Martin (Scheme 35).
Scheme 35

The phenyl seleno ester (81) was prepared in 83% yield through treatment of the acid (80) with diphenyl diselenide and tri-n-butyl phosphine. The acyl selenide derivative was subjected to the tin-mediated decarbonylation to yield (82) in 73% yield.

Having successfully demonstrated removal of the hydroxymethyl substituent from our cyclisation product (47) via the radical decarbonylation of an acyl selenide derivative, we were required to measure the enantiomeric integrity of our decarbonylation product (82). Deprotection of the BOC group from (82) would deliver (72), for which we have established suitable chiral HPLC conditions, thus enabling us to measure the e.e. of our radical decarbonylation product. Avoiding the use of typical acidic BOC cleavage conditions to ensure there was no possibility of racemisation, we followed a procedure utilising tetra-n-butylammonium fluoride (TBAF) to remove the BOC group from (82) (Scheme 36).

Scheme 36

Results and Discussion
The BOC-protected decarbonylated derivative (82) was heated under reflux in tetrahydrofuran with 10 equivalents of TBAF giving lactam (72) in 65% yield. We now measured the e.e. of (72) synthesised via the radical decarbonylation route using our standard chiral HPLC conditions (Figure 19).

![Chiral HPLC performed using a Chiracel OD-H column, 85:15 hexane:2-propanol, 0.6 ml/min.](image)

Figure 19. Chiral HPLC trace of (72) from radical decarbonylation

We were extremely pleased to observe the chiral HPLC trace for (72) from the radical decarbonylation (Figure 19) which demonstrated an e.e. ≥ 98% under the limit of detection of the HPLC equipment, demonstrating removal of the hydroxymethyl “auxiliary” from our cyclisation substrates with no loss of enantiomeric integrity.

2.5.4 Lactam Reduction

To examine the suitability of our previously used method (Section 2.2.3) for reduction of the lactam functionality from our indolizino[2,3-α]quinolizidine substrates, cyclisation product (47) was reacted under the conditions outlined in Scheme 37 to produce the clean reduction product (83) in 74% yield.
2.6 Application of N-Acyliminium Cyclisation Methodology in the Synthesis of Indole Alkaloids

2.6.1 Total Synthesis of (12bS)-(−)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine

In our research to date we have been able to demonstrate the stereoselective synthesis of both indolizino[8,7-b]indole and indolizino[2,3-a]quinolizidine derivatives through the application of our novel N-acyliminium cyclisation methodology. As noted in Section 2.1.1 the indolizino[2,3-a]quinolizidine template (1) comprises the tetracyclic skeleton of numerous interesting indole targets.

To demonstrate the potential synthetic utility of our new methodology in the target synthesis of complex indole alkaloids and their synthetic analogues, we initially undertook the synthesis of a simple indole alkaloid, (12bS)-(−)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (84).
The indole alkaloid (84), isolated in 1966, is found as the main constituent in the leaves of a New Guinea tree, *Dracontomelum mangiferum* B1, which belongs to the family Anacardiaceae.\(^6\)

In order to access the natural S-enantiomer of the target we were required to work with template (50), which was synthesised from D-tryptophan (Section 2.3.4). Our synthetic route to the natural product would initially require application of our tin-mediated decarbonylation strategy for removal of the hydroxymethyl group from (50) (Scheme 38).

\[\text{Scheme 38}\]
The indolizino[2,3-a]quinolizidine derivative (50) was first oxidised with IBX to produce the corresponding aldehyde (85) in 60% yield. Protection of (85) was accomplished as before through treatment with Et₃N, DMAP and (Boc)₂O to give (86) in 63% yield. Compound (86) was oxidised to the carboxylic acid derivative (87) with sodium chlorite in 70% yield from which we generated the acyl selenide (88) in a yield of 66%. Finally, we performed the tin-mediated radical decarbonylation reaction producing the indolizino[2,3-a]quinolizidine derivative (89) in 98% yield (Scheme 38).

Elaboration of compound (89) to the natural product (84) was achieved via deprotection of the indole nitrogen with TBAF giving (90) in 63% yield followed by reductive removal of the lactam carbonyl group with lithium aluminium hydride producing the target compound (84) in 96% yield (Scheme 39).

Elaboration of compound (89) to the natural product (84) was achieved via deprotection of the indole nitrogen with TBAF giving (90) in 63% yield followed by reductive removal of the lactam carbonyl group with lithium aluminium hydride producing the target compound (84) in 96% yield (Scheme 39).

Target $S$-(-)-(84) was found to have an $e.e. > 95\%$ and the same absolute configuration as the natural product by comparison of optical rotation data\textsuperscript{66} (lit. $[\alpha]_D = -84 (c = 1, \text{MeOH})$).\textsuperscript{67,68} Furthermore, we were able to obtain an X-ray crystal structure of (84) confirming the structure of the product (Figure 20).
2.6.2 Total Synthesis of Both Enantiomers of Deplancheine

*R-(+)-Deplancheine* (91) was isolated in 1980 by Husson and co-workers from the stem and bark of the New Caledonian plant *Alstonia deplanchei*. Deplancheine (91) has an unusual structure in lacking the three carbon unit usually attached to C(15) in the corynantheine-type alkaloids.

The (±)-form of deplancheine was synthesised as a model compound six years before the report of the isolation of the (+)-base from natural sources, which established the $E$-configuration of the ethylidene group. The $R$ configuration of indole alkaloids derived from amino acids is uncommon and has been attributed to the enzyme biogenesis of these alkaloids.

After the structural elucidation of deplancheine a number of total syntheses were reported, but all of these approaches produced racemic material. For example, Joule utilised the cyano-adduct (92) which on treatment with acetic acid undergoes...
cyclisation to produce enol ether (93). This compound is elaborated to (±)-(91) through deprotection of the enol-ether and wittig reaction (Scheme 40).

In 1982 Overman\textsuperscript{72b} reported the stereospecific iminium ion-vinylsilane cyclisation of (94) via intermediate (95) producing racemic (91) (Scheme 41).

Results and Discussion
There has been one asymmetric synthesis of unnatural $S$-(-)-(91) carried out by Myers and co-workers in 1986. It was the asymmetric synthesis of $S$-(91) by Myers that established the correct absolute configuration of naturally occurring (91) to be $R$.

Our route toward $R$-(91) utilises our enantiomerically pure radical decarbonylation product (82) as a key intermediate. The first stage of the transformation to $R$-(91) involved the introduction of the ethylidene group via the three-step procedure detailed in Scheme 42.

The lithium enolate from treatment of (82) with LDA undergoes aldol reaction with acetaldehyde, followed by activation of the hydroxyl group by mesylation and finally DBN-induced elimination to give the desired target (96) in 65% yield over the three steps (Scheme 42). We found that whereas a THF/DCM solvent mixture in the elimination step gave only a 4.7:1 ratio of isomers in favour of the desired $E$-product (96), if the elimination was carried out in THF alone the $E$-regioisomer of the ethylidene product (96) was obtained exclusively.

Conversion of (96) to the natural product simply required deprotection of the indole nitrogen and reduction of the lactam carbonyl (Scheme 43).
Deprotection of the BOC protecting group from (96) was achieved in 63% yield using TBAF generating lactam (97). Selective reduction of the lactam functionality in the presence of the ethylidene moiety followed the method described by Martin,\textsuperscript{29} which is an adaptation of the Borch protocol.\textsuperscript{75} Selective reduction was successful producing the natural product \(R-(91)\) in 77% yield (Scheme 43).

Target \(R-(+)-(91)\) was found to have an e.e. > 95% and the same absolute configuration as the natural product by comparison of optical rotation data (lit. \([\alpha]_D = 56 \pm 2 \, (c = 1, \text{CHCl}_3)\)).\textsuperscript{69}

We were able to obtain an X-ray crystal structure of the natural product which is shown in Figure 21. Interestingly, a spacer water molecule acts as an intramolecular hydrogen bond acceptor and donor linking two molecules of the natural product together in the unit cell.
A 400 MHz $^1$H NMR spectrum of $R$-(91) (Figure 22) was identical to that of a $^1$H NMR spectrum of racemic (91) (Figure 23), kindly provided by Professor Larry Overman from his synthesis of ($\pm$)-(91) in 1982.\textsuperscript{72b}

**Figure 21. Crystal Structure of $R$-(91)**

**Figure 22. $^1$H NMR spectrum of $R$-(91)**
To verify our asymmetric synthesis of R-(91) and to demonstrate the potential synthetic utility of our methodology we have also undertaken an asymmetric synthesis of the S-enantiomer of the natural product (91). The route (Scheme 44) mirrors that described in Scheme 43, but utilises intermediate (89), which was prepared by manipulation of key building block (50), synthesised starting from D-tryptophan (48) as the original substrate. Furthermore, in the final step of the synthesis, the selective reduction of the lactam carbonyl in the presence of the ethylidene moiety, we have applied two methodologies; the protocol we applied in the synthesis of R-(91) from Martin, and diisobutylaluminium hydride (DIBAL) as used by Myers.

Introduction of the ethylidene group into the radical decarbonylation product (89) involved our standard three step procedure of aldol reaction followed by activation and elimination of the resulting hydroxyl group generating (98) in 71% yield. Deprotection of the BOC group from (98) was achieved through treatment with TBAF producing (99) in 58% yield. Lactam (99) undergoes selective reduction through treatment with Meerwein's reagent followed by sodium borohydride producing S-(91) in 64% yield. In addition, DIBAL reduction of (99) was successful and the target compound S-(91) was isolated again in a yield of 64% (Scheme 44).

Figure 23. $^1$H NMR spectrum of (±)-(91)
1. LDA, CH$_3$CHO
   THF, -78°C to RT, 24 h

2. Et$_3$N, MsCl
   DCM, -40°C to RT, 3 h
3. DBN
   THF, RT, 16 h

THF, Δ, 9 h

1. Me$_3$OBF$_4$
   2,6-t-Bu$_2$Py
   DCM, RT, 21 h
2. NaBH$_4$
   MeOH
   0°C, 0.5 h

DIBAL
DME
0°C to RT

S-(91)

[α]$_D$ = -58.4 (c = 1, CHCl$_3$)

[α]$_D$ = -52.4 (c = 1, CHCl$_3$)

Scheme 44

In both cases target S-(-)-(91) was found to have an e.e. > 95% by comparison of optical rotation data (lit. [α]$_D$ = -56 ± 2 (c = 1, CHCl$_3$)).

2.6.3 Conclusion

In summary, we have developed a facile and highly stereoselective approach to the important indolizino[8,7-b]indole and indolizino[2,3-a]quinolizidine templates from readily available non-racemic substrates. The key ring-forming step involves the cyclisation of a pendent aromatic substituent onto an N-acyliminium intermediate.

We have successfully demonstrated removal of the pendent hydroxymethyl “auxiliary” from both systems demonstrating the potential for application of our novel
cyclisation methodology in target synthesis. In addition, we have functionalised our indolizino[2,3-\textit{a}]quinolizidine derivatives through application of Michael addition chemistry, which may have future utility in the synthesis of some complex indole alkaloids.

Finally, we were able to utilise our methodology in the asymmetric synthesis of a simple indole alkaloid (84), as well as construction of both enantiomers of deplancheine (91) with high enantiomeric purity.

Schemes 45 to 52 give an overview of some of the important transformations described throughout this thesis.

- Stereoselective synthesis of tetracyclic indolizino[8,7-\textit{b}]indole derivatives through condensation of an optically pure amino alcohol and a keto-acid substrate (Scheme 45).
• Stereoselective synthesis of indolizino[8,7-b]indole derivatives through cyclisation of an imide intermediate (Scheme 46).

Scheme 46

• Stereoselective synthesis of indolizino[2,3-a]quinolizidine derivatives via cyclisation of a chiral bicyclic lactam intermediate (Scheme 47).

Scheme 47

• Epimerisation of indolizino[2,3-a]quinolizidine derivatives (Scheme 48).

Scheme 48
- Functionalisation of indolizino[2,3-a]quinolizidine derivatives via conjugate addition reactions (Scheme 49).

\[
\begin{align*}
\text{Nucleophile} & \quad \text{Nucleophile} \\
(60) & \quad (\text{Nu})
\end{align*}
\]

Scheme 49

- Removal of hydroxymethyl "auxiliary" from indolizino[2,3-a]quinolizidine derivatives via radical decarbonylation of an acyl selenide (Scheme 50).

\[
\begin{align*}
\text{n-Bu}_3\text{SnH} & \quad \text{AIBN} \\
\text{Toluene} & \quad 80^\circ\text{C}, 2\text{ h}
\end{align*}
\]

Scheme 50

- Regioselective introduction of an ethyldene moiety into indolizino[2,3-a]quinolizidine substrates (Scheme 51).

\[
\begin{align*}
\text{THF, -78^\circ\text{C} to RT, 24 h} & \quad \text{THF, RT, 16 h} \\
(82) & \quad (96)
\end{align*}
\]

Scheme 51
• Selective reduction of lactam functionality in the presence of an ethyldene moiety (Scheme 52).

Results and Discussion

Future work will focus on extending the methodology described to other, more complex indole alkaloid targets.
Chapter 3

Experimental
3.1 General Information

3.1.1 Solvents and Reagents

All solvents, where necessary, were dried and stored over 4Å molecular sieves prior to use.

Reagent chemicals were purchased from Lancaster Chemical Synthesis Ltd., Aldrich Chemical Company Ltd., Acros (Fischer) Chemicals Ltd., Avocado and Strem Chemicals UK and were distilled or recrystallised as required.

3.1.2 Chromatographic Procedures

Analytical thin layer chromatography (TLC) was conducted using aluminium-backed plates coated with 0.2 mm silica. Plates were visualised under UV light (254 nm) as well as through staining with potassium permanganate, 2,4-dinitrophenylhydrazine or phosphomolybdic acid. Flash column chromatography was conducted using Merck Kiesgel (70-230 Mesh ASTM). Samples were applied as saturated solutions in an appropriate solvent or pre-adsorbed onto the minimum quantity of silica gel. Pressure was applied to the column by the use of hand bellows.

Chiral HPLC was performed using a Thermoseparations modular machine (V100 UV Detector, P200 pump and TSP Chromatographic integrator) using a Chira Cel OD-H column (250 x 4.6 mm) purchased from Merck.

3.1.3 Spectra

Infra-red spectroscopy (IR) was conducted in the range of 4000-600 cm⁻¹, using a Perkin-Elmer Fourier Transform Paragon 1000 Spectrophotometer (with internal calibration). Samples were run as nujol mulls or dissolved in an appropriate solvent and applied as a thin film to the IR plates. Liquid samples were applied neat to the plates and run as thin films.
Nuclear magnetic resonance (NMR) spectra ($^1$H and $^{13}$C) were recorded using either a Bruker AC-250 or DPX-400 spectrometer. Multiplicities were recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), double doublets (dd), doublet of double doublets (ddd) and multiplets (m). All NMR samples were made up in deuterated solvents with all values quoted in ppm relative to tetramethylsilane (TMS) as an internal standard. Coupling constants ($J$ values) are reported in Hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the $^1$H NMR spectra.

Mass spectra (high/low resolution) were recorded on a Jeol-SX102 instrument.

3.1.4 Other Data

Elemental analyses were conducted on a Perkin-Elmer 2400 CHN Elemental Analyser. Melting points were determined using an electrical 9100 Thermal Melting Point instrument. Optical rotations were performed using an Optical Activity PolAar 2001 instrument and are reported in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. A Bruker SMART 1000 CCD diffractometer $\omega$ rotation with narrow frames was used to collect X-ray data. Yields (unless otherwise stated) are quoted for isolated pure products.
3.2 Synthesis of Indolizino[8,7-b]indoles

(2S)-2-Amino-3-(1H-indol-3-yl)propan-1-ol (11)<sup>76</sup>

Chlorotrimethylsilane (12.4 ml, 97.9 mmol) was added to a solution of lithium borohydride (1.07 g, 49.0 mmol) in anhydrous tetrahydrofuran (75.0 ml) under a nitrogen atmosphere over the course of 2 minutes. L-tryptophan (10) (5.0 g, 24.5 mmol) was added portionwise to the mixture over 5 minutes. After 24 hours stirring at room temperature the mixture was treated with methanol (30.0 ml), which was added cautiously. The methanol was evaporated and the resulting oil treated with 20% potassium hydroxide solution (20.0 ml). The solution was washed with ethyl acetate (3 x 100 ml) and the combined organic phases dried over anhydrous magnesium sulphate, filtered and the solvent removed to yield a light brown oil (3.26 g, 70%) which required no further purification; \( \nu_{\text{max}}(\text{thin film})/\text{cm}^{-1} \) 3278 (NH); \( \delta_H(250 \text{ MHz}; \text{DMSO}) \) 2.56 (1H, dd, \( J \) 13.8, 6.3, CH(H)CHNH<sub>2</sub>) 2.79 (1H, dd, \( J \) 12.5, 5, CH(H)CHNH<sub>2</sub>) 2.95-3.06 (1H, m, CHNH<sub>2</sub>) 3.20 (1H, dd, \( J \) 17.5, 7.5, CH(H)OH) 3.35 (1H, dd, \( J \) 8.8, 6.3, CH(H)OH) 6.96 (1H, t, \( J \) 7.5, ArH) 7.05 (1H, t, \( J \) 7.5, ArH) 7.14 (1H, s, CHNH) 7.34 (1H, d, \( J \) 10, ArH) 7.54 (1H, d, \( J \) 7.5, ArH) 10.83 (1H, br, s, NH); \( \delta_C(100 \text{ MHz}; \text{DMSO}) \) 29.4 (CH<sub>2</sub>), 54.1 (CH), 65.7 (CH<sub>2</sub>), 111.2 (CH), 111.5 (C), 118.0 (CH), 118.4 (CH), 120.7 (CH), 123.1 (CH), 127.5 (C), 136.1 (C); MS (El) \( m/z \) 190 (\( M^+ \), 2.95%); (Found: \( M^+ \), 190.11068. C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O requires 190.11061).
(5S,11bS)-5-(Hydroxymethyl)-11b-methyl-2,3,5,6,11,11b-hexahydro-1H-pyrrolo[2,1-a]b-carbolin-3-one (14)

(2S)-2-Amino-3-(1H-indol-3-yl)propan-1-ol (11) (2.3 g, 12.1 mmol) and Levulinic acid (12) (1.40 g, 12.1 mmol) were added to toluene (150 ml) and heated at reflux under Dean-Stark conditions for 48 hours. The reaction was cooled to room temperature and the solvent was removed by rotary evaporation. The resulting solid was adsorbed onto silica gel and purified by flash column chromatography over silica gel using 8:2 ethyl acetate:light petroleum as eluent to produce an off-white solid (1.79 g, 55%), a small portion of which was recrystallised from dichloromethane/hexane to yield colourless needles; Mp 212-214 °C; [α]D = -229.8 (c = 1.2, CH2Cl2) (Found: C, 70.99; H, 6.67; N, 10.26; C16H18N2O2 requires C, 71.09; H, 6.71; N, 10.36%); νmax (thin film, DCM)/cm⁻¹ 3269 (NH), 1655 (C=O); δH(250 MHz; CDCl3) 1.65 (3H, s, CH3), 2.18-2.35 (2H, m, CH2CH2CO), 2.48 (1H, ddd, J 17.5, 7.5, 2.5, CH(H)CO), 2.67-2.81 (1H, m, CH(H)CO), 2.67-2.81 (1H, m, CH(H)CHN), 3.04 (1H, dd, J 16.3, 11.3, CH(H)CHN), 3.64-3.76 (1H, m, CH2CH2OH), 4.15-4.20 (2H, m, CH2OH), 5.12 (1H, t, J 7.5, OH), 7.13-7.20 (2H, m, ArH), 7.35 (1H, d, J 7.5, ArH), 7.48 (1H, d, J 7.5, ArH), 8.03 (1H, br, s, NH); δc(100 MHz; CDCl3) 24.3 (CH2), 25.4 (CH3), 31.3 (CH2), 32.7 (CH2), 55.5 (CH), 62.4 (C), 62.8 (CH2), 107.0 (C), 111.1 (CH), 118.6 (CH), 119.9 (CH), 122.3 (CH), 126.6 (C), 136.4 (C), 137.3 (C), 174.8 (NC=O); MS (EI) m/z 270 [M⁺, 30.8%] (Found: M⁺, 270.13639. C16H18N2O2 requires 270.13683).
1-[(1S)-2-Hydroxy-1-(1H-indol-3-ylmethyl)ethyl]tetrahydro-1H-pyrrole-2,5-dione (16)

(2S)-2-amino-3-(1H-indol-3-yl)propan-1-ol (11) (3.91 g, 20.6 mmol) and succinic anhydride (15) (2.1 g, 20.6 mmol) were stirred in toluene (100 ml) under nitrogen. To the resulting solution was added triethylamine (3 ml) and the mixture was heated under reflux for 18 hours. After this time the solvent was removed by rotary evaporation to yield a dark brown oil which was adsorbed onto silica gel and purified by flash column chromatography over silica gel, eluting with 3:2 ethyl acetate:light petroleum, to give the target compound (2.29 g, 54%), a small portion of which was recrystallised from dichloromethane to give clear crystals; Mp 144-147 °C; [α]D = -73.1 (c = 1.3, CH2Cl2) (Found: C, 65.80; H, 5.86; N, 10.29; C13H16N2O3 requires C, 66.16; H, 5.92; N, 10.29%); v_max (thin film, DCM)/cm⁻¹: 3408 (OH), 1694 (Imide C=O); δ_C (400 MHz; CDCl3) 2.45-2.61 (4H, m, COCH₂CH₂CO), 3.21-3.32 (2H, m, CH₂C=CH), 3.84 (1H, dd, J 7.5, 2.5, CH(H)OH), 4.02-4.06 (1H, m, CH(H)OH), 4.59 (1H, ddd, J 7.5, 5, 2.5, CHCH₂OH), 7.08 (1H, d, J 2.5, C=CH), 7.10-7.14 (1H, m, ArH), 7.16-7.20 (1H, m, ArH), 7.33 (1H, d, J 5, ArH), 7.62 (1H, d, J 5, ArH), 8.13 (1H, br, s, NH); OH not visible; δ_C (100 MHz; CDCl3) 23.6 (CH₃), 28.0 (2×CH₂), 55.4 (CH), 62.3 (CH₂), 111.2 (CH), 111.4 (C), 118.5 (CH), 119.6 (CH), 122.1 (CH), 122.9 (CH), 127.4 (C), 136.1 (C), 178.4 (2×C=O); MS (EI) m/z 272 [M⁺, 12.4%] (Found: M⁺ 272.05311. C₁₃H₁₆N₂O₃ requires 272.05349).
1-[(1S)-2-hydroxy-1-(1H-indol-3-ylmethyl)ethyl]tetrahydro-1H-pyrrole-2,5-dione (16) (0.50 g, 1.84 mmol) was dissolved in absolute ethanol (25 ml) under nitrogen at room temperature. The solution was cooled to 0 °C and sodium borohydride (0.70 g, 18.4 mmol) was added with stirring. 2 M HCl in absolute ethanol (0.93 ml, 1.84 mmol) was added slowly by syringe over a 3 hour period. The solution was then acidified to pH 1-3 by addition of 2 M HCl in absolute ethanol over a 15 minute period, affording a white suspension which was stirred for an additional 20 hours at room temperature. The mixture was quenched by the addition of saturated aqueous sodium bicarbonate solution (50 ml) and extracted with dichloromethane (3 x 50 ml). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed by rotary evaporation. Crude 250 MHz 1H NMR revealed formation of the product as a 9:1 mixture of diastereoisomers which were purified by flash column chromatography over silica gel eluting with ethyl acetate (0.21 g, 45%). The major isomer (18) was isolated as a white solid by crystallisation from ethanol; Mp 265-269 °C; [α]D = +144.8 (c = 0.42, EtOH), νmax(KBr disc)/cm⁻¹ 3269 (NH), 1666 (NC=O); δH(400 MHz; DMSO) 1.78-1.82 (1H, m, CH(H)CH₂C=O), 2.25-2.31 (1H, m, CH₂CH(H)C=O), 2.49-2.56 (1H, m, CH₂CH(H)C=O), 2.73 (1H, dd, J 8, 4, C=CCH(H)), 2.81 (1H, d, J 16, C=CCH(H)), 3.35-3.37 (2H, m, CH₂OH), 4.49 (1H, dd, J 12, 8, NCH₂CH₂OH), 4.83-4.87 (2H, m, C=CCH and OH), 6.95-6.99 (1H, m, ArH), 7.04-7.08 (1H, m, ArH), 7.32 (1H, d, J 8, ArH), 7.40 (1H, d, J 8, ArH), 11.0 (1H, br, s, NH); δC(100 MHz; DMSO) 21.1 (CH₂), 25.4 (CH₂), 31.0 (CH₂), 48.0 (CH), 50.7 (CH), 60.1 (CH₂), 104.1 (C), 111.0 (CH), 117.7 (CH), 118.4 (CH), 120.9 (CH), 126.7 (C), 133.4 (C), 136.1 (C), 172.6 (NC=O); MS (El) m/z 256 [M⁺, 95.0%] (Found: M⁺, 256.12145. C₁₅H₁₆N₂O₂ requires 256.12118).
To a solution of (5S,11bS)-5-(hydroxymethyl)-11b-methyl-2,3,5,6,11,11b-hexahydro-1H-pyrrolo[2,1-α]b-carbolin-3-one (14) (1.18 g, 4.37 mmol) in dimethylsulfoxide (20 ml) was added IBX (2.43 g, 8.74 mmol) with stirring under nitrogen. After 24 hours the solvent was removed and the resulting solid was re-suspended in ethyl acetate (250 ml), before filtering through a small pad of celite. The filtrate was washed with water (3 × 250 ml), the organic phase was then dried over anhydrous magnesium sulphate, filtered and evaporated to dryness to yield the target compound which was purified by flash column chromatography over silica gel using ethyl acetate as eluent. The purified aldehyde was afforded as an off-white solid (1.05 g, 90%); Mp 169-170 °C; [α]_D = -91.3 (c = 3.2, CH₂Cl₂); ν_{max}(thin film, DCM)/cm⁻¹ 3285 (NH), 1719 (CHO), 1670 (NC=O); δ_{H}(400 MHz; CDCl₃) 1.74 (3H, s, CH₃), 2.29-2.38 (1H, m, CH(H)CH₂CO), 2.29-2.38 (1H, m, CH₂CH(H)CO), 2.45-2.67 (1H, m, CH(H)CH₂CO), 2.45-2.67 (1H, m, CH₂CH(H)CO), 3.05 (1H, dd, J 16, 4, CH(H)CHN), 3.14 (1H, dd, J 14, 4, CH(H)CHN), 3.91 (1H, dd, J 12, 4, CHCHO), 7.11-7.18 (1H, m, ArH), 7.20-7.26 (1H, m, ArH), 7.33 (1H, d, J 8, ArH), 7.49 (1H, d, J 8, ArH), 8.23 (1H, br, s, NH), 10.1 (1H, s, CHO); δ_{C}(100 MHz; CDCl₃) 20.5 (CH₂), 27.4 (CH₃), 29.2 (CH₂), 32.6 (CH₂), 58.8 (CH), 61.1 (C), 107.5 (C), 111.1 (CH), 118.6 (CH), 120.1 (CH), 122.6 (CH), 128.3 (C), 136.2 (C), 136.7 (C), 177.7 (NC=O), 196.3 (RCHO); MS (EI) m/z 268 [M⁺, 47.3%] (Found: M⁺, 268.12124. C₁₆H₁₆N₂O₂ requires 268.12118).

