Novel synthetic routes
towards polycyclic alkaloids
and tetracycline ring systems

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Novel Synthetic Routes towards Polycyclic Alkaloids and Tetracycline Ring Systems

by

Liam John Duffy
BSc (Hons)

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy at Loughborough University

June 2008
Abstract

Novel and complementary routes for the selective preparation of either the 2,11 b-cis (B) or trans (C) series of functionalised benzo[a]quinolizidines have been developed and reported in close collaboration with the Bosch group. The common aromatic core, chiral β-aminoalcohol (A), allows access to either (B) or (C) via judicious choice of substrate sub-structure for lactamisation. The key cyclisation step in both instances involves the attack of a pendent aromatic nucleophile onto an N-acyliminium intermediate.

Also described in this thesis is the first asymmetric synthesis of the dodecahydrobenz[a]indolo[3,2-h]quinolizine ring system (E), a common sub-structure of several bioactive indole alkaloids. Our approach furnishes the pentacyclic indole core of the manadomanzamine skeleton with complete control over the relative and absolute stereochemistries at the three contiguous chiral centres at positions 1, 10 and 24.

The source of indole and chiral auxiliary, (S)-tryptophanol (D) has also been elaborated towards a functionalised analogue (F) with a synthetic ‘handle’ for further derivatisation. Synthetic routes towards the tetracycline class of compounds have also been investigated.

Acknowledgements

I have to begin by thanking my supervisor Prof. Steve Allin for giving me the opportunity to carry out this PhD and continually supporting and guiding my efforts. I would again like to thank Prof. Steve Allin and also Prof. Phil Page for the financial support received from Charnwood Molecular. I am also very grateful to Dr. Mike McKenzie for all of his help, particularly during my time at Charnwood.

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Finally I would like to thank my family, especially my grandparents for their support and my sister Louise for showing me the way to a better life. The biggest thanks is saved for the most important people in my life, my partner Kerry Lachojski, who I thank for 10 wonderful years and my baby girl, sorry sweetheart, I cant address you personally as we haven't decided on your name yet.
Contents

Chapter 1 – Introduction

1.0 N-Acyliminium Ions

1.1 Brief History

1.1.1 Generation of N-Acyliminium Ions and Synthesis of their Precursors 1
1.1.2 Structure and Reactivity of N-Acyliminium Ions 6
1.1.3 Mechanistic Aspects 7
1.1.4 Detection of N-Acyliminium Ion Intermediates by NMR Spectroscopy 8

1.2 Intramolecular N-Acyliminium Amidoalkylations

1.2.1 Iminium Cyclisations versus Acyliminium Cyclisations 9
1.2.2 Cyclisation of Benzenoid Nucleophiles 10
1.2.3 Cyclisation of Indole Nucleophiles 12
1.2.4 Cyclization of Pyrrole, Imidazole and Pyridine nucleophiles 14
1.2.5 Effect of Substituent on the Iminium Ion 15
1.2.6 Formation of Five-Membered and Seven-Membered Rings 17

1.3 Unsaturated Bicyclic Lactams

1.3.1 Conjugate Additions

1.3.1.1 Organocuprate Conjugate Addition 21
1.3.1.2 Enolate Conjugate Addition 24
1.3.1.3 Epoxidation by Conjugate Addition 25
1.3.1.4 Amines Conjugate Addition 27

1.4 Polyfunctionalised Bicyclic Lactams 28

1.5 The Benzoquinolizidine Alkaloids

1.5.1 Stereoselective Synthesis of the Tetrahydroisoquinoline Ring System 31
1.5.2 Stereoselective Synthesis of Benzoquinolizidine Alkaloids 33

Contents
1.5.3 Related Synthetic Targets

1.6 The Manadomanzamine Alkaloids
1.6.1 Background Information
1.6.2 Proposed Biogenetic Pathway of Manadomanzamines A and B
1.6.3 Racemic Preparation of the Dodecahydrobenz[a]indolo[3,2-h]quinolizine System

1.7 Stereoselective Synthesis of Indole Alkaloids

References
Chapter 3 – Introduction

3.0 The Tetracycline Antibiotics
3.1 Background Information
3.2 Synthetic Approaches to the Tetracyclines
  3.2.1 Myers’ Asymmetric Total Syntheses of the Tetracyclines
3.3 Structurally Related Linear Systems
  3.3.1 The Angucycline Antibiotics

References

Chapter 4 – Results and Discussion

Contents
4.0 A Novel Iterative Route towards the Tetracycline Antibiotics
4.1 Preparation of a Bicyclic Linear-Fused Adduct
4.2 Oxidation of the Bicyclic Linear-Fused Adduct
4.3 Benzylic Oxidation Review
4.4 Screening of Protecting Groups
4.5 Synthesis of Structurally Related Linear Systems
4.6 Fries Rearrangement Route
4.7 A Mixed Claisen/Fries Strategy
4.8 Conclusion

References

Chapter 5 – Experimental

5.0 General Information
5.1 Stereoselective Synthesis of the Tetrahydro-1H-pyrido[2,1-a] isoquinoline Ring System
5.2 Functionalisation of the Dimethoxytetrahydro-1H-pyrido[2,1-a] isoquinoline Ring System
5.3 Asymmetric Construction of the Dodecahydrobenz[a]indolo[3,2-h] quinolizine Ring System
5.4 Development of a Functionalised Dodecahydrobenz[a]indolo[3,2-h] quinolizine Ring System
5.5 Application of a Claisen/RCM protocol
5.6 Application of a mixed Claisen/ortho-Fries strategy

Chapter 6 – Appendix

6.0 X-Ray Crystallography Data
6.1 Publications

Contents
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
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<tr>
<td>AIBN</td>
<td>2,2’-Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
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<tr>
<td>BOC</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
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<td>b.p.</td>
<td>Boiling point</td>
</tr>
<tr>
<td>br</td>
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<tr>
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<td>d</td>
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<td>DMAP</td>
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<tr>
<td>DMF</td>
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</tr>
<tr>
<td>DMSO</td>
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<tr>
<td>e.e.</td>
<td>Enantiomeric excess</td>
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<td>RCM</td>
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<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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CHAPTER ONE:
POLYCYCLIC ALKALOIDS
INTRODUCTION
1.0  \textit{N}-Acyliminium Ions

1.1  Brief History

Significant progress in the enhancement of the chemo-, regio- and stereoselectivity of both classical and modern reagents in the last few decades has been paralleled by advances in organic synthesis.\textsuperscript{1} Both Mannich reagent (1), and amidoalkylating reagent (2), also known as an \textit{N}-acyliminium ion and primarily designed to facilitate Mannich-type condensations\textsuperscript{2}, have proved versatile synthetic tools. With respect to the latter, an impressive number of synthetic applications have been demonstrated utilizing intermolecular processes.\textsuperscript{3,4} In contrast, examination of the intramolecular carbon-carbon bond forming reactions of the \textit{N}-acyliminium ion has demonstrated a new dimension in the reactivity and selectivity tendencies of amidoalkylating reagents.

\[
\begin{align*}
\text{(1)} & \quad \begin{array}{c}
R^2 = \text{N} \\
R^3 & R^4
\end{array} \\
\text{(2)} & \quad \begin{array}{c}
R^2 = \text{N} \\
R^3 & O \\
R^4 & R^4
\end{array}
\end{align*}
\]

1.1.1  Generation of \textit{N}-Acyliminium Ions and Synthesis of their Precursors

The first detailed account on the generation of the \textit{N}-acyliminium ions and synthesis of their precursors was reported by Zaug and Martin\textsuperscript{5} in 1965. In subsequent years these methods have been refined and new methods added, resulting in five principle synthetic pathways to arrive at \textit{N}-acyliminium ions as illustrated in \textbf{Scheme 1}.
Route a) Oxidation of Amides

The key step in this method is the removal of hydride from the α-carbon of an amide which formally leads to an N-acyliminium ion. Several research groups have developed an extremely efficient electrochemical method to facilitate this transformation.\textsuperscript{6-8} The mechanism (Scheme 2) involves initial removal of an electron from the lone pair on nitrogen to generate cation radical (4). The subsequent removal of a proton and further electron affords the corresponding N-acyliminium ion (5). This electrochemical oxidation is carried out in the presence of a nucleophile, usually methanol, in order to immediately trap the N-acyliminium ion to yield α-methoxyalkyl amide (6). The scope of the reaction encompasses a wide structural variety of amides and carbamates and a more comprehensive study has since been reported.\textsuperscript{9}
Route b) Electrophilic Addition to Enamides

Lenz\textsuperscript{10} reported that acylation of an imine (7) with either an acid chloride or anhydride, followed by elimination of HX generates the enamide (8). Protonation of the enamide furnishes the corresponding \(N\)-acyliminium ion (9) (Scheme 3).
Route c) N-Protonation of N-Acylimines

This particular method carries more mechanistic rather than synthetic interest due to the relative instability of N-acylimines (rapidly tautomerize to corresponding enamides if possible). Wurthwein and co-workers\textsuperscript{11} investigated the protonation of imine (10) and produced convincing evidence for the N-acyliminium ion structure (11), as shown in Scheme 4.

![Scheme 4](image)

Route d) N-Acylation of Imines (Schiff Bases)

Imines are easily obtainable in high yields by condensation of the corresponding aldehydes or ketones with primary amines.\textsuperscript{12} Their acylation with suitable reactive carboxylic acid derivatives such as acid chlorides or anhydrides was reported as early as 1914 by James and Judd.\textsuperscript{13} The N-acylation of benzaniline (12) with benzoyl chloride (13) furnished the crystalline precursor (14), which was readily hydrolysed in water to give benzaldehyde (16) and benzanilide (17) (Scheme 5). The lability of the carbon-chlorine bond illustrates the tendency for the N-acyliminium ion (15) to be formed in this system.\textsuperscript{14}
Route e) Heterolysis of Amides

Heterolysis of α-substituted amides is the most frequently employed method for the generation of synthetically useful N-acyliminium ions. In the majority of cases the leaving group is an oxygen substituent, but can also be a sulfur, nitrogen, phosphorus or halogen substituent. In order to generate the N-acyliminium ion (19) from the α-oxyalkyl amide precursor (18) where R is alkyl or hydrogen (Scheme 6), a Brönsted or Lewis acid activator is generally employed. In the case where R is acetyl or methanesulfonyl, no such catalyst is required.
1.1.2 Structure and Reactivity of N-Acyliminium Ions

It has been well established throughout the last two decades that the Mannich intermediate (20) can be made considerably more reactive via substitution with electron withdrawing groups at nitrogen, thus enhancing its cationic character. Of these modified cations, the N-acyl derivative (21) and the carbamate (22) have been the most widely exploited. Examples of other electronegative substituents such as the amide (23) and N-tosyl (24) cations have been reviewed to a lesser extent. Numerous cyclic and linear forms can be distinguished, depending on the type of \( R^1, R^2 \) and \( R^3 \) and new variations such as the hydrazonium (25) have arisen.\(^{15}\)

\[
\begin{align*}
R^2 + & R^1 \quad 20 \ R = H, \text{ alkyl} \\
N & 21 \ R = \text{acyl} \\
R^3 & R \\
22 \ R = \text{COOR} \\
23 \ R = \text{CONR}_2 \\
24 \ R = \text{Tos} \\
25 \ R = \text{NR}_2
\end{align*}
\]

It is expected that the imino carbon atom in the amidoalkylating agent (21) is more electron-poor than in Mannich reagent (20) due to the presence of the strongly electron withdrawing carbonyl group. A study by Wurthwein\(^ {11} \) et al. of iminium salts (26) and (27) revealed that substitution of an N-methyl by an N-acetyl group produces an approximate downfield shift of 5 ppm with respect to the imino carbon absorption. This spectral evidence is indicative of N-acyliminium ions being more electrophilic than iminium ions, hence more reactive.

\[
\begin{align*}
\text{Ph} \quad & \text{Me} \\
\text{Ph} \quad & \text{H} \\
\text{SbCl}_6^- \\
(26) \\
\text{Ph} \quad & \text{Me} \\
\text{Ph} \quad & \text{H} \\
\text{SbCl}_6^- \\
(27)
\end{align*}
\]
1.1.3 Mechanistic Aspects

Reactions between N-acyliminium ions and nucleophiles (also termed amidoalkylation or Mannich-type condensations) have been frequently employed to introduce substituents at the α-carbon of an amine. The general schematic for the mechanism by which most amidoalkylations proceed is shown below (Scheme 7). Acidic catalysis generates equilibrium between precursor (28) and N-acyliminium ion (2). Substituted product (29) is obtained when N-acyliminium ion (2) reacts in an irreversible process with a nucleophile.

This scheme closely resembles that of an $S_N1$ process. A study by Zaugg and Martin\textsuperscript{17} led to the establishment of two extreme kinetic situations; (i) the formation of the N-acyliminium ion is rate limiting and (ii) the reaction of the nucleophile is rate limiting. The former situation implies that a more stable N-acyliminium leads to a faster reaction, whereas the latter case implies the opposite to be true. Other factors which influence the rate of amidoalkylation include the nature of the leaving group and the solvent.

An important side reaction in the chemistry of the N-acyliminium ion is the loss of a proton to give the corresponding enamide. In an acidic medium, this process may be reversible but this is not always the case. Dimeric structures can arise when enamides react as a nucleophile with the N-acyliminium ions still present. The problem of enamide...
formation and subsequent side reaction can arise if the N-acyliminium ion is not trapped fast enough by the nucleophile. The four main factors that facilitate such problems are:

- There is too much steric hindrance
- Stereoelectronic factors are unfavourable (intramolecular case)
- A medium or large sized ring is to be formed
- The nucleophile is not very reactive

1.1.4 Detection of N-Acyliminium Ion Intermediates by NMR Spectroscopy

Whereas iminium salts are frequently isolable, their N-acyliminium counterparts are seldom isolated due to both limited stability and high reactivity, and are almost always generated in situ. As a result, there have only been two reports in the literature of transient N-acyliminium intermediates being observed by dynamic NMR. Yamamoto and Nakada demonstrated that treatment of alkoxy carbamate (30) at -55 °C with Lewis acid in the presence of TfO produces a clean 13C NMR spectrum of the corresponding N-acyliminium ion intermediate (31) as shown in Scheme 8.

![Scheme 8](image-url)
In a more recent study, it was found that the bis(homoallyl) hydroxylactam (32) could be treated with BF$_3$·OEt$_2$ at 25 °C to produce a clean $^{13}$C NMR spectrum of the N-acyliminium ion (33). The slow cyclisation (1 h) of this intermediate to fluoro compound (34) highlighted unexpected stability, which may be explained by the greater electron withdrawing ability of the amide carbonyl compared to the carbamate.

\[ \text{(32)} \quad \text{(33)} \quad \text{(34)} \]

1.2 Intramolecular N-Acyliminium Amidoalkylations

1.2.1 Iminium Cyclisations versus Acyliminium Cyclisations

Cyclisations involving iminium cations such as the venerable Mannich reaction\textsuperscript{20}, the Bischler-Napieralski reaction\textsuperscript{21} and the Pictet-Spengler reaction\textsuperscript{22} are well reviewed and established. In contrast, a more recent development has been the emergence of cyclisations that proceed via N-acyliminium species (Scheme 9). Both types of intermediates have been extensively employed in the synthesis of alkaloidal and related systems, including several early uses of N-acyliminium ions in amidoalkylation reactions.\textsuperscript{2}
1.2.2 Cyclisation of Benzenoid Nucleophiles

The reactions of N-acyliminium ions with tethered $\pi$ bonds have proved a most versatile and important tool for the construction of complex nitrogen containing heterocycles. The first example of this kind was reported by Von Braun et al\textsuperscript{23} while investigating the ring closure of sulfonamide glycine derivatives by AlCl\textsubscript{3} catalysed decarbonylation (Scheme 10).

The major breakthrough in synthetic application of intramolecular amidoalkylations occurred in the early 1950s, when the reaction was applied in alkaloid synthesis.\textsuperscript{11} Interest in this field was stimulated by the pioneering work of both Belleau\textsuperscript{24} and Mondon\textsuperscript{25} on the synthesis of Erythrina alkaloids by ring closure of $N$-acyliminium ions (35a) ($R^1 = O$, $R^2 = H_2$) and (35b) ($R^1 = H_2$, $R^2 = O$).
The genus *Erythrina* is widely distributed in tropical and subtropical regions of the world and has traditionally been used in indigenous folk medicine. Extracts from the flowers, seeds, and bark of the genus have yielded a family of *Erythrinan* alkaloids which exhibit numerous pharmacological effects including sedative, hypotensive and neuromuscular blocking. The vast majority of naturally occurring *Erythrina* alkaloids possess the common tetracyclic framework and substitution pattern of (36).

![Chemical Structure](image)

Allin and James reported a novel, stereoselective approach to a fused tetracyclic ring core of the *Erythrinane* system in 92% yield via an asymmetric, intramolecular *N*-acyliminium mediated cyclisation. Treatment of bicyclic lactam (37) with the Lewis acid TiCl$_4$ gave the target core (38) presumably from the *N*-acyliminium ion (39) (Scheme 11).

![Chemical Structure](image)
1.2.3 Cyclisation of Indole Nucleophiles

Of equal importance in initiating studies in this field was the synthesis of yohimbine by Van Tamelen et al.,\textsuperscript{28} which incorporated a critical acid-catalyzed ring closure of the \( N \)-acyliminium ion (40). The reaction proceeded remarkably easily thus highlighting the reactivity of an electron-rich aromatic pyrrole ring in such cyclisations.

Indole type cyclisations via an intermediate \( N \)-acyliminium ion have been used in the synthesis of many indole alkaloids. The highly reactive nature of the indole \( \pi \)-nucleophile makes this category stand out as a unique collection of illustrative examples. The synthesis of tetrahydro[12H]pyrroloazepinoindole as reported by Wawzonek and
Maynard\textsuperscript{29} was facilitated by a key cyclisation of this type. The hydroxylactam precursor (41) was subjected to acid activation in order to generate the N-acyliminium ion (42), which gave direct access to the tetracyclic product (43) via an intramolecular cyclisation (Scheme 12).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_12.png}
\caption{Scheme 12}
\end{figure}

More recently, Allin and Thomas demonstrated both a novel and facile asymmetric approach to both enantiomers of the indole alkaloid deplancheine.\textsuperscript{30} The key ring forming step in the construction of the indolo[2,3-a]quinolizine framework involved cyclisation of an indole nucleophile onto an acid-induced N-acyliminium ion (46). Simple treatment of a mixture of bicyclic lactams (44a/b) with 2M HCl furnished indolo[2,3-a]quinolizine target (45) as a single diastereoisomer in 97\% yield (Scheme 13).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_13.png}
\caption{Scheme 13}
\end{figure}
1.2.4 Cyclization of Pyrrole, Imidazole and Pyridine nucleophiles

*N*-Substituted pyrroles linked to an *N*-acyliminium ion via the pyrrole α-position react cleanly at the α-position as shown previously (Scheme 13). Similarly, *N*-acyliminium ions linked to the pyrrole nitrogen undergo cyclisation at the α-position to generate five, six, seven and even eight-membered rings. Scheme 14 highlights the difficulty in forming a five-membered ring, as signified by the low yield of (48), but also the possibility of *N*-acyliminium cyclisation at the α-position.

Scheme 14

\[
\begin{array}{c}
\text{(47)} \\
\text{HCO}_2\text{H} \\
3 \text{days}
\end{array} \rightarrow 
\begin{array}{c}
\text{(48) (27 %)}
\end{array}
\]

Scheme 15 gives a clear indication of the high reactivity of the pyrrole nucleus for *N*-acyliminium cyclisations. In this case, cyclisation involving the phenyl nucleophile in order to generate a five-membered ring does not occur; rather, the pyrrole nucleophile attacks to furnish a new eight-membered ring (50). It is a remarkable feat to form an eight-membered ring in such high yield (92 %) and under such mild conditions (23 °C, 1 h) (Scheme 15).

Scheme 15

\[
\begin{array}{c}
\text{(49)} \\
\text{TFA, (2 drops)} \\
\text{DCM, 1 h}
\end{array} \rightarrow 
\begin{array}{c}
\text{(50) (92 %)}
\end{array}
\]
The role of other heterocyclic nucleophiles in the cyclisation of N-acyliminium ions has been reviewed.\cite{31} There is a reported example of an N-acyliminium cyclisation onto an imidazole.\cite{33} Reaction of histamine with 4-oxodecanoyl chloride in pyridine affords a mixture of amide (51) and tricyclic structures (52) and (53) which are acid catalysed cyclisation products of (51). Prolonged heating in 10 % aqueous acetic acid gave essentially pure (53) (Scheme 16).

\[
\begin{align*}
\text{(51)} & & \text{(52)} & & \text{(53)} \\
\end{align*}
\]

In contrast to the pyrrole nucleus, which has been shown to be a highly reactive nucleophile for N-acyliminium cyclisations e.g. Scheme 15, one would expect an electron-deficient heterocycle such as pyridine to be unreactive. Indeed, this can explain the limited depth of examples of pyridine in cationic π-cyclisation reactions in the literature, despite its frequent occurrence in a plethora of biologically active heterocycles. However, N-acyliminium reactions do proceed when the pyridine nucleus is activated at the 2-position as highlighted in Scheme 17.\cite{34}

\[
\begin{align*}
\text{(54)} & & \text{(55)} \\
\end{align*}
\]
The 2-methoxy substituted lactam (54) failed to undergo cyclisation in the presence of a wide range of Lewis acids including TiCl₄, SnCl₄ and BF₃·OEt₂, with only starting material recovered in each case. Refluxing the lactam in the presence of a catalytic amount of protic acid in benzene, however, furnished the target tetracycle (55) in 70 % yield.

1.2.5 Effect of Substituent on the Iminium Ion

In N-acyliminium ion cyclisations, the nature of the substituent either on the carbon or nitrogen of the iminium unit generally has negligible effect on the reaction outcome. There are instances however, in which more reactive N-acyliminium species have a significant impact. Intermediates that bear an electron-withdrawing group on the carbon atom, or those devoid of steric hindrance at the carbon atom, or those with more electron-deficient N-acyl groups, may result in higher yields and/or allow for milder conditions.

It has been demonstrated that for certain hydroxyisoindolinones with standard substituents such as phenyl or hydrogen, disparate reactivity exists, especially with ring strain in the cyclisation (Scheme 18).³⁵

![Scheme 18](image)

In the case of (56) where the iminium carbon bears an electron withdrawing phenyl group and where n = 1, cyclisation proceeds in high yield in stark comparison to the analogous
hydrogen substituent compound (57), which fails to cyclise. Since the corresponding cyclisations to six-membered rings supply good yields irrespective of substituent, it appears that the substituent effect is directly accentuated by ring strain.

Okano et al.\textsuperscript{36} demonstrated that if the electrophilicity of the iminium carbon is sufficiently enhanced, then the reactivity of the nucleophile can be lessened with no great effect (Scheme 19).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=\textwidth]{scheme19.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 19}

The presence of a trifluoromethyl group at the iminium carbon of (60) results in a quantitative yield of cyclised pyrroloisoquinolines (61/62), even though the arene nucleophile is a less reactive chlorophenyl group.

1.2.6 Formation of Five-Membered and Seven-Membered Rings

The formation of five-membered rings by N-acyliminium ion cyclisation can be problematic as highlighted previously (Scheme 18). This difficulty is illustrated by the failure of (63) and (64) to cyclise under various acidic conditions (Scheme 20).\textsuperscript{37}
On the other hand, five-membered rings are formed more readily from spirocyclisation of $N$-acyliminium species as highlighted by the cyclisation of $N$-arylglycinamide based ions to 3-aminoindolin-2-ones (Scheme 21).³⁸

Formation of seven-membered rings in cyclisations can be troublesome but there are several successful examples.³³ One prevalent example is illustrated in Scheme 22 where there are competing phenyl and thiophene $\pi$-nucleophiles. Upon subjection of (65) to trifluoroacetic acid, cyclisation occurred exclusively on the phenyl ring in 80% yield. No cyclisation took place on the thiophene ring (at the 4-position) thus reflecting the difficulty in forming a new five-membered ring, especially for a 5,5-fused product.³⁹
Another notable example of seven-membered ring generation utilizing an N-acyliminium precursor was reported by Nakatsuka et al.\textsuperscript{40} Azepinoindoles were prepared as exemplified in Scheme 23.