[Bis(triphenylphosphine)]rhodium(I) carbonyl chloride (20) (0.64 g, 0.93 mmol) was added to anhydrous p-xylene (30 ml) under a nitrogen atmosphere and the mixture warmed to 80 °C with stirring until the rhodium complex dissolved. [5S,11bS]-11b-methyl-oxo-2,3,5,6,11,11b-hexahydro-1H-pyrrolo[2,1-a]b-carboline-5-carbaldehyde (23) (0.25 g, 0.93 mmol) was added and the mixture heated at reflux under nitrogen. After 120 hours the solvent was evaporated and the crude material purified by flash column chromatography over silica gel using ethyl acetate as eluent to yield (11bS)-11b-methyl-2,3,11,11b-tetrahydro-1H-pyrrolo[2,1-a]b-carbolin-3-one (25) (0.03 g, 12%). In addition (0.09 g, 38%) of (11bS)-11b-methyl-2,3,5,6,11,11b-hexahydro-1H-pyrrolo[2,1-a]b-carbolin-3-one (24) was isolated; Data for (11bS)-11b-methyl-2,3,11,11b-tetrahydro-1H-pyrrolo[2,1-a]b-carbolin-3-one (25); Mp 184-186 °C; [α]D = -341.8 (c = 1.1, MeOH); \( \nu_{\text{max}} \) (thin film, DCM)/cm\(^{-1}\) 3215 (NH), 1685 (NC=O); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 1.40 (3H, s, CH\(_3\)), 2.44-2.61 (2H, m, CH\(_2\)CH\(_2\)CO), 2.44-2.61 (1H, m, CH\(_2\)CH(H)CO), 2.68-2.80 (1H, m, CH\(_2\)CH(H)CO), 6.34 (1H, d, J 8, NCH=CH), 6.74 (1H, d, J 8, NCH=CH), 7.16-7.19 (2H, m, ArH), 7.36 (1H, d, J 8, ArH), 7.60 (1H, m, J 16, ArH), 8.40 (1H, br, s, NH); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 24.4 (CH\(_3\)), 29.7 (CH\(_2\)), 32.3 (CH\(_2\)), 61.0 (C), 106.4 (CH), 107.5 (C), 111.5 (CH), 115.4 (CH), 118.5 (CH), 120.7 (CH), 122.3 (CH), 123.8 (C), 135.9 (C), 136.1 (C), 172.8 (NC=O); MS (El) \( m/z \) 238 [M\(^+\), 3.12%] (Found: M\(^+\), 238.11021. C\(_{15}\)H\(_{14}\)N\(_2\)O requires 238.11061).
(11bS)-11b-Methyl-2,3,5,6,11,11b-hexahydro-1H-pyrrolo[2,1-a]b-carbolin-3-one (24)

(11bS)-11b-methyl-2,3,11,11b-tetrahydro-1H-pyrrolo[2,1-a]b-carbolin-3-one (25) (0.03 g, 0.13 mmol) was dissolved in absolute ethanol (20 ml) and the reaction was purged with nitrogen. A catalytic amount of 10% palladium/charcoal was added to the mixture, a balloon filled with hydrogen was fitted and the system purged with hydrogen. The mixture was then stirred for a further 48 hours at room temperature. After this time, the mixture was filtered through celite and the reaction vessel washed with dichloromethane and poured onto the celite. The filtrate was concentrated and purified by flash column chromatography over silica gel with ethyl acetate to yield the product (0.03 g, 85%); Mp 140-142 °C; [α]D = -238.8 (c = 1, MeOH); νmax (thin film, DCM)/cm⁻¹ 1683 (NC=O); δH (400 MHz; CDCl₃) 1.51 (3H, s, CH₃), 2.06-2.12 (1H, m, CH(H)CH₂CO), 2.17-2.22 (1H, m, CH(H)CH₂CO), 2.34 (1H, ddd, J 16, 12, 4, CH(H)CO), 2.52-2.61 (1H, m, CH(H)CO), 2.69-2.81 (2H, m, CH₂CH₂N), 2.98-3.05 (1H, m, CH(H)N), 4.36-4.41 (1H, m, CH(H)N), 7.12-7.21 (2H, m, ArH), 7.34 (1H, d, J 12, ArH), 7.49 (1H, m, J 12, ArH), 8.22 (1H, br, s, NH); δC (100 MHz; CDCl₃) 21.2 (CH₂), 25.4 (CH₂), 30.7 (CH₂), 32.8 (CH₂), 35.0 (CH₂), 59.5 (C), 106.9 (C), 111.0 (CH), 118.6 (CH), 119.8 (CH), 122.2 (CH), 126.7 (C), 136.1 (C), 137.7 (C), 172.8 (NC=O); MS (EI) m/z 240 [M⁺, 22.7%] (Found: M⁺, 240.12621. C₁₅H₁₆N₂O requires 240.12626).

A solution of (SS,11bS)-S-(hydroxymethyl)-11b-methyl-2,3,5,6,11,11b-hexahydro-1H-pyrrolo[2,1-α]b-carbolin-3-one (14) (0.20 g, 0.74 mmol) in anhydrous toluene (15 ml) and dichloromethane (10 ml) was stirred at room temperature under nitrogen with sodium bis(methoxyethoxy)aluminium hydride (0.74 ml of a 65% solution in toluene) for 20 hours. The reaction mixture was quenched by careful addition of saturated aqueous sodium potassium tartrate (25 ml). The organic layer was separated and the salt extracted with dichloromethane (3 × 30 ml). The organic phases were dried with anhydrous sodium sulphate, filtered and the solvent removed on the rotary evaporator. The resulting solid was adsorbed onto silica gel and purified by flash column chromatography over silica gel using 8:2 dichloromethane:methanol as eluent to produce a light brown solid (0.13 g, 68%); Mp 103-107 °C; [α]D = -48.1 (c = 0.27, CH2Cl2); νmax(thin film, DCM)/cm⁻¹ 3400 (NH), 3278 (OH), δH(250 MHz; CDCl3) 1.54 (3H, s, CH3), 1.58-1.66 (1H, m, CH(H)CCH3), 1.80-1.92 (1H, m, CH(H)CCH3), 1.97-2.09 (1H, m, CH(H)CH2CCH3), 2.15-2.25 (1H, m, CH(H)CH2CCH3), 2.52 (1H, dd, J 15, 5, CH(H)CHN), 2.60 (1H, dd, J 15, 5, CH(H)CHN), 2.72 (1H, dd, J 16.3, 8.8, CH(H)N), 2.95-3.04 (1H, m, CH(H)N), 3.43-3.46 (1H, m, CHN), 3.68-3.76 (2H, m, CH2OH), 7.06-7.18 (2H, m, ArH), 7.32 (1H, d, J 7.5, ArH), 7.45 (1H, d, J 7.5, ArH), 7.95 (1H, br, s, NH2); δc(100 MHz; CDCl3) 17.3 (CH2), 20.6 (CH2), 26.0 (CH3), 36.7 (CH2), 41.9 (CH2), 53.1 (CH), 61.0 (C), 62.3 (CH2), 105.5 (C), 109.9 (CH), 117.1 (CH), 118.4 (CH), 120.6 (CH), 125.9 (C), 135.1 (C), 137.5 (C); MS (El) m/z 256.157 [M⁺, 0.47%] (Found: M⁺, 256.15790. C16H20N2O requires 256.15756).
A solution of (11bS)-11b-methyl-2,3,5,6,11,11b-hexahydro-1H-pyrrolo[2,1-a]b-carboline-3-one (24) (0.10 g, 0.42 mmol) in anhydrous toluene (20 ml) was stirred at room temperature under nitrogen with sodium bis(methoxyethoxy)aluminium hydride (0.5 ml of a 65% solution in toluene) for 20 hours. The reaction mixture was quenched by careful addition of saturated aqueous sodium potassium tartrate (25 ml). The organic layer was separated and the salt extracted with dichloromethane (3 x 30 ml). To the organic fraction was added water (100 ml) and the mixture acidified with 2 M HCl whilst stirring. The layers were separated and the aqueous layer was washed with dichloromethane (3 x 30 ml). The aqueous layer was basified with saturated sodium bicarbonate solution and extracted with dichloromethane (3 x 30 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and the solvent removed on the rotary evaporator. The crude product was chromatographed over silica gel using ethyl acetate to yield the product as a pale yellow oil (0.06 g, 67%) (27% overall yield from aldehyde); [α]D = -87.3 (c = 1.2, CH2Cl2); νmax (thin film, DCM)/cm−1 3372 (NH); δH (400 MHz; CDCl3) 1.52 (3H, s, CH3), 1.54-1.57 (1H, m, CH2CH(CH)CH2N), 1.81-1.83 (1H, m, CH2CH(H)CH2N), 2.00-2.05 (1H, m, CH(H)CH2CH2N), 2.09-2.13 (1H, m, CH(H)CH2CH2N), 2.52-2.56 (1H, m, CH2CH(H)C=C), 2.83-2.94 (1H, m, CH2CH(H)C=C), 3.07-3.12 (1H, m, CH2CH2CH(H)N), 3.20-3.25 (2H, m, CH2CH2C=CH), 7.00-7.10 (2H, m, ArH), 7.25 (1H, d, J 8, ArH), 7.40 (1H, d, J 8, ArH), 8.22 (1H, br, s, NH); δC (100 MHz; CDCl3) 15.0 (CH2), 21.0 (CH2), 26.1 (CH3), 36.8 (CH2), 41.1 (CH2), 47.9 (CH2), 60.0 (C), 105.5 (C), 109.9 (CH), 117.2 (CH), 118.4 (CH), 120.7 (CH), 126.0 (C), 135.0 (C), 136.8 (C); MS (EI) m/z 226 (M+, 12.8%) (Found: M+, 226.14670. C15H18N2 requires 226.14700).
3.3 Synthesis of Indolizino[2,3-a]quinolizidines

Methyl-5-hydroxypentanoate (44)\(^{38}\)

![Chemical structure](image)

Concentrated H\(_2\)SO\(_4\) (10 drops) was added to a stirred solution of δ-valerolactone (43) (10.0 g, 99.9 mmol) in methanol (100 ml). The resultant mixture was heated under reflux for 6 hours and then cooled in an ice/salt bath. Sodium bicarbonate (2.0 g) was added, stirred for 10 minutes, filtered and the solvent removed under reduced pressure. This yielded a colourless oil (13.3 g, 98%), which was used without further purification; \(\nu\)\(_{\text{max}}\) (thin film)/cm\(^{-1}\) 3410 (OH), 2951, 2872 (sp\(^3\) CH), 1736 (COOCH\(_3\)); \(\delta\)\(_H\) (400 MHz; CDCl\(_3\)) 1.53-1.60 (2H, m, CH\(_2\)CH\(_2\)OH), 1.65-1.73 (2H, m, CH\(_2\)CH\(_2\)CH\(_2\)OH), 2.34 (2H, t, J 8, CH\(_2\)COOCH\(_3\)), 3.62 (2H, t, J 8, CH\(_2\)OH), 3.65 (3H, s, OCH\(_3\)), 3.79 (1H, br, s, OH); \(\delta\)\(_C\) (100 MHz; CDCl\(_3\)) 21.8 (CH\(_2\)), 32.4 (CH\(_2\)), 34.1 (CH\(_3\)), 51.9 (CH\(_3\)), 62.1 (CH\(_2\)), 174.8 (C=O); MS (El) \(m/z\) 132 [M\(^+\), 2.13%] (Found: M\(^+\), 132.07894. C\(_6\)H\(_{12}\)O\(_3\) requires 132.07865).
Methyl-5-oxopentanoate (45)\(^3\)

Methyl-5-hydroxypentanoate (44) (11.9 g, 91.5 mmol) was slowly added to a suspension of PCC (29.6 g, 137.3 mmol) and celite (29.6 g) in anhydrous dichloromethane (180 ml), and the resulting mixture was stirred at room temperature for 2 hours. The solution was decanted and the solids were washed with diethyl ether (3 \(\times\) 100 ml). The combined organic washings were filtered through an alumina column to afford Methyl-5-oxopentanoate (45) as a pale green oil (8.0 g, 68%) which was used without further purification; \(v_{\text{max}}\) (thin film) / cm\(^{-1}\) 2953, 2843 (sp\(^3\) CH), 1734 (COOCH\(_3\)), 1437 (sp\(^3\) CH); \(\delta H\) (400 MHz; CDCl\(_3\)) 1.87-1.99 (2H, m, CH\(_2\)CHO), 2.55 (2H, t, \(J\) 7.6, CH\(_2\)CHO), 2.83 (2H, t, \(J\) 7.3, CH\(_2\)CH\(_2\)CHO), 3.60 (3H, s, OCH\(_3\)), 9.76 (1H, s, CHO); \(\delta C\) (100 MHz; CDCl\(_3\)) 15.3 (CH\(_2\)), 30.9 (CH\(_2\)), 40.8 (CH\(_2\)), 49.3 (CH\(_2\)), 171.2 (C=O), 199.5 (C=O); MS (EI) \(m/z\) 130 [M\(^+\), 5.48%] (Found: M\(^+\), 130.06275. C\(_6\)H\(_{10}\)O\(_3\) requires 130.06300).
(3S,8aS)-3-(1H-Indol-3-ylmethyl)perhydropyrido[2,1-b][1,3]oxazol-5-one (46a)

(2S)-2-amino-3-(1H-indol-3-yl)propan-1-ol (11) (3.0 g, 15.8 mmol) and Methyl-5-oxopentanoate (45) (2.1 g, 15.8 mmol) were added to toluene (150 ml) and refluxed under Dean-Stark conditions for 48 hours. The mixture was cooled to room temperature and the solvent removed under reduced pressure to yield the target compound. Crude 250 MHz ¹H NMR revealed the formation of (46) as a 5:1 mixture of diastereoisomers. These diastereoisomers were purified and separated by flash column chromatography over silica gel using ethyl acetate as eluent (2.90 g, 69%).

**Major isomer (46a)** isolated as a yellow solid which was recrystallised from dichloromethane to yield colourless needles; Mp 152-156 °C; [α]D = -39.1 (c = 1.7, CH2Cl2) (Found: C, 71.04; H, 6.69; N, 10.27; C16H18N2O2 requires C, 71.09; H, 6.71; N, 10.36%); νmax(thin film, DCM)/cm⁻¹ 3274 (NH), 1628 (NC=O); δH(400 MHz; CDCl3) 1.43-1.57 (1H, m, CH(H)CH2CH2C=O), 1.67-1.77 (1H, m, CH2CH(H)CH2C=O), 1.96-2.01 (1H, m, CH2CH(H)CH2C=O), 2.24-2.28 (1H, m, CH(H)CH2CH2C=O), 2.41-2.45 (2H, m, CH2C=O), 2.68 (1H, dd, J 16, 8, CH(H)C=O), 3.67-3.76 (1H, m, CH(H)C=O), 3.67-3.76 (1H, m, CH(H)O), 4.03 (1H, d, J 8, CH(H)O), 4.28-4.33 (1H, m, NCHCH2O), 4.68 (1H, dd, J 12, 4, NCHCH2O), 7.03 (1H, d, J 4, C=CHNH), 7.05-7.22 (2H, m, ArH), 7.36 (1H, d, J 8, ArH), 7.82 (1H, d, J 8, ArH), 8.24 (1H, br, s, NH); δC(100 MHz; CDCl3) 17.6 (CH), 27.0 (CH2), 28.4 (CH2), 56.1 (CH), 70.0 (CH2), 89.0 (CH), 111.1 (CH), 112.6 (C), 119.4 (CH), 119.6 (CH), 122.2 (CH), 122.4 (CH), 127.7 (C), 136.2 (C), 168.1 (NC=O); MS (ES) m/z 270 [M⁺, 100%] (Found: M⁺, 270.13690. C16H18N2O2 requires 270.13683).

**Minor isomer (46b)** isolated as a pale yellow oil; [α]D = +14.3 (c = 2.0, CH2Cl2) (Found: C, 70.97; H, 6.69; N, 10.35; C16H18N2O2 requires C, 71.09; H, 6.71; N, 10.36%); νmax(thin film, DCM)/cm⁻¹ 3279 (NH), 1628 (NC=O); δH(400 MHz; CDCl3)
1.33-1.42 (1H, m, CH(H)CH₂CH₂C=O), 1.51-1.59 (1H, m, CH₂CH(H)CH₂C=O),
1.80-1.88 (1H, m, CH₂CH(H)CH₂C=O), 2.14-2.18 (1H, m, CH(H)CH₂CH₂C=O),
2.27-2.37 (1H, m, CH(H)C=O), 2.53 (1H, dd, J 16, 8, CH(H)C=O), 3.05 (1H, dd, J
16, 8, CH(H)C=C), 3.32 (1H, dd, J 16, 4, CH(H)C=C), 3.69 (1H, dd, J 8.8, 7.2,
CH(H)O), 4.04-4.09 (1H, m, CH(H)O), 4.46 (1H, dd, J 8, 4, NCHOCH₂), 4.60-4.67
(1H, m, NCHCH₂O), 7.01 (1H, d, J 4, C=CH₂NH), 7.10-7.14 (1H, m, ArH), 7.17-7.21
(1H, m, ArH), 7.36 (1H, d, J 8, ArH), 7.69 (1H, d, J 8, ArH), 8.34 (1H, br, s, NH);
δc (100 MHz; CDCl₃) 14.2 (CH₂), 27.6 (CH₂), 28.2 (CH₂), 31.4 (CH₂), 54.5 (CH),
69.7 (CH₂), 87.3 (CH), 111.1 (CH), 111.2 (C), 119.2 (CH), 119.5 (CH), 122.2 (CH),
122.6 (CH), 127.8 (C), 136.3 (C), 168.8 (NC=O); MS (EI) m/z 270 [M⁺, 23.3%]
(Found: M⁺, 270.13690. CI₁₆H₁₈N₂O₂ requires 270.13683).

Experimental
(6S,12bR)-6-(Hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carboline-4-one (47)

(3S,8aS)-3-(1H-Indol-3-ylmethyl)perhydropyrido[2,1-b][1,3]oxazol-5-one (46a/b) (5:1 mixture of isomers) (1.0 g, 3.70 mmol) was dissolved in dry dichloromethane (40 ml) under a nitrogen atmosphere. The mixture was cooled to -78 °C and 1.5 equivalents of titanium tetrachloride (0.6 ml, 5.6 mmol) were added dropwise by syringe. The mixture was allowed to warm slowly to room temperature over a period of 20 hours. The reaction mixture was quenched with saturated ammonium chloride solution (40 ml), extracted with ethyl acetate (3 x 40 ml) and dried using anhydrous magnesium sulphate. The solvent was removed by rotary evaporation and crude 250 MHz $^1$H NMR revealed formation of the product as a 5:2 mixture of diastereoisomers (0.54 g, 54%) which were separated by flash column chromatography over silica gel using ethyl acetate as eluent.

Major isomer (47) isolated as a white solid which was recrystallised from absolute ethanol to yield the target compound as colourless block-like crystals; Mp 288-290 °C; $[\alpha]_D = +128.8$ (c = 0.50, EtOH) (Found: C, 70.75; H, 6.67; N, 10.28; C$_{16}$H$_{18}$N$_2$O$_2$ requires C, 71.09; H, 6.71; N, 10.36%); $\nu_{max}$(thin film, DCM)/cm$^{-1}$ 3277 (NH), 1618 (NC=O); $\delta_{H}$(400 MHz; DMSO) 1.52-1.62 (1H, m, CH(H)CH$_2$CH$_2$C=O), 1.73-1.86 (2H, m, CH$_2$CH$_2$C=O), 2.26-2.43 (2H, m, CH$_2$C=O), 2.59-2.63 (1H, m, CH(H)CH$_2$CH$_2$C=O), 2.66 (1H, ddd, J 16, 8, 4, C=CCH(H)), 2.80 (1H, d, J 16, C=CCH(H)), 3.35-3.37 (2H, m, CH$_2$OH), 4.65 (1H, d, J 8, NCHC=CH), 4.81 (1H, t, J 4, OCH$_2$), 5.22 (1H, q, J 7.5, NCHCH$_2$OH), 6.95-6.99 (1H, m, ArH), 7.04-7.08 (1H, m, ArH), 7.32 (1H, d, J 8, ArH), 7.40 (1H, d, J 8, ArH), 10.09 (1H, br, s, NH); $\delta_{C}$(100 MHz; DMSO) 19.4 (CH$_2$), 21.0 (CH$_2$), 29.0 (CH$_2$), 32.7 (CH$_2$), 48.2 (CH), 50.6 (CH), 60.2 (CH$_2$), 105.1 (C), 111.4 (CH), 118.1 (CH), 118.8 (CH), 121.3 (CH), 127.1 (C), 138.4 (C), 148.8 (C), 152.3 (C), 165.4 (C), 197.6 (C), 205.4 (C).
133.7 (C), 136.7 (C), 168.8 (NC=O); MS (El) m/z 270 [M⁺, 100%] (Found: M⁺, 270.13626. C₁₆H₁₈N₂O₂ requires 270.13683).

Minor isomer (57) isolated as light brown crystalline solid, a small portion of which was recrystallised from absolute ethanol to give colourless crystals; Mₚ 246-247 °C; [α]₀ = +16.0 (c = 0.55, DMSO) (Found: C, 71.00; H, 6.73; N, 10.33; C₁₆H₁₈N₂O₂ requires C, 71.09; H, 6.71; N, 10.36%); v_max(KBr disc)/cm⁻¹ 3277 (NH), 1618 (NC=O); δₜₚ(400 MHz; DMSO) 1.58-1.72 (1H, m, CH(H)CH₂C=O), 1.59-1.72 (1H, m, C=CCHCH(H)), 1.85-1.91 (1H, m, CH(H)CH₂C=O), 2.16-2.22 (1H, m, CH(H)C=O), 2.43-2.56 (1H, m, C=CCHCH(H)), 2.43-2.56 (1H, m, CH(H)C=O), 2.65-2.70 (C=CCH(H)), 3.11 (1H, dd, J 12, 6, C=CCH(H)), 3.28-3.34 (1H, m, CH(H)OH), 3.36-3.42 (1H, m, CH(H)OH), 4.24-4.30 (1H, m, NCHCH₂OH), 4.78-4.82 (1H, m, C=CCH), 4.88 (1H, t, J 8, OH), 6.98 (1H, t, J 8, ArH), 7.05 (1H, t, J 8, ArH), 7.32 (1H, d, J 8, ArH), 7.42 (1H, d, J 8, ArH), 10.9 (1H, br, s, NH); δ_C(100 MHz; DMSO) 17.5 (CH₂), 20.6 (CH₂), 27.4 (CH₂), 32.0 (CH₂), 52.3 (CH), 54.7 (CH), 61.3 (CH₂), 106.0 (C), 111.2 (CH), 117.7 (CH), 118.5 (CH), 120.8 (CH), 126.7 (C), 133.3 (C), 136.2 (C), 171.8 (NC=O); MS (El) m/z 270 [M⁺, 84.1%] (Found: M⁺, 270.13690. C₁₆H₁₈N₂O₂ requires 270.13683).
(6S,12bR)-6-(Hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (47) (From cyclisation of (46a/b) with 2 M HCl in absolute ethanol)

\[ \text{(3S,8aS)-3-(1H-Indol-3-ylmethyl)perhydropyrido[2,1-b][1,3]oxazol-5-one (46a/b)} \]

(3.1 g, 11.5 mmol) was dissolved in absolute ethanol (100 ml) under a nitrogen atmosphere. The resulting solution was acidified to pH 1 by the addition of 2 M HCl in ethanol and the mixture was stirred for a further 20 hours at room temperature. After this time the reaction was quenched by addition of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 x 150 ml). The organic fraction was dried over anhydrous magnesium sulphate and the solvent removed by rotary evaporation to yield a light brown solid (3.0 g, 97%). Crude 250 MHz \(^1\)H NMR revealed formation of (47) as a single diastereoisomer, which was recrystallised from absolute ethanol to yield the target compound as colourless block-like crystals; which had identical spectral properties as the major compound prepared via titanium tetrachloride mediated cyclisation of (46a/b).
Chlorotrimethylsilane (12.4 ml, 97.9 mmol) was added to a solution of lithium borohydride (1.07 g, 49.0 mmol) in anhydrous tetrahydrofuran (75.0 ml) under a nitrogen atmosphere over the course of 2 minutes. D-tryptophan (5.0 g, 24.5 mmol) was added portionwise to the mixture over 5 minutes. After 24 hours stirring at room temperature the mixture was treated with methanol (30.0 ml), which was added cautiously. The methanol was evaporated and the resulting oil treated with 20% potassium hydroxide solution (20.0 ml). The solution was washed with ethyl acetate (3 × 100 ml) and the combined organic phases dried with anhydrous magnesium sulphate, filtered and the solvent removed to yield a light brown oil (3.26 g, 70%) which required no further purification; νmax (thin film)/cm⁻¹ 3278 (NH); ²H(250 MHz; DMSO) 2.57 (1H, dd, J 15.0, 7.5, CH(H)CHNH₂) 2.79 (1H, dd, J 15.0, 5, CH(H)CHNH₂) 2.93-3.03 (1H, m, CHNH₂) 3.22 (1H, dd, J 10.0, 5, CH(H)OH) 3.36 (1H, dd, J 12.5, 5, CH(H)OH) 6.93-6.99 (1H, m, ArH) 7.03-7.07 (1H, m, ArH) 7.14-7.15 (1H, m, CHNH) 7.32-7.34 (1H, m, ArH) 7.52-7.54 (1H, m, ArH) 10.83 (1H, br, s, NH); δC(100 MHz; DMSO) 29.4 (CH₂), 53.5 (CH), 65.7 (CH₂), 111.2 (CH), 111.5 (C), 118.0 (CH), 118.3 (CH), 120.7 (CH), 123.2 (CH), 127.5 (C), 136.1 (C); MS (EI) m/z 190 (M⁺, 6.23%); (Found: M⁺, 190.11068. C₁₁H₁₄N₂O requires 190.11061).
(3R,8aR)-3-(1H-Indol-3-ylmethyl)perhydropyrido[2,1-b][1,3]oxazol-5-one (49)

(2R)-2-amino-3-(1H-indol-3-yl)propan-1-ol (48) (3.0 g, 0.02 mmol) and Methyl-5-oxopentanoate (45) (2.1 g, 0.02 mmol) were added to toluene (150 ml) and refluxed under Dean-Stark conditions for 48 hours. The mixture was cooled to room temperature and the solvent removed under reduced pressure to yield the target compound as a 5:1 mixture of diastereoisomers. These diastereoisomers were purified and separated by flash column chromatography over silica gel using ethyl acetate as eluent (2.90 g, 68%).

**Major isomer** (49) isolated as a pale yellow oil; [α]D = +15.6 (c = 2.0, CH2Cl2) (Found: C, 70.92; H, 6.64; N, 10.29; C16H18N2O2 requires C, 71.09; H, 6.71; N, 10.36%); νmax (thin film, DCM)/cm⁻¹ 3276 (NH), 1620 (NC=O); δH (400 MHz; CDCl3) 1.43-1.52 (1H, m, CH(H)CH2CH2C=O), 1.64-1.70 (1H, m, CH2CH(H)CH2C=O), 1.93-1.98 (1H, m, CH2CH(H)CH2C=O), 2.21-2.25 (1H, m, CH(H)CH2CH2C=O), 2.40-2.43 (2H, m, CH2C=O), 2.66 (1H, dd, J 16, 8, CH(H)C=C), 3.62-3.73 (1H, m, CH(H)C=C), 3.62-3.73 (1H, m, CH(H)O), 4.01 (1H, d, J 12, CH(H)O), 4.24-4.29 (1H, m, NCHCH2O), 4.64 (1H, dd, J 8, 4, NCHOCH2), 7.0 (1H, d, J 4, C=CHNH), 7.08-7.19 (2H, m, ArH), 7.34 (1H, d, J 8, ArH), 7.79 (1H, d, J 8, ArH), 8.51 (1H, br, s, NH); δC (100 MHz; CDCl3) 17.5 (CH2), 27.0 (CH2), 28.4 (CH2), 30.9 (CH2), 56.2 (CH), 69.9 (CH2), 89.0 (CH), 111.1 (CH), 112.3 (C), 119.2 (CH), 119.5 (CH), 122.1 (CH), 122.5 (CH), 127.7 (C), 136.3 (C), 168.4 (NC=O); MS (EI) m/z 270 [M⁺, 42.2%] (Found: M⁺, 270.13690. C16H18N2O2 requires 270.13690).

**Minor isomer** isolated as a pale yellow oil; [α]D = -9.9 (c = 13.5, CH2Cl2) (Found: C, 70.86; H, 6.66; N, 10.18; C16H18N2O2 requires C, 71.09; H, 6.71; N, 10.36%); νmax (thin film, DCM)/cm⁻¹ 3276 (NH), 1620 (NC=O); δH (400 MHz; CDCl3) 1.27-1.37 (1H, m, CH(H)CH2CH2C=O), 1.44-1.48 (1H, m, CH2CH(H)CH2C=O), 1.75-1.80 (1H, m, CH2CH(H)CH2C=O), 2.07-2.11 (1H, m, CH(H)CH2CH2C=O), 2.25-2.34
(1H, m, CH(H)C=O), 2.51 (1H, dd, J 16, 8, CH(H)C=O), 3.03 (1H, dd, J 16, 8, CH(H)C=C), 3.28 (1H, dd, J 16, 4, CH(H)C=C), 3.64 (1H, dd, J 8, 8, CH(H)O), 3.98-4.03 (1H, m, CH(H)O), 4.38 (1H, dd, J 8, 4, NCHOCH₂), 4.56-4.63 (1H, m, NCHCH₂O), 6.93 (1H, d, J 4, C=CHNH), 7.04-7.08 (1H, m, ArH), 7.12-7.16 (1H, m, ArH), 7.32 (1H, d, J 8, ArH), 7.66 (1H, d, J 8, ArH), 9.1 (1H, br, s, NH); δC(100 MHz; CDCl₃) 17.1 (CH₂), 27.5 (CH₂), 28.1 (CH₂), 31.4 (CH₂), 54.6 (CH), 69.6 (CH₂), 87.3 (CH), 110.5 (CH), 111.4 (C), 119.0 (CH), 119.3 (CH), 122.0 (CH), 123.0 (CH), 127.8 (C), 136.5 (C), 169.2 (NC=O); MS (EI) m/z 270 [M⁺, 42.9%] (Found: M⁺, 270.13690. C₁₆H₁₈N₂O₂ requires 270.13683).
(6R,12bS)-6-(Hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carboline-4-one (50)

(3R,8aR)-3-(1H-Indol-3-ylmethyl)perhydropyrido[2,1-b][1,3]oxazol-5-one (49) (3.1 g, 11.5 mmol) was dissolved in absolute ethanol (100 ml) under a nitrogen atmosphere. The resulting solution was acidified to pH 1 by the addition of 2 M HCl in ethanol and the mixture was stirred for a further 20 hours at room temperature. After this time the reaction was quenched by addition of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 x 150 ml). The organic fraction was dried over anhydrous magnesium sulphate and the solvent removed by rotary evaporation to yield a white solid (3.0 g, 97%), a portion of which was recrystallised from absolute ethanol to yield the target compound as colourless block-like crystals; Mp 280-282 ℃; [α]D = -129.9 (c = 1.9, DMSO) (Found: C, 70.91; H, 6.68; N, 10.28; C16H18N2O2 requires C, 71.09; H, 6.71; N, 10.36%); v̇max (thin film, DCM)/cm⁻¹ 3277 (NH), 1618 (NC=O); δ̇H(400 MHz; DMSO) 1.53-1.63 (1H, m, CH(H)CH₂CH₂C=O), 1.64-1.73 (2H, m, CH₂CH₂C=O), 2.26-2.42 (2H, m, CH₂C=O), 2.59-2.65 (1H, m, CH(H)CH₂CH₂C=O), 2.67 (1H, ddd, J 16, 8, 4, C=CCH(H)), 2.80 (1H, d, J 16, C=CCH(H)), 3.36-3.40 (2H, m, CH₂OH), 4.64-4.66 (1H, m, NCHCH₂OH), 4.82 (1H, t, J 6, OH), 5.24 (1H, q, J 8, NCH₂OH), 6.95-6.99 (1H, m, ArH), 7.04-7.08 (1H, m, ArH), 7.32 (1H, d, J 8, ArH), 7.41 (1H, d, J 8, ArH), 10.09 (1H, br, s, NH); δC(100 MHz; DMSO) 19.0 (CH₃), 20.7 (CH₂), 28.6 (CH₂), 32.3 (CH₂), 47.9 (CH), 50.3 (CH), 59.9 (CH₂), 104.8 (C), 111.1 (CH), 117.7 (CH), 118.5 (CH), 120.9 (CH), 126.8 (C), 133.3 (C), 136.4 (C), 168.5 (NC=O); MS (EI) m/z 270 [M⁺, 98.2%] (Found: M⁺, 270.13690. C₁₆H₁₈N₂O₂ requires 270.13683).
(6S,12bS)-6-(Hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (57)

(6S,12bR)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (47) (0.5 g, 1.9 mmol) was refluxed in toluene (50 ml) in the presence of trifluoroacetic acid (1.4 ml, 19 mmol) for 24 hours. The solution was cooled to room temperature and the reaction was quenched by the addition of saturated sodium bicarbonate solution (50 ml). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. Crude 400 MHz 1H NMR revealed formation of the product as a single diastereoisomer (0.46 g, 90%), a small portion of which was recrystallised from absolute ethanol to give colourless crystals; which had identical spectral properties as the compound prepared via titanium tetrachloride mediated cyclisation of (46a/b); Mp 246-247 °C; [α]D = +16.0 (c = 0.55, DMSO) (Found: C, 71.00; H, 6.73; N, 10.33; C16H18N2O2 requires C, 71.09; H, 6.71; N, 10.36%); δmax(KBr disc)/cm⁻¹ 3277 (NH), 1618 (NC=O); δH(400 MHz; DMSO) 1.58-1.72 (1H, m, CH(H)CH2C=O), 2.16-2.22 (1H, m, CH(H)C=O), 2.65-2.70 (C=CCH(H)), 3.11 (1H, dd, J 12, 6, C=CCH(H)), 3.28-3.34 (1H, m, CH(H)OH), 3.36-3.42 (1H, m, CH(H)OH), 4.24-4.30 (1H, m, NCH2CH2OH), 4.78-4.82 (1H, m, C=CCH), 4.88 (1H, t, J 8, OCH), 6.98 (1H, t, J 8, ArH), 7.05 (1H, d, J 8, ArH), 7.32 (1H, d, J 8, ArH), 7.42 (1H, d, J 8, ArH), 10.9 (1H, br, s, NH); δc(100 MHz; DMSO) 17.5 (CH2), 20.6 (CH2), 27.4 (CH2), 32.0 (CH2), 52.3 (CH), 54.7 (CH), 61.3 (CH2), 106.0 (C), 111.2 (CH), 117.7 (CH), 118.5 (CH), 120.8 (CH), 126.7 (C), 133.3 (C), 136.2 (C), 171.8 (NC=O); MS (El) m/z 270 [M⁺, 84.1%] (Found: M⁺, 270.13690. C16H18N2O2 requires 270.13683).
3.4 Functionalisation of Indolizino[2,3-a]quinolizidine Substrates

(6S,12bR)-12-(Phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (58)

Sodium hydride (60% dispersion in mineral oil) (0.58 g, 14.4 mmol) was weighed into a dry round bottom flask under nitrogen. The solid was washed with hexane (3 x 10 ml) to remove the mineral oil. The sodium hydride was re-suspended in anhydrous dimethylformamide (15 ml) and cooled to 0 °C with an ice bath. To this mixture was added a solution of (6S,12bR)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (47) (1.95 g, 7.2 mmol) in anhydrous dimethylformamide (15 ml) via cannula. The resulting mixture was stirred for a further 30 minutes at room temperature after which time benzyl bromide (2.7 g, 1.9 ml, 15.8 mmol) was added. After 1 hour stirring at room temperature the reaction was quenched by the addition of ice water (30 ml) and extracted with diethyl ether (3 x 30 ml). The combined ether fractions were dried with anhydrous magnesium sulphate, filtered and the solvent removed by rotary evaporation. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 3:2 hexane:ethyl acetate to give the target compound as a pale yellow foam (2.9 g, 90%); Mp 111-114 °C; [α]D = +95.8 (c = 2.0, CH2Cl2); νmax(thin film, DCM)/cm⁻¹ 1635 (NC=O); δH(400 MHz; CDCl3) 1.40-1.46 (1H, m, CH(H)CH2CH2C=O), 1.65-1.73 (2H, m, CH2CH2C=O), 2.26-2.43 (1H, m, CH(H)CH2CH2C=O), 2.26-2.43 (2H, m, CH2C=O), 2.26-2.43 (2H, m, CH2C=O), 2.80 (1H, ddd, J 16, 8, 4, C=CCH(H)), 2.94 (1H, d, J 16, C=CCH(H)), 3.19-3.29 (2H, m, CH2OBn), 4.36 (2H, s, OCH2Ph), 4.50 (1H, d, J 12, NHC=CH), 5.33 (1H, d, J 20, NCH(H)Ph), 5.43 (1H, m, NHCCH2OBn), 5.53 (1H, d, J 20, NCH(H)Ph), 6.83-6.85 (2H, m, ArH), 7.04-7.12 (2H, m, ArH), 7.13-7.24 (8H, m, ArH), 7.26-7.28 (1H, m, ArH), 7.51-7.53 (1H, m, ArH); δC(100 MHz; CDCl3) 18.6 (CH2), 21.5 (CH2), 29.7 (CH2), 31.4 (CH2), 45.2

Experimental
(CH), 46.7 (CH2), 50.5 (CH), 67.7 (CH2), 71.6 (CH2), 106.3 (C), 110.1 (CH), 118.0 (CH), 119.2 (CH), 121.5 (CH), 125.7 (2×CH), 126.5 (C), 126.9 (CH), 127.0 (2×CH), 127.2 (CH), 128.0 (2×CH), 128.5 (2×CH), 134.0 (C), 137.8 (C), 138.0 (C), 138.4 (C), 169.2 (NC=O); MS (El) m/z 450 [M+, 44.2%] (Found: M+, 450.23060. C30H30N2O2 requires 450.23073).
To a stirred solution of diisopropylamine (0.42 g, 0.59 ml, 4.2 mmol) in anhydrous tetrahydrofuran (5.0 ml) was added n-butyllithium (2.5 M solution in hexanes) (1.70 ml, 4.2 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred for 15 minutes at 0 °C and then cooled to -78 °C whereupon a solution of (6S,12bR)-12-(phenylmethyl)-6-[(phenylmethyl)oxy]methyl)-1,4,6,7,12,12b-hexahydropyrido[2,1-a]b-carbolin-4-one (58) (1.89 g, 4.2 mmol) in anhydrous tetrahydrofuran (15 ml) was added via cannula. The resulting mixture was stirred for a further 1 hour at -78 °C after which time phenylselenenylbromide (1.1 g, 4.6 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise via syringe. The reaction was allowed to warm slowly from -78 °C to room temperature with stirring. After 24 hours the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (40 ml) and extracted with diethyl ether (3 x 50 ml). The combined ether extracts were washed with saturated aqueous ammonium chloride solution (100 ml), dried with anhydrous sodium sulphate. The solvent was removed by rotary evaporation to yield the crude selenide (59) (2.5 g), which was used without further purification.

The crude selenide (59) (2.5 g) was dissolved in methanol (220 ml) and water (45 ml). To the resulting solution was added sodium metaperiodate (2.4 g, 9.7 mmol) and sodium bicarbonate (0.42 g, 5.0 mmol) and the solution was stirred vigorously at room temperature for 18 hours. After this time the reaction was poured into a mixture of saturated aqueous sodium bicarbonate solution (200 ml) and diethyl ether (250 ml). The ether layer was washed with water (200 ml), then brine (200 ml) and dried over anhydrous magnesium sulphate. The solvent was removed by rotary evaporation and the crude product was adsorbed onto silica gel and purified by flash column...
chromatography over silica gel eluting with 3:2 hexane:ethyl acetate to give the target compound as a pale yellow foam (1.6 g, 85%); Mp 76-78 °C; $[\alpha]_D = +195.1$ (c = 1.5, CH$_2$Cl$_2$); \(\nu_{\text{max}}(\text{thin film, DCM})/\text{cm}^{-1} 1662 (\text{NC}=\text{O})\); \(\delta_\eta(400 \text{ MHz; CDCl}_3) 2.21-2.30 (1H, m, CH(H)CH=CHC=O), 2.52-2.59 (1H, m, CH(H)CH=CHC=O), 3.02 (1H, ddd, J 16, 8, 4, CH(H)CHN), 3.15 (1H, d, J 16, CH(H)CHN), 3.30-3.38 (2H, m, CH$_2$OBn), 4.45 (2H, s, OCH$_2$Ph), 4.59-4.63 (1H, m, C=CCH), 5.23 (2H, dd, J 36, 16, NCH$_2$Ph), 5.42-5.46 (1H, m, NCHCH$_2$OBn), 6.06 (1H, dd, J 8, 4, CH=CHC=O), 6.49-6.50 (1H, m, CH=CHC=O), 6.83-6.85 (2H, m, ArH), 7.14-7.23 (11H, m, ArH), 7.60-7.62 (1H, m, ArH); \(\delta_c(100 \text{ MHz; CDCl}_3) 21.9 \text{ (CH)}_2, 32.0 \text{ (CH)}_2, 47.3 \text{ (CH)}, 48.3 \text{ (CH)}_2, 49.8 \text{ (CH)}, 68.0 \text{ (CH)}_2, 72.5 \text{ (CH)}_2, 107.6 \text{ (C)}, 109.8 \text{ (CH)}, 118.7 \text{ (CH)}, 119.9 \text{ (CH)}, 122.3 \text{ (CH)}, 125.6 (2\times \text{CH}), 125.9 \text{ (CH)}, 127.0 \text{ (C)}, 127.3 (2\times \text{CH}), 127.3 \text{ (CH)}, 127.5 \text{ (CH)}, 128.2 (2\times \text{CH}), 128.9 (2\times \text{CH}), 132.6 \text{ (C)}, 137.0 \text{ (C)}, 138.1 \text{ (C)}, 138.2 \text{ (C)}, 138.2 \text{ (CH)}, 164.9 \text{ (NC}=\text{O}); \text{MS (El) } m/z 448 [M]^+, 100.0\% \) (Found: M$^+$, 448.21406. C$_{30}$H$_{28}$N$_2$O$_2$ requires 448.21507).
Sodium hydride (60% dispersion in mineral oil) (0.15 g, 3.7 mmol) was weighed into a dry round bottom flask under nitrogen. The solid was washed with hexane (3 x 10 ml) to remove the mineral oil. The sodium hydride was re-suspended in anhydrous dimethylformamide (15 ml) and cooled to 0 °C with an ice bath. To this mixture was added a solution of (6S,12bR)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (47) (1.0 g, 3.7 mmol) in anhydrous dimethylformamide (15 ml) via cannula. The resulting mixture was stirred for a further 30 minutes at room temperature after which time benzyl bromide (0.7 g, 0.5 ml, 4.1 mmol) was added. After 1 hour stirring at room temperature the reaction was quenched by the addition of ice water (30 ml) and extracted with diethyl ether (3 x 30 ml). The combined ether fractions were dried with anhydrous magnesium sulphate, filtered and the solvent removed by rotary evaporation. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with ethyl acetate to give the target compound as a white powder (1.1 g, 83%); Mp 231-233 °C; [α]D = +140.8 (c = 1.31, CH2Cl2); νmax(thin film, DCM)/cm⁻¹ 3406 (OH), 1615 (NC=O); δq(400 MHz; CDCl3) 1.56-1.66 (1H, m, C=CCHCH(H)), 1.77-1.88 (2H, m, CH₂CH₂C=O), 2.32-2.38 (1H, m, C=CCHCH(H)), 2.42-2.51 (1H, m, CH(H)C=O), 2.54-2.60 (1H, m, CH(H)C=O), 2.86 (1H, d, J 16, C=CCH(H)), 3.01 (1H, ddd, J 16, 8, 4, C=CCH(H)), 3.41 (1H, t, J 12, C(H)OH), 3.47 (1H, t, J 12, C(H)OH), 3.59 (1H, dd, J 8, 4, C<H(H)OH), 4.60-4.62 (1H, m, C=CCH), 5.32 (2H, dd, J 48, 20, NCH₂Ph), 5.46-5.52 (1H, m, NCH₂CH₂OH), 6.94-6.96 (2H, m, ArH), 7.13-7.18 (3H, m, ArH), 7.26-7.31 (3H, m, ArH), 7.53-7.56 (1H, m, ArH); δc(100 MHz; CDCl3) 19.3 (CH₂), 21.8 (CH₂), 30.5 (CH₂), 31.9 (CH₂), 47.7 (CH₂), 49.1 (CH), 51.1 (CH), 62.8 (CH₂), 107.5 (C), 109.9 (CH), 118.4 (CH), 119.9 (CH), 122.3 (CH), 125.7 (2×CH), 126.8 (C), 127.6
(CH), 128.9 (2×CH), 133.0 (C), 137.2 (C), 138.3 (C), 172.2 (NC=O); MS (EI) m/z
360 [M⁺, 100%] (Found: M⁺, 360.18397. C₂₃H₂₄N₂O₂ requires 360.18378).
To a solution of 1,3-dithiane (0.05 g, 0.40 mmol) in anhydrous tetrahydrofuran (8.0 ml) at -78 °C under a nitrogen atmosphere was added n-butyllithium (2.5 M solution in hexanes) (0.16 ml, 0.4 mmol) dropwise. The resulting pale yellow solution was stirred for a further 30 minutes at -78 °C after which time a solution of (6S,12bR)-12-(phenylmethyl)-6-[(phenylmethyl)oxy]methyl]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (62a) (0.15 g, 0.33 mmol) in anhydrous tetrahydrofuran (5.0 ml) was added via cannula at -78 °C. The resulting mixture was allowed to warm slowly (overnight) to room temperature. The reaction was quenched by the addition of water (15 ml) and extracted with diethyl ether (3 x 15 ml). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. Crude 250 MHz 1H NMR revealed the formation of the product as a single diastereoisomer. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 3:2 hexane:ethyl acetate yielding the product as a pale yellow oil (0.1 g, 52%); [α]D = +44.7 (c = 0.6, CH2Cl2); νmax(thin film, DCM)/cm⁻¹ 1652 (NC=O); δH (400 MHz; CDCl3) 1.67-1.76 (1H, m, C=CCHCH(H)), 1.78-1.86 (1H, m, CH(H)C=O), 2.02-2.08 (1H, m, CH(H)C=O), 2.28-2.34 (1H, m, CHCHS), 2.45-2.50 (1H, m, C=CCHCH(H)), 2.56-2.85 (6H, m, S(CH2)3S), 2.99-3.00 (2H, m, C=CCH2), 3.29-3.39 (2H, m, CH2OBn), 3.97 (1H, d, J 8, SCHS), 4.45 (2H, dd, J 24, 12, OCH2Ph), 4.63-4.66 (1H, m, C=CCH), 5.41 (2H, dd, J 40, 16, NCH2Ph), 5.51-5.57 (1H, m, NCHCH2OBn), 6.84-6.86 (2H, m, ArH), 7.14-7.15 (11H, m, ArH), 7.56-7.59 (1H, m, ArH); δC(100 MHz; CDCl3) 22.0 (CH2), 26.2 (CH2), 30.5 (CH2), 30.6 (CH2), 34.1 (CH2), 34.5 (CH), 35.3 (CH2), 46.7 (CH), 143
47.7 (CH$_2$), 48.5 (CH), 52.6 (CH), 69.0 (CH$_2$), 73.0 (CH$_2$), 107.8 (C), 110.2 (CH), 118.9 (CH), 120.2 (CH), 122.6 (CH), 126.1 (2×CH), 127.5 (C), 127.7 (CH), 127.8 (2×CH), 127.8 (CH), 128.7 (2×CH), 129.1 (2×CH), 133.4 (C), 137.9 (C), 138.7 (2×C), 170.6 (NC=O); MS (El) m/z 568 [M$^+$, 37.2%] (Found: M$^+$, 568.22078. C$_{34}$H$_{38}$N$_2$O$_2$S$_2$ requires 568.22182).
Diethyl2-((2S,6S,12bR)-4-oxo-12-(phenylmethyl)-6-(((phenylmethyl)oxy)methyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-2-yl)propanedioate (62b)