Rather interestingly, enamide (68) as either the Z or E isomer, cyclised exclusively at the indole 4-position to furnish (69). This is in spite of the reactive indole 2-position being available for six-membered ring formation.
1.3 Unsaturated Bicyclic Lactams

Bicyclic lactams provide an extremely versatile chiral, non-racemic tool for the generation of a plethora of optically pure carbocycles and heterocycles. Their application to total synthesis has demonstrated that lactams provide access to a wide variety of structural features with excellent stereocontrol. The preparation of α,β-unsaturated carbonyl compounds is an important transformation, allowing further functionalisation of substrates. The predominant method to access such compounds involves the oxidative elimination of an appropriate selenoxide as developed by Reich. The α-phenylselenocarbonyl compound (70) can be accessed via an appropriate lithium enolate and phenyl selenyl bromide. Oxidative conditions promotes elimination to yield the α,β-unsaturated product (71) and phenyl selenic acid as a by-product (Scheme 24).

![Scheme 24](image-url)
1.3.1 Conjugate Additions

1.3.1.1 Organocuprate Conjugate Addition

The conjugate addition of organocuprates to electrophilic olefins has scarcely been utilised in a chiral sense.\textsuperscript{43} House \textit{et al.} carried out the addition of organocuprates on unsaturated lactam (72) in order to investigate any diastereoselective pattern and hence address the task. Rapid enone reduction was observed on attempting the addition of Gilman-type cuprates to yield saturated lactam (73) (Scheme 25).\textsuperscript{44}

\[
\text{Scheme 25}
\]

Diels-Alder cycloadditions to the bicyclic lactam were found to only be successful when an \(\alpha\)-carboalkoxy group was introduced.\textsuperscript{45} Subsequent addition of the standard ‘Gilman reagent’ to the same bicyclic lactam template (74) furnished the \(\beta\)-substituted lactam (75) in a 3:1 (trans:cis) diastereomeric ratio. Further studies revealed that the use of a lower order cyanocuprate produced a diastereomeric ratio >95:5 (trans:cis) (Scheme 26), (Table 1). It is rationalised that the angular methyl group effectively blocks the approaching cuprate on the \(\beta\) face thus promoting the \textit{endo} addition that is observed.

\[
\text{Scheme 26}
\]
The removal of the carbomethoxy group used initially to activate the addition, from the β-substituted lactam (75), has proved problematic. The viability of the procedure was limited by the rapid epimerisation noted upon alkaline hydrolysis to give the decarboxylated product. This disadvantage was ultimately overcome by changing to a benzyl ester (76), which could be easily removed via hydrogenolysis followed by decarboxylation in refluxing toluene to give (77) (Scheme 27). Pyrrolidine system (78) was obtained via reductive removal of the auxiliary over two steps.

Reagents: a) Pd/C, H₂ b) reflux c) AlH₃ d) NH₄HCO₂⁻, Pd/C

Scheme 27

More recently, Bosch et al. have established that unsaturated lactams (80a) and (80b), derived from the same chiral inductor, (R)-phenylglycinol, undergo conjugate addition of cyanocuprates with opposite facial selectivity. The resulting C-7/C-8a trans isomers (81a) and (81b) arise due to the difference in configuration at the C-8a stereocentre (Scheme 28).

Chapter 1 Introduction
The stereochemical outcome was explained by considering the difference in the conformation of the piperidine ring for lactams (80a) and (80b), with nucleophilic attack of the cyanocuprate proceeding via stereoelectronic control, axial to the electrophilic carbon of the enone. Rather interestingly, the same group also discovered that γ-substitution of C-7/C-8a trans lactam (S1b) with an ethyl group facilitates entry to C-7/C-8 cis isomers through similar additions (S3a/b) (Scheme 29). This allowed for entry to enantiopure cis-3-alkyl-4-arylpiperidines (S4a/b), with the stereochemical outcome of the conjugate additions to γ-substituted α,β-unsaturated δ-lactam (82) being in stark contrast to the trans isomers usually formed.49

![Scheme 28](image)

![Scheme 29](image)
1.3.1.2 Enolate Conjugate Addition

In contrast to the cuprate additions summarised in the previous section, the conjugate addition of stabilised anions to α,β-unsaturated carbonyl compounds is a reversible process. This gives rise to thermodynamic control for the addition, which could result in a different stereochemical outcome than for that observed for the irreversible addition of a cyanocuprate. Amat et al. investigated the addition of the enolate derived from ethyl 1,3-dithiolane-2-carboxylate to the diastereomeric lactams trans (86a) and cis (86b), (Scheme 30).

It was found that without the presence of an ethyl group at the γ-position, addition occurs with the same stereoselectivity as the addition of cyanocuprates to the related trans and cis lactams (80a) and (80b) (Scheme 28). The conjugate addition of the enolate of ethyl 1,3-dithiolane-2-carboxylate to the γ-ethyl substituted derivative of (86b), cis (88), took place with high facial selectivity to give a cis relationship at C-7/C-8a (Scheme 31).
The dramatic influence exerted by the γ-ethyl substituent on the stereochemical outcome of the conjugate addition of enolates is exemplified by comparison of (89) with the C-7/C-8a trans relationship observed for the same addition to related desethyl cis lactam (87b), (Scheme 30). The resulting C-7/C-8 trans product (89) is the thermodynamically more stable isomer and its formation is facilitated by the reversible nature of the enolate addition. This is complementary to the C-7/C-8 cis products (83a/b), (Scheme 29), which were accessed via kinetically controlled addition of a cyanocuprate to unsaturated lactam (82). The additional activating alkoxycarbonyl group incorporated into (82) was subsequently removed by employing a hydrogenation/decarboxylation sequence.

1.3.1.3 Epoxidation by Conjugate Addition

The versatility of unsaturated α,β-unsaturated lactam (74) was further demonstrated by Van Rheenan et al. who reported oxygen addition to the template using tertiary amine N-oxides.51 The Upjohn process for the dihydroxylation of unsaturated systems (catalytic OsO₄, N-methylmorpholine oxide) was employed, and the α-epoxide (90) isolated in high yield rather than the expected diol. The stereochemical outcome of this reaction was consistent with blocking of the β-face by the methyl substituent as α-face entry was exclusively observed (Scheme 32). Further studies revealed that osmium tetroxide was unnecessary and that NMO could be replaced with triethylamine-N-oxide. Epoxidation of the α-face of a variety of doubly activated α,β-unsaturated bicyclic lactams proved successful.52
Amat has shown that epoxidation of the $\alpha,\beta$-unsaturated bicyclic lactam is not limited to the bicyclo [3.3.0] system. The $\alpha,\beta$-epoxy lactam (94) has been obtained from the [4.3.0] bicyclic lactam (91) via treatment of the intermediate $\alpha$-selenyl bicyclic lactam (92) with $m$-CPBA (Scheme 33). It was reasoned that the $\alpha,\beta$-unsaturated lactam (93) would be formed as an elimination product of the selenoxide of (92). This was followed by epoxidation with $m$-CPBA to furnish $\beta$-epoxide (94).

The facial selectivity appears to be governed by the angular substituent present, with the presence of an angular hydrogen allowing for $\beta$-epoxidation. In the case where oxidation
of the intermediate selenide was achieved with ozone, the corresponding α,β-unsaturated lactam (93) was exclusively isolated. 46

1.3.1.4 Amines Conjugate Addition

High facial selectivity has also been observed for the addition of amines to the α,β-unsaturated lactam (72) (Scheme 34). In order to facilitate efficient amine addition, two crucial conditions have been identified; (a) the presence of water to drive amine addition to completion and (b) reaction with 8 equivalents of the amine. 54

Upon changing to a secondary amine i.e. increasing steric bulk, the selectivity of the endo-exo addition increased from 19:1 to >98:2 (Scheme 35), (Table 2). This indicated that the bulkier nucleophiles were sensitive to facial selectivity (Entries 1, 5). When the angular substituent of the lactam was changed from a methyl to a phenyl group (Entries 2 and 4), the selectivities for the reaction with the same primary amine changed from 19:1 to >98:2. 46

Chapter 1 Introduction
### Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^1$</th>
<th>Amine</th>
<th>Yield (%)</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>PhCH$_2$NH$_2$</td>
<td>84</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>H$_2$N$_2$Ph</td>
<td>83</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>H$_2$N$_2$Ph</td>
<td>85</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>H$_2$N$_2$Ph</td>
<td>89</td>
<td>98:2</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>HN</td>
<td>89</td>
<td>98:2</td>
</tr>
</tbody>
</table>

1.4 Polyfunctionalised Bicyclic Lactams

In contrast to the previous section (1.3) which describes the functionalisation of unsaturated bicyclic lactams via conjugate addition reactions, this section examines the incorporation of functionality prior to lactamisation. Bosch et al.\textsuperscript{55} have extensively studied the formation of polysubstituted bicyclic lactams from chiral 1,3 and 1,2 aminoalcohols, for example, (95) and (96, 97) respectively, with racemic or prochiral $\delta$-oxoacid derivatives (98-104) (Figure 1).

![Figure 1](image_url)
All of the cyclocondensation reactions undertaken involved a dynamic kinetic resolution (DKR) and/or differentiation of enantiotopic or diastereotopic ester groups effected by aminocarboxylic acids (95-97). The study encompassed a wide range of δ-oxoacid derivatives including unbranched aldehydes (98) and ketones (100), racemic aldehydes (99) and racemic ketones (101). Prochiral aldehydo-diesters bearing enantiotopic ester groups (102, 104) and racemic aldehydo-diesters containing diastereotopic ester groups (103) were also screened with the results summarised in Table 3.

<table>
<thead>
<tr>
<th>Synthons</th>
<th>Products</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
<th>a:b ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>rac-(95) + (98)</td>
<td>H₃C₆H₄NO₂⁻ + H₂C₆H₄NO₂⁻</td>
<td>H</td>
<td>H</td>
<td>-</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>rac-(95) + (99)</td>
<td>H₂C₆H₄NO₂⁻ + H₂C₆H₄NO₂⁻</td>
<td>H</td>
<td>Et</td>
<td>-</td>
<td>80</td>
<td>1:1³</td>
</tr>
<tr>
<td>rac-(95) + (100)</td>
<td>H₂C₆H₄NO₂⁻ + H₂C₆H₄NO₂⁻</td>
<td>CH₃</td>
<td>H</td>
<td>-</td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td>rac-(95) + (101)</td>
<td>H₂C₆H₄NO₂⁻ + H₂C₆H₄NO₂⁻</td>
<td>CH₃</td>
<td>Et</td>
<td>-</td>
<td>45</td>
<td>9:1⁴</td>
</tr>
<tr>
<td>(96) + (98)</td>
<td>H₂C₆H₄N²⁻ + H₂C₆H₄N²⁻</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>70</td>
<td>4:1</td>
</tr>
<tr>
<td>(96) + (99)</td>
<td>H₂C₆H₄N²⁻ + H₂C₆H₄N²⁻</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>87</td>
<td>7:5:3³</td>
</tr>
<tr>
<td>(96) + (102)</td>
<td>H₂C₆H₄N²⁻ + H₂C₆H₄N²⁻</td>
<td>H</td>
<td>H</td>
<td>X</td>
<td>78</td>
<td>4:1</td>
</tr>
<tr>
<td>(96) + (100)</td>
<td>H₂C₆H₄N²⁻ + H₂C₆H₄N²⁻</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>99</td>
<td>1:10</td>
</tr>
<tr>
<td>(96) + (101)</td>
<td>H₂C₆H₄N²⁻ + H₂C₆H₄N²⁻</td>
<td>CH₃</td>
<td>Et</td>
<td>H</td>
<td>74</td>
<td>1:8³</td>
</tr>
<tr>
<td>(97) + (99)</td>
<td>Ph₂CO₂⁻ + Ph₂CO₂⁻</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>78</td>
<td>1:9</td>
</tr>
<tr>
<td>(97) + (102)</td>
<td>Ph₂CO₂⁻ + Ph₂CO₂⁻</td>
<td>H</td>
<td>H</td>
<td>X</td>
<td>86</td>
<td>1:14</td>
</tr>
<tr>
<td>(97) + (103)</td>
<td>Ph₂CO₂⁻ + Ph₂CO₂⁻</td>
<td>H</td>
<td>Et</td>
<td>X</td>
<td>77</td>
<td>1:15³</td>
</tr>
<tr>
<td>(97) + (104)</td>
<td>Ph₂CO₂⁻ + Ph₂CO₂⁻</td>
<td>H</td>
<td>Y</td>
<td>H</td>
<td>80</td>
<td>1:20</td>
</tr>
<tr>
<td>(97) + (101)</td>
<td>Ph₂CO₂⁻ + Ph₂CO₂⁻</td>
<td>CH₃</td>
<td>Et</td>
<td>H</td>
<td>81</td>
<td>3:2</td>
</tr>
</tbody>
</table>

X = CH₃CO₂Me, Y = (CH₂)₂CO₂Me. ³Trace amounts of epimer at piperidine α-position detected. ⁴a:b:c ratio (c is the epimers of b at piperidine α-position). ⁵Trace amounts of epimer at piperidine β-position detected. ⁶Minor amounts of epimer at piperidine γ-position isolated.
For the reaction of aminophenol rac-(95) with racemic aldehyde (99), no stereoselectivity was observed, whereas condensation with racemic ketone (101) furnished the corresponding tricyclic lactams rac-(108) with good stereoselectivity (a/b diastereomeric ratio 9:1). The moderate yield attained for rac-(108) (45 %) was accounted for by the isolation of considerable amounts of 2-vinylphenol.

The application of conformationally rigid cis-1-amino-2-indanol (96) in the cyclocondensation reactions proved more successful, particularly with ketones (100, 101). Tetracyclic lactams (109) and (111) were generated as the major products in good yield from aldehydes (98) and (102) respectively, with a stereoselectivity similar to that previously observed with phenylglycinol.57 However, in the case of racemic aldehyde (99), no dynamic kinetic resolution (DKR) was observed. Interestingly, formation of enantiopure lactam (111) involved the enantioselective desymmetrisation of two enantiotopic ester groups.

In contrast, reaction of (96) with both prochiral ketone (100) and racemic ketone (101) gave much higher stereoselectivity than for the analogous reactions with phenylglycinol.57 The dynamic kinetic resolution of the isomerisable stereocentre α to the ketone carbonyl is highlighted by the formation of enantiopure lactam (113b), isolated in 61 % following column chromatography.

The use of aminoa1cohol (97) resulted in optimal yields and stereoselectivities for the cyclocondensation reactions involving aldehyde substrates (99) and (102-104). The reaction of (97) with racemic aldehyde (99) gave a 1:9 a/b stereoisomeric mixture of lactams (114) in 78 % yield, clearly indicating the occurrence of a DKR. The analogous condensation with racemic ketone (101) however, proceeded with low stereoselectivity (3:2 118a/b) and hence it was concluded that no DKR had taken place.

The prochiral aldehydo-diesters (102) and (104) produced 1:14 and 1:20 a/b stereoisomeric mixtures of the respective lactam esters (115) and (117) in excellent yield, indicating highly enantioselective desymmetrisations during condensation with (97).
correlation with these findings, racemic oxodiester (103) underwent highly stereoselective condensation with aminoalcohol (97) to furnish one of the eight possible stereoisomeric lactams (116b), which was isolated in 69% yield. This example rather impressively demonstrates the construction of three stereogenic centres with a well-defined absolute configuration in only a single step. The highly stereoselective process involves DKR, with epimerization of the configurationally labile stereocentre in the substrate and also the desymmetrisation of two diastereotopic acetate chains.

1.5 The Benzoquinolizidine Alkaloids

1.5.1 Stereoselective Synthesis of the Tetrahydroisoquinoline Ring System

The benzo[a]quinolizidine class of Alangium alkaloids are based on a fused tricyclic tetrahydroisoquinoline core (ABC ring) comprising of benzyl and piperidine subunits with 3,4-disubstitution at piperidine unit, C (119).

![Diagram of compound 119](image)

The potential of phenyl containing 5,6-bicyclic lactams derived from chiral amino alcohols as precursors to functionalized benzo[a]quinolizidine alkaloids has yet to be fully explored. Protoemetinol (120) is an attractive synthetic target primarily due to its biological activity but also as a synthetic base unit for related alkaloids (122) and (123).
Protoemetinol and one of its analogues, ankorine (121), have potent anti-inflammatory properties. Such characteristics offer scope for the treatment of chronic inflammatory diseases such as tuberculosis and rheumatoid arthritis. They have been traditionally employed as a medicinal herb in China and can be extracted from the leaves of *Alangium lamarckii*.\(^{59}\) Psychotrine (122) and O-methylpsychotrine (123) have been demonstrated clinically to be potent inhibitors of the HIV transcriptase\(^{60}\) enzyme thus preventing multiplication of the virus. Both alkaloids can be extracted from species within the *Alangiaceae* plant family. *Alangine* (124), a recently isolated natural product also from *A. lamarckii* differs stereochemically from compounds (120)-(123) in that it has trans relative stereochemistry at positions 2 and 11b.\(^{61}\)
Allin and Vaidya utilised chiral bicyclic lactam substrates as precursors in a stereoselective approach towards the tetrahydroisoquinoline ring system. The approach allows the introduction of asymmetry during the key ring-closing step; the stereoselective cyclisations of a bicyclic lactam substrate (125) via an N-acyliminium intermediate (127) (Scheme 36).

![Chemical Structures](image)

Scheme 36

The desired tricyclic tetrahydroisoquinoline ring system (126) was isolated as a single diastereoisomer in 68 % yield. The use of bicyclic lactams derived from β-amino alcohols containing fused 5,5 and 5,6 ring systems in asymmetric synthesis has been extensive. This is believed to be the first application of the corresponding fused 5,6 system (125) as a precursor in an N-acyliminium mediated cyclisation leading to the tetrahydroisoquinoline ring system.

1.5.2 Stereoselective Synthesis of Benzoquinolizidine Alkaloids

Hirai et al. have reported on the stereoselective synthesis of the Ipecac alkaloid (-)-protoemetinol. The key step in the efficient synthesis involves a stereoselective intramolecular Michael reaction (Scheme 37).

Chapter 1 Introduction
Scheme 37

Reagents: a) ethyl 4-bromobut-2-enoate, Zn dust, CH₃CN, rt. b) 20% oxalic acid, MeOH. c) 4-methyleneoxetan-2-one, (C₂H₅)₂O, rt. d) NaOEt, MeOH, rt. e) i) ethanedithiol, TFA, reflux ii) raney nickel, EtOH f) LiAlH₄.

1.5.3 Related Synthetic Targets

(+)–Tetrabenazine (128) used clinically for the management of movement disorders, functions to deplete brain mono-amine levels via inhibition of the vesicular monoamine transporter type 2 (VMAT2). In humans, tetrabenazine (128) is rapidly and extensively metabolized by reduction of the 2-keto group, producing α- and β-dihydrotetrabenazine
These alcohols also have high in vitro affinity for the VMAT2, and are likely the pharmacologically active agents in the mammalian brain.\textsuperscript{66}

1.6 The Manadomanzamine Alkaloids

1.6.1 Background Information

Since the mid 1980s there has been a dramatic re-emergence of cases of tuberculosis around the world, with the WHO estimating that one-third of the world’s population is currently infected, with 3.1 million deaths annually.\textsuperscript{67} The rapidly increasing threat posed by tuberculosis globally, particularly to women, adolescents and AIDS victims has stimulated a renewal of interest in discovering novel antituberculosis agents.

In 2003, Hamann and co-workers identified two novel manzamine based alkaloids as potential marine-derived anti-infective leads.\textsuperscript{68} Indeed, both manadomanzamine A (130) and manadomanzamine B (131), isolable from the Indonesian sponge \textit{Acanthostrongylophora} \textit{sp.}, exhibit significant activity against \textit{Mycobacterium tuberculosis} (Mt\textit{b}). Impressive MIC values of 1.9 and 1.5 \(\mu\text{g/ml}\) were attained for (130) and (131) respectively, and significant activities against both human immunodeficiency virus (HIV-1) and AIDS opportunistic infections (OIs) were also documented.
1.6.2 Proposed Biogenetic Pathway of Manadomanzamines A and B

Manadomanzamines A (130) and B (131) represent an unprecedented rearrangement of the manzamine skeleton and thus the alkaloids are suggested to derive from the more prevalent manzamines (Scheme 38).
Manzamine B (132) is first reduced to tetrahydromanzamine B (133) and then oxidation of C-22 to form the imine (134) is followed by hydrolysis of the C-22–N-21 bond to furnish aldehyde (135). The aldehyde is, in turn, condensed with N-2 to construct the new ring (136), and N-21 attacks at C-12 leading to ring opening of the epoxide. The non-stereoselective addition of the 2-ketopropyl is thought to occur either before the cleavage of the C-22–N-21 bond or after forming the C-22–N-2 bond.
1.6.3 Racemic Preparation of the Dodecahydrobenz[a]indolo[3,2-h]quinolizine System

The pentacyclic dodecahydrobenz[a]indolo[3,2-h]quinolizine ring system, sometimes referred to as an ‘inside yohimbane’ has previously been prepared in racemic fashion by Morrison et al. The system was accessed via condensation of tryptamine (137) with 2-formylcyclohexanecarboxylic acid (138) and with subsequent LiAlH₄ reduction of the lactam carbonyl functionality (Scheme 39).

Fractional crystallization of the crude lactam afforded a 60% yield of two trans epimers assigned as (139a) and (139b). It was proposed that reduction of these lactams gave the trans series of inside yohimbanes (140a) and (140b), as earlier preparation of (138) had revealed a significant trans bias.
1.7 Stereoselective Synthesis of Indole Alkaloids

The indolo[2,3-a]quinolizidine ring system (141) is a common core of a plethora of highly bioactive indole alkaloids and has thus generated great interest as a target heterocycle.

Deplancheine (142) is an alkaloid isolated from the New Caledonian plant *Alstonia* deplanchei. Geissoschizine (143) is a pivotal biosynthetic intermediate for many monoterpenoid indole alkaloids and is of the corynantheoid class. Vellosimine (144), a sarpagine alkaloid, has been associated with curare-like activity.

Recent examples of the construction of this heterocycle include the use of the asymmetric Pictet-Spengler reaction in the synthesis of (+)-geissoschizine (143), and the diastereoselective vinylogous Mannich reaction employed by Martin, similarly towards (143). Other approaches of note include a Fischer indole synthesis undertaken by Montgomery and an application of the Bischler-Napieralski reaction, also by Martin et al.
Allin et al. have recently developed a stereoselective synthesis of the indolo[2,3-\(a\)]quinolizidine scaffold utilizing an indole nucleophile in a \(N\)-acyliminium cyclisation as previously described (Scheme 13).\(^3\)

The hydroxymethyl auxiliary group was removed via a series of oxidative steps, culminating in a tin mediated decarbonylation of the phenyl seleno ester (146) (Scheme 40).\(^3\)

![Scheme 40](image)

The presence of the lactam carbonyl moiety in the key BOC-protected building block (147) allows for divergence towards a range of natural product targets via selective chemistries (Scheme 41).
In route 1, the ethylidene moiety was inserted through a three-step procedure, commencing with generation of the lithium enolate of (147) and subsequent aldol reaction with acetaldehyde. Hydroxyl group activation was achieved by mesitylation and then followed by DBN-induced elimination to give BOC-protected (148). TBAF was employed in order to liberate the indole nitrogen and finally the lactam carbonyl group removed as previously reported by Martin. The desired target, (R)-(+)−deplancheine (142) was isolated with an ee of >95%. 