To a pre-dried round bottom flask under nitrogen was added absolute ethanol (5.0 ml). Sodium metal (0.05 g, 2.2 mmol) was added portionwise to the ethanol at room temperature with stirring. When all the sodium metal had dissolved, diethylmalonate (0.32 g, 0.30 ml, 2.0 mmol) was added to the sodium ethoxide solution dropwise via syringe. The resulting solution was stirred at room temperature for 10 minutes and then cooled to 0 °C in an ice bath. To the sodiomalonate solution was added (6S,12bR)-12-(phenylmethyl)-6-(((phenylmethyl)oxy)methyl)-1,4,6,7,12,12b-hexahydropyrido[2,1-a]b-carbolin-4-one (60) (0.30 g, 0.67 mmol) in absolute ethanol (5.0 ml) dropwise via syringe at 0 °C and the mixture was allowed to warm slowly (overnight) to room temperature. After this time the reaction was quenched with water (20 ml) and extracted with diethyl ether (3 × 20 ml). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. Crude 250 MHz 1H NMR revealed the formation of the product as a single diastereoisomer. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 3:2 hexane:ethyl acetate to give the target compound as a yellow oil (0.08 g, 20%); [α]D = +62.4 (c = 2.0, CH2Cl2); νmax(thin film, DCM)/cm⁻¹ 1746 (Malonate C=O), 1667 (NC=O); δH(400 MHz; CDCl3) 1.17-1.24 (6H, m, 2 x OCH₂CH₃), 1.80-1.88 (1H, m, C=CCHCH(H)), 2.19-2.25 (1H, m, C=CCHCH(H)), 2.47 (1H, dd, J 16, 12, CH(H)C=O), 2.58 (1H, dd, J 16, 8, CH(H)C=O), 2.63-2.73 (1H, m, CHCH(CO₂Et)₂), 2.95-3.00 (1H, m, C=CCH(H)), 3.06 (1H, d, J 16, C=CCH(H)), 3.26-3.36 (2H, m, CH₂OBn), 3.38 (1H, d, J 8, CH(CO₂Et)₂), 4.12 (4H, q, J 8, 2 x OCH₂CH₃), 4.39-4.47 (2H, m, OCH₂Ph), 4.72-4.75 (1H, m, C=CCH(H)), 5.32 (2H, dd, J 44, 16, NCH₂Ph), 5.43-5.48 (1H, m, NCHCH₂OBn), 6.84-6.86 (2H, m, ArH), 7.14-7.23 (11H, m, ArH), 7.57-7.59 (1H, m,
ArH); $\delta_c(100\ \text{MHz}; \text{CDCl}_3)$ 14.0 (2×CH$_3$), 21.5 (CH$_2$), 29.5 (CH), 33.8 (CH$_2$), 35.8 (CH$_2$), 46.7 (CH), 46.9 (CH$_2$), 47.8 (CH), 55.1 (CH), 61.6 (CH$_2$), 61.7 (CH$_2$), 68.4 (CH$_2$), 72.6 (CH$_2$), 107.3 (C), 109.9 (CH), 118.5 (CH), 119.8 (CH), 122.1 (CH), 125.6 (2×CH), 127.0 (C), 127.3 (CH), 127.4 (2×CH), 127.4 (CH), 128.2 (2×CH), 128.7 (2×CH), 132.8 (C), 137.5 (C), 138.1 (C), 138.2 (C), 167.8 (Malonate C=O), 168.1 (Malonate C=O), 170.4 (NC=O); MS (El) $m/z$ 608 [M$, 83.1\%$] (Found: M$, 608.28769$. C$_{37}$H$_{40}$N$_2$O$_6$ requires 608.28864).
A 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran (6.7 ml, 6.7 mmol) was added to a suspension of copper cyanide (0.30 g, 3.4 mmol) in anhydrous tetrahydrofuran (12.0 ml) at -78 °C with stirring. The reaction mixture was warmed to 0 °C for 3 minutes and then re-cooled to -78 °C. A solution of (6S,12bR)-12-(phenylmethyl)-6-[(phenylmethyl)oxy]methyl]-1,4,6,7,12,12b-hexahydropyrido[2,1-a]b-carbolin-4-one (60) (0.30 g, 0.67 mmol) in anhydrous tetrahydrofuran (8.0 ml) was added via cannula at -78 ºC. After a further 5 minutes chlorotrimethylsilane (0.43 ml, 3.4 mmol) was added and the resulting suspension was warmed slowly (overnight) to room temperature. After this time a mixture of saturated aqueous ammonium chloride solution (10.0 ml) and water (10.0 ml) was added and stirring continued for 20 minutes. A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (2.0 ml) was added and stirring continued for a further 15 minutes. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 x 40 ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. Crude 250 MHz 1H NMR revealed the formation of the product as a single diastereoisomer. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 3:1 hexane:ethyl acetate to give the target compound as a pale yellow solid (0.21 g, 65%); Mp 148-151 ºC; [α]D = +37.8 (c = 2.0, CH2Cl2); vmax(thin film, DCM)/cm⁻¹ 3080 (Vinyl CH), 1615 (NC=O), 1642 (Vinyl CH=CH); δH(400 MHz; CDCl3) 1.82-1.90 (1H, m, C=CHCH(H)), 2.16-2.27 (1H, m, C=CHCH(H)), 2.47-2.53 (1H, m, CH(H)=O), 2.59 (1H, d, J 8, CH(H)=O), 2.63-2.66 (1H, m, CHCH=CH2), 2.90 (1H, d, J 16, C=CH(H)), 3.01 (1H, dd, J 16, 8, 4, C=CH(H)), 3.31 (2H, d, J 8, CH2OBn), 4.37-4.43 (2H, m, OCH2Ph), 4.47-4.51 (1H, m, C=CH), 4.97-5.02 (2H, m, CH=CH2), 5.17 (1H, d, J 16, NCH(H)Ph), 5.24 (1H, d, J 16,
NCH(H)Ph), 5.62-5.66 (1H, m, NCHCH$_2$OBn), 5.69-5.77 (1H, m, CH=CH$_2$), 6.87-6.89 (2H, m, ArH), 7.13-7.25 (11H, m, ArH), 7.55-7.57 (1H, m, ArH); $\delta_c$(100 MHz; CDCl$_3$) 22.4 (CH$_2$), 33.1 (CH), 35.3 (CH$_2$), 36.5 (CH$_2$), 46.5 (CH), 47.9 (CH), 48.2 (CH$_2$), 68.7 (CH$_2$), 73.0 (CH$_2$), 108.6 (C), 110.1 (CH), 116.1 (CH$_2$), 118.8 (CH), 120.3 (CH), 122.6 (CH), 126.2 (2×CH), 127.4 (C), 127.9 (CH), 127.9 (2×CH), 128.0 (CH), 128.6 (2×CH), 129.3 (2×CH), 133.7 (C), 137.6 (C), 138.6 (C), 138.8 (C), 139.5 (CH), 170.5 (NC=O); MS (El) $m/z$ 476 [M$^+$, 70.7%] (Found: M$^+$, 476.24597. C$_{32}$H$_{32}$N$_2$O$_2$ requires 476.24638).
(6S,12bS)-12-(Phenylmethyl)-6-{(phenylmethyl)oxy}methyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (63)

Sodium hydride (60% dispersion in mineral oil) (0.24 g, 6.0 mmol) was weighed into a dry round bottom flask under nitrogen. The solid was washed with hexane (3 × 10 ml) to remove the mineral oil. The sodium hydride was re-suspended in anhydrous dimethylformamide (15 ml) and cooled to 0 °C with an ice bath. To this mixture was added a solution of (6S,12bS)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (57) (0.80 g, 3.0 mmol) in anhydrous dimethylformamide (15 ml) via cannula. The resulting mixture was stirred for a further 30 minutes at room temperature after which time benzyl bromide (1.1 g, 0.80 ml, 6.6 mmol) was added. After 2 hours stirring at room temperature the reaction was quenched by the addition of ice water (30 ml) and extracted with diethyl ether (3 × 30 ml). The combined ether fractions were washed with anhydrous magnesium sulphate, filtered and the solvent removed by rotary evaporation. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 3:2 hexane:ethyl acetate to give the target compound as a clear oil (0.9 g, 70%); [α]D = +80.0 (c = 0.5, CH2Cl2); νmax (thin film, DCM)/cm⁻¹ 1653 (NC=O); δH(400 MHz; CDCl3) 1.62-1.75 (1H, m, CH(H)CH2C=O), 1.62-1.75 (1H, m, C=CCHCH(H)), 1.85-1.92 (1H, m, CH(H)CH2C=O), 2.31-2.36 (1H, m, C=CCHCH(H)), 2.43-2.57 (2H, m, CH2C=O), 3.07 (1H, ddd, J 16, 8, 4, C=CCH(H)), 3.30 (1H, dd, J 16, 4, C=CCH(H)), 3.74 (1H, dd, J 12, 4, CH(H)OBn), 3.82-3.86 (1H, m, CH(H)OBn), 4.62 (2H, s, OCH2Ph), 4.65-4.69 (1H, m, C=CCH), 4.82-4.88 (1H, m, NCH2CH2OBn), 5.40 (2H, dd, J 40, 20, NCH2Ph), 7.00-7.02 (2H, m, ArH), 7.23-7.25 (3H, m, ArH), 7.30-7.40 (8H, m, ArH), 7.65-7.67 (1H, m, ArH); δc(100 MHz; CDCl3) 17.9 (CH2), 22.1 (CH2), 28.8 (CH2), 32.1 (CH2), 47.9 (CH2), 51.3 (CH), 52.6 (CH), 71.1 (CH2), 72.7 (CH2), 108.9 (C), 109.4 (CH), 118.4 (CH), 119.7 (CH), 122.1 (CH), 125.6 (2×CH), 126.6 (C), 127.3 (CH), 127.4 (CH), 127.4 (2×CH), 128.1

Experimental
(2×CH), 128.8 (2×CH), 134.6 (C), 137.1 (C), 138.2 (C), 138.3 (C), 173.6 (NC=O);
MS (EI) m/z 450 [M+, 21.7%] (Found: M+, 450.23114. C₃₀H₃₀N₂O₂ requires 450.23073).
To a stirred solution of diisopropylamine (0.16 g, 0.23 ml, 1.6 mmol) in anhydrous tetrahydrofuran (5.0 ml) was added n-butyllithium (2.5 M solution in hexanes) (0.7 ml, 1.6 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred for 15 minutes at 0 °C and then cooled to -78 °C whereupon a solution of (6S,12bS)-12-(phenylmethyl)-6-[(phenylmethyl)oxy]methyl]-1,4,6,7,12,12b-hexahydropyrido[2,1-a]b-carbolin-4-one (63) (0.70 g, 1.6 mmol) in anhydrous tetrahydrofuran (10 ml) was added via cannula. The resulting mixture was stirred for a further 1 hour at -78 °C after which time phenylselenenylbromide (0.42 g, 1.8 mmol) in anhydrous tetrahydrofuran (6.0 ml) was added dropwise via syringe. The reaction was allowed to warm slowly from -78 °C to room temperature with stirring. After 24 hours the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (40 ml) and extracted with diethyl ether (3 × 50 ml). The combined ether extracts were washed with saturated aqueous ammonium chloride solution (100 ml), dried with anhydrous sodium sulphate. The solvent was removed by rotary evaporation to yield the crude selenide (64) (1.0 g), which was used without further purification.

The crude selenide (64) (1.0 g) was dissolved in methanol (100 ml) and water (20 ml). To the resulting solution was added sodium metaperiodate (1.0 g, 3.7 mmol) and sodium bicarbonate (0.16 g, 1.9 mmol) and the solution was stirred vigorously at room temperature for 18 hours. After this time the reaction was poured into a mixture of saturated aqueous sodium bicarbonate solution (200 ml) and diethyl ether (250 ml). The ether layer was washed with water (200 ml), then brine (200 ml) and dried over anhydrous magnesium sulphate. The solvent was removed by rotary evaporation and the crude product was adsorbed onto silica gel and purified by flash column
chromatography over silica gel eluting with 3:2 hexane:ethyl acetate to give the target compound as a pale yellow oil (0.5 g, 70%); $[\alpha]_D = -76$ (c = 1.0, CH$_2$Cl$_2$); $\nu_{max}$ (thin film, DCM)/cm$^{-1}$ 1678 (NC=O); $\delta_{t}$ (400 MHz; CDCl$_3$) 2.06-2.15 (1H, m, CH(H)CH=CH), 2.46-2.53 (1H, m, CH(H)CH=CH), 2.89 (1H, d, $J$ 16; 8, 4, C=CCH(H)), 3.21-3.25 (1H, m, C=CCH(H)), 3.40 (2H, d, $J$ 8, CH$_2$OBn), 4.40 (2H, dd, $J$ 16, 12, OCH$_2$Ph), 4.70-4.74 (1H, m, C=CCH), 5.07-5.12 (1H, m, NCHCH$_2$OBn), 5.23 (2H, s, NCH$_2$Ph), 5.96 (1H, dd, $J$ 8, 4, CH=CH=O), 6.36-6.40 (1H, m, CH=CH=O), 6.80-6.81 (2H, m, ArH), 7.06-7.20 (11H, m, ArH), 7.50-7.53 (1H, m, ArH); $\delta_{c}$ (100 MHz; CDCl$_3$) 21.3 (CH$_2$), 30.9 (CH$_2$), 48.0 (CH$_2$), 49.0 (CH), 52.0 (CH), 71.3 (CH$_2$), 72.6 (CH$_2$), 108.5 (C), 109.4 (CH), 118.5 (CH), 119.9 (CH), 122.4 (CH), 125.4 (2\times CH), 126.5 (C), 126.7 (CH), 127.3 (CH), 127.3 (2\times CH), 127.5 (CH), 128.1 (2\times CH), 128.9 (2\times CH), 130.8 (C), 137.2 (C), 138.2 (C), 138.5 (C), 139.8 (CH), 166.0 (NC=O); MS (EI) $m/z$ 448 [$M^+$, 21.9%] (Found: $M^+$, 448.21473.

C$_{30}$H$_{28}$N$_2$O$_2$ requires 448.21508).

Experimental
A 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran (6.7 ml, 6.7 mmol) was added to a suspension of copper cyanide (0.30 g, 3.4 mmol) in anhydrous tetrahydrofuran (12.0 ml) at -78 °C with stirring. The reaction mixture was warmed to 0 °C for 3 minutes and then re-cooled to -78 °C. A solution of (6S,12bS)-12-(phenylmethyl)-6-[(phenylmethyl)oxy]methyl]-1,4,6,7,12,12b-hexahydropyrido[2,1-a]b-carbolin-4-one (66) (0.30 g, 0.67 mmol) in anhydrous tetrahydrofuran (8.0 ml) was added via cannula at -78 °C. After a further 5 minutes chlorotrimethylsilane (0.43 ml, 3.4 mmol) was added and the resulting suspension was warmed slowly (overnight) to room temperature. After this time a mixture of saturated aqueous ammonium chloride solution (10.0 ml) and water (10.0 ml) was added and stirring continued for 20 minutes. A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (2.0 ml) was added and stirring continued for a further 15 minutes. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 40 ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. Crude 250 MHz ¹H NMR revealed the formation of the product as a single diastereoisomer. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 3:1 hexane:ethyl acetate to give the target compound as a yellow oil (0.17 g, 53%); [α]D = +4.0 (c = 2.0, CH2Cl2); νmax (thin film, DCM)/cm⁻¹ 3059 (Vinyl CH), 1653 (NC=O), 1669 (Vinyl CH₂=CH); δH (400 MHz; CDCl3) 1.84-1.93 (2H, m, C=CCH₂CH₂), 2.25 (1H, dd, J 16, 12, CH(H)C=O), 2.33-2.44 (2H, m, CH(H)C=O + CHCH=CH₂), 2.86-2.91 (1H, m, C=CCH(H)), 3.13 (1H, dd, J 16, 4, C=CCH(H)), 3.62 (1H, dd, J 12, 8, CH(H)OBn), 3.71 (1H, dd, J 8, 8, CH(H)OBn), 4.45 (2H, dd, J 12, 8, OCH₂Ph), 4.54-4.59 (2H, m, C=CCH + NCHCH₂OBn), 4.80 (2H, dd, J 34, 14, CH=CH₂), 5.24 (2H, dd, J 36, 16, NCH₂Ph), 5.43-5.52 (1H, m, CH=CH₂), 6.85-6.87

Experimental
(2H, m, ArH), 7.04-7.20 (11H, m, ArH), 7.48-7.50 (1H, m, ArH); δC(100 MHz; CDCl₃) 22.4 (CH₂), 33.9 (CH), 34.6 (CH₂), 38.0 (CH₂), 48.1 (CH₂), 52.3 (CH), 52.4 (CH), 71.4 (CH₂), 72.9 (CH₂), 109.4 (CH), 110.0 (C), 114.1 (CH₂), 118.5 (CH), 119.8 (CH), 122.3 (CH), 125.7 (2×CH), 126.6 (C), 127.4 (CH), 127.5 (2×CH), 127.5 (CH), 128.2 (2×CH), 128.9 (2×CH), 132.4 (C), 137.1 (C), 138.3 (C), 138.5 (C), 140.2 (CH), 173.0 (NC=O); MS (EI) m/z 476 [M⁺, 40.8%] (Found: M⁺, 476.24597. C₃₂H₃₂N₂O₂ requires 476.24638).
To a stirred solution of diisopropylamine (0.21 g, 0.30 ml, 1.78 mmol) in anhydrous tetrahydrofuran (5.0 ml) was added n-butyllithium (2.5 M solution in hexanes) (0.70 ml, 1.78 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred for 15 minutes at 0 °C and then cooled to -78 °C whereupon ethyl 1,3-dithiolane-2-carboxylate (0.37 g, 0.30 ml, 1.78 mmol) was added by syringe and stirring continued for a further 15 minutes. After this time a solution of (6S,12bS)-12-(phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,4,6,7,12,12b-hexahydropyrido[2,1-a]b-carbolin-4-one (65) (0.40 g, 0.89 mmol) in anhydrous tetrahydrofuran (10.0 ml) was added via cannula at -78 °C. The resulting mixture was allowed to warm slowly (overnight) to room temperature. The reaction was quenched by the addition of water (25 ml) and extracted with ethyl acetate (3 × 25 ml). The organic extracts were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. Crude 250 MHz 1H NMR revealed the formation of the product as a single diastereoisomer. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 3:2 hexane:ethyl acetate yielding the product as a pale yellow oil (0.31 g, 55%); [α]D = +376 (c = 0.5, CH2Cl2); νmax (thin film, DCM)/cm⁻¹ 1734 (ester C=O), 1662 (NC=O); δH (400 MHz; CDCl3) 1.17 (3H, t, J 8, CO2CHzCH3), 1.75-1.84 (1H, m, C=CCHCH(H)), 2.03-2.08 (1H, m, C=CCHCH(H)), 2.64-2.74 (2H, m, CH2C=O), 2.86-2.94 (2H, m, SCH(H) + CHCH2C=O), 2.96-2.99 (1H, m, C=CCH(H)), 3.15-3.19 (1H, m, C=CCH(H)), 3.21-3.37 (3H, m, SCH2 + SCH(H)), 3.44-3.54 (2H, m, CH2OBn), 4.06 (2H, q, J 8, CO2CHzCH3) 4.51 (2H, dd, J 16, 12, OCH2Ph), 4.79-4.82 (1H, m, C=CCH), 5.22-5.27 (1H, m, NCHCH2OBn), 5.37 (2H, dd, J 36, 20, NCH2Ph), 6.93-6.95 (2H, m, NCHCH2OBn).
ArH), 7.09-7.11 (1H, m, ArH), 7.14-7.16 (1H, m, ArH), 7.21-7.29 (8H, m, ArH), 7.56-7.58 (1H, m, ArH); δC(100 MHz; CDCl3) 13.8 (CH₃), 21.3 (CH₂), 35.2 (CH₂), 36.6 (CH₂), 37.2 (CH), 39.8 (CH₂), 39.9 (CH₂), 47.9 (CH₂), 47.9 (CH), 50.5 (CH), 62.4 (CH₂), 70.7 (CH₂), 72.8 (CH₂), 75.2 (C), 107.4 (C), 109.7 (CH), 118.5 (CH), 119.8 (CH), 122.3 (CH), 125.4 (2×CH), 126.8 (C), 127.2 (CH), 127.4 (CH), 127.5 (2×CH), 128.3 (2×CH), 128.8 (2×CH), 131.3 (C), 137.4 (C), 138.1 (C), 138.4 (C), 171.2 (NC=O), 173.2 (ester C=O); MS (EI) m/z 626 [M⁺, 14.4%] (Found: M⁺, 626.2278). C₃₆H₃₈N₄O₄S₂ requires 626.22730).
(6R,12bS)-12-(Phenylmethyl)-6-([(phenylmethyl)oxy]methyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-\(a\)]b-carbolin-4-one (67)

Sodium hydride (60% dispersion in mineral oil) (0.58 g, 14.4 mmol) was weighed into a dry round bottom flask under nitrogen. The solid was washed with hexane (3 \(\times\) 10 ml) to remove the mineral oil. The sodium hydride was re-suspended in anhydrous dimethylformamide (15 ml) and cooled to 0 °C with an ice bath. To this mixture was added a solution of (6R,12bS)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-\(a\)]b-carbolin-4-one (50) (1.95 g, 7.2 mmol) in anhydrous dimethylformamide (15 ml) via cannula. The resulting mixture was stirred for a further 30 minutes at room temperature after which time benzyl bromide (2.7 g, 1.9 ml, 15.8 mmol) was added. After 1 hour stirring at room temperature the reaction was quenched by the addition of ice water (30 ml) and extracted with diethyl ether (3 \(\times\) 30 ml). The combined ether fractions were dried with anhydrous magnesium sulphate, filtered and the solvent removed by rotary evaporation. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 3:2 hexane:ethyl acetate to give the target compound as a pale yellow foam (2.9 g, 90%); Mp 116-119 °C; \([\alpha]_D = -117.4\) (c = 2.0, CH\(_2\)Cl\(_2\)); \(\nu_{\text{max}}\) (thin film, DCM)/cm\(^{-1}\) 1639 (NC=O); \(\delta_h\) (400 MHz; CDCl\(_3\)) 1.52-1.62 (1H, m, \(\text{CH}(\text{H})\text{CH}_2\text{CH}_2\text{C} = \text{O}\)), 1.64-1.87 (2H, m, \(\text{CH}_2\text{CH}_2\text{C} = \text{O}\)), 2.30-2.35 (1H, m, \(\text{CH}(\text{H})\text{CH}_2\text{CH}_2\text{C} = \text{O}\)), 2.41-2.60 (2H, m, \(\text{CH}_2\text{C} = \text{O}\)), 2.90-2.94 (1H, m, C=\(\text{CCH}(\text{H})\)), 3.0 (1H, ddd, J 16, 8, 4, C=\(\text{CCH}(\text{H})\)), 3.31-3.39 (2H, m, \(\text{CH}_2\text{OBo}n\)), 4.36-4.41 (1H, m, N\(\text{CHC} = \text{C}\)), 4.43 (2H, dd, J 28, 12, O\(\text{CH}_2\text{Ph}\)), 5.26 (2H, dd, J 52, 20 N\(\text{CH}_2\text{Ph}\)), 5.66-5.71 (1H, m, N\(\text{CHC} = \text{C}\)), 6.86-6.89 (2H, m, Ar\(\text{H}\)), 7.14-7.25 (11H, m, Ar\(\text{H}\)), 7.55-7.58 (1H, m, Ar\(\text{H}\)); \(\delta_c\) (100 MHz; CDCl\(_3\)) 19.3 (\(\text{CH}_2\)), 22.0 (\(\text{CH}_2\)), 30.4 (\(\text{CH}_2\)), 32.0 (\(\text{CH}_2\)), 45.9 (\(\text{CH}\)), 47.7 (\(\text{CH}_2\)), 51.3 (\(\text{CH}\)), 68.3 (\(\text{CH}_2\)), 72.5 (\(\text{CH}_2\)), 107.8 (C), 109.8 (CH), 118.5 (CH), 119.8 (CH), 122.2 (CH), 125.7 (2\(\times\)CH), 127.0 (C), 127.4 (CH), 127.5 (2\(\times\)CH), 127.5 (CH), 128.3 (2\(\times\)CH), 128.9 (2\(\times\)CH), 133.4 (C), 137.2 (C), 138.2
(C), 138.3 (C), 170.4 (N\(\text{C}=\text{O}\)); MS (El) \(m/z\) 450 \([M^+, 41.8\%]\) (Found: \(M^+\), 450.23114. \(\text{C}_{20}\text{H}_{20}\text{N}_{2}\text{O}_2\) requires 450.23073).
(6R,12bS)-12-((phenylmethyl)-6-\{(phenylmethyl)oxy\}methyl}-1,4,6,7,12,12b-
hexahydropyrido[2,1-a]b-carbolin-4-one (69)

To a stirred solution of diisopropylamine (0.42 g, 0.59 ml, 4.2 mmol) in anhydrous
tetrahydrofuran (5.0 ml) was added n-butyllithium (2.5 M solution in hexanes) (1.70
ml, 4.2 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred for
15 minutes at 0 °C and then cooled to -78 °C whereupon a solution of (6R,12bS)-12-
(phenylmethyl)-6-\{(phenylmethyl)oxy\}methyl}-1,2,3,4,6,7,12,12b-
octahydropyrido[2,1-a]b-carbolin-4-one (67) (1.89 g, 4.2 mmol) in anhydrous
tetrahydrofuran (15 ml) was added via cannula. The resulting mixture was stirred for a
further 1 hour at -78 °C after which time phenylselenenylbromide (1.1 g, 4.6 mmol) in
anhydrous tetrahydrofuran (10 ml) was added dropwise by syringe. The reaction was
allowed to warm slowly from -78 °C to room temperature with stirring. After 24
hours the reaction was quenched by the addition of saturated aqueous ammonium
chloride solution (40 ml) and extracted with diethyl ether (3 x 50 ml). The combined
erther extracts were washed with saturated aqueous ammonium chloride solution (100
ml), dried with anhydrous sodium sulphate. The solvent was removed by rotary
evacuation to yield the crude selenide (68) (2.5 g), which was used without further
purification.

The crude selenide (68) (2.5 g) was dissolved in methanol (220 ml) and water (45 ml).
To the resulting solution was added sodium metaperiodate (2.4 g, 9.7 mmol) and
sodium bicarbonate (0.42 g, 5.0 mmol) and the solution was stirred vigorously at
room temperature for 18 hours. After this time the reaction was poured into a mixture
of saturated aqueous sodium bicarbonate solution (200 ml) and diethyl ether (250 ml).
The ether layer was washed with water (200 ml), then brine (200 ml) and dried over
anhydrous magnesium sulphate. The solvent was removed by rotary evaporation and
the crude product was adsorbed onto silica gel and purified by flash column
chromatography over silica gel eluting with 3:2 hexane:ethyl acetate to give the target compound as a pale yellow foam (1.6 g, 85%); Mp 67-69 °C; [α]D = -265.6 (c = 1.0, CH2Cl2); νmax (thin film, DCM)/cm⁻¹: 1651 (C=N); δH (400 MHz; CDCl3) 2.20-2.29 (1H, m, CH(H)CH=CHC=O), 2.32-2.59 (1H, m, CH(H)CH=CHC=O), 3.02 (1H, ddd, J 16, 8, 4, CH(H)CHN), 3.15 (1H, d, J 16, CH(H)CHN), 3.29-3.39 (2H, m, CH2OBn), 4.44 (2H, s, OCH2Ph), 4.58-4.62 (1H, m, C=CCH), 5.22 (2H, dd, J 36, 16, NCH2Ph), 5.41-5.46 (1H, m, NCHCH2OBn), 6.06 (1H, dd, J 8, 4, CH=CHC=O), 6.49-6.53 (1H, m, CH=CHC=O), 6.82-6.85 (2H, m, ArH), 7.11-7.23 (11H, m, ArH), 7.59-7.62 (1H, m, ArH); δC (100 MHz; CDCl3) 22.0 (CH2), 32.0 (CH2), 46.1 (CH), 47.3 (CH2), 49.8 (CH), 68.1 (CH2), 72.6 (CH2), 107.7 (C), 109.8 (CH), 118.7 (CH), 119.9 (CH), 122.3 (CH), 125.6 (2×CH), 125.9 (CH), 127.0 (C), 127.3 (2×CH), 127.3 (CH), 127.5 (CH), 128.2 (2×CH), 129.1 (2×CH), 132.6 (C), 137.0 (C), 138.2 (C), 138.2 (C), 138.3 (CH), 164.8 (C=O); MS (El) m/z 448 [M⁺, 100.0%] (Found: M⁺, 448.21580. C30H28N2O2 requires 448.21508).
(2R,6R,12bS)-2-Eth-1-enyl-12-(phenylmethyl)-6-{[(phenylmethyl)oxy]methyl}-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (70)

A 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran (6.7 ml, 6.7 mmol) was added to a suspension of copper cyanide (0.30 g, 3.4 mmol) in anhydrous tetrahydrofuran (12.0 ml) at -78 °C with stirring. The reaction mixture was warmed to 0 °C for 3 minutes and then re-cooled to -78 °C. A solution of (6R,12bS)-12-(phenylmethyl)-6-{{[(phenylmethyl)oxy]methyl}-1,4,6,7,12,12b-hexahydropyrido[2,1-a]b-carbolin-4-one (69) (0.30 g, 0.67 mmol) in anhydrous tetrahydrofuran (8.0 ml) was added via cannula at -78 °C. After a further 5 minutes chlorotrimethylsilane (0.43 ml, 3.4 mmol) was added and the resulting suspension was warmed slowly (overnight) to room temperature. After this time a mixture of saturated aqueous ammonium chloride solution (10.0 ml) and water (10.0 ml) was added and stirring continued for 20 minutes. A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (2.0 ml) was added and stirring continued for a further 15 minutes. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 x 40 ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. Crude 250 MHz 1H NMR revealed the formation of the product as a single diastereoisomer. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 3:1 hexane:ethyl acetate to give the target compound as a pale yellow oil (0.22 g, 70%); [α]D = -42.5 (c = 1.6, CH2Cl2); νmax (thin film, DCM)/cm⁻¹ 1636 (NC=O); δh (400 MHz; CDCl3) 1.83-1.90 (1H, m, C=CHCH2), 2.47-2.67 (2H, m, CH=CH2), 2.88-2.93 (1H, m, C=CH(H)), 3.01 (1H, ddd, J 16, 4, 4, C=CH(H)), 3.32 (2H, d, J 8, CH2OBn), 4.37-4.44 (2H, m, OCH2Ph), 4.47-4.51 (1H, m, C=CH(H)), 4.97-5.03 (2H, m, CH=CH2), 5.18 (1H, d, J 20, NCH(H)Ph), 5.32 (1H, d, J 20, NCH(H)Ph), 5.61-5.67 (1H, m, NCH2OBn), 5.69-5.78 (1H, m, CH=CH2), 6.86-6.90 (2H, m, NCH2OBn)
ArH), 7.13-7.24 (1H, m, ArH), 7.53-7.57 (1H, m, ArH); $\delta_C$(100 MHz; CDCl$_3$) 21.9 (CH$_2$), 32.7 (CH), 34.9 (CH$_2$), 36.1 (CH$_2$), 46.2 (CH), 47.5 (CH), 47.7 (CH$_2$), 68.3 (CH$_2$), 72.6 (CH$_2$), 108.2 (C), 109.7 (CH), 115.6 (CH$_2$), 118.4 (CH), 119.8 (CH), 122.2 (CH), 125.8 (2×CH), 127.0 (C), 127.4 (CH), 127.5 (2×CH), 127.6 (CH), 128.2 (2×CH), 128.9 (2×CH), 133.3 (C), 137.2 (C), 138.2 (C), 138.4 (C), 139.2 (CH), 170.2 (NC=O); MS (EI) $m/z$ 476 [M$^+$, 64.6%] (Found: M$^+$, 476.24597. C$_{32}$H$_{32}$N$_2$O$_2$ requires 476.24638).
3.5 Manipulation of Indolizino[2,3-α]quinolizidine Substrates

\[(6S,12bR)-4-Oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-α]b-carbolin-6-carbaldehyde (71)\]

To a solution of \((6S,12bR)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-α]b-carbolin-4-one (47) (1.0 g, 3.7 mmol)\) in dimethylsulfoxide (10 ml) was added IBX (1.13 g, 4.1 mmol) with stirring under nitrogen. After 24 hours stirring at room temperature the solvent was removed and the resulting solid was re-suspended in ethyl acetate (250 ml), before filtering through a small pad of celite. The filtrate was washed with water (3 × 250 ml), the organic phase was then dried with anhydrous magnesium sulphate, filtered and evaporated to dryness to yield the target compound which was purified by flash column chromatography over silica gel using ethyl acetate as eluent. The purified aldehyde was afforded as a pale yellow foam (0.69 g, 70%); \(\text{Mp 98-102 °C; } [α]_D = +99.0 \text{ (c = 0.9, CH}_2\text{Cl}_2); \nu_{\text{max}}\text{(thin film, DCM)/cm}^{-1} 3279 (\text{NH}), 1733 (\text{CHO}), 1615 (\text{NC}=\text{O}); \delta_{\text{H}}(400 \text{ MHz; CDCl}_3) 1.74 (1\text{H, ddd, } J = 24, 12, 4, \text{CH(H)}\text{CH}_2\text{CH}_2\text{C}=\text{O}), 2.02-2.05 (2\text{H, m, CH}_2\text{CH}_2\text{C}=\text{O}), 2.41-2.47 (1\text{H, m, CH(H)}\text{CH}_2\text{CH}_2\text{C}=\text{O}), 2.47-2.55 (1\text{H, m, CH(H)}\text{C}=\text{O}), 2.70-2.76 (1\text{H, m, CH(H)}\text{C}=\text{O}), 3.07-3.13 (1\text{H, m, CH(H)}\text{CHCHO}), 3.39-3.46 (1\text{H, m, CH(H)}\text{CHCHO}), 4.93 (1\text{H, d, } J = 12, \text{C}=\text{CCH}), 5.99 (1\text{H, d, } J = 8, \text{CHCHO}), 7.13-7.22 (2\text{H, m, ArH}), 7.33 (1\text{H, d, } J = 12, \text{ArH}), 7.54 (1\text{H, d, } J = 4, \text{ArH}), 7.85 (1\text{H, br, s, NH}), 9.51 (1\text{H, s, CHO}); \delta_{\text{C}}(100 \text{ MHz; CDCl}_3) 19.5 (\text{CH}_2), 20.0 (\text{CH}_2), 29.7 (\text{CH}_2), 32.0 (\text{CH}_2), 52.1 (\text{CH}), 56.7 (\text{CH}), 106.5 (\text{C}), 111.0 (\text{CH}), 118.4 (\text{CH}), 120.1 (\text{CH}), 122.6 (\text{CH}), 126.5 (\text{C}), 132.6 (\text{C}), 136.4 (\text{C}), 170.2 (\text{NC}=\text{O}), 199.3 (\text{CHO}); \text{MS (El) } m/z 268 [M^+] 86.2\%\) (Found: M^+, 268.12124. \text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2 \text{requires } 268.12118).
(12bR)-1,2,3,4,6,7,12,12b-Octahydropyrido[2,1-a]b-carbolin-4-one (72)

[Bis(triphenylphosphine)]rhodium (I) carbonyl chloride (20) (0.77 g, 1.11 mmol) was added to mesitylene (25 ml) under nitrogen and the mixture warmed to 80 °C with stirring until the rhodium complex dissolved. (6S,12bR)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-6-carbaldehyde (71) (0.30 g, 1.11 mmol) was added and the mixture heated at reflux under nitrogen. After 21 hours the solvent was removed and the crude material purified by flash column chromatography over silica gel using ethyl acetate as eluent to give the product as an off-white solid (0.16 g, 60%); Mp 228-230 °C; [α]D = +216.4 (c = 1.0, CHCl3); νmax (thin film, DCM)/cm⁻¹ 1651 (NC=O); δH (400 MHz; CDCl3) 1.76-1.89 (1H, m, CH(H)CH₂CH₂C=O), 1.95-2.01 (1H, m, CH(H)CH₂C=O), 2.36-2.47 (1H, m, CH(H)CH₂CH₂C=O), 2.36-2.47 (1H, m, CH(H)C=O), 2.57-2.62 (1H, m, CH(H)C=O), 2.72-2.82 (1H, m, CH(H)CH₂N), 2.84-2.89 (1H, m, CH(H)CH₂N), 2.84-2.89 (1H, m, CH(H)N), 4.77-4.81 (1H, m, C=CH₂), 5.14-5.22 (1H, m, CH(H)N), 7.11-7.21 (2H, m, ArH), 7.35 (1H, d, J = 8, ArH), 7.50 (1H, d, J = 8, ArH), 7.79 (1H, br, s, NH); δc (100 MHz; CDCl3) 19.8 (CH₂), 21.4 (CH₂), 29.5 (CH₂), 32.8 (CH₂), 40.5 (CH₂), 54.7 (CH), 109.5 (C), 111.0 (CH), 118.4 (CH), 119.8 (CH), 122.1 (CH), 126.8 (C), 133.3 (C), 136.3 (C), 169.3 (NC=O); MS (EI) m/z 240 [M⁺, 100.0%] (Found: M⁺, 240.12633. C₁₅H₁₆N₂O requires 240.12626).

(e.e. = 94%; determined by chiral HPLC using a Chira Cel OD-H column, 85:15 hexane:2-propanol, 0.6 ml/min).
1,1-Dimethylethyl(6S,12bR)-6-formyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (79)

(6S,12bR)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-6-carbaldehyde (71) (4.3 g, 16.0 mmol) was dissolved in anhydrous tetrahydrofuran (40.0 ml) under nitrogen. Triethylamine (4.5 ml, 32.0 mmol), N,N-Dimethylaminopyridine (0.4 g, 3.2 mmol) and Di-tert-butyl dicarbonate (4.5 g, 20.8 mmol) were added successively and the resulting solution was stirred at room temperature under nitrogen for 4 hours. After this time the volatiles were removed by rotary evaporation and the resulting residue was re-dissolved in ethyl acetate (200 ml) and washed successively with saturated aqueous ammonium chloride (2 × 200 ml), saturated aqueous sodium bicarbonate (2 × 200 ml) and brine (200 ml). The organic layer was dried over anhydrous magnesium sulphate, the solvent removed under rotary evaporation and the crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel using 3:2 ethyl acetate:hexane as eluent. The product was isolated as a yellow oil (5.8 g, 98%); [α]D = +249.6 (c = 1.0, CHCl3); νmax (thin film, DCM)/cm⁻¹ 1645 (NC=O), 1729 (CHO); δH (400 MHz; CDCl3) 1.40-1.50 (1H, m, C=CCHCH(H)), 1.68 (9H, s, OC(CH3)3), 1.94-2.06 (2H, m, CH2CH2C=O), 2.51-2.60 (1H, m, CH(H)C=O), 2.61-2.66 (1H, m, C=CHCH(H)), 2.72-2.79 (1H, m, CH(H)C=O), 2.97 (1H, ddd, J 16, 8, 4, C=CCH(H)), 3.36-3.41 (1H, m, C=CCH(H)), 3.93-3.95 (1H, m, NCHCHO), 7.25-7.34 (2H, m, ArH), 7.47-7.49 (1H, m, ArH), 8.03-8.07 (1H, m, ArH), 9.54 (1H, s, CHO); δC (100 MHz; CDCl3) 19.4 (CH2), 20.6 (CH2), 28.2 (3×CH3), 30.6 (CH2), 31.7 (CH2), 54.1 (CH), 56.2 (CH), 84.6 (C), 114.7 (C), 115.7 (CH), 118.3 (CH), 123.1 (CH), 125.0 (CH), 128.1 (C), 134.5 (C), 136.9 (C), 149.8 (NC(O)OBu), 171.1 (NC=O), 199.1 (CHO); MS (EI) m/z 368 [M⁺, 27.8%] (Found: M⁺, 368.17367. C21H24N2O4 requires 368.17361).
(6S,12bR)-12-{{(1,1-Dimethylethyl)oxy}carbonyl}-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylic acid (80)

A solution of 1,1-dimethylethyl(6S,12bR)-6-formyl-4-oxo-1,2,3,4,6,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (79) (2.6 g, 7.1 mmol) in acetonitrile (35.0 ml), tert-butyl alcohol (130.0 ml) and 1-methyl-1-cyclohexene (63.0 ml) was stirred rapidly as it was cooled to 0 °C. A solution of sodium chlorite (6.3 g, 54.7 mmol) and sodium dihydrogen phosphate (6.3 g, 49.7 mmol) in water (130.0 ml) was added dropwise over a period of 10 minutes at 0 °C. The solution was then allowed to stir at room temperature for a further 18 hours. After this time the reaction was partitioned between ethyl acetate (300 ml) and brine (200 ml). The ethyl acetate layer was then washed with 1 M aqueous sodium dithionite solution (100 ml). The organic layer was dried over anhydrous magnesium sulphate and evaporated to dryness to give the target compound which was purified by flash column chromatography over silica gel eluting with ethyl acetate yielding a yellow oil (2.24 g, 83%); [α]D = +159.2 (c = 3.0, CHCl3); νmax (thin film, DCM)/cm⁻¹ 3379 (OH), 1640 (NC=O); δH(400 MHz; CDCl3) 1.41-1.45 (1H, m, C=CCHCH(H)), 1.67 (9H, s, OC(CH3)3), 1.88-1.92 (2H, m, CH2CH2C=O), 2.47-2.61 (1H, m, CH(H)C=O), 2.47-2.61 (1H, m, C=CCHCH(H)), 2.65-2.72 (1H, m, CH(H)C=O), 2.89-2.95 (1H, m, C=CCH(H)), 3.38-3.42 (1H, m, C=CCH(H)), 5.32-5.35 (1H, m, C=CCH), 6.03-6.05 (1H, m, NCHCO2H), 7.22-7.32 (2H, m, ArH), 7.44-7.46 (1H, m, ArH), 8.04 (1H, d, J 8, ArH); δC(100 MHz; CDCl3) 19.1 (CH2), 23.1 (CH2), 28.2 (3×CH3), 30.4 (CH2), 31.4 (CH2), 49.5 (CH), 53.9 (CH), 84.5 (C), 114.9 (C), 115.7 (CH), 118.4 (CH), 123.0 (CH), 124.8 (CH), 128.3 (C), 134.0 (C), 136.8 (C), 149.9 (NC(O)O'Bu), 171.8 (NC=O), 174.6 (C(O)OH); MS (El) m/z 384 [M⁺, 2.0%] (Found: M⁺, 384.16768. C21H24N2O5 requires 384.16852).
1,1-Dimethylethyl(6S,12bR)-4-oxo-6-(phenylseleno)carbonyl]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-α]b-carbolin-12-carboxylate (81)

To a flask containing (6S,12bR)-12-[(1,1-dimethylethyl)oxy]carbonyl]-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-α]b-carbolin-12-carboxylic acid (80) (2.24 g, 5.83 mmol) under nitrogen was added anhydrous dichloromethane (30.0 ml) followed by diphenyldiselenide (2.8 g, 8.7 mmol). The resulting mixture was cooled to 0 °C and tributylphosphine (90% grade) (3.6 ml, 11.7 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirring continued for a further 18 hours at room temperature. Dichloromethane (100 ml) and water (100 ml) were added and the aqueous layer was extracted with a further (100 ml) of dichloromethane. The combined organic fractions were washed with brine (100 ml), dried over anhydrous magnesium sulphate and evaporated to dryness to give the crude product which was purified by flash column chromatography over silica gel eluting with 8:2 hexane:ethyl acetate, then 3:2 ethyl acetate:hexane giving the target compound as a pale yellow foam (2.5 g, 83%); Mp 75-78 °C; [α]D = +93.6 (c = 2.0, CHCl3); \( \nu_{max} \) (thin film, DCM)/cm\(^{-1} \) 1726 (COSePh); \( \delta \) (400 MHz; CDCl3) 1.43-1.54 (1H, m, C=CCHCH(H)), 1.69 (9H, s, OC(CH3)3), 1.97-2.13 (2H, m, CH2CH2C=O), 2.59-2.68 (1H, m, C=CCHCH(H)), 2.59-2.68 (1H, m, CH(H)C=O), 2.78-2.85 (1H, m, CH(CH)C=O), 2.86-2.92 (1H, m, C=CCH(H)), 3.47-3.51 (1H, m, C=CCH(H)), 5.56-5.59 (1H, m, C=CCH), 6.15-6.17 (1H, m, NCHCOSePh), 6.15-6.17 (1H, m, ArH), 7.22-7.30 (5H, m, ArH), 7.38-7.40 (2H, m, ArH), 7.43-7.46 (1H, m, ArH), 8.04-8.06 (1H, m, ArH); \( \delta \) (100 MHz; CDCl3) 19.0 (CH2), 22.3 (CH2), 28.2 (3×CH3), 31.0 (CH2), 31.7 (CH2), 54.1 (CH), 59.6 (CH), 84.4 (C), 114.8 (C), 115.6 (CH), 118.4 (CH), 123.1 (CH), 124.9 (CH), 125.3 (C), 128.3 (C), 128.9 (CH), 129.2 (2×CH), 133.4 (C), 135.9 (2×CH), 136.7 (C), 149.9 (NC(O)O'Bu), 171.7 (NC=O), 200.3 (COSePh); MS (Cl) m/z 525 [MH+, 6.3%] (Found: MH+, 525.13013. C27H28N2O4Se requires 525.12143).
1,1-Dimethylethyl(12bR)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-\(\alpha\)]b-carbolin-12-carboxylate (82)

A three-necked flask fitted with a condenser, glass stopper and a suba seal was flushed with nitrogen. A solution of 1,1-dimethylethyl(6S,12bR)-4-oxo-6-[(phenylseleno)carbonyl]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-\(\alpha\)]b-carbolin-12-carboxylate (81) (2.5 g, 4.8 mmol) in anhydrous toluene (25.0 ml) was added via cannula. The solution was then degassed with nitrogen for 15 minutes before adding tri-\(n\)-butyltin hydride (5.1 ml, 19.2 mmol) by syringe. The resulting mixture was heated to 80 °C in an oil bath whereupon azobisisobutyronitrile (0.16 g, 0.96 mmol) was added portionwise over a 2 hour period at 80 °C. After 2 hours stirring at 80 °C the mixture was cooled to room temperature and the solvent removed on the rotary evaporator. The resulting crude oil was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with hexane followed by 3:1 ethyl acetate:hexane. The target compound was isolated as a colourless oil (1.17 g, 73%); \([\alpha]_D = +328.8\) (c = 2, CH2Cl2); \(\nu_{\max}\) (thin film, DCM)/cm\(^{-1}\) 1700 (NC=O(O)\(\text{Bu}^+\)); \(\delta\) (CDCl3) 1.41-1.46 (1H, m, C=CCHCH(H)), 1.69 (9H, s, OC(CH3)3), 1.89-1.95 (2H, m, CH2CH2C=O), 2.39-2.48 (1H, m, CH(H)C=O), 2.59-2.68 (1H, m, C=CCHCH(H)), 2.59-2.68 (1H, m, CH(H)C=O), 2.70-2.79 (2H, m, CH2CH2N), 2.81-2.84 (1H, m, CH(H)N), 5.08-5.17 (1H, m, CH(H)N), 5.08-5.17 (1H, m, C=CCH), 7.23-7.33 (2H, m, ArH), 7.43-7.45 (1H, m, ArH), 8.04-8.06 (1H, m, ArH); \(\delta\) (CDCl3) 19.5 (CH2), 21.7 (CH2), 28.2 (3\times CH3), 30.2 (CH2), 32.2 (CH2), 39.0 (CH2), 56.1 (CH), 84.3 (C), 115.5 (CH), 118.3 (CH), 118.4 (C), 123.0 (CH), 124.6 (CH), 128.7 (C), 135.3 (C), 136.8 (C), 150.2 (NC(O)O\(\text{Bu}^+\)), 169.9 (NC=O); MS (EI) \(m/z\) 340 [M\(^+\), 14.9%] (Found: M\(^+\), 340.17801. C20H24N2O3 requires 340.17869).
(12bR)-1,2,3,4,6,7,12,12b-Octahydropyrido[2,1-α]b-carbolin-4-one (72)

1,1-dimethylethyl(12bR)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-α]b-carbolin-
12-carboxylate (82) (0.05 g, 0.15 mmol) was dissolved in anhydrous tetrahydrofuran
(8.0 ml) under a nitrogen atmosphere. A 1.0 M solution of tetrabutylammonium
fluoride in tetrahydrofuran (1.5 ml, 1.5 mmol) was then added and the mixture was
heated under reflux for 9 hours. After this time the mixture was cooled to room
temperature and water (30.0 ml) was added. The mixture was extracted with ethyl
acetate (2 × 50.0 ml) and the organic fractions were dried over anhydrous magnesium
sulphate and the solvent removed on the rotary evaporator. The crude product was
adsorbed onto silica gel and purified by flash column chromatography over silica gel
using ethyl acetate as eluent to give the target compound as an off-white solid (0.02 g,
65%), which had identical spectral properties to the compound prepared through
rhodium decarbonylation of (71).