The alternative route towards the indole alkaloid derivative (+)-12b-epidevinylantirhine (route 2) begins with the introduction of α,β-unsaturation in order to facilitate Michael addition at the 2-position. A suitable nucleophile, in this case 1,3-dithiolane-2-carboxylate was lithiated and added to afford key intermediate (150) as a single diastereoisomer in 47% yield. Desulfurisation of the dithioacetal with nickel boride was followed by formic acid deprotection of the indole nitrogen. Finally, global reduction of
the methyl ester and lactam carbonyl with lithium aluminium hydride furnished the desired target (151) in 50 % yield. 79
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Chapter 1 References
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CHAPTER TWO:

POLYCYCLIC ALKALOIDS

RESULTS AND DISCUSSION
2.0 Stereoselective Synthesis of Polycyclic Alkaloid Templates

2.1 Stereoselective Synthesis of the Tetrahydro-$1H$-pyrido[2,1-$a$]isoquinoline Ring System

Access to the tetrahydroisoquinoline core of the benzo[$a$]quinolizidine class of alkaloids is now well established within our group. Methodology developed by Allin and Vaidya\textsuperscript{62} allowed access to (152) and (126) in reasonable yield and with excellent diastereoselectivity. More recently, Allin and Thomas\textsuperscript{30} have successfully manipulated the indolo[2,3-$a$]quinolizidine template in order to furnish both enantiomers of the indole alkaloid deplancheine (Scheme 41). It was envisaged that a coupling of these methodologies would facilitate novel entry to the biologically active benzo[$a$]quinolizidine family of alkaloids (Figure 4).

(+)-Protoemetinol (120) and alangine (124) differ in the type of carbon substituents on the heterocyclic ring with the key point being that they exhibit the opposite relative stereochemistry at the 2 and 11$b$ positions.

Figure 4

Chapter 2 Results and Discussion

47
The three step procedure employed to obtain the benzo[a]quinolizidine derivative (152) from (S)-phenylalaninol is illustrated in Scheme 42.

![Scheme 42](Image)

The synthesis began with the reduction of the readily available (S)-phenylalanine (153) using lithium borohydride and chlorotrimethylsilane to yield enantiomerically pure β-aminoalcohol (154). It is hypothesised that the reduction proceeds via a borane-tetrahydrofuran complex (157) with chlorotrimethylsilane assisting to act as the reducing agent (Scheme 43). The amino alcohol was obtained in 95% yield and required no further purification.

![Scheme 43](Image)

The β-aminoalcohol was condensed under Dean-Stark conditions with the appropriate keto-ester (155) for 48 hours to give a 4:1 diastereomeric ratio (with respect to the protons on C-2 and C-5 of (156)) in 50% yield. The major isomer (156a) has syn relative stereochemistry as confirmed by 1D NOE experiments (Figure 5).
With syn-(156a) isolated, focus was directed toward the intramolecular N-acyliminium cyclisation. Treatment of syn-(156a) with 1.5 eq of TiCl₄ at -10 °C in anhydrous DCM for 20 hours resulted in the isolation of cyclised product (152) as a single diastereoisomer in 65% yield. Interestingly, it was also found that subjecting anti-(156b) to identical reaction conditions produced the same diastereoisomer, irrelevant of the stereochemistry before the planar iminium was formed. Thus, in subsequent synthesis of (126), the chromatographic separation of bicyclic lactam diastereoisomers (125a) and (125b) was deemed unnecessary and the crude mixture of (125) was carried forward to the TiCl₄ mediated cyclisation reaction (Scheme 44).

2.2 Stereoselective Synthesis of the Dimethoxy-tetrahydro-1H-pyrido[2,1-a]isoquinoline Ring System

To prepare the dimethoxy derivative of previous tricyclic ring system (152), the synthetic steps as detailed in Scheme 44 were employed.
The synthesis began with the acid catalysed transesterification of δ-valerolactone (160) with methanol to produce the ring-opened target, methyl-5-hydroxypentanoate (161), in quantitative yield (Scheme 45). This was not purified as relactonisation is known to occur readily during distillation or aqueous work up.\textsuperscript{82}

The alcohol (161) was subsequently oxidised to the corresponding aldehyde methyl-5-oxopentanoate (155), using pyridinium chlorochromate in 68 % yield (Scheme 46). The aldehyde was taken forward to the cyclocondensation reaction with no further purification required.\textsuperscript{82}
Keto-ester (155) was condensed with amino alcohol (159) under Dean-Stark conditions to furnish a 6:1 (syn/anti) mixture of isolable bicyclic lactam diastereoisomers syn-(125a) and anti-(125b) in a reasonable combined yield of 62 %.81

As previously mentioned, both syn-(156a) and anti-(156b) led to the formation of the same, enantiomerically pure tricyclic product (152). Based on this knowledge, a crude mixture containing the syn and anti epimers of (125) was carried forward to the TiCl₄ mediated cyclisation. As expected, the reaction proceeded cleanly to the formation of a single diastereoisomer (126) in considerably higher yield (79 %) than (152) (62 %).

Assuming that the condensation reaction to produce the cyclised target (126) proceeds via the N-acyliminium intermediate (127), the mechanism would be that suggested in Scheme 46a. The enhanced nucleophilic character imparted on the aryl ring by the electron donating methoxy groups is believed to result in a more efficient ring closing onto the N-acyliminium ion (127).
Single crystal X-ray analysis was employed to confirm the stereochemical outcome of the cyclisation i.e. the syn relationship between the C-15 hydroxymethyl auxiliary and the C-5 proton (Figure 6). Furthermore, 1D NOE studies revealed no signal enhancement of H-15 when irradiating the H-5 signal and vice versa.

Chapter 2  Results and Discussion
2.3 Rationalisation for the Stereochemical Outcome of the Cyclisation Reactions

Felkin-Anh-like conformational models can be invoked in order to rationalise the stereochemical outcome of the cyclisation reactions of bicyclic lactams (125a/b) and (156a/b). The largest substituent of the stereocentre is positioned perpendicular to the carbonyl group to give two very distinct conformations. The conformational mode of the N-acyliminium ion (127) that arises from the TiCl₄ activation of the bicyclic lactam substrates (125a/b) and (156a/b) is depicted in Figure 7.⁸³
Figure 7

In the case of conformation A, which leads to the favoured products (126) and (152), the carbonyl moiety is 'eclipsed' in a 1,3-fashion by the relatively small hydrogen atom at the \( \beta \)-amino alcohol chiral centre. The steric positioning of the Lewis acid-complexed oxymethyl group here is favoured as the angular hydrogen atom at the imino carbon atom provides no sufficient steric bulk to interfere.

The alternative conformation B would give rise to the anti-epimers of (126) and (152) i.e. the minor products but neither is observed. In this case the benzyl group is positioned as the larger substituent leading to an unfavourable 1,3-destabilising interaction between the carbonyl group and the more bulky Lewis acid-complexed oxymethyl group. It is also thought possible that as TiCl\(_4\) is capable of multipoint coordination, some degree of chelation control i.e. complexation of the Lewis acid-complexed oxymethyl group to the carbonyl oxygen could occur.
2.4 Manipulation of the Dimethoxy-tetrahydro-1H-pyrido[2,1-a]isoquinoline Ring System

Having developed a synthetic route to the dimethoxy-tetrahydro-1H-pyrido[2,1-a]isoquinoline core, which forms the synthetic base of several biologically interesting benzo [a]-quinolizidine alkaloids, we decided to investigate template functionalisation. The presence of a reactive carbonyl group on the C ring provides a handle for derivatisation e.g. enolate derivatisation and potential conjugate addition to ring C (Figure 8). The presence of asymmetry in the molecule, set up by the cyclisation reaction, could provide stereocontrol for the aforementioned functionalisation reactions. It was reasoned that investigation of these elaborative procedures would determine the suitability of our template as an intermediate in the synthesis of target alkaloids.

![Figure 8]

2.4.1 Removal of the Hydroxymethyl Substituent

It was first decided to investigate the possibility of efficient removal of the hydroxymethyl ‘handle’ as it is not present in any of the benzo[a]quinolizidine alkaloid targets. This would also allow for investigation of C ring elaboration in an equivalent manner to protecting the hydroxymethyl group, which will also be examined. Our proposed route for removal of the hydroxymethyl group from (126) consisted of a four-step tin-mediated radical decarbonylation strategy (Scheme 47).
The initial step involved oxidation of (126) to produce the corresponding aldehyde (162). The aldehyde was obtained as a single diastereoisomer with the use of either Dess-Martin periodinane or its precursor IBX in yields of 63 % and 70 % respectively. The reagent of choice was IBX, not only due to the higher yield attained, but also owing to its facile formation from the cheap and readily available starting materials 2-iodobenzoic acid and potassium bromate. The aldehyde (162) was oxidised with sodium chlorite in straightforward fashion as previously demonstrated by the group on indole-based
templates, and acid (163) was isolated in a respectable 86% yield. Initial attempts to synthesise the phenyl seleno ester (164) with diphenyl diselenide and tri-n-butyl phosphine proved successful but in extremely poor yields (ca. 20-30%) under similar conditions to those employed by Martin. Yields were improved significantly by refluxing the reaction for 20 h, and acyl selenide (164) was isolated in 76% yield.

The phenyl seleno ester (164) was subjected to tin-mediated radical decarboxylation conditions in order to afford target (165) in similar fashion to previous examples by Martin. The target compound was isolated in excellent 81% yield having successfully demonstrated the removal of the hydroxymethyl substituent via an overall decarboxylation process.

2.4.2 Introduction of α,β-Unsaturation

The introduction of α,β-unsaturation was undertaken following methodology developed by Jones, Mundy and Whitehouse, whereby olefins can be readily accessed via syn elimination of the corresponding selenoxide. The procedure described by Reich to effect such a transformation was modified as detailed in Scheme 48.

\[
\begin{align*}
\text{LDA (3 eq)} & \quad \text{PhSeBr (1.5 eq)} \\
\text{THF} & \quad \text{-78 °C to rt} \\
\text{19 h} & \quad \text{SePh}
\end{align*}
\]

NOT ISOLATED

\[
\begin{align*}
\text{NaI} & \quad \text{MeOH, H}_2\text{O} \\
\text{rt, 20 h} & \quad \text{MeOH, H}_2\text{O}
\end{align*}
\]

Scheme 48

Chapter 2  Results and Discussion
The enolate of the decarboxylated product (165) was generated using LDA (3 eq) and trapped with phenylselenyl bromide (1.5 eq) at -78 °C to produce selenide (166). The selenide was not purified but directly treated with sodium metaperiodate to promote selenoxide syn elimination to give the desired α,β-unsaturated target (167) in 61% yield over 2 steps.

2.4.3 Conjugate Addition Study

With the α,β-unsaturated compound (167) in hand, our attention turned to the possible conjugate addition of a nucleophile which in turn could be further elaborated towards the desired alcohol chain. The nucleophile of choice was vinylmagnesium bromide as this has been previously highlighted as a suitable precursor for such a conversion via hydroboration. The 1,4-addition was effected by addition of vinylmagnesium bromide in the presence of stoichiometric amounts of CuCN and trimethylsilyl chloride as an accelerator (Scheme 49).

\[ \text{MeO} \quad \text{MeO} \quad \text{VinylMgBr (15 eq)} \quad \text{CuCN (7.5 eq)} \quad \text{TMSCI (7.5 eq)} \]
\[ \text{THF, -78 °C to 0 °C, then -78 °C, 24 h} \]

**Scheme 49**

The addition product (168) was isolated in 67% yield and as a single diastereoisomer, with the relative stereochemistry revealed by 1D NOE studies to be as shown in Figure 9. No positive NOE interaction was observed between the protons at positions 2 and 11b and, due to the formation of (168) as a single diastereoisomer, it was not possible to perform comparative NOE studies. We were however able to obtain more conclusive support for trans relative stereochemistry of protons 2 and 11b of the product through a positive 1D NOE interaction as indicated in Figure 9.
In the case of the nucleophilic species attacking from the opposite face, one would expect to observe the opposite NOE interactions to those mentioned. The stereochemical outcome of the conjugate addition could be explained by the preference of the nucleophilic species to adopt a pseudo-equatorial position on the lactam ring.

With target (120) in mind, we decided to attempt 1,4-addition with commercially available ethyl 1,3-dithiolane-2-carboxylate. Previous work in the group has demonstrated successful desulfurisation of the dithioacetal followed by reduction to yield the desired alcohol chain.\textsuperscript{79} Unfortunately, subjection of $\alpha,\beta$-unsaturated compound (167) to the lithiated dithiolane unit on several occasions failed to yield anything other than starting material, perhaps owing to the reversible nature of the addition (Scheme 50).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9}
\caption{Figure 9}
\end{figure}
In 2004, Vanderwal and Jacobsen\textsuperscript{90} reported a general procedure for the enantioselective hydration of $\alpha,\beta$-unsaturated imides by aluminium-catalyzed conjugate addition of oxime nucleophiles (Scheme 51). An $\alpha,\beta$-unsaturated imide (170) is treated with an oxime nucleophile to afford a crude oxime ether (172), which in turn yields catalytic hydrogenolysis product (173) in high yields without erosion of optical purity.

\begin{center}
\includegraphics[width=\textwidth]{Scheme_51.png}
\end{center}

**Scheme 51**

We envisaged that application of this methodology would allow introduction of the alcohol moiety at the C-3 position, concurrent with the functionality of tetrabenazine targets (128) and (129). Enantioselectivity was not considered important as the alcohol moiety would be oxidised to the corresponding ketone in the case of tetrabenazine (128) and could possibly be selectively reduced to produce $\alpha$ or $\beta$-dihydrotetrabenazine (129). Chlorinated, aromatic and ethereal solvents were all described as poor media for the oxime addition and therefore removed from our screening (Scheme 52). Unfortunately, all attempts to access oxime ether (174) failed to yield anything other than starting material.
After these disappointing results, we decided to investigate the viability of epoxidation in order to introduce oxygen at the 2 position. We first attempted to form epoxide \((175)\) using standard electrophilic peracid conditions, but only starting material was recovered, presumably due to the electron deficiency of the conjugated alkene \((167)\). However, epoxidation with a standard nucleophilic epoxidising species, hydrogen peroxide (2 eq) with sodium hydroxide (2 eq) in water, also failed to yield target \((175)\) (Scheme 53).
2.4.4 Protection of the Hydroxymethyl Substituent

In view of the fact that the opposite stereochemistry at the 2 position of (168) is required to proceed toward our initial target (-)-protemetinol (120), a new strategy was devised for the 1,4-addition. It was thought possible that facial selectivity could be reversed by leaving the hydroxymethyl substituent intact and protecting with a group of extreme steric bulk. Protection of the hydroxymethyl was carried out with imidazole (3 eq) followed by DMAP (0.1 eq) and TBDPSCI (1.5 eq) to give (176) in almost quantitative yield (Scheme 54).91

\begin{center}
\begin{tikzpicture}
\node at (0,0) {meo \quad meo \quad \text{imidazole (3 eq)}}; \node at (1.5,0) {\quad \text{DMAP (0.1 eq)} \quad \text{TBDPSCI (1.5 eq)}}; \node at (0,-1) {meo \quad meo \quad meo \quad meo \quad \text{otbdps}}; \node at (1.5,-1) {meo \quad meo \quad meo \quad meo \quad \text{otbdps}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 54}
To TBDPS protected compound (176) was added LDA (3 eq) and then PhSeBr (1.5 eq) at -78 °C to furnish selenide (177). The limited solubility of (177) hindered selenoxide elimination, and as a result, the corresponding α,β-unsaturated compound (178) was only isolable in 42 % yield. It was possible however to recover virtually all of the unreacted selenide and repeat the process.

The conjugate addition product (179) was accessed using conditions similar to those previously described in the synthesis of the analogous compound (168), Scheme 49. Analysis of the crude ¹H-NMR spectrum of the product indicated the formation of a single diastereoisomer which was purified via column chromatography to give (179) exclusively in 70 % yield. The attempt to block the β-face from nucleophilic attack was confirmed to have failed by undertaking a 1D NOE study. As previously observed, no positive NOE interaction was seen for the protons at positions 2 and 11b. The positive NOE interaction between proton 11b and the vinyl proton (Figure 9) was evidence enough to assign the relative stereochemistry as cis.

In contrast to the axial attack of the vinyl cuprate under stereoelectronic control to give the kinetic product (179) (Scheme 54), the conjugate addition of the enolate of ethyl 1,3-dithiolane-2-carboxylate to unsaturated lactam (178) affords a 1:1 mixture of isomers (Scheme 55). It is reasoned that the conjugate addition may be reversible in this case and thus both isomers (180a) (2,11b, trans, kinetic) and (180b) (2,11b, cis, thermodynamic) are formed under the reaction conditions (-78 °C to rt, 24 h).
2.5 Amino Alcohol Scale Up Attempt

In order to produce amino alcohol (159) on a multi-gram scale for the preparation of the dimethoxytetrahydro-1H-pyrido[2,1-a]isoquinoline template, the steps detailed in Scheme 56 were undertaken.

Initial Boc protection of the amine of L-DOPA (181) with Et$_3$N (1.2 eq) followed by Boc$_2$O gave (182) in quantitative yield. Protection of the amine was necessary to facilitate regio-selective methylation in the subsequent step towards (183). The protected species was exposed to KOH (1.1 eq) followed by MeI (1.1 eq) to initially yield the ester. Secondly, the methoxy groups that are required in the target amino alcohol (159) were
introduced by simple repetition of addition of KOH (2.2 eq) followed by MeI (2.2 eq) to furnish (183) in a 76 % yield.

Elaboration of compound (183) to the target aminoalcohol (159) was achieved via reduction of the ester group with NaBH₄ (4 eq) giving (184) in excellent 89 % yield. This was followed by Boc-deprotection with TFA (20 eq) to produce target compound (159) in 84 % yield. ¹H-NMR analysis indicated the formation of an enantiomerically pure product, with no epimerization noted.

Although we have successfully demonstrated the synthesis of the target amino alcohol (159) from cheap, commercially available L-3-(3,4-dihydroxyphenyl)alanine, scaling up to 20g of starting material resulted in significant yield loss and therefore the route was deemed impractical.

2.6 Literature Approaches Towards Benzo[a]quinolizidine Systems

In a very similar approach to our group, Garcia et al.⁹² developed methodology for the construction of the benzo[a]quinolizidine skeleton involving either a Parham or N-acyliminium ion cyclisation. α,β-Unsaturation was introduced by an oxidative elimination of a selenoxide in order to facilitate screening of sulfur-stabilised anions (Scheme 57).
For the conjugate additions, 2-lithio-1,3-dithiane and bis-(phenylthio)methyl lithium were chosen as the group had previously shown their differing behaviour in 1,4-additions. The latter anion would be more stable whereas its acyclic structure allows rotation, optimising orbital overlap with the conjugate acceptor. It was observed that no reaction took place when conjugate acceptors (167) and (187) were added to the lithiated anions at -78 °C. Optimisation revealed that 1,4-addition occurred when the anion was allowed to reach room temperature with subsequent quenching with (167) or (187) (Table 4). This could possibly account for the failure of lithiated ethyl 1,3-dithiolane-2-carboxylate to undergo addition to (167) as illustrated in Scheme 50.
(167), (187) → \( \text{a)} \) (Table 4)

\[
\begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array}
\end{array}
\]

\[
\begin{array}{c}
\begin{array}{c}
\text{R}^1 \text{S} \text{R}^2
\end{array}
\end{array}
\]

Reagents: \( \text{a)} \) (R\(_2\)S\(_2\))CHLi, - 78 °C, 1 h.

Scheme 58

<table>
<thead>
<tr>
<th>Entry</th>
<th>RLI</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>t (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>dr trans/cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhS\rightarrow Li PhS</td>
<td>H</td>
<td>Ph</td>
<td>16</td>
<td>189a</td>
<td>5(^a)</td>
<td>&lt;5:95</td>
</tr>
<tr>
<td>2</td>
<td>PhS\rightarrow Li PhS</td>
<td>H</td>
<td>Ph</td>
<td>5</td>
<td>189a</td>
<td>70</td>
<td>&lt;5:95</td>
</tr>
<tr>
<td>3</td>
<td>(\text{S}\rightarrow\text{S}\rightarrow\text{Li})</td>
<td>H</td>
<td>-(CH(_2)_3(-</td>
<td>5</td>
<td>189b</td>
<td>85</td>
<td>&lt;5:95</td>
</tr>
<tr>
<td>4</td>
<td>PhS\rightarrow Li PhS</td>
<td>Me</td>
<td>Ph</td>
<td>16</td>
<td>190a:191a</td>
<td>93</td>
<td>80:20</td>
</tr>
<tr>
<td>5</td>
<td>(\text{S}\rightarrow\text{S}\rightarrow\text{Li})</td>
<td>Me</td>
<td>-(CH(_2)_3(-</td>
<td>16</td>
<td>190b:191b</td>
<td>84</td>
<td>85:15</td>
</tr>
<tr>
<td>6</td>
<td>(\text{S}\rightarrow\text{S}\rightarrow\text{Li})</td>
<td>Me</td>
<td>-(CH(_2)_3(-</td>
<td>5</td>
<td>190b:191b</td>
<td>75</td>
<td>88:12</td>
</tr>
</tbody>
</table>

\(^a\) Cyclopropane derivative obtained in 68 %.

Table 4

Chapter 2  Results and Discussion  67
Thus, benzo[a]quinolizinones (167) and (187) undergo conjugate addition of sulfur-stabilised anions with opposite facial selectivity. These results are in agreement with those published by Amat and Bosch, who have examined the factors controlling facial selectivity in the 1,4-addition of several nucleophiles to phenylglycinol-derived unsaturated bicyclic lactams. Similar effects have been observed by Allin for conjugate addition reactions on various indolo[2,3-a]quinolizine templates.

In the case where R = H (167), nucleophilic attack proceeds under stereoelectronic control, parallel with respect to the axial hydrogen 11b (exo attack). This gives rise to a 1,3-syn diaxial interaction between the substituents in the resulting intermediate A (Figure 10). However for (187) (R = Me), also a conformationally rigid lactam, anti-parallel attack to yield the more stable trans diastereoisomer through an intermediate such as B is observed. This is promoted by the unfavourable 1,3-syn diaxial interaction in the intermediate or the transition state leading to it.

![Diagram](image_url)

**Figure 10**
Of great importance in this area is the enantioselective two-step route to polyfunctionalised benz[a]quinolizidines developed by Amat and Bosch. The approach involves the stereoselective condensation of a racemic or prochiral δ-oxo(di)ester (192a-c) with (3,4-dimethoxyphenyl)alaninol (159). The resulting masked N-acyliminium ion present in the bicyclic lactams (193a-c) generated facilitates stereocontrolled cyclisation on the aromatic ring (Scheme 59). The amino alcohol used not only serves as the chiral inductor for the cyclocondensation; it is also used to assemble the final target polycyclic products.

Scheme 59

Cyclocondensation of amino alcohol (159) with racemic γ-alkyl δ-oxoester (192a), which contains a stereocentre capable of epimerization, gave (193a) as the major product out of
the four possible enantiopure stereoisomeric lactams. The process involved a dynamic kinetic resolution (DKR) of the racemic substrate with minor amounts of the diastereoisomer at the 8 and 8a positions formed. Oxodiester (192b) was similarly condensed to furnish enantiopure lactam (193b) in 67% yield with minor amounts of the diastereoisomer at the 7 and 8a positions. The process involved the desymmetrisation of the two enantiotopic ester chains. More interestingly, treatment of racemic δ-oxoester (192c) with amino alcohol (159) constructed three stereogenic centres in a single stereoselective step to give 60% of (193c). Of the other seven possible stereoisomeric lactams, only the diastereoisomer at the 2, 8 and 8a positions was isolated in a minor amount.