(e.e. = 98%; determined by chiral HPLC using a Chira Cel OD-H column, 85:15
hexane:2-propanol, 0.6 ml/min).
A solution of \((6S,12bR)-6\)-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-\(a\)]b-carbolin-4-one (47) (0.30 g, 1.11 mmol) in anhydrous toluene (10.0 ml) and tetrahydrofuran (15.0 ml) was stirred at room temperature under nitrogen with sodium bis(methoxyethoxy)aluminium hydride (1.1 ml of a 65\% solution in toluene) for 20 hours. The reaction mixture was quenched by careful addition of saturated aqueous sodium potassium tartrate (25 ml). The organic layer was separated and the salt extracted with ethyl acetate (3 \times 50 ml). The organic phase was dried with anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. The crude product was purified by flash column chromatography over silica gel eluting with 10\% methanol:ethyl acetate to yield the product as a yellow solid (0.21 g, 74\%); Mp 101-104 °C; \([\alpha]_D = +57.6 \ (c = 1.0, \text{DMSO}); \nu_{\text{max}}\) (thin film, DCM)/cm\(^{-1}\) 3357 (OH); \(\delta\)\(_{\text{H}}\) (400 MHz; DMSO) 1.31-1.55 (1H, m, \(\text{CH(H)CH}_2\text{N}\)), 1.59-1.62 (1H, m, \(\text{CH(H)CH}_2\text{N}\)), 1.72-1.75 (1H, m, \(\text{C=CCHCH}_2\text{H(H)}\)), 2.19-2.22 (1H, m, \(\text{C=CCHCH(H)}\)), 2.74-2.77 (2H, m, \(\text{CH}_2\text{CHCH}_2\text{OH}\)), 3.03-3.05 (1H, m, \(\text{NCHCH}_2\text{OH}\)), 3.23-3.28 (1H, m, \(\text{CH(H)OH}\)), 3.49-3.52 (IH, m, \(\text{C=CCH}\)), 3.56-3.59 (1H, m, \(\text{C=CCH}\)), 3.71-3.73 (1H, m, \(\text{CH(H)OH}\)), 4.42 (1H, br, s, \(\text{OH}\)), 6.91-6.95 (1H, m, \(\text{ArH}\)), 6.98-7.02 (1H, m, \(\text{ArH}\)), 7.27 (1H, d, \(\text{J = 8, ArH}\)), 7.35 (1H, d, \(\text{J = 8, ArH}\)), 10.6 (1H, br, s, \(\text{NH}\)); \(\delta\)\(_{\text{C}}\) (100 MHz; DMSO) 22.4 (\(\text{CH}_2\)), 24.0 (\(\text{CH}_2\)), 26.0 (\(\text{CH}_2\)), 30.8 (\(\text{CH}_2\)), 52.0 (\(\text{CH}_2\)), 53.4 (\(\text{CH}\)), 56.5 (\(\text{CH}_2\)), 60.6 (\(\text{CH}\)), 104.5 (\(\text{C}\)), 110.8 (\(\text{CH}\)), 117.4 (\(\text{CH}\)), 118.0 (\(\text{CH}\)), 120.1 (\(\text{CH}\)), 127.3 (\(\text{C}\)), 135.2 (\(\text{C}\)), 136.1 (\(\text{C}\)); MS (El) \(m/z\) 256 [\(\text{M}^+\), 5.6\%] (Found: \(\text{M}^+\), 256.15729. \(\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}\) requires 256.15756).
3.6 Total Synthesis of a Simple Indole Alkaloid

\[(6R,12bS)-4-Oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-6-carbaldehyde (85)\]

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\[\text{To a solution of } (6R,12bS)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (50) (5.0 g, 18.5 mmol) in dimethylsulfoxide (40 ml) was added IBX (15.4 g, 55.5 mmol) with stirring under nitrogen. After 24 hours stirring at room temperature the solvent was removed and the resulting solid was re-suspended in ethyl acetate (250 ml), before filtering through a small pad of celite. The filtrate was washed with water (3 x 250 ml), the organic phase was then dried with anhydrous magnesium sulphate, filtered and evaporated to dryness to yield the target compound which was purified by flash column chromatography over silica gel using ethyl acetate as eluent. The purified aldehyde was afforded as a pale yellow foam (3.0 g, 60%); Mp 97.5-99 °C; [\alpha]D = -201.3 (c = 1.2, CH2Cl2); \nu_{max}(\text{thin film, DCM})/cm^{-1} 3271 (NH), 1727 (CHO), 1617 (NC=O); \delta_{t}(400 MHz; CDCl3) 1.66-1.77 (1H, m, CH(H)CH2CH2CH2C=O), 1.99-2.05 (2H, m, CH2CH2C=O), 2.40-2.48 (1H, m, CH(H)CH2CH2C=O), 2.49-2.54 (1H, m, CH(H)C=O), 2.69-2.76 (1H, m, CH(H)C=O), 3.10 (1H, ddd, J 16, 8, 4, CH(H)CHCHO), 3.41-3.47 (1H, m, CH(H)CHCHO), 4.89-4.93 (1H, m, C=CCH), 5.97-5.99 (1H, m, CHCHO), 7.11-7.24 (2H, m, ArH), 7.30-7.32 (1H, m, ArH), 7.53-7.55 (1H, m, ArH), 8.15 (1H, br, s, NH), 9.49 (1H, s, CHO); \delta_{c}(100 MHz; CDCl3) 19.5 (CH2), 20.0 (CH2), 29.6 (CH2), 32.0 (CH2), 52.2 (CH), 56.8 (CH), 106.4 (C), 111.1 (CH), 118.3 (CH), 120.0 (CH), 122.6 (CH), 126.5 (C), 132.7 (C), 136.5 (C), 170.4 (NC=O), 199.3 (CHO); MS (EI) m/z 268 [M+], 75.9% (Found: M+, 268.12130. C16H16N2O2 requires 268.12118).\]
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1,1-Dimethylethyl(6R,12bS)-6-formyl-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (86)

(6R,12bS)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-6-carbaldehyde (85) (3.5 g, 13.1 mmol) was dissolved in anhydrous tetrahydrofuran (40.0 ml) under nitrogen. Triethylamine (3.7 ml, 26.2 mmol), N,N-Dimethylaminopyridine (0.35 g, 2.7 mmol) and Di-tert-butyl dicarbonate (3.8 g, 17.1 mmol) were added successively and the resulting solution was stirred at room temperature under nitrogen for 4 hours. After this time the volatiles were removed by rotary evaporation and the resulting residue was re-dissolved in ethyl acetate (200 ml) and washed successively with saturated aqueous ammonium chloride (2 x 200 ml), saturated aqueous sodium bicarbonate (2 x 200 ml) and brine (200 ml). The organic layer was dried over anhydrous magnesium sulphate, the solvent removed under rotary evaporation and the crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel using 3:2 ethyl acetate:hexane as eluent. The product was isolated as a yellow oil (2.6 g, 63%); [α]D = -925.3 (c = 3.0, CH2Cl2); v_{max}(thin film, DCM)/cm^{-1} 1729 (CHO), 1653 (NC=O); δ_{H}(400 MHz; CDCl3) 1.41-1.50 (1H, m, C=CCHCH(H)), 1.67 (9H, s, OC(CH3)3), 1.96-2.04 (2H, m, CH2CH2C=O), 2.50-2.59 (1H, m, CH(H)C=O), 2.61-2.65 (1H, m, C=CCHCH(H)), 2.71-2.78 (1H, m, CH(H)C=O), 2.96 (1H, ddd, J 16, 8, 4, C=CCH(H)), 3.35-3.40 (1H, m, C=CCH(H)), 5.26-5.29 (1H, m, C=CCH), 5.92-5.94 (1H, m, NCHCHO), 7.24-7.34 (2H, m, ArH), 7.47-7.49 (1H, m, ArH), 8.04-8.06 (1H, m, ArH), 9.52 (1H, s, CHO); δ_{C}(100 MHz; CDCl3) 19.3 (CH2), 20.5 (CH2), 28.4 (3×CH3), 30.6 (CH2), 31.7 (CH2), 54.0 (CH), 56.1 (CH), 84.6 (C), 114.7 (C), 115.7 (CH), 118.2 (CH), 123.1 (CH), 125.0 (CH), 128.1 (C), 134.5 (C), 136.9 (C), 149.8 (NC(O)O'Bu), 170.9 (NC=O), 199.1 (CHO); MS (EI) m/z 368 [M^+], 54.1% (Found: M^+, 368.17367. C21H24N2O4 requires 368.17361).

Experimental
A solution of 1,1-dimethylethyl(6R,12bS)-6-formyl-4-oxo-1,2,3,4,6,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (86) (2.6 g, 7.1 mmol) in acetonitrile (35.0 ml), tert-butyl alcohol (130.0 ml) and 1-methyl-1-cyclohexene (63.0 ml) was stirred rapidly as it was cooled to 0 °C. A solution of sodium chlorite (80% grade) (6.3 g, 54.7 mmol) and sodium dihydrogen phosphate (6.3 g, 49.7 mmol) in water (130.0 ml) was added dropwise over a period of 10 minutes at 0 °C. The solution was then allowed to stir at room temperature for a further 18 hours. After this time the reaction was partitioned between ethyl acetate (300 ml) and brine (200 ml). The ethyl acetate layer was then washed with 1 M aqueous sodium dithionite solution (100 ml). The organic layer was then washed with anhydrous magnesium sulphate and evaporated to dryness to give the target compound which was purified by flash column chromatography over silica gel eluting with ethyl acetate yielding a yellow oil (1.9 g, 70%); [α]_D = -530 (c = 1.0, CH2Cl2); ν_max (thin film, DCM)/cm⁻¹ 3379 (OH), 1640 (NC=O); δ_H (400 MHz; CDCl₃) 1.34-1.40 (1H, m, C=CHCH(H)), 1.64 (9H, s, OC(CH₃)₃), 1.82-1.91 (2H, m, CH₂CH₂C=O), 2.45-2.62 (1H, m, CH(H)C=O), 2.45-2.62 (1H, m, C=CHCH(H)), 2.45-2.62 (1H, m, CH(H)C=O), 2.83-2.89 (1H, m, C=CHCH), 2.83-2.89 (1H, m, C=CHCH), 3.35-3.41 (1H, m, C=CHCH(H)), 5.33-5.36 (1H, m, C=CHCH), 5.98-6.0 (1H, m, NCHCO₂H), 7.18-7.28 (2H, m, ArH), 7.39-7.41 (1H, m, ArH), 8.03 (1H, d, J 8, ArH); δ_C (100 MHz; CDCl₃) 19.0 (CH₂), 23.2 (CH₂), 28.2 (3×CH₃), 30.4 (CH₂), 31.3 (CH₂), 49.8 (CH), 51.4 (CH), 84.4 (C), 115.0 (C), 115.7 (CH), 118.4 (CH), 123.0 (CH), 124.8 (CH), 128.4 (C), 133.9 (C), 136.8 (C), 149.9 (NC(O)O'Bu), 172.1 (NC=O), 173.0 (C(O)OH); MS (EI) m/z 384 [M⁺, 2.0%] (Found: M⁺, 384.16768. C₂₁H₂₄N₂O₅ requires 384.16852).
1,1-Dimethylethyl(6R,12bS)-4-oxo-6-[(phenylseleno)carbonyl]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (88)

To a flask containing (6R,12bS)-12-[(1,1-dimethylethyl)oxy]carbonyl]-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylic acid (87) (1.9 g, 4.95 mmol) under nitrogen was added anhydrous dichloromethane (30.0 ml) followed by diphenylidiselenide (2.4 g, 7.5 mmol). The resulting mixture was cooled to 0 °C and tributylphosphine (90% grade) (3.1 ml, 10.1 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirring continued for a further 18 hours at room temperature. Dichloromethane (100 ml) and water (100 ml) were added and the aqueous layer was extracted with a further (100 ml) of dichloromethane. The combined organic fractions were washed with brine (100 ml), dried over anhydrous magnesium sulphate and evaporated to dryness to give the crude product which was purified by flash column chromatography over silica gel eluting with 8:2 hexane:ethyl acetate, then 3:2 ethyl acetate:hexane giving the target compound as a pale yellow foam (1.72 g, 66%); Mp 75-77 °C; [α]D = -84 (c = 1.0, CH2Cl2); νmax (thin film, DCM)/cm⁻¹ 1729 (COSePh), 1654 (NC=O); δH (400 MHz; CDCl3) 1.44-1.54 (1H, m, C=CHC(H)), 1.70 (9H, s, OC(CH3)3), 1.95-2.11 (2H, m, CH2CH2C=O), 2.60-2.68 (1H, m, C=CCHCH(H)), 2.60-2.68 (1H, m, C=CH(H)C=O), 2.78-2.85 (1H, m, CH(H)C=O), 2.87-2.93 (1H, m, C=CH(H)), 3.47-3.52 (1H, m, C=CH(H)), 5.56-5.59 (1H, m, C=CCH), 6.15-6.17 (1H, m, NCHCOSeph), 6.15-6.17 (1H, m, ArH), 7.24-7.32 (5H, m, ArH), 7.39-7.40 (2H, m, ArH), 7.43-7.46 (1H, m, ArH), 8.03-8.06 (1H, m, ArH); δC (100 MHz; CDCl3) 19.0 (CH2), 22.4 (CH2), 28.3 (3×CH3), 31.1 (CH2), 31.8 (CH2), 54.1 (CH), 59.6 (CH), 84.5 (C), 114.8 (C), 115.7 (CH), 118.4 (CH), 123.1 (CH), 124.9 (CH), 125.4 (C), 128.3 (C), 128.9 (CH), 129.2 (2×CH), 133.5 (C), 136.0 (2×CH), 136.8 (C), 149.9 (NC(O)O'Bu), 171.6 (NC=O), 200.3 (COSePh); MS (Cl) m/z 525 [MH+], 6.7% (Found: MH+, 525.13013. C27H28N2O4Se requires 525.12143).
1,1-Dimethylethyl(12bS)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (89)

A three-necked flask fitted with a condenser, glass stopper and a suba seal was flushed with nitrogen. A solution of 1,1-dimethylethyl(6R,12bS)-4-oxo-6-[(phenylseleno)carbonyl]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (88) (1.7 g, 3.2 mmol) in anhydrous toluene (20.0 ml) was added via cannula. The solution was then degassed with nitrogen for 15 minutes before adding tri-n-butyltin hydride (3.5 ml, 13.2 mmol) by syringe. The resulting mixture was heated to 80 °C in an oil bath whereupon azobisisobutyronitrile (0.1 g, 0.6 mmol) was added portionwise over a 2 hour period at 80 °C. After 2 hours stirring at 80 °C the mixture was cooled to room temperature and the solvent removed on the rotary evaporator. The resulting crude oil was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with hexane followed by 3:1 ethyl acetate:hexane. The target compound was isolated as a colourless oil (1.1 g, 98%); [α]D = -77.3 (c = 1.8, CH2Cl2); νmax(thin film, DCM)/cm⁻¹ 1732 (NC=O(O)\textsuperscript{(Bu)}), 1644 (NC=O); δH(400 MHz; CDCl₃) 1.32-1.42 (1H, m, C=CCHCH(H)), 1.67 (9H, s, OC(CH₃)₃), 1.79-1.86 (2H, m, CH₂CH₂C=O), 2.34-2.43 (1H, m, CH(H)C=O), 2.54-2.77 (1H, m, C=CCHCH(H)), 2.54-2.77 (1H, m, CH(H)C=O), 2.54-2.77 (2H, m, CH₂CH₂N), 2.54-2.77 (1H, m, CH(H)N), 5.05-5.15 (1H, m, CH(H)N), 5.05-5.15 (1H, m, C=CCH), 7.18-7.30 (2H, m, ArH), 7.37 (1H, d, J 8, ArH), 8.06 (1H, d, J 8, ArH); δC(100 MHz; CDCl₃) 19.5 (CH₃), 21.6 (CH₂), 28.1 (3xCH₃), 30.2 (CH₂), 32.1 (CH₂), 38.8 (CH₂), 56.0 (CH), 84.1 (C), 115.5 (CH), 118.2 (CH), 118.2 (C), 122.9 (CH), 124.5 (CH), 128.6 (C), 135.2 (C), 136.8 (C), 150.1 (NC(O)O\textsuperscript{(Bu)}), 169.4 (NC=O); MS (EI) m/z 340 [M⁺, 13.8%] (Found: M⁺, 340.17884. C₂₀H₂₄N₂O₃ requires 340.17862).
(12bS)-1,2,3,4,6,7,12,12b-Octahydropyrido[2,1-a]b-carbolin-4-one (90)

1,1-dimethylethyl(12bS)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (89) (0.23 g, 0.68 mmol) was dissolved in anhydrous tetrahydrofuran (10.0 ml) under a nitrogen atmosphere. A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (6.8 ml, 6.8 mmol) was then added and the mixture was heated under reflux for 9 hours. After this time the mixture was cooled to room temperature and water (40.0 ml) was added. The mixture was extracted with ethyl acetate (2 × 70.0 ml) and the organic fractions were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel using ethyl acetate as eluent to give the target compound as an off-white solid (0.1 g, 63%), Mp 238-240 °C; [α]D = -286 (c = 1.0, CHCl3); νmax (thin film, DCM)/cm⁻¹ 1651 (NC=O); δH(400 MHz; CDCl3) 1.76-1.89 (1H, m, CH(H)CH2C=O), 1.95-2.01 (1H, m, CH(H)CH2C=O), 2.36-2.47 (1H, m, CH(H)CH2CH2C=O), 2.36-2.47 (1H, m, CH(H)C=O), 2.57-2.62 (1H, m, CH(H)C=O), 2.72-2.82 (1H, m, CH(H)CH2N), 2.84-2.89 (1H, m, CH(H)CH2N), 4.76-4.80 (1H, m, C=CH2), 5.14-5.22 (1H, m, CH(N)), 7.11-7.21 (2H, m, ArH), 7.33-7.36 (1H, m, ArH), 7.51 (1H, d, J 8, ArH), 7.85 (1H, br, s, NH); δC(100 MHz; CDCl3) 19.4 (CH2), 21.0 (CH2), 29.1 (CH2), 32.5 (CH2), 40.1 (CH2), 54.4 (CH), 109.8 (C), 110.9 (CH), 118.5 (CH), 119.9 (CH), 122.2 (CH), 127.0 (C), 133.3 (C), 136.2 (C), 169.1 (NC=O); MS (El) m/z 240 [M⁺, 100.0%] (Found: M⁺, 240.12632. C13H16N2O requires 240.12626).

Experimental
Lithium aluminium hydride (0.07 g, 1.68 mmol) was weighed into a pre-dried three necked flask fitted with a condenser under a nitrogen atmosphere. Anhydrous tetrahydrofuran (13.0 ml) was added and the suspension was cooled to 0 °C with an ice bath. (12bS)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (90) (0.07 g, 1.68 mmol) in anhydrous tetrahydrofuran (4.0 ml) was added dropwise to the hydride solution at 0 °C. The resulting mixture was heated under reflux for 3 hours and then stirred at room temperature for a further 12 hours. Ether (5.0 ml) was added and the reaction was quenched by the careful addition of saturated aqueous sodium potassium tartrate solution. The mixture was stirred for another 1 hour before the addition of anhydrous magnesium sulphate prior to filtration though a celite pad. The reaction vessel was washed out with ethyl acetate and filtered through the celite pad. The filtrate was evaporated under reduced pressure to yield the crude product which was adsorbed onto silica gel and purified by flash column chromatography over silica gel using ethyl acetate as eluent to give the target compound as a yellow solid (0.09 g, 96%), a small portion of which was recrystallised from dichloromethane to yield yellow plate-like crystals; Mp 146-148 °C (lit.\textsuperscript{67-68} Mp 149-150 °C); [\alpha]\textsubscript{D} = -79.6 (c = 1.0, MeOH) (lit.\textsuperscript{67-68} [\alpha]\textsubscript{D} = -86.5 ± 2 (c = 1.0, MeOH)); \nu\textsubscript{max}(thin film, DCM)/cm\textsuperscript{-1} 3441 (NH); \delta\textsubscript{H}(400 MHz; CDCl\textsubscript{3}) 1.40-1.52 (1H, m, C=CCHCH\textsubscript{2}CH(H)), 1.57 (1H, ddd, J 24, 16, 4, C=CCHCH(H)), 1.69-1.77 (2H, m, C=CCH(CH\textsubscript{2})\textsubscript{2}CH\textsubscript{2}), 1.85-1.89 (1H, m, C=CCHCH\textsubscript{2}CH(H)), 2.02-2.05 (1H, m, C=CCHCH(H)), 2.37 (1H, dt, J 8, 4, C=CCH(CH\textsubscript{2})\textsubscript{3}CH(H)N), 2.58-2.73 (1H, m, C=CCH\textsubscript{2}CH(H)N), 2.58-2.73 (1H, m, C=CCH\textsubscript{2}CH\textsubscript{2}N), 2.96-3.02 (1H, m, C=CCH\textsubscript{2}CH\textsubscript{2}N), 3.02-3.08 (1H, m, C=CCH(CH\textsubscript{2})\textsubscript{3}CH(H)N), 3.21 (1H, d, J 8, C=CCH), 7.06-7.15 (2H, m, ArH), 7.28 (1H, d, J 8, ArH), 7.46 (1H, d, J 8, ArH), 7.73 (1H, br, s, NH); \delta\textsubscript{C}(100 MHz; CDCl\textsubscript{3}) 21.6 (CH\textsubscript{2}), 24.3 (CH\textsubscript{2}), 25.7 (CH\textsubscript{2}), 30.0 (CH\textsubscript{2}), 53.6 (CH\textsubscript{2}), 55.7 (CH\textsubscript{2}), 60.2 (CH), 108.2 (C), 110.7 (CH), 118.1 (CH), 119.4 (CH), 121.3 (CH), 127.5 (C), 135.1 (C), 136.0 (C); MS (EI) m/z 226 [M\textsuperscript{+}, 72.3%] (Found: M\textsuperscript{+}, 226.14700. C\textsubscript{15}H\textsubscript{18}N\textsubscript{2} requires 226.14700).

Experimental 177
3.7 Total Synthesis of Both Enantiomers of Deplancheine

1,1-Dimethylethyl(12bR)-3-[(E)ethylidene]-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (96)

To a stirred solution of diisopropylamine (1.3 ml, 8.8 mmol) in anhydrous tetrahydrofuran (10.0 ml) was added n-butyllithium (2.5 M solution in hexanes) (3.5 ml, 8.8 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred for 15 minutes at 0 °C and then cooled to -78 °C whereupon a solution of 1,1-dimethylethyl(12bR)-4-oxo-1,2,3,4,6,7,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (82) (1.0 g, 2.9 mmol) in anhydrous tetrahydrofuran (15.0 ml) was added via cannula. The resulting mixture was stirred for a further 30 minutes at -78 °C after which time acetaldehyde (1.6 ml, 29.0 mmol) was added dropwise by syringe. The reaction was allowed to warm to room temperature overnight and then quenched by the addition of saturated aqueous ammonium chloride solution (30.0 ml) and extracted with ethyl acetate (2 × 50 ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to yield a yellow oil. The crude oil was dissolved in anhydrous dichloromethane (15.0 ml) under a nitrogen atmosphere. Triethylamine (1.2 ml, 8.7 mmol) was added and the mixture cooled to -40 °C before adding methane sulfonyl chloride (0.34 ml, 4.4 mmol). After 20 minutes stirring at -40 °C the reaction was allowed to warm to room temperature and stirred for an additional 3 hours. After this time the solvent was removed and the mesylate dissolved in anhydrous tetrahydrofuran (35.0 ml) to which 1,5-diazabicyclo[4.3.0]non-5-ene (1.1 ml, 8.7 mmol) was added and stirred at room temperature for 16 hours. The solvent was removed and the residue re-dissolved in dichloromethane (80 ml) which was washed with saturated aqueous ammonium chloride solution (60 ml). The organic fraction was dried over anhydrous magnesium sulphate and evaporated to dryness to give the crude product. Crude 250 MHz $^1$H NMR revealed formation of the product as a single trans geometrical isomer which
was purified by flash column chromatography over silica gel using 5:1 hexane:ethyl acetate as eluent (0.70 g, 65%).

**Trans isomer (96)** isolated as a pale yellow oil; \([\alpha]_D = +140.4 \, (c = 2.0, \text{CH}_2\text{Cl}_2); \nu_{\text{max}}(\text{thin film, DCM})/\text{cm}^{-1} 1734 (\text{N}=\text{O}(\text{O})'\text{Bu}) 1591 (\text{C} = \text{C}); \delta_\text{H}(400 \, \text{MHz; CDCl}_3) 1.47-1.52 (1H, m, C=CHCH(H)), 1.70 (9H, s, OC(CH_3)_3), 1.78 (3H, dd, J 8, 4, C=CHCH_3), 2.40-2.49 (1H, m, C=CHCH_2CH(H)), 2.58-2.64 (1H, m, C=CHCH(H)), 2.71-2.72 (1H, m, C=CHCH_2CH(H)), 2.73-2.76 (2H, m, CH_2CH_2N), 2.84-2.90 (1H, m, CH(H)N), 5.13-5.23 (1H, m, CH(H)N), 5.13-5.23 (1H, m, C=CHCH), 7.00-7.05 (1H, m, C=CHCH_3), 7.23-7.32 (2H, m, ArH), 7.43-7.46 (1H, m, ArH), 8.06-8.08 (1H, m, ArH); \delta_\text{C}(100 \, \text{MHz; CDCl}_3) 13.7 (\text{CH}_3), 21.5 (\text{CH}_2), 23.4 (\text{CH}_2), 28.2 (3 \times \text{CH}_3), 30.3 (\text{CH}_2), 39.1 (\text{CH}_2), 55.1 (\text{CH}), 84.2 (\text{C}), 115.6 (\text{CH}), 118.2 (\text{C}), 118.3 (\text{CH}), 123.0 (\text{CH}), 124.5 (\text{CH}), 128.6 (\text{C}), 129.3 (\text{C}), 134.2 (\text{CH}), 135.0 (\text{C}), 136.7 (\text{C}), 150.2 (\text{NC}(\text{O})'\text{Bu}), 164.9 (\text{NC}=\text{O}); \text{MS} (\text{EI}) m/z 366 [M^+] 8.9\% (Found: M^+, 366.19484. \text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3 \text{requires 366.19434}).

When the DBN elimination was carried out in a 1:1 mixture of tetrahydrofuran and dichloromethane a 4.7:1 mixture of **trans:cis** geometrical isomers was obtained; these were separated by column chromatography over silica gel using 5:1 hexane:ethyl acetate as eluent.