The stereoselective cyclisation of lactams (193a-c) was promoted with either BF₃·Et₂O or TiCl₄ to give enantiopure benzo[a]quinolizidines (194a-c) (detectable by NMR spectroscopy). N-acyliminium ion cyclisations upon the 3,4-dimethoxybenzene ring are known to occur under kinetic conditions without stereochemical equilibration. This gives rise to the rationale that the 6,11b-trans relationship seen for (194a-c) is of a result of stereoelectronically controlled axial attack of the aromatic ring as shown in conformer A (Figure 11).

The alternative cyclisation via the chair-like conformation B is disfavoured due to the allylic 1,3-strain between the pseudoequatorial hydroxymethyl substituent (Lewis acid complexed) and the lactam carbonyl. The hydroxymethyl auxiliary plays a decisive role.

Chapter 2  Results and Discussion  70
as a stereocontrol element in determining the relative stereochemistry of chiral centre 11b generated through cyclisation. Such models are analogous to those proposed by our own research group.

**Scheme 60** depicts the removal of the hydroxymethyl appendage from (194b) to give the enantiopure cis-benzo[a]quinolizidine-2-acetate (195) that matches the relative cis stereochemistry of important targets such as protoemetinol (120) at centres 2 and 11b. This is complementary to the trans relative stereochemistry set up at the 2 and 11b positions by our group, which covers trans-type targets such as alangine (124).

The synthetic steps employed to oxidise to the carboxylic acid which is in turn converted into a seleno ester and radically decarbonylated, are those recently developed by Allin\(^{30}\) and also applied to the unfunctionalised piperidine derivative of (194b), (126) (Scheme 47).

### 2.7 Conclusion

In summary we have developed a facile and highly stereoselective approach to the important dimethoxytetrahydro-1H-pyrido[2,1-\(\alpha\)]isoquinoline ring system from readily available non-racemic substrates. The formation of an \(N\)-acyliminium intermediate allows for the key cyclisation via attack of a pendant aromatic substituent nucleophile.
We have also demonstrated the removal of the hydroxymethyl appendage from the system, highlighting the potential of our novel template for manipulation towards synthetic targets. Furthermore we have functionalised the C-3 position of our polycyclic template (126) through the application of Michael addition chemistry, which may constitute a key step in our future progression towards our targets.

Schemes 61 to 63 provide a rounded overview of the key transformations described throughout this chapter.

- Stereoselective synthesis of a dimethoxytetrahydro-1H-pyrido[2,1-a]isoquinoline derivative through cyclisation of an N-acyliminium intermediate (Scheme 61).

\[
\text{(125a/b) \xrightarrow{\text{MeO, TiCl}_4 (3 \text{ eq})} \text{DCM, -78 °C}} \quad \text{(126)}
\]

Scheme 61

- Removal of the pendant hydroxymethyl substituent from (126) via radical decarbonylation of an acyl selenide (Scheme 62).

\[
\text{MeO, Toluene} \quad \text{MeO, Toluene} \quad \text{MeO, Toluene}
\]

\[
\text{MeO \xrightarrow{\text{Tolene, 80 °C, 24 h}} \text{MeO}} \quad \text{MeO \xrightarrow{n-\text{Bu}_3\text{SnH}} \text{MeO}} \quad \text{MeO \xrightarrow{\text{AIBN}} \text{MeO}}
\]

\[
\text{(164) \xrightarrow{n-\text{Bu}_3\text{SnH}} \text{(165)}}
\]

Scheme 62

- Functionalisation of \(\alpha,\beta\)-unsaturated compound (167) via diastereoselective 1,4-addition of a vinyl group (Scheme 63).

Chapter 2  Results and Discussion  72
Scheme 63
2.8 Asymmetric Construction of the Dodecahydrobenz[a]indolo[3,2-h]quinolizine Ring System

2.8.1 Introduction

Access to the pentacyclic dodecahydrobenz[a]indolo[3,2-h]quinolizine ring system (196) is of great interest as this heterocyclic template is a common sub-structure of several bioactive indole alkaloids (Figure 12). Manadomanzamine A and B (130/131) exhibit strong activity against *Mycobacterium tuberculosis* and HIV-1 and Aids opportunistic infections.\(^{68}\)

Manzamine A (197) and related structures are highly potent, orally bioavailable antimalarial agents that are more effective than most currently available therapeutics, i.e. chloroquine and artemisinin.\(^{100}\) Manzamine B (132) was isolated by Higa and co-
workers in 1987 from the marine sponge *Haliclona* sp., collected from Okinawa. Its quite unique and complex structure contains a $\beta$-carboline and tetracyclic ring system as well as 11- and 13-membered aza-cycles with (Z)-olefins. Initial screening revealed cytotoxicity against P388 mouse leukaemia cells (IC50 6 $\mu$g/ml), but more material is required for a complete survey.

### 2.8.2 Synthetic Strategy

Our research group, and others, have reported a substantial body of work in recent years on the development of asymmetric routes towards important heterocyclic templates centred upon novel, highly diastereoselective $N$-acyliminium cyclisations. Allin *et al.* have recently applied this methodology in the successful construction of several indole alkaloid targets. Identical retrosynthetic principles were applied to the manadomanzamine core and consequently **Scheme 64** was devised.

![Scheme 64](image)

Pentacyclic target (196), with three contiguous stereocentres at ring positions 1, 10 and 24 was deconstructed to furnish (S)-tryptophanol (198) as both the source of indole moiety and chiral auxiliary. Also revealed is bi-functional aldehydo-acid (138), required to facilitate initial lactamisation and eventually become the octahydroisoquinolin-3(4H)-one component of the template.

Bi-functional substrate (138) was prepared using a procedure previously employed by Cook and co-workers whereby ketones are homologated via Wittig functionalisation and subsequent hydrolysis to yield the corresponding aldehyde (**Scheme 65**).
Commercially available ketone (199) was converted to the corresponding enol ether (200) in 64% yield using methyltriphenylphosphonium chloride (2 eq) and potassium tert-butoxide (3 eq). Subsequent treatment with 2M HCl served the dual purpose of ester and vinyl ether hydrolysis to furnish (138) as a mixture of cis and trans isomers (1:3) in quantitative yield. The preparation of (S)-tryptophanol on a multi-gram scale is routine within the group and this was prepared cleanly in 82% yield (Scheme 66).

Bosch and Amat have investigated the use of racemic multi-functional aldehyde substrates in stereoselective condensation reactions in some detail.\textsuperscript{56} In a similar fashion, aldehyde (138), a racemate, and (S)-tryptophanol were subjected to the standard Dean-Stark conditions in toluene for 24 h to give a 1:1 mixture of two readily separable diastereoisomers (202a/b) in 69% yield (Scheme 67).
The relative stereochemistry of (202a) was determined by NOE studies as summarised in Figure 13. The protons at ring positions 1 and 24 give a positive NOE to each other while neither gives an NOE to the proton at ring position 10. Further confirmation of the relative trans stereochemistry across the ring junction C-10 to C-24 is provided via the positive NOE interaction between the proton at C-1 and the proton of fixed stereochemistry from the chiral auxiliary.

Crucially, diastereoisomer (202a) has both the relative and absolute stereochemistry that matches that of the manadomanzamine natural products at the C-10 and C-24 positions. At this point, the stereochemistry revealed at the C-1 position bore no significance as it is this hemiaminal centre that is lost during formation of a planar iminium species in the key N-acyliminium-mediated cyclisation step. The relative stereochemistry of the second diastereoisomer (202b) was elucidated by X-ray crystallographic analysis and may prove useful in future analogue generation studies (Figure 14).
In order to rationalise the stereochemical outcome of each cyclocondensation, the formation of hemiaminal intermediates (203a) and (203b) from each enantiomer of aldehyde (138) was studied (Scheme 68).

Scheme 68

Chapter 2  Results and Discussion
In each case a trans-decalin like conformation is adopted in the reactive intermediate, with an all equatorial substitution pattern. These favoured arrangements serve to minimise diaxial interactions, with the H-atom at the hemiaminal centre for both (203a) and (203b) assuming an axial orientation prior to irreversible lactamisation.

2.8.4 Stereochemical Outcome of the Cyclisation Reactions

With bicyclic lactam (202a) in hand, we turned our attention to the key N-acyliminium cyclisation step in order to construct the pentacyclic manadomanzamine natural product framework. Subjection of masked N-acyliminium ion (202a) to 2M HCl in ethanol for 18 h at room temperature induced acid-catalysed cyclisation to give (204a) as a single diastereoisomer in 73\% yield (Scheme 69).

\[
\begin{array}{c}
\text{HN} & \text{O} & \text{N} & \text{SO} \\
\text{2M HCl} & \text{EtOH} & \text{rt, 18 h} & \text{H} \\
\text{(202a)} & \text{(204a)} & \text{(204a)}
\end{array}
\]

Scheme 69

NOE experiments were again undertaken to reveal that the relative and absolute stereochemistries at ring positions 1, 10, and 24 of (204a) matched that of the natural product. The hydroxymethyl (CH\text{2}) group gives a positive NOE to the proton at ring position 1 which in turn gives a positive NOE to the proton at position 24. Neither of protons 1 or 24 gives a positive NOE to the proton at ring position 10.

We proposed that the stereocontrol observed arises from conformation (205a) (Figure 15), which would allow for minimal A\text{1,3} strain between the lactam carbonyl group and
the H-atom at the stereogenic centre of the tryptophanol moiety. The indolyl nucleus subsequently attacks from a pro-equatorial orientation leading to a seemingly preferred axial positioning of all three H-atoms at the three contiguous chiral centres C-1, 10 and 24.

Identical conditions to those described for the cyclisation of (202a) (Scheme 69) were applied to lactam substrate (202b) which bares the desired relative trans stereochemistry across the ring junction C-10 to C-24 but not the correct absolute stereochemistry. Cyclisation proceeded cleanly to give a comparable 75 % yield of a single diastereoisomer as illustrated in Scheme 70.

In this instance NOE studies led to the stereochemical assignment above (204b) as protons at the 1 and 10 positions of the ring give a positive NOE to each other. The

Chapter 2  Results and Discussion  80
hydroxymethyl CH$_2$ also gives a positive NOE to the proton at the 1 position but no signal enhancement of either H-1 or H-10 was observed when irradiating the H-24 signal and vice versa.

In order to explain the stereochemical outcome observed, the transition state must lead to a pro-axial attack onto the N-acyliminium ion (Figure 16). Despite this requirement, the preferred conformation (205b) is adopted in order to minimize the A$^{(1,3)}$ strain between the H-atom at the stereogenic centre of the tryptophan moiety and lactam carbonyl group.$^{103}$

\[ \text{(205b)} \]

\textbf{Figure 16}

2.9 Development of a Functionalised Dodecahydrobenz[a]indolo[3,2-h]quinolizine Ring System

With successful construction of test template (204a) in hand, we needed to modify the aldehydo-acid substrate to incorporate a masked ketone functionality for subsequent enolate functionalisations of the A ring. Also, the ketone is required to introduce one of the two terminally-unsaturated alkylamine substituents that are put in place via reductive amination. Our full retrosynthetic analysis details the importance of such a handle in order to introduce RCM precursors (Scheme 71).
2.9.1 Modification of Wittig/Hydrolysis Homologation Route

It was initially envisaged that the starting material employed in the adapted Cook procedure\textsuperscript{102} (Scheme 65) to yield aldehydo-acid (138) could be simply fine-tuned to prepare our revised bifunctional target (211) with analogous chemistries. Commercially available 1,4-cyclohexanedione monoethylene acetal (208) was converted to the corresponding methyl ester (209a) by simple enolate formation with KHMDS (1.15 eq) and subsequent trapping with methyl bromoacetate (1.15 eq). Having obtained (209a) in 72 \% yield following flash column chromatography, repetition of the Wittig chemistry...
used to prepare vinyl ether (200) failed to deliver the analogous acetal-protected compound (210) (Scheme 72).

![Chemical Reaction Diagram](image)

**Scheme 72**

It was revealed by $^1$H-NMR and HMQC studies that the acetal protecting group was sensitive to the Wittig reagent and as a direct result; an intractable mixture of mono and bis-enol ethers was obtained. This in turn prevented our global hydrolysis strategy to reveal aldehydo-acid (211) with the desired A-ring ketone in place.

### 2.9.2 Adaptation of Darzens Procedure

The next step taken was to examine the Morrison protocol for the preparation of 2-formylocyclohexaneacetic acid (138) in the previously discussed synthesis of inside yohimbanes (Chapter 1, Scheme 39). In similar fashion to our Wittig/hydrolysis protocol, ethyl 2-(2-oxocyclohexyl)acetate (199) is the chosen starting material but the homologation is achieved via Darzen’s condensation to furnish glycidic ester (212). Base catalysed hydrolysis and decarboxylation gave a mixture of the corresponding lactone (213) and aldehyde (138). The mixture was refluxed with dilute acid to promote the
establishment of an equilibrium mixture of the cis and trans isomers of (138) with the trans isomer predominating ca. 1:3 respectively (Scheme 73).

(209b) was prepared through a suitable enolate alkylation using the previously established conditions (Scheme 72). Slight fine-tuning of the Darzen conditions was required, with crude epoxide (214) being formed in 74% yield using potassium tert-butoxide (1.5 eq) and ethyl chloroacetate (1.6 eq) in ether at low temperature. Rather unfortunately, (214) proved to be sensitive to chromatography and all attempts to promote the hydrolysis/decarboxylation sequence on crude (214) failed with either starting material recovered or an intractable mixture formed in each case (Scheme 74).
2.9.3 Development of a Hydroboration/Oxidation Protocol

With our initial strategies failing to deliver either an acetal protected or deprotected derivative of our initial substrate ethyl 2-(2-oxocyclohexyl)acetate (199), our attention was turned to attempting an in situ hydroboration/oxidation sequence. Application of standard Wittig conditions to keto-ester (209a) delivered the required alkene substrate (217) in quantitative yield. The first approach employed standard hydroboration conditions\textsuperscript{104}, but we were not able to effect oxidation of the boronated intermediate to produce (218) using hydrogen peroxide in sodium hydroxide. However, simple exchange of oxidising reagent from hydrogen peroxide to pyridinium chlorochromate, mirroring an in situ procedure applied to 1,4-cyclohexanedione monoethylene acetal (208) by Bonjoch,\textsuperscript{105} afforded key aldehyde (219) directly in 70% over 2 steps (Scheme 75).

\[
\begin{align*}
\text{(209a)} & \xrightarrow{\text{CH}_3\text{PPh}_3\text{Br, NaH, THF, rt}} \text{(217)} \\
\text{(217)} & \xrightarrow{\text{H}_3\text{B-SMe}_2, \text{NaOH, H}_2\text{O}_2, \text{THF, rt}} \text{(218)} \\
\text{(218)} & \xrightarrow{\text{oxidation}} \text{rac-(219)}
\end{align*}
\]

Scheme 75
2.9.4 Stereochemical Outcome of the Cyclocondensation Reactions

With acetal-protected bifunctional substrate (219) in hand, our focus turned to the proposed cyclocondensation reaction with (S)-tryptophanol in order to generate asymmetric building blocks (220a) and (220b). Application of Dean-Stark conditions afforded two readily separable diastereoisomers in a modest 45% yield as illustrated in Scheme 76. The ratio of isomers in the crude reaction mixture was confirmed as 1:1 by $^1$H-NMR studies, this being identical to the analogous lactams (202a/b) lacking A-ring functionalisation.

![Scheme 76](image)

The absolute stereochemistry of hexacyclic lactam (220a) was confirmed using 1D NOE studies, as all attempts to produce a crystal large enough to provide a sufficient repeat unit for X-ray analysis proved unsuccessful. Signal augmentation was observed for H-24 when irradiating the H-1 signal and *vice versa*. In addition, irradiation of the H-1 signal also highlights a positive NOE interaction with the proton of known stereochemistry from (S)-tryptophanol. No enhancement of the proton at the C-10 position is observed when irradiating either the H-1 or H-24 signal (Figure 17).
The absolute stereochemistry at the three contiguous centres C-1, 10 and 24 of (220a) matches that of the manadomanzamine natural product targets as did the test substrate (202a). Also in accordance with previous results, NOE studies revealed (220b) to have the opposite trans stereochemistry across the ring junction C-10-24 to (220a). When irradiating either H-1 or 24, a signal enrichment of the other is observed but unlike (220a), no positive NOE exists between the protons at the 1 and aminoalcohol stereocentre. Furthermore, no signal augmentation of the proton at the 10 position occurred when irradiating neighbouring protons 1 and 24 (Figure 18).
2.9.5 Stereochemical Outcome of the Cyclisation Reactions

In continuation of our previously established protocol for the highly diastereoselective cyclisation of an indolyl nucleus onto such N-acyliminium intermediates, 2 M HCl in ethanol at room temperature were the first conditions applied (Scheme 77). Despite the harsh reaction conditions, vigorous stirring for 18 h or above only afforded a 1:1 mixture of deacetalised cyclised product and deacetalised lactam for both (220a) and (220b). Optimisation of these conditions revealed that for (220a), heating at 50 °C for 3 h would promote complete deacetalisation and cyclisation and the same transformation was effected in a significantly longer 18 h reaction time for (220b).

Scheme 77

In the case of lactam (220a), it appears that although the overall cyclisation/deprotection yield is comparable with that of (220b) (56 % to 58 %), the pro-equatorial attack and/or
the deacetalisation step is favoured as completion time is significantly less (15 h) than for (220b). From a synthetic standpoint, although deacetalisation at this early stage does not constitute a major challenge as differentiation with the amide carbonyl is facile, we may wish to proceed with a masked ketone until the enolate chemistries are met. For this reason we decided to screen Lewis acid catalysts to investigate the possibility of acetal retention through the cyclisation. The reason for using (220b) as the test lactam was twofold, not only is it the least valuable from a synthetic standpoint, it also appears to be more resistant to cyclisation and thus is a good standard for (220a). A full summary of parameters applied to this synthetic difficulty is given in Table 5. It was found that regardless of the level of cyclisation, complete acetal cleavage was observed without exception.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lactam</th>
<th>Acid/Lewis acid</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(220a)</td>
<td>2M HCl</td>
<td>rt</td>
<td>18</td>
<td>(221a)/(222a) (1:1)</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>(220b)</td>
<td>2M HCl</td>
<td>rt</td>
<td>18</td>
<td>(221b)/(222b) (1:1)</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>(220a)</td>
<td>2M HCl</td>
<td>50</td>
<td>3</td>
<td>(222a)</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>(220b)</td>
<td>2M HCl</td>
<td>50</td>
<td>18</td>
<td>(222b)</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>(220b)</td>
<td>TiCl₄ (3 eq)</td>
<td>-10</td>
<td>16</td>
<td>(222b)</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>(220b)</td>
<td>BF₃·OEt₂ (3 eq)</td>
<td>rt</td>
<td>16</td>
<td>(221b)/(222b) (1:1)</td>
<td>53</td>
</tr>
</tbody>
</table>

Table 5

Structural elucidation was once again achieved via NOE studies to confirm that the three contiguous chiral centres present in (222a) matched that of the manadomanzamine natural product targets. Irradiation of the proton at ring position 1 gave a positive NOE to both the proton at position 24 and one of the hydroxymethyl CH₂ protons. These three protons therefore must be on the same face of the template, and with the chirality of the hydroxymethyl centre fixed, we can assign the stereochemistry as shown in Figure 19. Rather tellingly, no signal enhancement was recorded for H-10 whilst irradiating H-1.
The second diastereoisomer (222b) was again proven to have the opposite trans stereochemistry across the ring junction C-10-24 to the required isomer (222a). Irradiation of $H-1$ resulted in a signal enhancement of both $H-10$ and hydroxymethyl CH$_2$ i.e. a positive NOE. Furthermore, when irradiating $H-10$ a signal enrichment of $H-1$ is observed but no such relationship is observed between $H-10$ and $H-24$. The stereochemical outcome of this cyclisation is summarised in Figure 20.
2.9.6 Removal of Hydroxymethyl Auxiliary

There are several well established methods within the group for the removal of the chiral auxiliary that is not present in our alkaloidal targets. The most direct route, a one step procedure involving high grade Raney nickel, was most recently applied by Allin et al in the synthesis of the anti-tumour alkaloid (R)-(+)crispine A.\textsuperscript{106} Despite effecting hydroxymethyl removal in quantitative yield however, chiral shift $^1$H-NMR studies revealed that racemisation had taken place.

In the case of our pentacyclic core (222a), we rationalised that the proton at the fixed centre C-10 would provide stereocontrol in the event of scrambling aminal centre C-1 thus eliminating the previously observed racemisation of simpler templates. Despite preparing fresh Raney nickel in the laboratory, as it has been found critical to do so in our group, only an intractable mixture was observed when attempting the reaction (Scheme 78).

Scheme 78

The possibility of rhodium catalysed decarbonylation of the corresponding aldehyde of hydroxymethyl containing alkaloid templates has been studied extensively within our group.\textsuperscript{107} Most recently, this two-step procedure was employed by Allin et al\textsuperscript{106} in the successful synthesis of (R)-(+)crispine A with an $ee > 99\%$. Initial oxidation of the hydroxyl group was achieved via IBX oxidation to give aldehyde (223) in 75 \% yield following flash column chromatography (Scheme 79).

\textit{Chapter 2 Results and Discussion}
Despite using the previously optimised conditions for decarbonylation, of 5% chlorocarbonylbis(triphenylphosphine)rhodium (I) and 12% diphenylphosphinopropane and refluxing for 4 days, the reaction failed to proceed cleanly. Only a trace amount of target compound (206) was observed by $^1$H-NMR analysis of characteristic peaks within an irresolvable product mixture.

Due to time constraints the final and previously successful four-step removal strategy (Scheme 47), involving radical decarbonylation of an acyl selenide, was not attempted.

2.9.7 Conclusion

In summary, we have developed the first highly asymmetric syntheses of pentacyclic core templates of the manadomanzamine alkaloids. Both the initial test synthesis and subsequent development of a functionalised A-ring core allow the controlled formation of the correct relative and absolute stereochemistries at the C-1, 10 and 24 positions.

Schemes 80 to 82 outline the key transformations involved in construction of the manadomanzamine heterocyclic skeleton and are described in more detail throughout this chapter.
• An *in-situ* hydroboration/oxidation protocol to liberate key trans-aldehyde rac-(219) (Scheme 80).

![Scheme 80](image)

• Stereoselective condensation of (S)-tryptophanol (198) and rac-(219) to afford key asymmetric building block (220a) (Scheme 81).

![Scheme 81](image)

• *N*-acyliminium mediated cyclisation of lactam (220a) to furnish functionalised core (222a) with the required stereochemistry at the three contiguous centres C-1, 10 and 24 (Scheme 82).
Scheme 82
References


CHAPTER THREE:
TETRACYCLINE RING SYSTEMS
INTRODUCTION
3.0 The Tetracycline Antibiotics

3.1 Background Information

The seemingly insurmountable challenge of the total synthesis of elaborate natural products which are potent antimicrobial agents has long intrigued synthetic chemists. Classically, such complex antibiotics are only accessible via multi-step manipulation of isolated natural products (semi-synthesis). The absence of a practical synthetic route restricts the quest for analogues that might be studied as new antibiotic candidates.\textsuperscript{108}

The tetracycline class of antibiotic is characterized by a common scaffold of four linearly fused six membered rings with a high density of polar functionality, labelled A to D. The A-ring is typically highly functionalized and cis-fused to the B-ring, the C-ring contains a tetrasubstituted stereogenic centre and the D-ring is aromatic. This combination is exemplified by (-)-tetracycline (Figure 21).\textsuperscript{109}

![Figure 21](image)

The tetracyclines are broad spectrum antibiotics and as a result have been extensively clinically employed in human and veterinary medicine over the past 50 years.\textsuperscript{110} This has inevitably led to the emergence of resistant strains of pathogenic bacteria, heightening resurgent interest in studying the mechanisms of resistance and in developing new antibiotics.\textsuperscript{111}
Aureomycin (224) (chlortetracycline) was the first member of the tetracyclines to be discovered, isolated from a culture of *Streptomyces aureofaciens* by Duggar in 1948. Just two years later, Finlay *et al.* described methods for the isolation and purification of a new broad spectrum antibiotic terramycin (225) (oxytetracycline) yielded from *Streptomyces rimosus*. The third known natural antibiotic in the series is demeclocycline (226) (demethylchlortetracycline).