**Cis isomer** isolated as a yellow oil; \([\alpha]_D = +218.4 \, (c = 4.0, \text{CH}_2\text{Cl}_2); \nu_{\text{max}}(\text{thin film, DCM})/\text{cm}^{-1} 1731 (\text{N}=\text{O}(\text{O})'\text{Bu}) 1660 (\text{C} = \text{C}); \delta_\text{H}(400 \, \text{MHz; CDCl}_3) 1.22-1.533 (2H, m, C=CHCH_2), 1.69 (9H, s, OC(CH_3)_3), 2.15-2.18 (3H, m, C=CHCH_3), 2.47-2.52 (1H, m, C=CHCH_2CH(H)), 2.57-2.62 (1H, m, C=CHCH_2CH(H)), 2.73-2.78 (2H, m, CH_2CH_2N), 2.80-2.88 (1H, m, CH(H)N), 5.06-5.18 (1H, m, CH(H)N), 5.06-5.18 (1H, m, C=CHCH), 5.92-5.97 (1H, m, C=CHCH_3), 7.23-7.32 (2H, m, ArH), 7.44-7.47 (1H, m, ArH), 8.04-8.06 (1H, m, ArH); \delta_\text{C}(100 \, \text{MHz; CDCl}_3) 15.8 (\text{CH}_3), 21.6 (\text{CH}_2), 28.2 (3 \times \text{CH}_3), 30.3 (\text{CH}_2), 30.6 (\text{CH}_2), 38.8 (\text{CH}_2), 55.7 (\text{CH}), 84.2 (\text{C}), 115.5 (\text{CH}), 118.3 (\text{CH}), 118.4 (\text{C}), 123.0 (\text{CH}), 124.5 (\text{CH}), 128.7 (\text{C}), 128.7 (\text{C}), 135.4 (\text{CH}), 136.8 (\text{C}), 136.8 (\text{CH}), 150.2 (\text{NC}(\text{O})'\text{Bu}), 165.4 (\text{NC}=\text{O}); \text{MS} (\text{EI}) m/z 366 [M^+] 13.1\% (Found: M^+, 366.19395. \text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3 \text{requires 366.19434}).
1,1-dimethylethyl(12bR)-3-[(E)ethylidene]-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (96) (0.7 g, 1.91 mmol) was dissolved in anhydrous tetrahydrofuran (8.0 ml) under a nitrogen atmosphere. A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (19.1 ml, 19.1 mmol) was then added and the mixture was heated under reflux for 9 hours. After this time the mixture was cooled to room temperature and water (30.0 ml) was added. The mixture was extracted with ethyl acetate (2 × 50.0 ml) and the organic fractions were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel using 3:1 hexane:ethyl acetate as eluent to give the target compound as a yellow solid (0.32 g, 63%), a portion of which was recrystallised from diethyl ether to give a yellow crystalline solid; Mp 198-202 °C; [α]D = +77.2 (c = 1.0, CH2Cl2); νmax (thin film, DCM)/cm⁻¹ 3238 (NH), 1746 (NC=O); δH (400 MHz; CDCl3) 1.72-1.82 (1H, m, C=CHCH(H)), 1.77 (3H, dd, J 8, 4, C=CHCH3), 2.31-2.41 (1H, m, C=CHCH2CH(H)), 2.50-2.58 (1H, m, C=CHCH(H)), 2.77-2.97 (4H, m, C=CHCH2CH(H) + CH2CH3N + CH(H)N), 4.81-4.84 (1H, m, C=CH), 5.18-5.25 (1H, m, CH(H)N), 7.00-7.06 (1H, m, C=CH3), 7.09-7.19 (2H, m, ArH), 7.31-7.34 (1H, m, ArH), 7.49-7.51 (1H, m, ArH) 8.57 (1H, br, s, NH); δC (100 MHz; CDCl3) 13.7 (CH3), 21.1 (CH2), 22.7 (CH2), 28.9 (CH2), 40.6 (CH2), 54.0 (CH), 109.4 (C), 111.0 (CH), 118.3 (C), 119.6 (CH), 122.0 (CH), 126.8 (C), 129.2 (C), 133.4 (C), 134.1 (CH), 136.4 (C), 164.7 (NC=O); MS (EI) m/z 266 [M⁺, 100%] (Found: M⁺, 266.14191. C17H18N2O requires 266.14191).
A slurry of (12bR)-3-[(E)ethylidene]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (97) (0.32 g, 1.2 mmol) and trimethyloxonium tetrafluoroborate (0.48 g, 3.3 mmol) in anhydrous dichloromethane (40.0 ml) containing 2,6-di-tert-butylpyridine (0.80 ml, 3.5 mmol) was stirred at room temperature under nitrogen for 21 hours. After this time the reaction was cooled to 0 °C and anhydrous methanol (16.0 ml) was added. After 15 minutes sodium borohydride (0.48 g, 12.0 mmol) was added carefully and the mixture stirred at 0 °C for a further 30 minutes. The reaction was warmed to room temperature and saturated aqueous sodium bicarbonate solution (40.0 ml) and ethyl acetate (40.0 ml) were added. The layers were separated and the aqueous layer extracted with ethyl acetate (2 × 30.0 ml). The combined organic fractions were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to give the crude product which was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 98:2 ethyl acetate:triethylamine. The target compound was isolated as a yellow solid (0.23 g, 77 %), a portion of which was recrystallised from dichloromethane to yield yellow needles; Mp 139.5-140.5 °C (lit.69 Mp 140 °C); [α]D = +52.0 (c = 1.0, CHCl3) (lit.69 [α]D = 56 ± 2 (c = 1.0, CHCl3)); νmax (thin film, DCM)/cm⁻¹ 3455 (NH); 51(400 MHz; CDCl3) 1.52-1.60 (1H, m, C=CCHCH(H)), 1.63 (3H, d, J 8, C=CHCH3), 1.95-2.02 (1H, m, C=CCHCH2CH(H)), 2.15-2.20 (1H, m, C=CCHCH(H)), 2.61-2.75 (2H, m, CH(H)CH2N + NCH(H)C=CHCH3), 2.80-2.84 (1H, m, C=CCHCH2CH(H)), 2.98-3.11 (3H, m, CH(H)CH2N + NCH(H)C=CHCH3 + CH(H)N), 3.32-3.35 (1H, m, CH(H)N), 3.38-3.41 (1H, m, C=CHCH3), 5.43 (1H, q, J 8, C=CHCH3), 7.06-7.15 (2H, m, ArH), 7.30-7.33 (1H, m, ArH), 7.46-7.48 (1H, m, ArH), 7.76 (1H, br, s, NH); δC(100 MHz; CDCl3) 12.7 (CH3), 21.6 (CH2), 25.9 (CH2), 30.3 (CH2), 52.9 (CH2), 60.2 (CH), 63.5 (CH2), 108.4 (C), 110.7 (CH), 118.2 (CH), 119.4 (CH), 119.4 (CH), 119.4 (CH),
121.3 (CH), 127.4 (C), 134.0 (C), 134.6 (C), 136.0 (C); MS (EI) m/z 252 [M⁺, 98.6%]
(Found: M⁺, 252.16261. C₁₇H₂₀N₂ requires 252.16265).
1,1-Dimethylethyl(12bS)-3-[(E)ethylidene]-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (98)

To a stirred solution of diisopropylamine (1.1 ml, 7.9 mmol) in anhydrous tetrahydrofuran (10.0 ml) was added n-butyllithium (2.5 M solution in hexanes) (3.3 ml, 7.9 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred for 15 minutes at 0 °C and then cooled to -78 °C whereupon a solution of 1,1-dimethylethyl(12bS)-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (89) (0.9 g, 2.7 mmol) in anhydrous tetrahydrofuran (15.0 ml) was added via cannula. The resulting mixture was stirred for a further 30 minutes at -78 °C after which time acetaldehyde (1.5 ml, 27.0 mmol) was added dropwise by syringe. The reaction was allowed to warm to room temperature overnight and then quenched by the addition of saturated aqueous ammonium chloride solution (30.0 ml) and extracted with ethyl acetate (2 × 50 ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to yield a yellow oil. The crude oil was dissolved in anhydrous dichloromethane (15.0 ml) under a nitrogen atmosphere. Triethylamine (1.1 ml, 7.9 mmol) was added and the mixture cooled to -40 °C before adding methane sulfonyl chloride (0.31 ml, 4.0 mmol). After 20 minutes stirring at -40 °C the reaction was allowed to warm to room temperature and stirred for an additional 3 hours. After this time the solvent was removed and the mesylate dissolved in anhydrous tetrahydrofuran (35.0 ml) to which 1,5-diazabicyclo[4.3.0]non-5-ene (1.0 ml, 7.9 mmol) was added and stirred at room temperature for 16 hours. The solvent was removed and the residue re-dissolved in dichloromethane (80 ml) which was washed with saturated aqueous ammonium chloride solution (60 ml). The organic fraction was dried over anhydrous magnesium sulphate and evaporated to dryness to give the crude product. Crude 250 MHz ¹H NMR revealed formation of the product as a single trans geometrical isomer which was purified by flash column chromatography over silica gel using 5:1 hexane:ethyl acetate as eluent (0.69 g, 71%).
**Trans isomer (98)** isolated as a pale yellow oil; \([\alpha]_D = -181.9 \ (c = 3.0, \text{CH}_2\text{Cl}_2); v_{\text{max}}(\text{thin film, DCM})/\text{cm}^{-1} \ 1734 \ (\text{NC}=\text{O}(\text{O}^\text{Bu})) \ 1582 \ (\text{C}=\text{C}); \ \delta_\text{H}(400 \ \text{MHz}; \ \text{CDCl}_3) \ 1.42-1.53 \ (1\text{H, m, C}=\text{CCHCH}(\text{H})), \ 1.69 \ (9\text{H, s, OC(CH}_3)_3), \ 1.77 \ (3\text{H, d, } J \ 8, \ \text{C}=\text{CCH}_3), \ 2.39-2.47 \ (1\text{H, m, C}=\text{CCHCH}_2\text{CH}(\text{H})), \ 2.59-2.63 \ (1\text{H, m, C}=\text{CCHCH}_2\text{CH}(\text{H})), \ 2.71-2.72 \ (1\text{H, m, C}=\text{CCHCH}_2\text{CH}(\text{H})), \ 2.72-2.74 \ (2\text{H, m, CH}_2\text{CH}_2\text{N}), \ 2.82-2.89 \ (1\text{H, m, CH}(\text{H})\text{N}), \ 5.13-5.27 \ (1\text{H, m, CH}(\text{H})\text{N}), \ 5.13-5.27 \ (1\text{H, m, C}=\text{CCH}), \ 6.98-7.03 \ (1\text{H, m, C}=\text{CHCH}_3), \ 7.21-7.31 \ (2\text{H, m, ArH}), \ 7.42 \ (1\text{H, d, } J \ 8, \ \text{ArH}), \ 8.08 \ (1\text{H, d, } J \ 8, \ \text{ArH}); \ \delta_\text{C}(100 \ \text{MHz}; \ \text{CDCl}_3) \ 13.6 \ (\text{CH}_3), \ 21.5 \ (\text{CH}_2), \ 23.3 \ (\text{CH}_2), \ 28.2 \ (3\times\text{CH}_3), \ 30.3 \ (\text{CH}_2), \ 39.0 \ (\text{CH}_2), \ 55.1 \ (\text{CH}), \ 84.2 \ (\text{C}), \ 115.6 \ (\text{CH}), \ 118.1 \ (\text{C}), \ 118.2 \ (\text{CH}), \ 123.0 \ (\text{CH}), \ 124.5 \ (\text{CH}), \ 128.6 \ (\text{C}), \ 129.4 \ (\text{C}), \ 134.0 \ (\text{CH}), \ 135.0 \ (\text{C}), \ 136.7 \ (\text{C}), \ 150.0 \ (\text{NC}(\text{O})\text{O}^\text{Bu}), \ 164.7 \ (\text{NC}=\text{O}); \ \text{MS (EI) } m/z \ 366 \ [\text{M}^+, \ 14%] \ (\text{Found: M}^+, \ 366.19484. \ \text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3 \text{requires 366.19434}).
(12bS)-3-[(E)Ethylidene]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (99)

1,1-dimethylethyl(12bS)-3-[(E)ethylidene]-4-oxo-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-12-carboxylate (98) (0.69 g, 1.9 mmol) was dissolved in anhydrous tetrahydrofuran (5.0 ml) under a nitrogen atmosphere. A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (19.0 ml, 19.0 mmol) was then added and the mixture was heated under reflux for 9 hours. After this time the mixture was cooled to room temperature and water (30.0 ml) was added. The mixture was extracted with ethyl acetate (2 x 50.0 ml) and the organic fractions were dried over anhydrous magnesium sulphate and the solvent removed on the rotary evaporator. The crude product was adsorbed onto silica gel and purified by flash column chromatography over silica gel using 3:1 hexane:ethyl acetate as eluent to give the target compound as a yellow solid (0.29 g, 58%), a portion of which was recrystallised from diethyl ether to give a yellow solid; Mp 195-197 °C; [α]D = -43.6 (c = 1.0, CH2Cl2); νmax (thin film, CH2Cl2)/cm⁻¹ 3466 (NH), 1740 (NC=O); δH (400 MHz; CDCl3) 1.69-1.81 (1H, m, C=CCHCH(H)), 1.75 (3H, dd, J 8, 4, C=CHCH3), 2.29-2.39 (1H, m, C=CCH2CH(H)), 2.54-2.62 (1H, m, C=CCHCH(H)), 2.76-2.97 (4H, m, C=CCHCH2CH(H) + CH2CH2N + CH(H)N), 4.79-4.83 (1H, m, C=CCH), 5.20-5.24 (1H, m, CH(H)N), 7.00-7.06 (1H, m, C=CHCH3), 7.08-7.18 (2H, m, ArH), 7.31-7.33 (1H, m, ArH), 7.48-7.50 (1H, m, ArH) 8.83 (1H, br, s, NH); δC(100 MHz; CDCl3) 13.7 (CH3), 21.1 (CH2), 22.7 (CH2), 28.9 (CH2), 40.7 (CH2), 54.0 (CH), 109.3 (C), 111.1 (CH), 118.3 (C), 119.6 (CH), 121.9 (CH), 126.8 (C), 129.3 (C), 133.4 (C), 134.1 (CH), 136.5 (C), 164.8 (NC=O); MS (EI) m/z 266 [M⁺, 100%] (Found: M⁺, 266.14191. C17H18N2O requires 266.14191).
A slurry of (12bS)-3-[(E)ethylidene]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carboline-4-one (99) (0.15 g, 0.56 mmol) and trimethyloxonium tetrafluoroborate (0.23 g, 1.5 mmol) in anhydrous dichloromethane (19.0 ml) containing 2,6-di-tert-butylpyridine (0.36 ml, 1.6 mmol) was stirred at room temperature under nitrogen for 21 hours. After this time the reaction was cooled to 0 °C and anhydrous methanol (8.0 ml) was added. After 15 minutes sodium borohydride (0.22 g, 5.8 mmol) was added carefully and the mixture stirred at 0 °C for a further 30 minutes. The reaction was warmed to room temperature and saturated aqueous sodium bicarbonate solution (20.0 ml) and ethyl acetate (20.0 ml) were added. The layers were separated and the aqueous layer extracted with ethyl acetate (2 × 20.0 ml). The combined organic fractions were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to give the crude product which was adsorbed onto silica gel and purified by flash column chromatography over silica gel eluting with 98:2 ethyl acetate:triethylamine. The target compound was isolated as a yellow solid (0.09 g, 64%), a portion of which was recrystallised from dichloromethane to yield a yellow crystalline solid; Mp 136-138 °C (lit.73 Mp 139-140 °C); [α]D = -52.4 (c = 1.0, CHCl3) (lit.73 [α]D = -56 ± 2 (c = 1.0, CHCl3)); νmax(thin film, DCM)/cm⁻¹: 3455 (NH); δH(400 MHz; CDCl3) 1.50-1.60 (1H, m, C=CHCH(H)), 1.62 (3H, d, J 8, C=CHCH3), 1.94-2.01 (1H, m, C=CHCH2CH(H)), 2.13-2.18 (1H, m, C=CHCH2CH(H)), 2.61-2.74 (2H, m, CH(H)CH2N + NCH(H)C=CHCH3), 2.79-2.82 (1H, m, C=CHCH2CH(H)), 2.99-3.10 (3H, m, CH(H)CH2N + NCH(H)C=CHCH3 + CH(H)N), 3.32-3.35 (1H, m, CH(H)N), 3.37-3.40 (1H, m, C=CHCH3), 5.43 (1H, q, J 8, C=CHCH3), 7.06-7.15 (2H, m, ArH), 7.29-7.31 (1H, m, ArH), 7.46-7.48 (1H, m, ArH), 7.77 (1H, br, s, NH); δC(100 MHz; CDCl3) 12.7 (CH3), 21.6 (CH2), 25.9 (CH2), 30.3 (CH2), 52.9 (CH2), 60.2 (CH), 63.5 (CH2), 108.3 (C), 110.7 (CH), 118.2 (CH),
119.4 (CH), 119.4 (CH), 121.3 (CH), 127.4 (C), 134.0 (C), 134.7 (C), 136.0 (C); MS (EI) m/z 252 [M⁺, 100%] (Found: M⁺, 252.16261. \( \text{C}_{17}\text{H}_{20}\text{N}_2 \) requires 252.16265).
(12bS)-3-[(E)ethylidene]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carboline S-(91)73

(12bS)-3-[(E)ethylidene]-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carboline-4-one (99) (0.15 g, 0.56 mmol) was dissolved in anhydrous ethylene glycol dimethyl ether (12.0 ml) and the resulting solution was cooled to 0 °C. A 1.0 M solution of diisobutylaluminium hydride (4.1 ml, 4.1 mmol) was added dropwise at 0 °C before allowing the mixture to warm to room temperature and stirring for another 1 hour. After 1 hour stirring at room temperature the reaction was quenched with methanol (12.0 ml) and water (1.0 ml): Ethyl acetate (40.0 ml) and aqueous sodium potassium tartrate solution (40.0 ml) were added and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 20.0 ml). The combined organic fractions were dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to give the crude product which was adsorbed onto silica and purified by flash column chromatography over silica eluting with 98:2 ethyl acetate:triethylamine. The target compound was isolated as a yellow solid (0.09 g, 64%), a portion of which was recrystallised from dichloromethane to yield a yellow crystalline solid which was identical in all respects to the compound prepared by the alternative route except for [α]D = -58.4 (c = 1.0, CHCl3).

References 189
33. Ferreira R., *Brazil Med.*, 1949, 131

References
50. Khera J.S., 1st Year PhD report Loughborough University, 2003
76. Beilsteins Handbuch der Organischen Chemie, 22(5),12

References
4.1 X-ray Data

4.1.1 \((5S,11bS)-5\text{-}(\text{hydroxymethyl})-11b\text{-methyl}-2,3,5,6,11,11b\text{-hexahydro-1H-pyrrolo}[2,1\text{-}a]b\text{-carbolin-3-one (14)} \)

![Chemical Structure Diagram]

Table 1. Crystal data and structure refinement.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>(14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>(C_{16.25}H_{18.50}Cl_{0.50}N_2O_2)</td>
</tr>
<tr>
<td>Formula weight</td>
<td>291.56</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoK(\alpha), 0.71073 \text{ Å}</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>tetragonal, I4</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>(a = 19.5077(16) \text{ Å} \quad \alpha = 90^\circ)</td>
</tr>
<tr>
<td></td>
<td>(b = 19.5077(16) \text{ Å} \quad \beta = 90^\circ)</td>
</tr>
<tr>
<td></td>
<td>(c = 8.2691(10) \text{ Å} \quad \gamma = 90^\circ)</td>
</tr>
</tbody>
</table>
Cell volume
Z
Calculated density
Absorption coefficient $\mu$
$F(000)$
Crystal colour and size
Reflections for cell refinement
Data collection method

$\theta$ range for data collection
Index ranges
Completeness to $\theta = 26.00^\circ$
Intensity decay
Reflections collected
Independent reflections
Reflections with $F^2 > 2\sigma$
Absorption correction
Min. and max. transmission
Structure solution
Refinement method
Weighting parameters $a$, $b$
Data / restraints / parameters
Final $R$ indices [$F^2 > 2\sigma$]
$R$ indices (all data)
Goodness-of-fit on $F^2$
Absolute structure parameter
Largest and mean shift/su
Largest diff. peak and hole

Appendix
Table 2. Hydrogen bonds [Å and °].

<table>
<thead>
<tr>
<th>D–H...A</th>
<th>d(D–H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(2)–H(2)…O(2*)</td>
<td>0.88(3)</td>
<td>1.92(3)</td>
<td>2.788(3)</td>
<td>168(2)</td>
</tr>
<tr>
<td>O(2)–H(2A)…O(1)</td>
<td>0.90(3)</td>
<td>1.76(3)</td>
<td>2.597(2)</td>
<td>154(3)</td>
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Symmetry operations for equivalent atoms
* x,y,z−1
4.1.2 (3S,8aS)-3-(1H-Indol-3-ylmethyl)perhydropyrido[2,1-b][1,3]oxazol-5-one (46a)

Table 1. Crystal data and structure refinement.

<table>
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<th>Identification code</th>
<th>(46a)</th>
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<tbody>
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<td>Chemical formula</td>
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</tr>
<tr>
<td>Formula weight</td>
<td>270.32</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoK(\alpha), 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, (\text{I2})</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>(a = 13.1781(14) \text{ Å}) (\alpha = 90^\circ) (\beta = 98.163(2)^\circ)</td>
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<tr>
<td></td>
<td>(b = 6.5138(7) \text{ Å})</td>
</tr>
<tr>
<td></td>
<td>(c = 16.3036(18) \text{ Å}) (\gamma = 90^\circ)</td>
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<tr>
<td>Cell volume</td>
<td>1385.3(3) \text{ Å}^3</td>
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<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1.296 g/cm(^3)</td>
</tr>
<tr>
<td>Absorption coefficient (\mu)</td>
<td>0.086 mm(^{-1})</td>
</tr>
</tbody>
</table>
F(000) 576
Crystal colour and size colourless, 2.40 × 0.26 × 0.18 mm³
Reflections for cell refinement 3141 (θ range 2.52 to 28.92°)
Data collection method Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames
θ range for data collection 1.86 to 28.92°
Index ranges h –17 to 10, k –8 to 8, l –22 to 20
Completeness to θ = 26.00° 99.9 %
Intensity decay 0%
Reflections collected 5817
Independent reflections 3100 (Rint = 0.0389)
Reflections with F² > 2σ 2937
Absorption correction semi-empirical from equivalents
Min. and max. transmission 0.819 and 0.985
Structure solution direct methods
Refinement method Full-matrix least-squares on F²
Weighting parameters a, b 0.1396, 0.2705
Data / restraints / parameters 3100 / 1 / 184
Final R indices [F² > 2σ] R1 = 0.0716, wR2 = 0.1874
R indices (all data) R1 = 0.0733, wR2 = 0.1900
Goodness-of-fit on F² 1.113
Absolute structure parameter 1.3(17)
Largest and mean shift/su 0.001 and 0.000
Largest diff. peak and hole 0.189 and –0.298 e Å⁻³

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4.1.3 (6S,12bR)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (47)

Table 1. Crystal data and structure refinement.

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<td>Formula weight</td>
<td>270.32</td>
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<tr>
<td>Temperature</td>
<td>150(2) K</td>
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<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
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<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2₁</td>
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<td>Unit cell parameters</td>
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<td>698.45(10) Å³</td>
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<td>Z</td>
<td>2</td>
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Appendix
Calculated density
Absorption coefficient $\mu$
$F(000)$
Crystal colour and size
Reflections for cell refinement
Data collection method

$\theta$ range for data collection
Index ranges
Completeness to $\theta = 26.00^\circ$
Intensity decay
Reflections collected
Independent reflections
Reflections with $F^2 > 2\sigma$
Absorption correction
Min. and max. transmission
Structure solution
Refinement method
Weighting parameters $a$, $b$
Data / restraints / parameters
Final $R$ indices [$F^2 > 2\sigma$]
$R$ indices (all data)
Goodness-of-fit on $F^2$
Absolute structure parameter
Largest and mean shift/su
Largest diff. peak and hole

1.285 g/cm$^3$
0.086 mm$^{-1}$
288
colourless, $0.51 \times 0.30 \times 0.18$ mm$^3$
4666 ($\theta$ range 2.20 to 28.74$^\circ$)
Bruker SMART 1000 CCD diffractometer $\omega$ rotation with narrow frames
2.17 to 28.92$^\circ$
h $-10$ to $10$, $k$ $-12$ to $12$, $l$ $-13$ to $13$
99.9 %
0 %
6217
3182 ($R_{int} = 0.0126$)
3027
semi-empirical from equivalents
0.958 and 0.985
direct methods
Full-matrix least-squares on $F^2$
0.0490, 0.0836
3182 / 1 / 187
$R1 = 0.0311$, $wR2 = 0.0805$
$R1 = 0.0328$, $wR2 = 0.0821$
1.049
0.2(8)
0.000 and 0.000
0.193 and $-0.177$ e Å$^{-3}$
Table 2. Hydrogen bonds [Å and °].