![Chemical structures of Aureomycin, Terramycin, and Demeclocycline](image)

**Figure 22**

Second generation tetracyclines (those not available by purely microbiological techniques and synthetically manipulated) now play a major role in chemotherapy. Of these, the glycyclyclines are currently the only derivatives that exhibit antibacterial activity comparable to that of the early tetracyclines when they were first introduced. These compounds show potent activity against a broad spectrum of Gram-positive and Gram-negative bacteria, including tetracycline resistant strains. Two of the glycyclycline derivatives DMG-MINO (227) (9-aminominocycline) and DMG-DMDOT (228) (9-amino-6-demethyl-6-deoxytetracycline) (Figure 23), have been studied by several groups.
Several other unnatural, semi-synthetic tetracyclines are frequently utilized in a clinical sense, these include rolitetracycline (229) (pyrroloidinomethyltetracycline), methacycline (230) (6-methylenooxytetacycline), doxycycline (231) (6-deoxyoxytetacycline) and minocycline (232) (7-dimethylamino-6-demethyl-6-deoxytetacycline) (Figure 24).

Among the derivatives highlighted in Figure 24, those with the hydroxyl group removed from carbon 6 of the C-ring have shown particular clinical promise. These 6-deoxytetracyclines (231) and (232) exhibit greater stability and equal or greater potencies in antibacterial assays in comparison to their 6-hydroxy counterparts. However,
elaboration of natural tetracyclines is significantly limited in terms of scope and general synthetic routes to diverse tetracyclines prove elusive.

3.2 Synthetic Approaches to the Tetracyclines

Over the last 50 years there has been little variation in synthetic approaches toward the tetracycline antibiotics with the predominant area of research being limited to semi-synthesis. There is now, however, extensive literature built up around the subject stimulated by the arduous challenge that the number of proximate asymmetric centres presents. Bearing this in mind, it is deemed no small feat that all of the major tetracyclines have fallen to synthesis. The majority of approaches towards the total synthesis of tetracyclines have proceeded with a stepwise assembly of the ABCD ring system, commencing with either a D or CD-ring precursor, and are typically low yielding.

The first total synthesis of a tetracycline antibiotic was reported by Woodward and co-workers in 1968 starting with \textit{m}-methoxybenzoate (233) as the A-ring synthetic unit in the synthesis of (±)-6-demethyl-6-deoxytetracycline (234). Despite the length of synthesis and poor overall yield (25 steps, \textasciitilde0.002 \% yield), there is great historical significance in such a breakthrough (Scheme 83).
The Muxfeldt group achieved the total synthesis of (±)-terramycin (225) in 1979, adopting a novel approach with juglone (235) chosen as the starting material, a suitable CD ring precursor. The synthesis centered upon a key aldehyde (236) that could be either condensed with the corresponding oxazolone or thiazolone. The thiazoline derivative (237) was selected for simplicity and condensed with glutamate derivative (238) to construct the tetracycline core (239), and notably the A and B rings in the one step. This low-yielding but most elegant condensation created 3 new C-C bonds in a single step with the appropriate substitution as the highly crystalline desired diastereoisomer was obtained (Scheme 84).

Reagents: a) NaH, dimethyl oxalate, MeOH, DMF, 20-80 °C b) NaH, MeOH, DMF, 120 °C

Scheme 83

Chapter 3 Introduction
In 1996 the most efficient construction of the tetracycline ring system thus far was the synthesis of (±)-12a-deoxytetracycline (243) by the Stork laboratory (16 steps, 18 to 25% yield).\textsuperscript{123} Siloxyketal (241) was generated from the C ring ketone (240) with the desired simultaneous protection of the keto, tertiary hydroxyl and phenolic groups in ring C. Subsequent deprotonation initiates the cascade Dieckmann cyclisation to generate (242) in a respectable 59% yield considering the dual construction of the C and D rings. However, the absence of a hydroxyl group at the fusion point between the A and B rings is associated with greatly reduced antimicrobial activity.
3.2.1 Myers’ Asymmetric Total Syntheses of the Tetracyclines

In 2005 Myers reported a groundbreaking short and convergent enantioselective synthetic route to a diverse range of 6-deoxytetracycline antibiotics. The route was initiated by whole-cell microbial dihydroxylation of benzoic acid (which would become the B ring of the targeted 6-deoxytetracycline (231) using a mutant strain of *Alcaligenes eutrophus*. The stereogenic centre produced at the future ring junction position would elaborate all others in the target molecule. Diol (244) was obtained in a promising 79% yield and with >95% enantiomeric excess.

Innovatively, Myers’ group opted for initial construction of an AB-ring precursor enone (245) which could in turn be stereospecifically coupled to a D-ring precursor (246) via the Michael-Dieckmann reaction. This step simultaneously constructs the C ring thus
completing the four linearly fused ring scaffold of target (231). This approach allows for rapid and facile access to analogues via structural manipulation of the D-ring and also linear extensions to novel E-ring derivatives. Most significantly, of the four possible tetracycline diastereoisomers that in theory may have been yielded from this reaction, the analogues are formed as largely one diastereoisomer with stereochemistry that matches that of the natural product (Scheme 86).

Reagents: a) A. eutrophus B9 b) LDA, TMEDA, THF, then (245), -78 °C to 0 °C c) HF, MeCN d) H2/Pd, THF, MeOH

Scheme 86

Chapter 3 Introduction
Although the convergent approach is primarily designed to facilitate access to new, possibly more potent derivatives, Myers demonstrated the immense versatility of the strategy in the synthesis of (-)-tetracycline (Figure 21).\textsuperscript{124} It was devised to proceed from an AB-ring cursor (247) (10 steps from benzoic acid, 11 % yield, >95 % ee), previously employed in the synthesis of 6-deoxotetracycline analogues. The introduction of a phenylthio substituent in the α-position of the enone served to activate the molecule towards Diels-Alder cycloaddition. Heating a neat mixture of activated enone (248) with diene precursor (249) furnished the required endo-cycloadduct. Only four steps from the advanced position of having the tetracycline framework in place (250) were required in order to synthesise (-)-tetracycline (Figure 21) (Scheme 87).

\[ \text{Reagents: a) } \text{HPy·Br}_3, \text{ DCM, b) PhSH, DBU, DMF c) (249), neat, 85 \degree C} \]

\textbf{Scheme 87}
The distinct advantages of Myers' synthesis over all other previous attempts are indeed the simplicity of the starting materials and also the facile access it provides to a vast array of both natural and synthetically modified tetracyclines.

3.3 Structurally Related Linear Systems

3.3.1 The Angucycline Antibiotics

The angucyclines with a unique benz[a]anthraquinone as a common structure (Figure 25) are a rapidly growing new class of antibiotics. Urdamycinone B (251), urdamycin B (252), C104 (253) and aquamycin (254) exhibit a variety of biological activities including anti-tumour activity and enzyme inhibition.

In 1999 Matsuo and co-workers achieved the total synthesis of urdamycinone B, a prototypical member of the C-glycosylangucycline antibiotics via a novel and effective strategy without any protecting group in the sugar moiety. The synthetic approach
began with juglone (235) as a suitable CD-ring precursor, elaborated over 4 steps to yield glycosyl acceptor (255). The aryl C-glycosidation of (255) and the unprotected D-olivose (256) was realised by previously established methods, generating the desired β-C-glycoside (257). The A-ring was introduced as a constituent of the diene B-ring precursor (259) that underwent regioselective Diels-Alder cycloaddition with the unprotected dieneophile (258) to assemble the tetracyclic framework. Urdamycinone B (251) was synthesised in a further 3 steps from key intermediate (260) (Scheme 88).

Reagents: a) (256), TMSOT, MeCN, rt, 1 h b) H₂, 10% Pd/C, MeOH, rt, 1 h c) (259), B(OAc)₃, DCM, rt, 2 h d) DBU, DCM, rt, 0.5 h

Scheme 88

Chapter 3 Introduction
References


Chapter 3 References
CHAPTER FOUR:
TETRACYCLINE RING SYSTEMS
RESULTS AND DISCUSSION
4.0 A Novel Iterative Route towards the Tetracycline Antibiotics

In the ongoing quest to develop new tetracycline antibiotics in order to combat the inevitable emergence of bacterial resistance, it is most evident that recent synthetic advances in this area have been critical.

Our group has recently proposed a novel and versatile route towards linear-fused ring frameworks that could facilitate entry to the tetracycline and related natural product systems. The proposed route centres upon an innovative iterative protocol of aromatic Claisen rearrangement/ring closing metathesis (RCM) chemistries (Scheme 89).

\[ \text{Scheme 89} \]

Chapter 4 Results and Discussion
It was proposed that bis-allylation of diol (261), suitably protected at the 2 and 3 position would furnish diallyl ether (262) which would undergo Claisen rearrangement to yield hydroquinone (263). Alcohol protection and subsequent ring closing metathesis is expected to yield bicyclic linear fused adduct (264) which provides access to 1,4-napthalenediol (265) via sequential oxidation and rearomatisation. With (265) in hand, we believe it possible to construct further rings in a left-to-right fashion by recycling into the iterative process outlined, and ultimately obtain polycyclic templates such as (266).

In order to allow for functional group manipulation of the linear core at an advanced stage, alcohol protection is carried out following each Claisen rearrangement utilising complementary groups that would, at a later stage, enable selective deprotection of any pair of hydroxyl groups.

4.1 Preparation of a Bicyclic Linear-Fused Adduct

Scheme 90 depicts the successful elaboration of (267) towards the bicyclic linear-fused adduct (271) as recently demonstrated within the group. With the proposed Claisen/RCM strategies established as a viable synthetic protocol, the extended linear cores would be pursued.
Diallylation of 2,3-dimethylhydroquinone (267) using conventional conditions furnished the Claisen-precursor (268) in an excellent 92 % yield following flash column chromatography. Double aromatic Claisen rearrangement was achieved by employing methodology previously reported by Widenhoefer, whereby a bis-allyl ether such as (268) is refluxed in mesitylene for 24 hours.131 The resulting hydroquinone was obtained in a respectable 70 % yield, however it was shown to be unstable above 0 °C and consequently carried forward to the protection step without further purification.

Contrary to our preliminary results, Kotha et al.132 reported the thermal Claisen rearrangement of substrate (268) with quinone (272) as the product obtained (Scheme 91). However, this would appear to require an oxidation to occur in addition to rearrangement and subsequent analysis of our Claisen product (269) has confirmed the sole product of the reaction to be the required hydroquinone (269).

We initially chose to protect the alcohol moieties as the corresponding acetates using standard conditions to produce diacetate (270) in 90 % yield. In order to complete the first left-to-right elaboration of the linear ring system, a ring closing metathesis was performed using Grubbs 2nd generation catalyst.133 The bicyclic target (271) was isolated in an efficient 93 % yield following flash column chromatography.

Having accomplished the synthesis of key adduct (271), attention was turned to the subsequent oxidation and rearomatisation steps necessary to furnish 1,4-naphthalenediol (274). This would allow second entry into the cumulative process and hence construction.
of the third ring, a feat currently unreported in the literature to our knowledge (Scheme 92).

![Scheme 92]

4.2 Oxidation of the Bicyclic Linear-Fused Adduct

Numerous methods for the oxidation of unfunctionalised hydrocarbons have been developed over the years.\textsuperscript{134} The dual benzylic and allylic properties of the site at which we required the introduction of oxygen functionality were predicted to induce rapid oxidation. Due to a benzylic carbon being analogous to an allylic carbon in its reactivity, this offers the distinct advantage of increased scope as oxidative methods are applicable to both systems and many general procedures are frequently utilised.\textsuperscript{135}

Successful oxidation of diacetate adduct (271) to the diacetate of napthazarin (273) was reported as early as 1986 by Rodriguez and co-workers.\textsuperscript{136} However, when the method of adding substrate (271) to a solution of chromium trioxide in acetic acid at 0-5 °C was replicated, adduct (271) and elimination product (275) were recovered as a mixture (Scheme 93).
The preparation of naphthalenedione (273) via oxidation of the corresponding naphthalene diacetate derivative (271) has previously proved unsuccessful within the group (Table 6). Several methods, including those reported by Wiberg$^{137}$ and Rathore,$^{138}$ allylic oxidation through selenium dioxide in ethanol and benzylic oxidation via pyridinium chlorochromate respectively, have failed.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CrO$_3$/AcOH$^{136}$</td>
<td>(275)</td>
</tr>
<tr>
<td>2</td>
<td>SeO$_2$/t-BuOOH$^{139}$ (catalytic and stoichiometric)</td>
<td>(275)</td>
</tr>
<tr>
<td>3</td>
<td>SeO$_2$/EtOH</td>
<td>(275)</td>
</tr>
<tr>
<td>4</td>
<td>PCC</td>
<td>(275)</td>
</tr>
<tr>
<td>5</td>
<td>CrO$_3$/t-BuOOH$^{140}$</td>
<td>(275)</td>
</tr>
<tr>
<td>6</td>
<td>KMnO$_4$/Al$_2$O$_3$$^{141}$</td>
<td>(275)</td>
</tr>
</tbody>
</table>

Table 6
Andreu et al.\textsuperscript{142} recently reported a novel procedure for selective benzylic oxidation involving 10\% palladium on carbon and aqueous ammonium hydroxide solution in acetonitrile. Rather unfortunately, when this technique was applied to substrate (271) mainly starting material was recovered with a trace of naphthalene elimination product (275).

A final attempt to access the diacetate of napthazarin (273) was undertaken employing conditions previously described by Durham and Miller\textsuperscript{143}. Treatment of diacetate adduct (271) with chromium trioxide in a solution of pyridine and dichloromethane again failed to yield napthazarin (273) and furnished elimination product (275) (Scheme 93).

4.3 Benzylic Oxidation Review

The decision was taken to return to the originally proposed route and alternative methodologies to the allylic/benzylic oxidation were considered. It was most apparent that elimination was occurring \textit{via} the C=C of the second ring to yield the undesired naphthalene (275). Removal of the double bond and therefore allylic property of the reaction site would be offset by the high benzylic reactivity so it was decided to attempt oxidation of saturated substrate (276) (Scheme 94).

Catalytic hydrogenation of the ring closed substrate (271) was achieved using Pd/C under an atmosphere of hydrogen, delivering the desired saturated substrate (276) in

\begin{center}
\includegraphics[width=\textwidth]{scheme94.png}
\end{center}

\textbf{Scheme 94}

\textit{Chapter 4Results and Discussion}\n
115
quantitative yield. The subsequent oxidation was attempted using chromium (VI) oxide, believed to be the most harsh and effective method with excess oxidant over a range of temperatures (Table 7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Equivalents</th>
<th>Temperature</th>
<th>Mono(277) : Bis (277)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CrO₃</td>
<td>5</td>
<td>0-2 °C</td>
<td>8 : 1</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>CrO₃</td>
<td>5</td>
<td>rt</td>
<td>6 : 1</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>CrO₃</td>
<td>10</td>
<td>50 °C</td>
<td>1 : 6</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>CrO₃</td>
<td>10</td>
<td>60 °C</td>
<td>0 : 1</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>KMnO₄</td>
<td>12</td>
<td>rt</td>
<td>SM</td>
<td>82</td>
</tr>
</tbody>
</table>

Table 7

Having effected bis-oxidation of substrate (276) by employing optimum conditions (entry 3) deduced from simple modification of those reported previously¹³⁶, two major flaws were encountered. Firstly, the capricious nature of the reaction with yields varying between 52 and 91 % significantly limited reproducibility and secondly, all attempts at a scale greater than 800 mg resulted in little or no retrievable compound (<5%).

With di-ketone (277) now in hand, we were able to directly attempt the second iterative process as tautomerisation occurred readily to furnish 1,4-naphthalenediol (274) (Scheme 95).

Chapter 4  Results and Discussion
It was postulated that simple repetition of the conventional allylation conditions previously employed would allow access to the second cycle. However, only the corresponding deprotected tetraol (279) was isolable in 78% yield. Hasegawa et al. previously reported an analogous allylation in the presence of acetate protecting groups by heating to 60 °C in DMF but when these conditions were applied to 1,4-naphthalenediol (274) only starting material was recovered. Subsequent attempts to produce the allylated target (278) under various conditions are summarised in Table 8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone</td>
<td>K₂CO₃</td>
<td>(279)</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>K₂CO₃</td>
<td>SM</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>CsCO₃</td>
<td>(279)</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>K₂CO₂</td>
<td>SM</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>NaH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>Ag₂O</td>
<td>SM</td>
<td>76</td>
</tr>
</tbody>
</table>

Table 8
4.4 Screening of Protecting Groups

Central to the success of the proposed synthetic pathway is the ability to employ complementary protecting groups that would allow for selective deprotection in the latter stages. It was reasoned that the initial acetate protection had to be replaced by protection with a non-enolisable, base and moisture sensitive protecting group. Considering the iterative protocol, the protecting group would also have to exhibit inertness towards catalytic hydrogenation and moderate heating (50-60 °C) in acetic acid.

With these criteria in mind, it was decided to protect the alcohol moieties as their silyl-ether derivatives using standard conditions. This was undertaken with the addition of imidazole (2.4 eq) and DMAP (0.2 eq) to hydroquinone (269) followed by TBDMSCl (2.2 eq) to give a mixture of mono (280) and bis protected target (281) in 71 % yield (Scheme 96). Surprisingly, attempts to separate the mixture via flash column chromatography failed and therefore the strategy had to be abandoned as reacting the crude mixture would result in complexation of the phenolic –OH group to the metal catalyst.

\[
\text{OH} \quad \overset{\text{imidazole (2.4 eq)}}{\longrightarrow} \quad \overset{\text{DMAP (0.2 eq)}}{\longrightarrow} \quad \overset{\text{TBDMSCl (2.2 eq)}}{\longrightarrow} \quad \text{OH}
\]

\[
(269) \quad \overset{\text{DCM, 0 °C to rt, 8 h}}{\longrightarrow} \quad (280, 281)
\]

Scheme 96

It was envisaged that bis-methylation of hydroquinone (269) would allow for the second iteration and ultimately the key third ring in validating the process. This was effected via addition of KOH (2.5 eq) and then the electrophile methyl iodide (2.5 eq) to furnish product (282) in a 98 % yield. The subsequent step involved ring closing metathesis of dimethoxy derivative (282) using conditions previously described. The bicyclic target
(283) was obtained in disappointing 54 % yield as it immediately begins to aromatise to give the unwanted naphthalene derivate (284) (Scheme 97).

\[
\begin{align*}
\text{OH} & \quad \text{KOH (2.5 eq)} \\
\text{OH} & \quad \text{MeI (2.5 eq)} \\
\text{DMF} & \quad 0 \, ^\circ\text{C to rt, 4 h} \\
\text{OMe} & \quad \text{Grubbs 2} \\
\text{Toluene} & \quad \text{rt, 18 h} \\
\end{align*}
\]

Scheme 97

It was next decided to investigate the possibility of successfully completing a second cycle with benzoyl protecting groups in place. The benzoyl groups are analogous to the initially employed acetates, and offered the prospect of handling crystalline solids formed via \(\pi\)-stacking, which would be beneficial for handling and purification purposes.

Initial bis-benzoyl protection under standard conditions proved facile and bis-protected target (285) was isolated in 96 % yield following recrystallisation. Ring closure was achieved with Grubbs 2\textsuperscript{nd} generation catalyst in toluene for 24 hours to furnish bicyclic target (286) as a white crystalline solid that could be simply filtered and recrystallised in an encouraging 82 % yield. Catalytic hydrogenation of the ring closed substrate (286) was effected using Pd/C under hydrogen, with stirring at room temperature for 18 hours.

The saturated adduct (287) was obtained in 93 % yield and carried forward to a benzylic oxidation attempt using the only previously successful method of chromium (VI) oxide in

*Chapter 4  Results and Discussion* 119
acetic acid. Unfortunately, an intractable mixture was highlighted by crude $^1$H-NMR spectral analysis but with evidence of mono (288) and bis (289) oxidised, neither of which were isolable via flash column chromatography (Scheme 98).

![Scheme 98](image)

Further attempts to promote the oxidation were carried out under different methods and the results are summarised in Table 9.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SeO$_2$/t-BuOOH$^{139}$</td>
<td>mono-deprotected</td>
</tr>
<tr>
<td>2</td>
<td>SeO$_2$/EtOH$^{137}$</td>
<td>SM</td>
</tr>
<tr>
<td>3</td>
<td>PCC$^{138}$</td>
<td>mono-deprotected</td>
</tr>
<tr>
<td>4</td>
<td>KMnO$_4$/CH$_3$CN$^{144}$</td>
<td>SM + mono-deprotected</td>
</tr>
</tbody>
</table>

Table 9

Chapter 4  Results and Discussion 120
In a final attempt to validate the proposed linear route to the tetracycline core it was decided to proceed with protection of the alcohol moieties as methoxyethoxymethyl (MEM) ethers. This was achieved with the addition of sodium hydride (2.1 eq) followed by MEMCl (2.1 eq) to produce bis-protected (290) in excellent 92% yield. Routine ring closing metathesis afforded bicyclic adduct (291) in disappointing 41% yield following flash column chromatography.

It was noticed that the metathesis product was aromatising in a similar fashion to that of the methyl derivative and in future was subjected to catalytic hydrogenation without further purification. The saturated product was isolated in typically high yield for this conversion (97%) and subjected to chromium (VI) trioxide (10 eq) in an attempt to furnish the corresponding diketone. However, 1H-NMR spectral analysis revealed fully deprotected diol (293) to be the sole product of the reaction (Scheme 99).
4.5 Synthesis of Structurally Related Linear Systems

In order to demonstrate the versatility of the proposed left-to-right ring construction pathway, it was decided to apply the established chemistries to a suitable glycosyl acceptor precursor (juglone (235)). Following methodology previously reported by Masquelin et al., juglone was first O-methylated with methyl iodide (2 eq) using silver (I) oxide (1.5 eq) to yield (294) quantitatively. This was subsequently reduced with aqueous sodium dithionite, affording the corresponding hydroquinone intermediate (295) as an air sensitive solid in 87% yield.

Unfortunately, all attempts to synthesise diallyl ether (297) directly from hydroquinone ether (295) using standard conditions produced the mono-allylated species (296), with a trace amount of target (297) identifiable via $^1$H-NMR spectral analysis. To this crude product was added sodium hydride (1.1 eq) followed by allyl bromide (1.1 eq) to furnish rearrangement precursor (297) in 67% yield after recrystallisation from diethyl ether (Scheme 100). Unfortunately, time constraints did not allow for application of our Calisn/RCM strategy to this system.

![Scheme 100](image-url)
4.6 Fries Rearrangement Route

The Fries rearrangement of phenyl esters is the most efficient process for the preparation of hydroxyaryl ketones from corresponding phenols reported to date. The direct 2-acylation reaction usually requires stoichiometric amounts of strong Lewis acids such as aluminium (III) chloride. There are examples however, of milder catalysts like titanium (IV) chloride and lanthanide triflates being employed successfully to promote rearrangement. The process can also be driven photochemically with UV light, and this is simply termed the photo-Fries rearrangement.