<table>
<thead>
<tr>
<th>D–H…A</th>
<th>d(D–H)</th>
<th>d(H…A)</th>
<th>d(D…A)</th>
<th>(DHA)</th>
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<tbody>
<tr>
<td>N(12)–H(12)…O(15')</td>
<td>0.912(17)</td>
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<td>2.7765(14)</td>
<td>171.0(15)</td>
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<td>O(15)–H(15)…O(13'')</td>
<td>0.82(2)</td>
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Symmetry operations for equivalent atoms: ' −x,y+1/2,−z+1  " −x,y−1/2,−z
4.1.4 (6R,12bS)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carboline-4-one (50)

Table 1. Crystal data and structure refinement.

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<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
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<td>Crystal system, space group</td>
<td>monoclinic, p2₁</td>
</tr>
<tr>
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<td></td>
<td>( c = 9.9759(5) ) Å ( \gamma = 90^\circ )</td>
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<tr>
<td>Cell volume</td>
<td>693.19(6) Å³</td>
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<td>Z</td>
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</table>
Calculated density 1.295 g/cm$^3$
Absorption coefficient $\mu$ 0.086 mm$^{-1}$
F(000) 288
Crystal colour and size colourless, $0.14 \times 0.10 \times 0.08$ mm$^3$
Reflections for cell refinement 17065 ($\theta$ range 2.91 to 27.48$^\circ$)
Data collection method Enraf Nonius KappaCCD area detector
phi and omega scans to fill Ewald sphere
$\theta$ range for data collection 3.10 to 27.56$^\circ$
Index ranges $h -10$ to $10$, $k -11$ to $11$, $l -11$ to $12$
Completeness to $\theta = 26.50^\circ$ 99.7 %
Intensity decay 0%
Reflections collected 11109
Independent reflections 3159 ($R_{int} = 0.0632$)
Reflections with $F^2 > 2\sigma$ 2751
Absorption correction semi-empirical from equivalents
Min. and max. transmission 0.9880 and 0.9931
Structure solution direct methods
Refinement method Full-matrix least-squares on $F^2$
Weighting parameters a, b 0.0481, 0.1693
Data / restraints / parameters 3159 / 1 / 188
Final R indices [$F^2 > 2\sigma$] $R1 = 0.0435$, $wR2 = 0.0992$
R indices (all data) $R1 = 0.0545$, $wR2 = 0.1057$
Goodness-of-fit on $F^2$ 1.033
Absolute structure parameter $-0.7(12)$
Extinction coefficient 0.058(8)
Largest and mean shift/su 0.000 and 0.000
Largest diff. peak and hole 0.216 and $-0.169$ e Å$^{-3}$
Table 2. Hydrogen bonds [Å and °].

<table>
<thead>
<tr>
<th>D–H...A</th>
<th>d(D–H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(12)–H(12)...O(15A)</td>
<td>0.95(3)</td>
<td>1.84(3)</td>
<td>2.775(2)</td>
<td>170(2)</td>
</tr>
<tr>
<td>O(15)–H(15)...O(13B)</td>
<td>0.86(3)</td>
<td>1.78(3)</td>
<td>2.6312(19)</td>
<td>169(3)</td>
</tr>
</tbody>
</table>

Symmetry operations for equivalent atoms:
A  \(-x+1,y-1/2,-z+1\)  B  \(-x+1,y+1/2,-z+2\)
4.1.5 (6S,12bS)-6-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (57)

Table 1. Crystal data and structure refinement.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>(57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{16}H_{18}N_{2}O_{2}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>270.32</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>orthorhombic, P2_{1}2_{1}2_{1}</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>a = 6.8864(5) Å, α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 13.5051(10) Å, β = 90°</td>
</tr>
<tr>
<td></td>
<td>c = 14.4236(10) Å, γ = 90°</td>
</tr>
<tr>
<td>Cell volume</td>
<td>1341.42(17) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1.339 g/cm³</td>
</tr>
<tr>
<td>Property</td>
<td>Value</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Absorption coefficient $\mu$</td>
<td>0.089 mm$^{-1}$</td>
</tr>
<tr>
<td>$F(000)$</td>
<td>576</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>Colourless, 0.69 x 0.32 x 0.13 mm$^3$</td>
</tr>
<tr>
<td>Reflections for cell refinement</td>
<td>5922 ($\theta$ range 2.82 to 28.16$^\circ$)</td>
</tr>
<tr>
<td>Data collection method</td>
<td>Bruker SMART 1000 CCD diffractometer $\omega$ rotation with narrow frames</td>
</tr>
<tr>
<td>$\Theta$ range for data collection</td>
<td>2.07 to 28.80$^\circ$</td>
</tr>
<tr>
<td>Index ranges</td>
<td>h = -9 to 9, k = -17 to 17, l = -18 to 18</td>
</tr>
<tr>
<td>Completeness to $\theta$ = 26.00$^\circ$</td>
<td>100.0 %</td>
</tr>
<tr>
<td>Intensity decay</td>
<td>0%</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>11490</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3153 ($R_{int} = 0.0205$)</td>
</tr>
<tr>
<td>Reflections with $F^2 &gt; 2\sigma$</td>
<td>2899</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>semi-empirical from equivalents</td>
</tr>
<tr>
<td>Min. and max. transmission</td>
<td>0.941 and 0.989</td>
</tr>
<tr>
<td>Structure solution</td>
<td>direct methods</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on $F^2$</td>
</tr>
<tr>
<td>Weighting parameters $a, b$</td>
<td>0.0525, 0.1126</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3153 / 0 / 187</td>
</tr>
<tr>
<td>Final $R$ indices [$F^2 &gt; 2\sigma$]</td>
<td>$R_1 = 0.0333$, $wR_2 = 0.0837$</td>
</tr>
<tr>
<td>$R$ indices (all data)</td>
<td>$R_1 = 0.0373$, $wR_2 = 0.0865$</td>
</tr>
<tr>
<td>Goodness-of-fit on $F^2$</td>
<td>1.049</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.7(10)</td>
</tr>
<tr>
<td>Largest and mean shift/su</td>
<td>0.000 and 0.000</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.199 and -0.179 e Å$^{-3}$</td>
</tr>
</tbody>
</table>
Table 2. Hydrogen bonds [Å and °].

<table>
<thead>
<tr>
<th>D–H...A</th>
<th>d(D–H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(12)–H(12)...O(15')</td>
<td>0.861(16)</td>
<td>1.932(16)</td>
<td>2.7819(15)</td>
<td>168.9(15)</td>
</tr>
<tr>
<td>O(15)–H(15)...O(13&quot;)</td>
<td>0.79(2)</td>
<td>1.86(2)</td>
<td>2.6534(14)</td>
<td>176.4(19)</td>
</tr>
</tbody>
</table>

Symmetry operations for equivalent atoms

' -x+1,y+1/2,-z+1/2     " x-1,y,z
4.1.6 (12bR)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-a]b-carbolin-4-one (72)

Table 1. Crystal data and structure refinement.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>(72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{15}H_{13}N_{2}O</td>
</tr>
<tr>
<td>Formula weight</td>
<td>240.30</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>orthorhombic, Pbca</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>a = 12.2720(9) Å, α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 13.2782(10) Å, β = 90°</td>
</tr>
<tr>
<td></td>
<td>c = 15.0736(11) Å, γ = 90°</td>
</tr>
<tr>
<td>Cell volume</td>
<td>2456.2(3) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1.300 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient μ</td>
<td>0.083 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>1024</td>
</tr>
<tr>
<td>Crystal colour and size</td>
<td>yellow, 0.65 × 0.30 × 0.16 mm³</td>
</tr>
</tbody>
</table>
Reflections for cell refinement

Data collection method

θ range for data collection

Index ranges

Completeness to θ = 26.00°

Intensity decay

Reflections collected

Independent reflections

Reflections with F² > 2σ

Absorption correction

Min. and max. transmission

Structure solution

Refinement method

Weighting parameters a, b

Data / restraints / parameters

Final R indices [F² > 2σ]

R indices (all data)

Goodness-of-fit on F²

Largest and mean shift/su

Largest diff. peak and hole

Table 2. Hydrogen bonds [Å and °].

D–H...A   d(D–H)   d(H...A)   d(D...A)   <(DHA)

N(12)–H(12)...O(13')  0.902(17)  1.901(17)  2.7797(16)  163.9(15)

Symmetry operations for equivalent atoms

' -x+1/2, y+1/2, z

Appendix
4.1.7 (12bS)-(−)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (84)

![Chemical structure image]

Table 1. Crystal data and structure refinement.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>(84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{15}H_{19}N_2O_{0.50}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>235.32</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, C2</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>$a = 19.0934(15)$ Å $\alpha = 90^\circ$ $\beta = 91.481(2)^\circ$ $\gamma = 90^\circ$</td>
</tr>
<tr>
<td>Cell volume</td>
<td>1286.60(17) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Calculated density</td>
<td>1.215 g/cm³</td>
</tr>
<tr>
<td>Absorption coefficient $\mu$</td>
<td>0.075 mm⁻¹</td>
</tr>
</tbody>
</table>
F(000) 508
Crystal colour and size yellow, 0.82 x 0.64 x 0.29 mm³
Reflections for cell refinement 4199 (θ range 2.86 to 28.76°)
Data collection method Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames

θ range for data collection 1.96 to 28.77°
Index ranges h -25 to 24, k -8 to 8, l -13 to 13
Completeness to θ = 26.00° 99.8 %
Intensity decay 0%
Reflections collected 5681
Independent reflections 1681 (Rint = 0.0150)
Reflections with F²>2σ 1591
Absorption correction semi-empirical from equivalents
Min. and max. transmission 0.941 and 0.979
Structure solution direct methods
Refinement method Full-matrix least-squares on F²
Weighting parameters a, b 0.0514, 0.2871
Data / restraints / parameters 1681 / 1 / 166
Final R indices [F²>2σ] R1 = 0.0305, wR2 = 0.0808
R indices (all data) R1 = 0.0323, wR2 = 0.0828
Goodness-of-fit on F² 1.038
Absolute structure parameter -10(10)
Largest and mean shift/su 0.000 and 0.000
Largest diff. peak and hole 0.170 and -0.178 e Å⁻³
Table 2. Hydrogen bonds for [Å and °].

<table>
<thead>
<tr>
<th>D–H...A</th>
<th>d(D–H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(13)–H(13)...N(5A)</td>
<td>0.88(2)</td>
<td>2.17(2)</td>
<td>3.0360(15)</td>
<td>165(2)</td>
</tr>
<tr>
<td>N(12)–H(12)...O(13)</td>
<td>0.88(2)</td>
<td>2.14(2)</td>
<td>3.0211(17)</td>
<td>172.9(19)</td>
</tr>
</tbody>
</table>

Symmetry operations for equivalent atoms
A  x,y+1,z
Table 1. Crystal data and structure refinement.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>R-(91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical formula</td>
<td>C_{17}H_{21}N_{2}O_{0.50}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>261.36</td>
</tr>
<tr>
<td>Temperature</td>
<td>150(2) K</td>
</tr>
<tr>
<td>Radiation, wavelength</td>
<td>MoKα, 0.71073 Å</td>
</tr>
<tr>
<td>Crystal system, space group</td>
<td>monoclinic, P2_{1}</td>
</tr>
<tr>
<td>Unit cell parameters</td>
<td>a = 12.7620(16) Å, α = 90°</td>
</tr>
</tbody>
</table>
Cell volume \(1498.5(3) \text{ Å}^3\)

\(Z\) 4

Calculated density 1.158 g/cm\(^3\)

Absorption coefficient \(\mu\) 0.070 mm\(^{-1}\)

\(F(000)\) 564

Crystal colour and size yellow, 0.58 \(\times\) 0.24 \(\times\) 0.19 mm\(^3\)

Reflections for cell refinement 2638 (\(\theta\) range 2.39 to 26.93°)

Data collection method Bruker SMART 1000 CCD diffractometer \(\omega\) rotation with narrow frames

\(\theta\) range for data collection 1.61 to 25.00°

Index ranges \(h\) -15 to 14, \(k\) -7 to 8, \(l\) -20 to 20

Completeness to \(\theta = 25.00\)° 99.4 %

Intensity decay 0%

Reflections collected 8486

Independent reflections 4933 (\(R_{int} = 0.0318\))

Reflections with \(F^2 > 2\sigma\) 3705

Absorption correction semi-empirical from equivalents

Min. and max. transmission 0.960 and 0.987

Structure solution direct methods

Refinement method Full-matrix least-squares on \(F^2\)

Weighting parameters \(a, b\) 0.0439, 0.1475

Data / restraints / parameters 4933 / 1 / 367

Final \(R\) indices \([F^2 > 2\sigma]\) \(R_1 = 0.0429, \, wR_2 = 0.0918\)

\(R\) indices (all data) \(R_1 = 0.0687, \, wR_2 = 0.1051\)

Goodness-of-fit on \(F^2\) 1.017

Absolute structure parameter 0.4(19)

Extinction coefficient 0.0041(11)

Largest and mean shift/su 0.000 and 0.000

Largest diff. peak and hole 0.148 and -0.143 e Å\(^{-3}\)
Table 2. Hydrogen bonds [Å and °].

<table>
<thead>
<tr>
<th>D–H...A</th>
<th>d(D–H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(12)–H(12)...O(15)</td>
<td>0.92(3)</td>
<td>1.85(3)</td>
<td>2.766(3)</td>
<td>176(3)</td>
</tr>
<tr>
<td>O(15)–H(15A)...N(20)</td>
<td>0.93(3)</td>
<td>1.98(3)</td>
<td>2.894(3)</td>
<td>169(3)</td>
</tr>
<tr>
<td>O(15)–H(15B)...N(5A)</td>
<td>0.86(3)</td>
<td>2.00(4)</td>
<td>2.845(3)</td>
<td>167(3)</td>
</tr>
</tbody>
</table>

Symmetry operations for equivalent atoms
A  x,y+1,z
Stereoselective synthesis of the indolizinoindole ring system

Steven M. Allin,* Christopher I. Thomas,* James E. Allard, Matthew Dunton,*
Mark R. J. Elsegood* and Mark Edgar*

*Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK
†OSI Pharmaceuticals, Walton Road, Oxford OX4 6LT, UK

Received 10 December 2002; revised 14 January 2003; accepted 20 January 2003

Abstract—We report a novel, facile and stereoselective approach to the indolizino[8,7-b]indole ring system from a readily available, non-racemic chiral template.© 2003 Elsevier Science Ltd. All rights reserved.

Indolizino[8,7-b]indoles of general structure 1 are of interest to the pharmaceutical industry having been used as intermediates in the preparation of diuretic compounds, and are also known to exhibit analgesic and anti-inflammatory activity in their own right. Other, more functionalised, templates such as 1 have been shown to act as β-turn mimics and display high binding affinity and selectivity for CCK receptors. The lactam homologue 3 is perhaps of greater significance in natural product chemistry, sharing the same heterocyclic skeleton with a plethora of highly bioactive indole alkaloids, including tacamine, geissoschizine, and ajmalicine.

Over recent years, we have reported a new approach to a range of non-racemic heterocycles involving stereoselective cyclisation onto N-acyliminium intermediates as the key ring-forming step. Based on our novel and stereoselective approach to both the isoindoloisoquinoline and pyrroloisoquinoline ring systems, we recognised that a suitably substituted bicyclic lactam could act as a precursor for a stereoselective approach to the indolizino[8,7-b]indole ring system.

Our approach to the synthesis of the required bicyclic lactam substrate 5 followed the general method previously used in our group. The β-amino alcohol derivative of (S)-tryptophan was reacted under Dean-Stark conditions with the appropriate keto-acid for 45 h (Scheme 1). Under these reaction conditions we were able to isolate the expected bicyclic lactam 5 in only 3% yield. The major product of the reaction, isolated in 35% yield, was found to be the target indolizino[8,7-b]indole derivative 6.

Examination of the crude reaction mixture by 250 MHz 1H NMR spectroscopy revealed the formation of 6 as a single diastereoisomer.

The relative stereochemistry of product 6 was determined by single crystal X-ray analysis (Fig. 1), and was found to be as expected based on our experience of cyclisation reactions involving similar N-acyliminium precursors. Effectively, retention of configuration at the methyl-bearing chiral centre is observed if one considers bicyclic lactam 5 to be an intermediate.

Interestingly, compound 6 was observed to form two crystallographically unique hydrogen bonds: one intramolecular N(2)-H(2A)—O(1) (N(2)···O(2A)=2.57(3) Å, O(2A)-H(2A)-O(1)=124°) and one intermolecular N(2)-H(2)—O(2A) (N(2)···O(2A)=2.78(3) Å, N(2)-H(2)—O(2A)=168°) forming chains along the crystallographic c-direction.
Scheme 1.

![Scheme 1](image)

Figure 1. Crystal structure of 6, omitting most H atoms and the solvent molecule of crystallisation. The intra- and inter-molecular H-bonds are highlighted and the numbering scheme is defined.

Of course, one could envisage an alternative mechanism to explain the formation of 6 that avoids the intermediacy of bicyclic lactam 5: a stereoselective Pictet-Spengler reaction in which condensation of the β-amino alcohol and keto-acid substrate results in formation of a tetrahydro-β-carboline derivative which then undergoes lactam formation to yield 6 in the final step. To date, no intermediates have been observed by us that would support this hypothesis with our substrates.

An alternative approach to the indolizino[3,7-b]indole ring system was also investigated through formation and subsequent borohydride reduction of the imide intermediate 7, accessed in 54% yield from the required β-amino alcohol and succinic anhydride. In this approach, summarised in Scheme 2, the intermediate ethoxy-lactam derivative 8 was not isolated since, under the reaction conditions, direct cyclisation via an N-acyliminium intermediate was observed to yield the target heterocycle 9 in 45% yield and as a 9:1 mixture of diastereoisomers. The major diastereoisomer was isolated by crystallisation and the relative stereochemistry of this product was determined to be as shown in Scheme 2 by NOE studies. Again, the relative stereochemistry observed on cyclisation of the attacked aromatic nucleus was as expected based on previous results from our group.

As noted above, access to the six-membered lactam homologue through application of this methodology would be highly attractive as it would allow access to a wide range of desirable indole targets. With this in mind we successfully prepared the bicyclic lactam substrate 10 in 55% overall yield. The relative stereochemistry of the major diastereoisomer, represented in Scheme 3, was determined by NOE studies. Based on our previous work in a related area, these substrate diastereoisomers were not separated, but were treated with TiCl₄ to promote the stereoselective cyclisation reaction (Scheme 3).

We were pleased to isolate the cyclised product, 11, in 54% yield and 1H NMR analysis of the crude reaction mixture revealed the formation of this product as a 2:2 mixture of diastereoisomers. A comparative NOE study was undertaken on the isolated diastereoisomers to confirm that the relative stereochemistry of the major diastereoisomer is as shown in Scheme 3.

To demonstrate the potential synthetic utility of this new methodology we followed a method previously used by us to remove the hydroxymethyl auxiliary group (Scheme 4). Oxidation of 6 to the corresponding aldehyde was achieved in 90% yield using IBX (2,3-dioxo-1,2-benzisoxazole) or DMAP. Subsequent desaturation gave a mixture of enamide 12 and target lactam 13. This product mixture was subjected to catalytic hydrogenation to convert the unwanted enamide through to lactam 13. Finally, lactam reduction generated the tertiary amine derivative 14 in 27% overall yield from the aldehyde.

In summary, we report a facile and highly stereoselective approach to a range of indole-containing heterocycles from readily available non-racemic substrates. Current work is focused on extending this methodology to specific indole alkaloid targets, and our progress will be reported in due course.

Acknowledgements

Loughborough University and OSI Pharmaceuticals (joint studentship to C.I.T.), EPSRC (Quota studentship to J.E.A.).
References

6. For example, see Martin, S. F.; Clark, C. W.; Corbett, J. W. Org. Chem. 1995, 60, 2326-3242.
8. Compound 8 was observed to begin to convert to 6 on standing in an NMR tube in CDCl3 solvent.
9. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 158533).
11. The absence of an NOE between the protons situated at positions 5 and 11b of product 9 is consistent with the proposed structure. As we were unable to isolate the minor diastereoisomer we were unable to carry out a comparative NOE study. This result is in agreement with related work from our group (Ref. 7b).
12. We were able to perform a set of comparative NOE studies on the separable diastereoisomers of product 10. In the case of the major diastereoisomer, 10, an NOE was observed between protons at positions 3 and 5. In the case of the minor diastereoisomer, no NOE was observed. Both results are in accord with previous results from our group detailing the preparation of 5,6-fused bicycle lactams (Ref. 11).
14. We were able to perform a set of comparative NOE studies on the separable diastereoisomers of product 11. In the case of the minor diastereoisomer an NOE was observed between protons at positions 6 and 12b. In the case of the major diastereoisomer, 11, no NOE was observed.
Highly stereoselective synthesis of the indolo[2,3-a]quinolizine ring system and application to indole natural product synthesis

Steven M. Allin,* Christopher I. Thomas,* James E. Allard,* Kevin Doyleb and Mark R. J. Elsegood*ab

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bOSI Pharmaceuticals, Wantling Road, Oxford OX4 6LT, UK

Received 15 June 2004; revised 12 July 2004; accepted 24 July 2004. Available online 13 August 2004

Abstract—We report a novel, facile and highly stereoselective approach to the indolo[2,3-a]quinolizine ring system from a readily available, non-racemic chiral template. We demonstrate the potential for application of this methodology to natural product synthesis through conversion of the template to a simple indole alkaloid with high enantiomeric purity.

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The indolo[2,3-a]quinolizine ring system 1 is of great interest and significance since this heterocyclic template is found within a plethora of highly bioactive indole alkaloids, including geissoschizine 2,1 vellosimine 3,2 and ajmalicine 4.3 The presence of the lactam carbonyl in templates such as 1 would allow for possible further functionalisation en route to the natural product targets. Recent approaches to the construction of this heterocyclic target system by other groups have included the diastereoselective vinylogous Mannich reaction, 4 the Bischler-Napieralski reaction, 5 Fischer indole synthesis and the asymmetric Pictet–Spengler reaction. 7

We have recently developed a new and general approach for the stereoselective synthesis of a range of non-racemic heterocycles that involves the cyclisation of pendant aromatic substituents onto N-acyliminium intermediates as the key ring-forming step. 6 Based on our novel approach to the indolizino[8,7-b]indole ring system, 6 we recognised that a suitably substituted bicyclic lactam could act as a precursor in a stereoselective approach to the indolo[2,3-a]quinolizine ring system.

Our approach to the synthesis of the required bicyclic lactam substrate 5 followed the general method previously used in our group. 6 The β-amino alcohol derivative of (S)-tryptophan was reacted under Dean–Stark conditions in toluene with an appropriate functionalised substrate for 48 h (Scheme 1). Under these reaction conditions, we were able to isolate the expected bicyclic lactam in 69% yield as a 5:1 mixture of separable diastereoisomers, 5a and 5b.

The relative stereochemistry of the major diastereoisomer 5a was determined by single crystal X-ray analysis (Fig. 1). 8 This indole-containing bicyclic lactam is a novel example of the fused 5,6-ring systemfavoured by Amat et al. 9 and the relative stereochemistry observed for the major isomer 5a is consistent with results obtained both by these researchers and in our own previous work in other areas. 9b
In a previous communication, we noted briefly that treatment of the initial mixture of diastereoisomers of substrate 5 with TiCl₄ gave the desired indolo[2,3-a]quinolizine target 6 in 54% yield, but with only a poor level of product diastereoselectivity (5:2). We have now discovered that simply treating the mixture of bicyclic lactam substrate diastereoisomers, 5a and 5b, with 2 M HCl in ethanol at room temperature for 20 h gives an excellent yield of 95% for the cyclisation reaction, and leads to the formation of the desired indolo[2,3-a]quinolizine product as a single diastereoisomer (Scheme 2).

The relative stereochemistry of the single diastereoisomer 6 was determined by single crystal X-ray analysis (Fig. 2) and was found to be as favoured in the TiCl₄ mediated cyclisation reaction that had previously given only a 5:2 ratio of product diastereoisomers.

To highlight the potential synthetic utility of our new methodology in the target synthesis of complex indole alkaloids and their synthetic analogues, we undertook the synthesis of a simple indole alkaloid, (S)-(−)-1,2,3,4,6,7,12b-octahydroindolo[2,3-a]quinolizine, 11, the main constituent of Dreemonomelium w.lngferman B1. In order to access the natural (S)-enantiomer of the target we were required to work with the opposite stereochemical series of the template. Hence compound 7 was prepared as a single diastereoisomer from (R)-tryptophan by analogous chemistry to that described above.

To reduce the lactam carbonyl group completely the synthesis of the natural product. Target (S)-(−)-11 was found to have an ee of 99% and the same absolute configuration as the natural product by comparison of optical rotation data.

In summary, we report a facile and highly stereoselective approach to the important indolo[2,3-a]quinolizine template from readily available non-racemic substrates, and have demonstrated the structural modification of the template to deliver a simple indole alkaloid with high enantiomeric purity. Current work is focused on extending the methodology described in this paper to other, more complex indole alkaloid targets. Our progress will be reported in due course.
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References and notes

9. Crystallographic data (excluding structure factors) for the structures 6a (R = 0.072) and 6b (R = 0.031) in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 227217-227218).
12. (a) Compound 9 gave [α]D 20 = +28 (c 1, CHCl3). The same compound is quoted as having [α]D 20 = -223 (c 1, 0.2, CHCl3) at an ee of 90% at (b) Compound 11 [α]D 20 = -79.6 (c 1, MeOH); lit. [11][12] [α]D 20 = -84 (c 1, MeOH).

Appendix