It was initially postulated within our group that a double Fries rearrangement of phenyl ester (298) could yield metathesis precursor (300) after suitable bis-protection of (299) (Scheme 101). This would negate the need to pursue the problematic benzylic oxidation as earlier described in Section 4.3. The initial acrylate (298) was prepared in straightforward fashion from 2,3-dimethylhydroquinone (267) and acryloyl chloride in high yield following flash column chromatography.

There were several hurdles to overcome in achieving Fries rearrangement with a stoichiometric amount of AlCl₃, regioselectivity is known to be poor, and the harsh conditions required (neat, high temperature) for AlCl₃-mediated acylation can result in deacylation and side reactions. With these obstacles in mind, the conditions described
by Vukićević\textsuperscript{150} whereby doubling the quantity of AlCl\textsubscript{3} in dilute solutions at room temperature still allows the reaction to proceed were applied to substrate (298).\textsuperscript{136} Despite stirring bis-acrylate (298) with AlCl\textsubscript{3} in DCM for 24 hours at room temperature, \textsuperscript{1}H-NMR analysis of the product revealed starting material exclusively remained. An attempt using boron trifluoride diethyl etherate as the Lewis acid, this time in benzene also failed to yield any of the desired Fries product (299).

This initial failure prompted the use of TiCl\textsubscript{4} as catalyst at 140 °C for 2 hours in spite of the aforementioned complications (Scheme 102).

Unfortunately, the desired Claisen-precursor (299) was not formed, rather the harsh conditions resulted in mono-deacylation to give cleavage product (301). Our reservation that the first Fries rearrangement would render the second subsequent rearrangement unfavourable because of the inevitable ring deactivation may be correct. This would be in

\textit{Chapter 4 Results and Discussion} 124
agreement with the literature which discloses that bis-Fries rearrangement is not usually observed in similar cases.\textsuperscript{151}

4.7 A Mixed Claisen/Fries Strategy

An alternative rearrangement/metathesis strategy of combining a Claisen and ortho-Fries rearrangement was devised as both the double Fries and double Claisen protocols had failed to elaborate a third ring in left-to-right fashion (B ring). Although not truly iterative in nature, we envisaged proceeding with selective mono-allylation of juglone-like substrate (302). We have already deduced that stepwise derivatisation of (302) allows allylation to occur preferentially in the required position. Acylation using a suitable carbamoyl chloride liberates (303), ready to undergo a mixed Claisen/Fries procedure (Scheme 103).

\begin{center}
\includegraphics[width=\textwidth]{scheme103.png}
\end{center}

\textbf{Scheme 103}

\textit{Chapter 4 Results and Discussion}
Displacement of alkylamine with a vinyl organometallic would yield enone (305) which in turn should metathesise to give (306), such transformations are well known.\textsuperscript{152} Many of the synthetic steps required to convert advanced intermediate (306), which already incorporates rings D, C and B, into \((-\)-tetracycline (Figure 21) are analogous to previous syntheses (Schemes 83-87).

Commencing with juglone (235) as a suitable CD ring core, \(O\)-benzylation was achieved in 72 \% using silver (I) oxide (4 eq) and benzyl bromide (3 eq) in chloroform as previously described by Brimble.\textsuperscript{153} Subsequent reduction of (307) with an excess (8.5 eq) of aqueous sodium dithionite in EtOAc/H\textsubscript{2}O (1:1) was simply performed in a separating funnel with vigorous shaking. Benzylated hydroquinone (302) was isolated in 89 \% yield and required no further purification. Mono-allylated species (308) was produced cleanly in 83 \% yield under standard conditions. A stronger base (NaH, 2eq) was again required to access the more hindered hydroxyl, with subsequent addition of dimethylcarbamoyl chloride (2 eq) giving key intermediate dimethyl carbamate (303) in quantitative yield (Scheme 104).

\[ \text{Scheme 104} \]
With (270) in hand, ready for the mixed Claisen/Fries procedure, it was reasoned that the Claisen should be attempted first as from previous endeavours we were aware of the ring deactivation caused by the first Fries rearrangement. Scheme 105 outlines our initial attempt at a combined rearrangement strategy.

Successful [3,3]-sigmatropic rearrangement of allyl phenyl ether (303) was achieved thermally to give the required ortho-substituted phenol derivative (309) in 79 % yield. Before attempting the Fries component of the strategy, the free hydroxyl group of (311) was protected as its methyl derivative for simplicity in 90 % yield. Carbamate O-to-C 1,3-migration was attempted under the standard conditions of sec-BuLi/TMEDA (1.1 eq) metalation followed by slow warming to room temperature as reported by Snieckus. Rather disappointingly, only the starting material was recovered from the reaction mixture following flash column chromatography with no trace of Fries product (311).
Returning to key intermediate (303), the order of rearrangement was reversed with the ortho-anionic Fries being attempted first, again using the metalation conditions employed in Scheme 105. In this case we were able to trigger 1,3-carbamoyl rearrangement resulting in (312) in 51% yield following flash column chromatography (Scheme 106).

![Scheme 106]

However, as seen with previous attempts to initiate 1,3-rearrangement with the migrated amide already on the ring, the Claisen failed. Without time constraints, the next attempt to introduce the allyl group would have been via an ortho-metalation/alkylation strategy similar to that utilized by Snieckus in the synthesis of ochratoxin precursors (Scheme 107).  

![Scheme 107]
was metalated (2 eq of sec-BuLi/TMEDA) and subsequently transmetalated (MgBr2-Et2O), with the presumed Grignard intermediate treated with allyl bromide to afford (315) in 14% yield. Although mimicking this procedure would detract from the rearrangement element of our proposal, it would allow us to investigate diethylamine displacement, presumably with a vinyl organometallic. This would facilitate entry to an RCM precursor, allowing us to investigate the validity of our protocol with regards to B-ring construction.

4.8 Conclusion

In Summary, a new iterative strategy for the construction of linear fused carbon ring templates has been advanced significantly from its inception. The first double Claisen/metakthesis sequence has been proven and numerous examples of metathesis on related compounds have been provided. The benzylic/allylic oxidation process required to access a second cycle has been problematic but a low-yielding benzylic oxidation to liberate key diketone (277) has been achieved. Several protecting groups have been screened which will allow the operator to deprotect, at will, any chosen individual ring for derivatisation.

A mixed Claisen/anionic ortho-Fries route has been investigated with both a single Claisen and single ortho-Fries rearrangement being developed for this semi-iterative route. Schemes 108 to 112 depict the key transformations examined throughout the chapter.

- Double aromatic Claisen rearrangement of bis allyl ether (268).

```
\text{Scheme 108}
```

\textit{Chapter 4 Results and Discussion}
• Ring closing metathesis of Claisen products using Grubbs 2nd generation catalyst.

\[
\begin{align*}
\text{OAc} & \quad \text{Grubbs 2} \\
\text{THF} & \quad \text{rt, 24 h} \\
\end{align*}
\]

Scheme 109

• Bis-benzylic oxidation of bicyclic diacetate (276) to give diketone (277).

\[
\begin{align*}
\text{OAc} & \quad \text{CrO}_3 \text{ (excess)} \\
\text{AcOH, 60 °C} & \quad \text{OAc} \\
\end{align*}
\]

Scheme 110

• Single aromatic Claisen rearrangement of juglone derivative (303) for B-ring construction.

\[
\begin{align*}
\text{O} & \quad \text{Mesitylene} \\
\text{reflux, 24 h} & \quad \text{OH} \\
\end{align*}
\]

Scheme 111

• Anionic ortho-Fries rearrangement of dimethyl carbamate (303) towards B-ring construction.
Scheme 112
References


CHAPTER FIVE:

EXPERIMENTAL
5.0 General Information

All reactions described were carried out using commercial dry solvents with the exceptions of light petroleum, ethyl acetate (distilled over CaCl₂) and dichloromethane (distilled over phosphorus pentoxide). Light petroleum in all cases refers to the bp 40-60 °C fractions. Sodium hydride was obtained as 60% dispersion in mineral oil and subsequently isolated by washing with hexane in all cases. Melting points were determined using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. All infrared spectra were obtained from a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. All ¹H (400 MHz) and ¹³C (100 MHz) NMR spectra were collected on a Bruker DPX-400 spectrometer. Unless otherwise stated, all NMR samples were prepared as solutions in CDCl₃ with tetramethylsilane as the internal standard for ¹H-NMR spectra and CDCl₃ the standard for ¹³C-NMR spectra. Chemical shifts are quoted in parts per million (ppm) and the $J$ values in hertz (Hz). Mass spectra were either recorded on a Jeol JMS-SX102 quadrupole high-resolution mass spectrometer or by the EPSRC National Mass Spectrometry Service Centre at the University of Swansea. Merck Kieselgel 60 H silica was used for purification via column chromatography in all cases.

Chapter 5 Experimental
5.1 Stereoselective Synthesis of the Dimethoxy-tetrahydro-1H-pyrido[2,1-a]isoquinoline Ring System

Methyl-5-hydroxypentanoate (161).\textsuperscript{82}

\[
\begin{align*}
\text{O} & \\
\text{O}Me & \\
\text{OH} & 
\end{align*}
\]

To a stirred solution of \( \delta \)-valerolactone (160) (20.0 g, 200 mmol) in methanol (100 ml) was added 20 drops of concentrated sulphuric acid. The resulting solution was refluxed for 5 hours and then cooled in an ice bath. Sodium hydrogen carbonate (5 g) was added and the resulting suspension allowed to stir for 10 minutes and then filtered. Solvent was removed under reduced pressure to yield the target compound as a colourless oil which was carried forward without additional purification (25.01 g, 95%), \( \nu_{\text{max}} \) (thin film, neat)/cm\(^{-1}\) 3446 (OH), 1732 (C(O)OCH\(_3\)), 1168 (CO(O)CH\(_3\)); \( \delta \)\( H \) (250 MHz; CDCl\(_3\)) 1.52-1.59 (2H, m, CH\(_2\)CH\(_2\)OH), 1.61-1.73 (2H, m, CH\(_2\)CH\(_2\)CH\(_2\)OH), 2.05 (1H, br, s, 2.31 (2H, t, \( J \) 7.2, CH\(_2\)COOCH\(_3\)), 3.62 (2H, t, \( J \) 7.2, CH\(_2\)OH), 3.68 (3H, s, CH\(_3\)); \( \delta \)\( C \) (100 MHz; CDCl\(_3\)) 21.1 (CH\(_2\)), 32.0 (CH\(_2\)), 33.7 (CH\(_2\)), 51.6 (CH\(_3\)), 62.1 (CH\(_2\)), 173.9 (C); MS (El) \( m/z \) 132 [MH\(^+\), 7.5 %] (MH\(^+\), 133.0862. C\(_8\)H\(_{12}\)O\(_3\) requires 133.0865).
Methyl-5-oxopentanoate (155).\textsuperscript{82}

![Methyl-5-oxopentanoate](image)

Methyl-5-hydroxypentanoate (161) (11.8 g, 90.0 mmol) was slowly added to a suspension of pyridinium chlorochromate (29.0 g, 134.5 mmol) and Celite (29.0 g) in dry dichloromethane (185 ml). The resulting mixture was allowed to stir at room temperature for a further 3.5 hours. After this time the solution was decanted and the solids washed with diethyl ether (3 x 100 ml). The combined organic fractions were filtered through an alumina column and the solvent removed on the rotary evaporator to afford the target compound as a pale green oil (5.95 g, 52 %), $\nu_{\text{max}}$ (thin film, neat)/cm\textsuperscript{-1} 1733 (C(O)OCH\textsubscript{3}), 1166 (CO(O)CH\textsubscript{3}); $\delta_{\text{H}}$ (400 MHz; CDCl\textsubscript{3}) 1.92-1.97 (2H, m, CH\textsubscript{2}CH\textsubscript{2}OH), 2.35 (2H, t, $J$ 6.8, CH\textsubscript{2}COOMe), 2.52 (2H, t, $J$ 7.2, CH\textsubscript{2}CHO), 3.68 (3H, s, CH\textsubscript{3}), 9.78 (1H, s, CHO); $\delta_{\text{C}}$ (100 MHz; CDCl\textsubscript{3}) 17.3 (CH\textsubscript{2}), 32.9 (CH\textsubscript{2}), 42.9 (CH\textsubscript{2}), 51.6 (CH\textsubscript{3}), 173.3 (C), 201.6 (CH); MS (EI) $mlz$ 130 [MH\textsuperscript{+}, 33.1 %] (MH\textsuperscript{+}, 129.0552. C\textsubscript{6}H\textsubscript{10}O\textsubscript{3} requires 129.0553).
A solution of chlorotrimethylsilane (5.78 ml, 53.20 mmol) was added under nitrogen to a solution of lithium borohydride (13.30 ml of a 2.0 M solution in tetrahydrofuran, 26.60 mmol) in tetrahydrofuran (20 ml) over the course of 5 minutes. 3-(3,4-dimethoxyphenyl)-L-alanine (158) (3.00 g, 13.30 mmol) was added portion-wise to the mixture over 15 minutes and left to stir at room temperature for 24 hours. After this time methanol (30 ml) was added slowly to the resulting pale yellow solution and the solvents were removed under reduced pressure. The residue was treated with 20% aqueous potassium hydroxide solution and extracted with dichloromethane (3 x 50 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and evaporated to dryness to give the target compound as a white crystalline solid (2.48 g, 88%) which required no further purification. Mp 81-82 °C, Lit: Mp 78-79 °C; [α]D = -20.4 [c = 8.0, EtOH], Lit: [α]D = -21.5° [c = 8.0, EtOH]; v_max (thin film, CH₂Cl₂)/cm⁻¹ 3352 (OH); δ_H (250 MHz; CDCl₃) 1.91 (3H, br. S, OH and NH₂), 2.48 (1H, dd, J 13.5, 8.7 CH(H)CHNH₂), 2.71 (1H, dd, J 5.2, 13.6, CH(H)CHNH₂), 3.06-3.16 (1H, m, NH₂CH), 3.40 (1H, dd, J 7.2, 10.6, CH(H)OH), 3.64 (1H, dd, J 3.9, 13.1, CH(H)OH), 3.87 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 6.72-6.75 (2H, m, ArH), 6.80-6.83 (1H, m ArH); δ_C (100 MHz; CDCl₃) 42.2 (CH₂), 54.2 (CH), 55.9 (2 × CH₃), 66.3 (CH₂), 111.3 (CH), 112.2 (CH), 121.1 (CH), 131.1 (C), 147.6 (C), 148.9 (C); MS (EI) m/z 211 [M⁺, 8.9 %] (M⁺, 211.1205. C₁₁H₁₇N_O₃ requires 211.1208).
(3S)-3-(3,4-Dimethoxybenzyl)hexahydrooxazolo[3,2-a]pyridin-5-one (125a).81

Methyl-5-hydroxypentanoate (155) (1.53 g, 11.74 mmol) was slowly added to a solution of (S)-2-amino-3-(3,4-dimethoxyphenyl)propan-1-ol (159) (2.48 g, 11.74 mmol) in toluene (150 ml) and the resulting mixture was refluxed under Dean-Stark conditions for 48 hours. The reaction was allowed to cool to room temperature and the solvent removed on the rotary evaporator to yield a brown oil. 250 MHz 1H-NMR analysis of the crude product mixture revealed the formation of a 6:1 diastereomeric mixture of the desired bicyclic lactam. No further purification was necessary and the brown oil was taken directly onto the next step (3.01 g, 90 %), νmax (thin film, CH2Cl2)/cm⁻¹ 1623 (NCO), 1261 (CHOCH2); Major isomer: δH (400 MHz; CDCl3) 1.40-1.49 (1H, m, (CH(H))3CO), 1.64-1.74 (1H, m, (CH(H))3CO), 1.94-2.02 (1H, m, (CH(H))3CO), 2.20-2.27 (1H, m, (CH(H))3CO), 2.32-2.43 (2H, m, (CH(H))3CO), 2.52 (1H, dd, J 10, 13.2, CH(H)Ph), 3.53 (1H, dd, J 3.2, 13.6, CH(H)Ph), 3.74 (1H, ddd, J 1.6, 6.4, 9.6, OCH(H)), 3.86 (3H, s, OCH3), 3.88 (3H, s, OCH3), 4.03 (1H, dd J 1.2, 9.6, OCH(H)), 4.20 (1H, m, OCH2CH2CH2Ph), 4.69 (1H, dd, J 3.2, 9.6, (CH2)2CHOCH2), 6.71-6.82 (3H, m, ArH); Major isomer: δC (100 MHz; CDCl3) 17.5 (CH2), 28.4 (CH2), 31.1 (CH2), 36.6 (CH2), 55.9 (2 x CH3), 56.9 (CH), 69.2 (CH2), 89.0 (CH), 111.1 (CH), 112.6 (CH), 121.6 (CH), 130.7 (C), 147.7 (C), 148.9 (C), 168.0 (NCO); MS (El) m/z 291 [M⁺, 50.8 %] (M⁺, 291.1474. C16H21NO4 requires 291.1471).
Titanium tetrachloride (9.20 ml, 66.01 mmol) was added drop-wise under nitrogen to a stirred solution of (3S)-3-(3,4-dimethoxybenzyl)-hexahydrooxazolo[3,2-a]pyridin-5-one (125a/b) (2.75 g, 9.44 mmol) in anhydrous dichloromethane (100 ml) at -78 °C via syringe. The resulting blood-red suspension was allowed to warm to room temperature over 48 hours and then quenched by the addition of saturated aqueous ammonium chloride solution (30 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The resulting crude brown oil was adsorbed onto silica and purified by column chromatography using 3:1 ethyl acetate: light petroleum as eluent. The product was isolated as a white foam (2.20 g, 79 %), Mp 106-108 °C; [α]D = 94.0 [c = 1.0, CHCl3]; νmax (thin film, CH2Cl2/cm-1 3364 (OH) 1615 (NC=O); δH (400 MHz; CDCl3) 1.71-1.81 (1H, m, CH(H)CH2CH2CO), 1.88-1.97 (2H, m, CH2CH(H)CO and CH(H)Ph), 2.39-2.47 (2H, m, CH(H)CH2CH2CO and CH2CH(H)CO), 2.61 (1H, dt, J 5.3, 17.5, CH(H)CO), 2.67 (1H, dd, J 2.8, 16.0, CH(H)Ph), 3.02 (1H, dd, J 6.0, 16.0, CH(H)Ph), 3.53-3.63 (3H, m, CH2OH and OH) 3.86 (3H, s, OCH3), 3.87 (3H, s, OCH3), 4.58 (1H, dd, J 4.4, 10, CH2CHNCO), 5.17-5.23 (1H, m, CHCH2OH), 6.62 (1H, s, ArH), 6.66 (1H, s, ArH); δC (100 MHz; CDCl3) 19.2 (CH2), 29.1 (CH2), 30.6 (CH2), 32.2 (CH2), 49.0 (CH), 53.2 (CH), 55.9 (2 × CH3), 62.5 (CH2), 108.1 (CH), 111.8 (CH), 124.7 (C), 127.8 (C), 147.7 (C), 148.0 (C) 171.5 (NCO); MS (EI) m/z 291 [M+], 19.3 % (M+), 291.1469. C16H21NO4 requires 291.1471.
5.2 Functionalisation of the Dimethoxytetrahydro-1H-pyrido[2,1-\(a\)] isoquinoline Ring System

\((6S,11bR)-9,10\text{-Dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-}\(a\)\text{-}isoquinoline-6-carbaldehyde (162).}

\[
\text{MeO} \quad \text{MeO} \\
\text{H} \quad \text{O} \\
\text{H} \quad \text{N} \\
\text{N} \quad \text{O}
\]

A solution of \((6S,11bR)-6\text{-}(\text{hydroxymethyl})\text{-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-}\(a\))\text{-isoquinolin-4(11bH)-one (126) (2.00 g, 6.86 mmol) in anhydrous dichloromethane (50 ml) was added via cannula to a stirred solution of Dess-Martin periodinane (3.20 g, 7.55 mmol) in anhydrous dichloromethane (50 ml). The resulting mixture was allowed to stir at room temperature overnight. After this time the volatiles were removed by rotary evaporation and the resulting residue was re-dissolved in ethyl acetate (100 ml) and washed with saturated aqueous sodium bicarbonate (2 \(\times\) 100 ml). The organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness on the rotary evaporator to yield the crude product that was adsorbed onto silica and purified by column chromatography using ethyl acetate as eluent. The target compound was isolated as a yellow crystalline solid (1.39 g, 70 %), \text{Mp 112-115 °C; } [\alpha]_D = 64.4 \ [c = 1.0, \text{CH}_2\text{Cl}_2]; \nu_{\text{max}} \text{(thin film, CH}_2\text{Cl}_2)/\text{cm}^{-1} 1731 (\text{CHO}) 1644 (\text{NCO}), 1257 (\text{CHOCH}_2); \delta_{\text{H}} \ (400 \text{ MHz; CDCl}_3) 1.64-1.71 (3H, m, CCHCH(H) and CH\text{H}_2\text{CH}_2\text{CO}), 2.45-2.52 (2H, m, CH(H)CH and CCHCH(H)), 2.60-2.71 (1H, m, CH(H)CO), 3.03 (1H, dd, J 62.2, 16.0, CCH(H)CH), 3.16 (1H, dd, J 3.4, 15.8, CCH(H)CH), 3.85 (3H, s, OCH\text{H}_3), 3.87 (3H, s, OCH\text{H}_3), 4.71-4.74 (1H, dd, J 3.8, 11.2, CCH), 5.50-5.58 (1H, m, CHCHO), 6.60 (1H, s, ArH), 6.66 (1H, s, ArH), 9.54 (1H, s, CHO); \delta_{\text{C}} \ (100 \text{ MHz; CDCl}_3) 19.6 (\text{CH}_2) 27.3 (\text{CH}_2), 31.2 (\text{CH}_2), 31.8 (\text{CH}_2), 55.0 (\text{CH}), 55.9 (\text{CH}_3), 56.0 (\text{CH}_3), 57.0 (\text{CH}), 108.1 (\text{CH}), 111.1 (\text{CH}), 123.8 (C), 127.8 (C), 148.1 (C), 148.2 (C), 170.6 (\text{NCO}), 199.4 (\text{CHO}); \text{MS (El) } \text{m/z} 289 [M^+ , 19.3 \%] (M^+, 289.1310. C}_{16}\text{H}_{19}\text{NO}_4 \text{requires 289.1314].}
A solution of (6S,11bR)-9,10-dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline-6-carbaldehyde (162) (4.25 g, 14.69 mmol) in acetonitrile (42 ml), tert-butyl alcohol (155.0 ml) and 1-methyl-1-cyclohexene (75.0 ml) was stirred rapidly as it was cooled to 0 °C. A solution of sodium chlorite (80 % grade) (12.78 g, 113.11 mmol) and sodium dihydrogen phosphate (12.34 g, 102.83 mmol) in water (155.0 ml) was added drop-wise over a period of 20 minutes at 0 °C. The solution was then allowed to stir at room temperature for a further 18 hours. After this time the reaction mixture was added to brine (200 ml) and the solution acidified to pH 2 by addition of 1M hydrochloric acid. The resulting mixture was extracted with ethyl acetate (2 × 100 ml) and then washed with 1M aqueous sodium dithionite solution (150 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and the solvent removed on the rotary evaporator to give the crude product which was purified by flash column chromatography over silica eluting with ethyl acetate affording a white solid (3.86 g, 86 %), Mp 95-97 °C; [a]D = 68.0 [c = 1.0, CHCl3]; νmax (thin film, CH2Cl2)/cm⁻¹ 3432 (OH) 1634 (NC=O); δH (400 MHz; CDCl3) 1.58-1.59 (1H, m, CCHCH(H)), 1.84-1.88 (2H, m, CH₂CH₂CO), 2.32-2.37 (2H, m, CH₂CO), 2.52-2.56 (1H, m, CCHCH(H)) 2.95 (1H, dd, J 5.9, 15.8, CCH(H)CH), 3.08 (1H, dd, J 3.4, 15.8, CC(H)HCH), 3.86 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 4.71 (1H, dd, J 3.9, 11.1 CCH), 5.60-5.62 (1H, m, CHCO₂H), 6.63 (1H, s, ArH), 6.64 (1H, s, ArH); δC (100 MHz; CDCl3) 19.2 (CH₂), 29.9 (CH₂) 31.1 (CH₂), 31.5 (CH₂), 50.6 (CH), 54.7 (CH), 55.9 (CH₃), 56.0 (CH₃), 108.4 (CH), 111.4 (CH), 124.1 (C), 127.7 (C), 148.0 (C), 148.1 (C), 171.5 (NCO), 174.4 (CO₂H). MS (EI) m/z 305 [MH⁺, 95.1 %] (MH⁺, 305.1260. C₁₆H₁₉NOS requires 305.1263).
Se-Phenyl (6S,11bR)-9,10-Dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline-6-carboselenoate (164).

To a solution of (6S,11bR)-9,10-dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline-6-carboxylic acid (163) (2.57 g, 8.42 mmol) in anhydrous dichloromethane (80.0 ml) under nitrogen was added diphenyldiselenide (3.94 g, 12.63 mmol). The resulting mixture was cooled to 0 °C and tributylphosphine (90 % grade) (4.15 ml, 16.83 mmol) was added drop-wise. The mixture was heated under reflux for a further 20 hours with stirring. After this time dichloromethane (100 ml) and water were added and the aqueous layer was extracted with a further portion of dichloromethane (100 ml). The combined organic fractions were washed with brine (200 ml), dried over anhydrous magnesium sulfate and volatiles removed under reduced pressure. The resulting crude oil was adsorbed onto silica and purified by flash column chromatography eluting with 1:1 ethyl acetate:light petroleum to give the target compound as a white foam (2.85 g, 76 %). Mp 120-123 °C; [α]D = -34.8 [c = 1.0, CHCl3]; νmax (thin film, CH2Cl2)/cm⁻¹ 1716 (COSePh), 1646 (NCO); δH (400 MHz; CDCl3) 1.76-1.79 (1H, m, CCHCH(H)), 2.00-2.06 (2H, m, CH2CH2CO), 2.47-2.58 (2H, m, CCHCH(H) and CH(H)CO), 2.74 (1H, dt, J 6.0, 17.0 CH(H)CO), 3.04 (1H, dd, J 6.0, 16.0, CCH(H)CH), 3.23 (1H, dd, J 4.0, 16.0, CCH(H)CH), 3.86 (3H, s, OCH3), 3.87 (3H, s, OCH3), 4.91 (1H, dd, J 4.0, 11.0, CCH), 5.82-5.84 (1H, m, CHCOSeph), 6.63 (2H, s, ArH), 7.30-7.42 (5H, m, ArH); δC (100 MHz; CDCl3) 19.1 (CH2), 29.7 (CH2), 31.3 (CH2), 32.0 (CH2), 55.0 (CH), 55.9 (CH3), 56.1 (CH3), 60.5 (CH), 108.1 (CH), 111.3 (CH), 123.9 (C), 125.3 (C), 127.5 (C), 128.9 (CH), 129.3 (2 × CH), 136.0 (2 × CH), 148.1, (2 × C), 171.1 (NCO), 200.7 (COSePh). MS (El) m/z 445 [MH⁺, 11.5 %] (MH⁺, 445.0865. C22H23NO4Se requires 445.0865).
(R)-9,10-Dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (165).

A three-necked flask was fitted with a condenser, glass stopper and a suba seal and was flushed with nitrogen. A solution of Se-phenyl-(6S,11bR)-9,10-dimethoxy-4-oxo-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline-6-carboselenoate (164) (0.45 g, 1.02 mmol) in anhydrous toluene (20 ml) was added via cannula. The solution was then degassed with nitrogen for 15 minutes before adding tri-n-butyltin hydride (1.07 ml, 4.05 mmol) via syringe. The resulting mixture was heated to 80°C in an oil bath and azobisisobutyronitrile (0.03 g, 0.20 mmol) was added portion-wise over a 2 hour period at 80°C. After a further 2 hours stirring at 80°C the mixture was allowed to cool to room temperature and evaporated to dryness. The resulting crude oil was adsorbed onto silica and purified by flash column chromatography over silica eluting with light petroleum followed by 3:1 ethyl acetate:light petroleum. The target compound was isolated as a white solid (0.25 g, 94 %), Mp 108-110°C; [α]D = 249.2 [c = 1.0, CHCl3]; νmax (thin film, CH2Cl2)/cm⁻¹ 1636 (NCO); δH (400 MHz; CDCl3) 1.65-1.72 (1H, m, CCHCH(H)), 1.83-1.96 (2H, m, CH₂CH₂CO), 2.33-2.41 (1H, m, CH(CH)CO), 2.50-2.59 (2H, m, CCHCH(H) and CH(CH)CO), 2.60-2.66 (1H, m, CCH(H)), 2.77-2.84 (1H, m, CH(H)N), 2.87-2.91 (1H, m, CCH(H)), 3.87 (6H, s, 2 x OCH₃), 4.62 (1H, dd, J 4.0, 10.0, CCH), 4.86-4.91 (1H, m, CH(H)N), 6.62 (1H, s, ArH), 6.68 (1H, s, ArH); δC (100 MHz; CDCl3) 19.6 (CH₂), 28.5 (CH₂) 31.0 (CH₂), 32.2 (CH₂), 39.6 (CH₂), 55.9 (CH₃), 56.0 (CH₃), 56.7 (CH), 108.1 (CH), 111.5 (CH), 127.2 (C), 129.1 (C), 147.6 (C), 147.7 (C), 169.3 (NCO). MS (EI) m/z 261 [M⁺, 75.0 %] (M⁺, 261.1365. C₁₅H₁₉N₃O₃ requires 261.1365).
To a stirred solution of diisopropylamine (1.17 g, 1.62 ml, 11.60 mmol) in anhydrous tetrahydrofuran (20 ml) was added n-butyllithium (2.5 M solution in hexanes) (4.64 ml, 11.60 mmol) drop-wise under nitrogen at 0 °C. The reaction mixture was stirred for 15 minutes at 0 °C and then cooled to −78 °C whereupon a solution of (R)-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (165) (1.01 g, 3.83 mmol) in anhydrous tetrahydrofuran (20 ml) was added via cannula. To the resulting mixture was added phenylselenylbromide (1.36 g, 5.80 mmol) in anhydrous tetrahydrofuran (20 ml) drop-wise 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 (50 ml) and extracted with diethyl ether (3 × 50 ml). The combined ether extracts were washed with saturated aqueous ammonium chloride solution (100 ml) and dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation to yield the crude selenide (1.23 g), which was used without further purification.

The crude selenide was dissolved in methanol (100 ml) and water (50 ml). To the resulting solution was added sodium metaperiodate (1.88 g, 8.90 mmol) and sodium hydrogen carbonate (0.39 g, 4.60 mmol) and the solution was stirred vigorously at room temperature for 20 hours. After this time the reaction was added to a mixture of saturated aqueous sodium bicarbonate solution (150 ml) and diethyl ether (200 ml). The ether layer was washed with water (150 ml), then brine (150 ml) and dried over anhydrous magnesium sulphate. Volatiles were removed under reduced pressure and the crude product adsorbed onto silica and purified by flash column chromatography over silica eluting with 1:1 ethyl acetate:light petroleum to afford the target compound as a white foam (0.61 g, 61 %), Mp 108-109 °C; [α]D = 272.0 [c = 1.0, CHCl3]; νmax (thin film,
CH\textsubscript{2}Cl\textsubscript{2})/cm\textsuperscript{-1} 1663 (NCO), 1610. (C=C); \(\delta\textsubscript{H} (400 \text{ MHz}; \text{CDCl}_3) 2.26-2.35 \text{ (1H, m, CCH\textsubscript{3}CH(H)), 2.69-2.77 \text{ (2H, m, CCHCH(H) and CCH(H)), 2.80-2.91 \text{ (2H, m, CCH(H) and CCH(H)), 3.87 \text{ (3H, s, OCH\textsubscript{3})}, 3.88 \text{ (3H, s, OCH\textsubscript{3})}, 4.71-4.80 \text{ (2H, m, CCH and CH(H)N), 6.06 \text{ (1H, dd, } J 3.0, 10.0, CHCO), 6.66 \text{ (1H, s, ArH), 6.66 \text{ (1H, s, ArH), 6.67-6.70 \text{ (1H, m, CHCHCO); } \delta\textsubscript{C} (100 \text{ MHz; CDCl}_3) 29.0 \text{ (CH\textsubscript{2}), 33.7 \text{ (CH\textsubscript{2}) 38.0 \text{ (CH\textsubscript{2})}, 54.4 \text{ (CH), 55.9 \text{ (CH\textsubscript{3})}, 56.1 \text{ (CH\textsubscript{3})}, 108.6 \text{ (CH), 111.5 \text{ (CH), 125.6 \text{ (CH), 127.1 \text{ (C), 127.6 \text{ (C), 138.8 \text{ (CH), 147.9 \text{ (C), 148.0 \text{ (C), 164.8 \text{ (NC=O). MS (EI) } m/z 259 [MH\textsuperscript{+}, 100 \text{ %}] (MH\textsuperscript{+}, 259.1287. C\textsubscript{15}H\textsubscript{17}NO\textsubscript{3} requires 259.1288).}}) \text{ Experimental} \text{ 145}
(2R,11bR)-9,10-Dimethoxy-2-vinyl-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (168).

A 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran (8.88 ml, 8.88 mmol) was added to a suspension of copper cyanide (0.60 g, 6.65 mmol) in anhydrous tetrahydrofuran (10.0 ml) at -78 °C with stirring. The reaction mixture was warmed to 0 °C for 15 minutes and then re-cooled to -78 °C. A solution of (R)-9,10-dimethoxy-6,7-dihydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (167) (0.23 g, 0.89 mmol) in anhydrous tetrahydrofuran (10.0 ml) was added via cannula at -78 °C. After a further 5 minutes chlorotrimethylsilane (0.84 ml, 6.65 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 (15.0 ml) and water (15.0 ml) was added and stirring continued for 15 minutes. A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (2.0 ml) was added and stirring continued for 15 minutes. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 x 40 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and the solvent removed on the rotary evaporator. Crude 400 MHz 1H-NMR revealed the formation of the product as a single diastereoisomer. The crude product was adsorbed onto silica and purified by flash column chromatography eluting with 2:1 light petroleum:ethyl acetate to give the target compound as a pale yellow oil (0.17 g, 67 %), [α]D = 43.0 [c = 1.0, CHCl3]; νmax (thin film, CH2Cl2)/cm⁻¹: 2921 (Vinyl CH), 1645 (Vinyl CH2=CH), 1615 (NC=O); δH (400 MHz; CDCl3) 2.02-2.08 (1H, m, CCHCH(H)), 2.30-2.37 (1H, m, CCHCH(H)), 2.54 (2H, t, J 4.0, CH2CO), 2.63 (1H, dt, J 2.8, 15.2, CCH(H)), 2.67-2.73 (1H, m, CCH2CO), 2.78-2.85 (1H, m, CCH2CH(H)), 2.91-2.90 (1H, m, CCH(H)), 3.86 (3H, s, OCH3), 3.87 (3H, s, OCH3), 4.63-4.66 (1H, dd, J 5.2, 8.8, CCH), 4.85 (1H, ddd, J 2.4, 5.2, 12.4, CCH2CH(H)), 5.12-5.18 (2H, m, CH=CH2), 5.91-6.00 (1H, m, CH=CH2), 6.62 (1H, s, ArH), 6.64 (1H, s, ArH); δC (100 MHz; CDCl3) 28.5 (CH2), 33.1 (CH), 34.8 (CH2), 36.3 (CH2), 40.1 (CH) 53.5 (CH),

Chapter 5 Experimental 146
55.9 (CH₃), 56.1 (CH₃), 107.8 (CH), 11.7 (CH), 115.4 (CH₂), 127.6 (C), 129.0 (C), 139.4 (CH), 146.8 (C), 146.9 (C) 169.0 (NCO); MS (EI) m/z 287 [MH⁺, 7.5 %] (MH⁺, 288.1594. C₁₇H₂₁NO₃ requires 288.1594).
To a stirred solution of (6S,11bR)-6-(hydroxymethyl)-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (126) (1.02 g, 3.51 mmol) in dichloromethane (50.0 ml) at 0 °C was added imidazole (0.72 g, 10.53 mmol). To this mixture was added 4-dimethylaminopyridine (0.04 g, 0.35 mmol) followed by drop-wise addition of tert-butyldiphenylsilyl chloride (1.45 g, 1.37 ml, 5.27 mmol). The resulting mixture was allowed to warm to room temperature over 16 hours. After this time water (50 ml) was added and the organic phase separated. The aqueous phase was extracted with dichloromethane (3 x 50 ml) and the combined organic fractions dried over anhydrous magnesium sulfate, filtered and the solvent removed by rotary evaporation. The crude product was adsorbed onto silica and purified by flash column chromatography over silica eluting with 1:1 ethyl acetate:light petroleum. The target compound was isolated as a white foam (1.80 g, 97 %), Mp 66-69 °C; [a]D = 65.0 [c = 1.0, CHCl3]; νmax (thin film, CH2Cl2)/cm⁻¹ 1634 (NCO) 1111 (COSi); δH (400 MHz; CDCl3) 1.01 (9H, s, C(CH3)3), 1.59-1.69 (1H, m, CCHCH(H)), 1.74-1.84 (1H, m, CH(H)CH2CO), 1.88-1.95 (1H, m, CH(H)CH2CO), 2.34-2.40 (1H, m, CCHCH(H)), 2.44 (1H, dd, J 7.2, 10.8, CH(H)CO), 2.52-2.58 (1H, m, CH(H)CO), 2.78 (1H, dd, J 2.0, 16.0, CCH(H)CH), 2.97 (1H, dd, J 6.0, 16.0, CCH(H)CH), 3.61 (2H, d, 7.6, CH2OSi), 3.85 (6H, s, 2 x OCH3), 4.34 (1H, dd, J 4.0, 10.4, CCH), 5.34-5.40 (1H, m, CHCH2OSi), 6.54 (1H, s, ArH), 6.58 (1H, s, ArH), 7.26-7.61 (10H, m, C(CH3)3); δC (100 MHz; CDCl3) 19.2 (C(CH3)3), 19.5 (CH2), 26.7 ((CH3)3), 28.7 (CH2), 31.2 (CH2), 32.3 (CH2), 47.6 (CH), 53.6 (CH), 55.9 (CH3), 56.1 (CH3), 62.0 (CH2), 108.1 (CH), 111.9 (CH), 124.8 (C), 127.6 (2 x CH), 127.7 (2 x CH), 128.2 (C), 129.6 (CH), 129.7 (CH), 133.2 (C), 133.4 (C), 135.6 (4 x CH), 147.5 (C), 147.9 (C), 170.0 (NCO); MS (El) m/z 529 [MH⁺, 14.5 %] (MH⁺, 530.2720. C32H39N04Si requires 530.2721).

To a stirred solution of diisopropylamine (1.03 g, 1.44 ml, 10.19 mmol) in anhydrous tetrahydrofuran (30 ml) was added n-butyllithium (2.5 M solution in hexanes) (4.08 ml, 10.19 mmol) drop-wise under nitrogen at 0 °C. The reaction mixture was stirred for 15 minutes at 0 °C and then cooled to −78 °C whereupon a solution of (6S,11bR)-6-((tert-butyldiphenylsilyloxy)methyl)-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (176) (1.80 g, 3.40 mmol) in anhydrous tetrahydrofuran (30 ml) was added via cannula. To the resulting mixture was added phenylselenyl bromide (1.20 g, 5.10 mmol) in anhydrous tetrahydrofuran (20 ml) 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 (50 ml) and extracted with diethyl ether (3 × 50 ml). The combined ether extracts were washed with saturated aqueous ammonium chloride solution (100 ml) and dried with anhydrous magnesium sulfate. The solvent was removed by rotary evaporation to yield the crude selenide (2.30 g), which was used without further purification.

The crude selenide was dissolved in methanol (100 ml) and water (50 ml). To the resulting solution was added sodium metaperiodate (1.67 g, 7.82 mmol) and sodium hydrogen carbonate (0.34 g, 4.08 mmol) and the solution was stirred vigorously at room temperature for 20 hours. After this time the reaction was added to a mixture of saturated aqueous sodium bicarbonate solution (150 ml) and diethyl ether (200 ml). The ether layer was washed with water (150 ml), then brine (150 ml) and dried over anhydrous magnesium sulfate. Volatiles were removed under reduced pressure and the crude product adsorbed onto silica and purified by flash column chromatography over silica.

Chapter 5 Experimental
eluting with 1:1 ethyl acetate:light petroleum to afford the target compound as a white foam (0.43 g, 42 %), Mp 81-84 °C; [α]D = 238.0 [c = 1.0, CHCl3]; v_max (thin film, CH2Cl2)/cm⁻¹ 1661 (NC=O) 1111 (COSi); δ_H (400 MHz; CDCl3) 1.00 (9H, s, (CH3)3), 2.21-2.30 (1H, m, CCHCH(H)), 2.61 (1H, ddd, J 4.4, 6.4, 17.6, CCHCH(H)), 3.01 (2H, d, J 3.6 CCH(H)CH), 3.46 (1H, t, J 9.2, CH2OSi), 3.60 (1H, q, J 7.6, CH2OSi), 3.86 (3H, s, OCH3), 3.87 (3H, s, OCH3), 4.49 (1H, dd, J 4.4, 14.0, CCH), 5.19-5.22 (1H, m, CHCH2OSi), 6.05 (1H, dd, J 2.4, 9.6, CHCO), 6.48 (1H, s, ArH), 6.61-6.66 (2H, m, CHCHCO and ArH), 7.21-7.58 (10H, m, C(CH3)3)); δ_C (100 MHz; CDCl3) 19.1 (C(CH3)3), 26.7 ((CH3)2), 29.3 (CH2), 33.9 (CH2), 47.2 (CH), 52.7 (CH), 55.9 (CH3), 56.1 (CH3), 61.2 (CH2), 108.5 (CH), 112.1 (CH), 124.3 (C), 125.9 (CH), 126.9 (C), 127.5 (2 × CH), 127.7 (2 × CH), 129.5 (CH), 129.6 (CH), 133.2 (2 × C), 135.5 (2 × CH), 135.6 (2 × CH), 138.9 (CH), 147.8 (C), 148.2 (C), 164.7 (NCO); MS (FAB) m/z 527 [MH⁺, 19.9 %] (MH⁺, 526.2420. C32H37N04Si requires 526.2414).
(2S,6S,11bR)-6-((tert-Butyldiphenylsilyloxy)methyl)-9,10-dimethoxy-2-vinyl-2,3,6,7-

A 1.0 M solution of vinylmagnesium bromide in tetrahydrofuran (17.05 ml, 17.05 mmol) was added to a suspension of copper cyanide (0.76 g, 8.53 mmol) in anhydrous tetrahydrofuran (20 ml) at -78 °C with stirring. The reaction mixture was warmed to 0 °C for 15 minutes and then re-cooled to -78 °C. A solution of (6S,11bR)-6-((tert-butyldiphenylsilyloxy)methyl)-9,10-dimethoxy-6,7-dihydro-1H-pyrido[2,1-a] isoquinolin-4(11bH)-one (178) (0.60 g, 1.14 mmol) in anhydrous tetrahydrofuran (20 ml) was added via cannula at -78 °C. After a further 5 minutes chlorotrimethylsilane (1.08 ml, 8.53 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 (25 ml) and water (25 ml) was added and stirring continued for 15 minutes. A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (4.0 ml) was added and stirring continued for 15 minutes. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 x 50 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and the solvent removed on the rotary evaporator. Crude 400 MHz $^1$H-NMR revealed the formation of the product as a single diastereoisomer. The crude product was adsorbed onto silica and purified by flash column chromatography eluting with 1:1 light petroleum:ethyl acetate to give the target compound as a pale yellow oil (0.44 g, 70 %), $[\alpha]_D = 19.6$ [c = 1.0, CHCl$_3$]; $\nu_{max}$ (thin film, neat)/cm$^{-1}$ 1661 (NC=O) 1111 (COSi); $\delta_H$ (400 MHz; CDCl$_3$) 1.00 (9H, s, (CH$_3$)$_3$), 2.05-2.17 (2H, m, CCHCH$_2$), 2.48 (1H, dd, J 6.8, 17.2, CH(H)CO), 2.55 (1H, dd, J 5.6, 16.8, CH(H)CO), 2.70-2.74 (1H, m, CHCH$_2$CO), 2.88-3.00 (2H, m, CH$_2$OSi), 3.63-3.71 (2H, m, CCH$_2$CH), 3.86 (6H, s, 2 x OCH$_3$), 4.53-4.56 (1H, m, CCH), 5.07-5.15 (3H, CH=CH$_2$ and CHCH$_2$OSi), 5.89-5.97 (1H, m, CH=CH$_2$), 6.57 (1H, s, ArH), 6.63 (1H, s, 

Chapter 5  Experimental
ArH), 7.26-7.61 (10H, m, C(CH₃)₃); δ_C (100 MHz; CDCl₃) 19.2 (C(CH₃)₃), 26.8 ((CH₃)₃), 29.0 (CH₂), 33.1 (CH), 34.6 (CH₂), 37.1 (CH₂), 48.8 (CH), 50.7 (CH), 56.0 (CH₃), 56.2 (CH₃), 62.8 (CH₂), 107.6 (CH), 112.0 (CH), 115.1 (CH₂), 126.1 (C), 127.6 (2 × CH), 127.7 (2 × CH), 128.7 (C), 129.7 (CH), 133.2 (C), 133.3 (C), 135.6 (2 × CH), 135.6 (2 × CH), 140.0 (CH), 147.5 (C), 148.1 (C), 169.2 (NCO); MS (El) m/z 555 [MH⁺, 15.5 %] (MH⁺, 555.2874. C₃₄H₄₁NO₄Si requires 555.2878).

Chapter 5  Experimental
Ethyl 2-(((6S,11bR)-6-(tert-butyldiphenylsilyloxy)methyl)-9,10-dimethoxy-4-oxo-
2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl)-1,3-dithiolane-2-
carboxylate (180)

To a stirred solution of diisopropylamine (0.27 ml, 0.95 mmol) in anhydrous
tetrahydrofuran (5 ml) was added n-butyllithium (2.5 M solution in hexanes) (0.76 ml,
1.90 mmol) dropwise under nitrogen at 0 °C. The reaction mixture was stirred for 15
minutes at 0 °C and then cooled to -78 °C whereupon ethyl 1,3-dithiolane-2-carboxylate
(0.16 ml, 1.14 mmol) was added via syringe and stirring was continued for a further 30
minutes. After this time a solution of (6S,11bR)-6-(tert-butyldiphenylsilyloxy)methyl)-
9,10-dimethoxy-6,7-dihydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (178) (500 mgs,
0.95 mmol) in anhydrous tetrahydrofuran (10 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 x 25 ml). The organic extracts were dried over anhydrous magnesium sulfate, filtered
and the solvent removed on the rotary evaporator. Crude 400 MHz ¹H-NMR analysis
revealed the formation of (180a/b) as a 1:1 mixture of diastereoisomers. These
diastereoisomers were purified but with only one isomer isolable by flash column
chromatography over silica using 5:1 light petroleum:ethyl acetate as eluent to yield a
yellow solid (188 mgs, 28 %), Mp 89-91 °C; [α]D = 182.0 [c = 1.5, CHCl3]; νmax (thin
film, CH2Cl2/cm⁻¹, 1732 (C(=O)OCH3), 1667 (NCO), 1112 (CO(O)CH3); δH (400 MHz;
CDCl3) 1.00 (9H, s, (CH3)3), 1.30 (3H, t, J 7.2, OCH2CH3), 1.99-2.22 (2H, m, CCHCH2),
2.89 (1H, dd, J 6.0, 16.4, CC(H)HCH), 3.00 (1H, dd, J 6.0, 16.4, CCH(CH)H), 3.19-3.29
(4H, m, SCH2CH2S), 3.33-3.45 (2H, m, CH2CO), 3.54-3.63 (2H, m, CH2OSi), 3.67-3.71
(1H, m, CHCH2CO), 3.86 (6H, s, 2 x OCH3), 4.24 (2H, q, J 8.4, OCH2CH3), 4.69 (1H,
dd, J 3.6, 10.4, CCH), 5.06-5.09 (1H, m, CHCH2OSi), 6.57 (1H, s, ArH), 6.61 (1H, s,
ArH), 7.25-7.59 (10H, m, C(CH$_3$)$_3$); $\delta_{\text{C}}$(100 MHz; CDCl$_3$) 14.0 (CH$_3$), 19.2 (C(CH$_3$)$_3$), 26.8 (C(CH$_3$)$_3$), 28.8 (CH$_2$), 35.0 (CH$_2$), 37.1 (CH), 38.3 (CH$_2$), 38.5 (CH$_2$), 39.4 (CH$_2$), 49.0 (CH), 51.3 (CH), 55.9 (CH$_3$), 56.4 (CH$_3$), 62.3 (CH$_2$), 62.7 (CH$_2$), 75.2 (C) 108.4 (CH), 112.1 (CH), 124.9 (C), 127.1 (C), 127.6 (2 × CH), 127.7 (2 × CH), 129.6 (CH), 129.7 (CH), 133.1 (2 × C), 135.5 (2 × CH), 135.6 (2 × CH), 147.8 (C), 148.3 (C), 166.5 (NCO), 171.2 (CO); MS (FAB) m/z 705 \([\text{M}^+, 21.0 \%]\) (M$^+$, 705.2621. C$_{38}$H$_{47}$NO$_6$S$_2$Si requires 705.2614).

Chapter 5  Experimental  154
(S)-2-(tert-Butoxycarbonyl)-3-(3,4-dihydroxyphenyl)propanoic acid (182).

\[ \text{HO-CH(NH)CH(OH)-C(OH)CH(OH)} \]

A solution of L-3-(3,4-dihydroxyphenyl)alanine (181) (3.0 g, 15.21 mmol) in water (100 ml) was stirred rapidly as it was cooled to 0 °C. Triethylamine (2.54 ml, 18.25 mmol) and di-tert-butyl dicarbonate (3.49 g, 18.25 mmol) as a solution in dioxane (100 ml) were added successively and the resulting mixture was allowed to warm to room temperature and stir for a further 24 hours. Volatiles were removed under reduced pressure and the aqueous portion extracted with ethyl acetate (3 x 50 ml) at an adjusted pH of 2. The combined organic fractions were washed successively with saturated aqueous sodium bicarbonate (50 ml) and brine (50 ml) and dried over anhydrous magnesium sulfate. Solvents were removed on the rotary evaporator to yield a light brown solid (4.48 g, 99 %) which was suitable for further reactions. Mp 139-141 °C; \([\alpha]_D = 40.0 [c = 1.0, \text{H}_2\text{O}]\);

\[ \text{V}_{\text{max}} \text{(thin film, CH}_2\text{Cl}_2)/\text{cm}^{-1} 3331 \text{(OH), 1682 (C(O)OH); } \delta_{\text{H}} \text{(400 MHz; CDCl}_3) 1.33 \] (9H, s, OC(CH\(_3\)\(_3\)), 2.63 (1H, dd, \(J = 9.6, 13.8, \text{CH(H)CH(NH)}\)), 2.81 (1H, dd, \(J = 4.4, 13.7, \text{CH(H)CH(NH)}\)), 3.94-4.01 (1H, m, NHCH), 6.45-6.47 (1H, m, ArH), 6.59-6.61 (2H, m ArH); \(\delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 28.2 ((CH\(_3\)_3)), 36.6 (CH\(_2\)), 57.0 (CH), 78.0 (C), 115.3 (CH), 116.6 (CH), 119.9 (CH), 128.9 (C), 143.8 (C), 144.9 (C), 155.5 (NC(O)O\(_t\)Bu), 174.0 (CHCO\(_2\)H); MS (EI) \text{m/z} 297 [M\(^+\), 3.2 %] \(\text{(M}\(^+\), 297.1217. C}_{14}\text{H}_{19}\text{NO}_6 \) requires 297.1212).
Finely ground potassium hydroxide (0.93 g, 16.59 mmol) was added portion wise to a solution of (S)-2-(tert-butoxycarbonyl)-3-(3,4-dihydroxyphenyl)propanoic acid (182) (4.48 g, 15.08 mmol) in dimethylformamide at 0 °C and stirred for 10 minutes. After this time methyl iodide (1.08 ml, 16.59 mmol) was added drop-wise and the solution was then allowed to stir at room temperature for 0.5 hours. The resulting mixture was cooled to 0 °C and finely ground potassium hydroxide (1.86 g, 33.18 mmol) was added portion-wise and allowed to stir for 15 minutes before drop-wise addition of methyl iodide (2.16 ml, 33.18 mmol). The reaction was allowed to warm to room temperature overnight and then added to ice (100 g) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated to yield a light brown oil. The crude oil was adsorbed onto silica and purified by column chromatography using 3:1 hexane: ethyl acetate as eluent. The product was isolated as a white solid (3.87 g, 76 %), Mp 123-125 °C; [α]D = 43.5 [c = 1.0, CH2Cl2]; v_max (thin film, CH2Cl2)/cm⁻¹ 1746 (NCO(O)Bu), 1713 (C(O)OCH3), 1262, 1160 (2 x C-O) δH (400 MHz; DMSO) 1.30 (9H, s, OC(CH3)3), 2.76 (1H, dd, J 9.9, 13.7, CH(H)CHNH), 2.90 (1H, dd, J 5.1, 13.8, CH(H)CHNH), 3.60 (3H, s, COOCH3), 3.70 (3H, s, COCH3), 3.72 (3H, s, COCH3) 4.10-4.16 (1H, m, NHCH), 6.70-6.74 (1H, m, ArH), 6.83-6.85 (2H, m ArH); δC (100 MHz; DMSO) 28.1 ((CH3)3), 36.0 (CH2), 51.8 (CH3), 55.3 (CH), 55.4 (CH3), 55.5 (CH3), 79.2 (CH), 111.6 (CH), 112.9 (CH), 121.1 (CH), 129.8 (C), 147.4 (C), 148.4 (C), 172.7 (NC(O)OBu), 174.0 (CHCO2CH3); MS (El) m/z 339 [M⁺, 5.6 %] (M⁺, 339.1677. C17H25N06 requires 339.1682).
(S)-tert-Butyl 3-(3,4-dimethoxyphenyl)-1-hydroxypropan-2-ylcarbamate (184).

To a stirred solution of (S)-methyl 2-(tert-butoxycarbonyl)-3-(3,4-dimethoxyphenyl)propanoate (183) (3.30 g, 9.73 mmol) in absolute ethanol (150 ml) at 0 °C was added sodium borohydride (1.47 g, 33.58 mmol) portion wise. The solution was allowed to warm to room temperature overnight and then cooled back down to 0 °C. The reaction was quenched with successive addition of concentrated hydrochloric acid (2 ml) and water (15 ml). Ethanol was removed under reduced pressure and the reaction partitioned between ethyl acetate (150 ml) and brine (150 ml). The ethyl acetate layer was dried over anhydrous magnesium sulfate and evaporated to dryness to afford a crude solid. Recrystallisation from ethyl acetate gave white crystals (2.70 g, 89 %), Mp 91-93 °C; [α]D = 29.2 [c = 1.0, CH2Cl2]; νmax (thin film, CH2Cl2)/cm⁻¹ 3366 (OH), 1684 (NCO(OiBu)), 1261, 1158, (2 x C-O); δH (400 MHz; CDCl3) 1.42 (9H, s, OC(CH3)3), 2.67 (1H, dd, J 13.6, 8.4 CH(H)CHNH2), 2.78 (1H, dd, J 6.8, 14.0, CH(H)CHNH2), 3.55 (1H, dd, J 5.1, 11.0, CH(H)OH), 3.64 (1H, dd, J 6.1, 11.3, CH(H)OH), 3.86 (3H, s, CH3), 3.87 (3H, s, CH3), 4.80-4.82 (1H, m, NHCH) 6.73-6.76 (2H, m, ArH), 6.77-6.81 (1H, m ArH); δC (100 MHz; CDCl3) 28.4 ((CH3)3), 37.0 (CH2), 53.6 (CH), 55.8 (CH3), 55.9 (CH3), 64.3 (CH2), 77.3 (C), 111.2 (CH), 112.2 (CH), 121.3 (CH), 130.8 (C), 147.6 (C), 148.9 (C), 156.2 (NC(O)OiBu); MS (EI) m/z 311 [M⁺, 18.7 %] (M⁺, 311.1737. C16H25NO5 requires 311.1733).

Chapter 5 Experimental 157
5.3 Asymmetric Construction of the Dodecahydrobenz[a]indolo[3,2-h]quinolizine Ring System

Ethyl 2-(2-(methoxymethylene)cyclohexyl)acetate (200).

\[
\begin{array}{c}
\text{OMe} \\
\text{OEt}
\end{array}
\]

(Methoxymethyl)triphenylphosphonium chloride (7.45 g, 21.72 mmol) was added to potassium tert-butoxide (3.66 g, 32.58 mmol) and dissolved in anhydrous toluene (100 ml). The subsequent orange solution was stirred at room temperature for 1.5 hours to give a blood-red solution. To this solution was added ethyl 2-cyclohexanoneacetate (199) (1.96 ml, 10.86 mmol) drop-wise over a 10 minute period and the reaction mixture left to stir for a further 18 hours. The reaction was quenched with the careful addition of water (20 ml) followed by a further 80 ml and then extracted into ethyl acetate (3 x 50 ml). The combined organic fractions were washed with brine (2 x 50 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield a yellow solid. The solid was suspended in diethyl ether to crash out triphenylphosphine oxide and the collected filtrate was adsorbed directly onto silica. The crude product was purified by flash column chromatography over silica eluting with 4:1 light petroleum:ethyl acetate to furnish the target compound as a colourless oil (1.47 g, 64 %), \( \nu_{\text{max}} \) (thin film, CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 1734 (C=O), 1232 (C-O); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 1.23-1.27 (3H, m, OCH\(_2\)CH\(_3\)), 1.36-1.39 (1H, m, CHC(H)H), 1.43-1.52 (3H, m, CCH\(_2\)CH\(_2\) and CHCH\(_2\)C(H)H), 1.59-1.69 (2H, m, CHCH\(_2\)CH(H) and CHCH\(_2\)CH(H)), 2.12-2.16 (1H, m, CC(H)H), 2.22-2.27 (1H, m, CCH(H)), 2.30-2.35 (1H, m, CHC(H)HCO), 2.44-2.50 (1H, m, CHCH(H)CO), 2.51-2.58 (1H, m, CCHCH\(_2\)), 3.52 (3H, s, OCH\(_3\)), 4.09-4.16 (2H, m, OCH\(_2\)CH\(_3\)), 5.75 (1H, s, CCHOCH\(_3\)); \( \delta_{\text{C}} \) (100MHz; CDCl\(_3\)) 14.2 (CH\(_3\)), 23.2 (CH\(_2\)), 23.6 (CH\(_2\)), 26.7 (CH\(_2\)), 33.0 (CH\(_2\)), 36.0 (CH), 37.8 (CH\(_2\)), 59.1 (CH\(_3\)), 60.0 (CH\(_2\)), 119.3 (C), 139.3 (CH), 172.8 (CO); MS (FAB) \text{m/z} 212 [M\(^+\), 77.9 %] (M\(^+\), 212.1415. C\(_{12}\)H\(_{20}\)O\(_3\) requires 212.1413).
2-((1S,2R)-2-formylycyclohexyl)acetic acid rac-(138).\textsuperscript{70}

![Chemical structure](image)

Ethyl 2-(2-(methoxymethylene)cyclohexyl)acetate (200) (700 mgs, 3.30 mmol) was dissolved in a 3:1 mixture of tetrahydrofuran (30 ml) and water (10 ml). To this vigorously stirred solution was added 2M hydrochloric acid until a pH of 1 was attained and then the reaction was heated at 55 °C for 6 hours. After this time the tetrahydrofuran was removed under reduced pressure and the resulting solution diluted with water (20 ml) and extracted with ethyl acetate (5 × 30 ml). The combined organics were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford a crude yellow oil. The oil was purified via flash column chromatography over silica, eluting with 2:1 ethyl acetate:light petroleum to yield a colourless oil (553 mgs, 99 %), $\nu_{\text{max}}$ (thin film, CH$_2$Cl$_2$)/cm$^{-1}$ 3221 (OH), 1720 (C=O); $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 1.05-2.74 (12 H, br, m, OHCHCHCH$_2$CH$_2$CH$_2$CH$_2$CHCH$_2$), 5.74 (1H, d, $J$ 1.6, CHO); $\delta_{\text{C}}$ (100MHz; CDCl$_3$) 24.9 (CH$_2$), 25.5 (CH$_2$), 29.2 (CH$_2$), 32.7 (CH$_2$), 35.9 (CH), 40.6 (CH$_2$), 49.1 (CH), 112.4 (CH), 179.1 (CO); MS (FAB) $m/z$ 170 [MH$^+$, 14.8 %] (MH$^+$, 170.0863. C$_9$H$_{14}$O$_3$ requires 170.0865).

Chapter 5  Experimental  159
(S)-2-Amino-3-(1H-indol-3-yl)propan-1-ol (198)

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 ml) under a nitrogen atmosphere over the course of 2 minutes. L-tryptophan (201) (5.0 g, 24.5 mmol) was added portion-wise to the mixture over 5 minutes. After 24 hours stirring at room temperature the mixture was treated with methanol (30 ml), which was added in a cautious manner. All volatiles were removed under reduced pressure on the rotary evaporator to yield an oil that was treated with 20% potassium hydroxide solution (20 ml). The solution was washed with ethyl acetate (3 × 100 ml) and the combined organic phases dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a light brown foam (3.82 g, 82%) which required no further purification; νmax (thin film, CH2Cl2)/cm⁻¹ 3275 (NH); δH (400 MHz; DMSO) 2.60 (1H, dd, J 7.2, 14.1, C(H)HCHNH2), 2.74-2.92 (1H, m, C(H)HCHNH2), 2.97-3.09 (1H, m, CHNH2), 3.21-3.29 (1H, m, C(H)HOH), 3.40 (1H, dd, J 4.6, 10.2, CH(H)OH), 6.99 (1H, t, J 6.7, ArH), 7.08 (1H, t, J 7.4 ArH), 7.15 (1H, s, CHNH), 7.37 (1H, d, J 7.9, ArH), 7.57 (1H, d, J 7.6 ArH), 10.90 (1H, br, s, NH); δC (100 MHz; DMSO) 29.7 (CH2), 53.9 (CH), 66.1 (CH2), 111.7 (CH), 111.8 (C), 118.7 (CH), 118.8 (CH), 121.1 (CH), 123.4 (CH), 127.3 (C), 136.5 (C); MS (FAB) m/z 190 [MH⁺, 66.1%] (MH⁺, 190.1182). C11H14N2O4 requires 190.1184).
3S,6aS,10aR,10bS)-3-((1H-Indol-3-yl)methyl)octahydro-2H-oxazolo[2,3-a]isoquinolin-5(3H)-one (202a).

(S)-2-Amino-3-(1H-indol-3-yl)propan-1-ol (198) (564 mgs, 2.76 mmol) and 2-((1S,2R)-2-formylcyclohexyl)acetic acid rac-(138) (470 mgs, 2.76 mmol) were added to toluene (30 ml) and refluxed under Dean-Stark conditions for 24 hours. The mixture was allowed to cool to room temperature and the solvent removed under reduced pressure to yield the target compound. Crude 400 MHz $^1$H-NMR analysis revealed the formation of (202) as a 1:1 mixture of diastereoisomers. These diastereoisomers were purified and separated by flash column chromatography over silica using 4:1 light petroleum:ethyl acetate as eluent (619 mgs, 69 %).

Natural product isomer (202a) isolated as a white solid; Mp 214-216 °C; [a]$_D$ = 13.9 [c = 1.0, CH$_2$Cl$_2$], $\nu$$_{max}$ (thin film, CH$_2$Cl$_2$)/cm$^{-1}$ 1632 (NCO), 1298 (C-O); $\delta$$_H$ (400 MHz; CDCl$_3$) 1.02-1.10 (2H, m, NCHCHC(H)H and COCH$_2$CHC(H)H), 1.22-1.35 (3H, m, NCHCH and NCHCHCH$_2$C(H)H and COCH$_2$CHCH$_2$C(H)H), 1.44-1.54 (1H, m, COCH$_2$CH), 1.76-1.83 (3H, m, NCHCHCH$_2$CH(H) and COCH$_2$CHCH(H) and COCH$_2$CHCH$_2$CH(H)), 2.00-2.16 (2H, m, NCHCHCH(H) and COC(H)H), 2.52 (1H, dd, J 6.0, 17.6 COCH(H)), 2.61 (1H, dd, J 10.4, 14.0 CHCC(H)H), 3.63-3.67 (1H, CHOC(H)H), 3.78 (1H, d, J 13.6, CHCCH(H)), 4.01 (1H, d, J 9.2, CHOCH(H)), 4.26-4.30 (1H, m, CHCCH$_2$CH), 4.32 (1H, d, J 8.4, NCH), 7.00 (1H, d, J 2.0, NHCH), 7.12 (1H, t, J 7.2, ArH), 7.18 (1H, t, J 7.6, ArH), 7.34 (1H, d, J 8.0, ArH), 7.82 (1H, d, J 7.6, ArH), 8.32 (1H, s, NH); $\delta$$_C$ (100MHz; CDCl$_3$) 24.8 (CH$_2$), 25.6 (CH$_2$), 26.9 (CH$_2$), 27.5 (CH$_2$), 32.4 (CH$_2$), 34.5 (CH), 39.3 (CH$_2$), 43.6 (CH), 56.3 (CH), 70.2 (CH$_2$), 92.8 (CH), 111.1 (CH), 112.6 (C), 119.4 (CH), 119.5 (CH), 122.1 (CH), 122.4 (CH), 127.7 (C),

Chapter 5  Experimental  161
136.3 (C), 167.6 (NCO); MS (FAB) m/z 324 [MH⁺, 100%] (MH⁺, 324.1920. C₂₀H₂₄N₂O₂ requires 324.1916).
(3S,6αR,10αS,10bR)-3-((1H-Indol-3-yl)methyl)octahydro-2H-oxazolo[2,3-a]isoquinolin-5(3H)-one (202b).

(S)-2-Amino-3-(1H-indol-3-yl)propan-1-ol (198) (564 mgs, 2.76 mmol) and 2-((1S,2R)-2-formylcyclohexyl)acetic acid rac-(138) (470 mgs, 2.76 mmol) were added to toluene (30 ml) and refluxed under Dean-Stark conditions for 24 hours. The mixture was allowed to cool to room temperature and the solvent removed under reduced pressure to yield the target compound. Crude 400 MHz 1H-NMR analysis revealed the formation of (202) as a 1:1 mixture of diastereoisomers. These diastereoisomers were purified and separated by flash column chromatography over silica using 4:1 light petroleum:ethyl acetate as eluent (619 mgs, 69%).

Second isomer (202b) isolated as a white solid; Mp 190-192 °C; [α]D = 11.5 [c = 1.0, CH2Cl2]; νmax (thin film, CH2Cl2)/cm⁻¹ 1631 (NCO), 1244 (C-O); δH (400 MHz; CDCl₃) 0.96-1.03 (2H, m, NCHCHC(H)H and COCH₂CHC(H)H), 1.14-1.27 (3H, m, NCHCH and NCHCH₂CH₂C(H)H and COCH₃CHCH₂C(H)H), 1.37-1.48 (1H, m, COCH₂CH), 1.70-1.82 (3H, m, NCHCH₂CH(CH₃) and COCH₂CHCH(CH₃) and COCH₂CHCH₂CH(CH₃)), 1.98 (1H, d, J 11.6, NCHCH(CH₃)), 2.03 (1H, d, J 11.6, COC(H)H), 2.57 (1H, dd, J 5.6, 18.0, COCH(H)), 3.00 (1H, dd, J 8.8, 14.4, CHCC(H)H), 3.35 (1H, dd, J 3.2, 14.0, CHCC(H)), 3.67 (1H, dd, J 7.2, 8.8, CHOC(H)H), 4.04 (1H, dd, J 7.6, 8.8, CHOCH(H)), 4.15 (1H, d, J 8.4, NCH), 4.57-4.63 (1H, m, CHCCH₂CH), 6.99 (1H, d, J 2.0, NHCH), 7.09-7.20 (2H, m, ArH), 7.34 (1H, d, J 8.0, ArH), 7.70 (1H, d, J 8.0, ArH), 8.41, (1H, s, NH); δC (100MHz; CDCl₃) 24.8 (CH₂), 25.3 (CH₂), 27.5 (CH₂), 28.3 (CH₂), 32.3 (CH₂), 33.0 (CH), 39.0 (CH₂), 43.1 (CH), 54.8 (CH), 70.0 (CH₂), 91.5 (CH), 111.0 (C), 111.2 (CH), 119.1 (CH), 119.5 (CH), 122.1 (CH), 122.6 (CH),
127.7 (C), 136.3 (C), 168.4 (NCO); MS (FAB) m/z 324 [MH$^+$, 13.1%] (MH$^+$, 324.1920.
C$_{20}$H$_{24}$N$_{2}$O$_{2}$ requires 324.1916).
7-Hydroxymethyl-1,3,4,4a'S,5,7'S,8,13,13b'R,13c'R-decahydro-2H-6a,13-diaza-indeno[1,2-c]phenanthren-6-one (204a)

35,6aS,10aR,10bS)-3-((1H-Indol-3-yl)methyl)octahydro-2H-oxazolo[2,3-a]isoquinolin-5(3H)-one (202a) (200 mgs, 0.62 mmol) was dissolved in a solution of 2M hydrochloric acid in absolute ethanol (8 ml) and the mixture stirred for a further 18 h at room temperature. After this time the reaction was quenched by addition of saturated aqueous sodium bicarbonate (15 ml) and extracted with ethyl acetate (3 × 20 ml). The organic fraction was dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield a crude yellow solid. Crude 400 MHz 1H-NMR analysis revealed the formation of (204a) exclusively and purification via flash column chromatography over silica with ethyl acetate as eluent gave the target compound as an off-white solid (145 mgs, 73 %).

Natural product isomer (204a) isolated as a white solid; Mp 187-189 °C; [α]D = 15.1 [c = 1.0, CH2Cl2]; vmax (thin film, CH2Cl2)/cm−1 3415 (OH), 1653 (NCO); δH (400 MHz; DMSO) 0.95-1.45 (1H, m COCH2CHC(H)H), 1.24-1.42 (3H, m, NCHCHC(H)H and NCHCHCH2C(H)H and COCH2CHCH2C(H)H), 1.49-1.63 (2H, m, NCHCH and COCH2CH), 1.69-1.77 (2H, br, COCH2CHCH2CH(H) and COCH2CHCH2CH(H)), 1.82-1.88 (1H, br, NCHCHCH2CH(H)), 1.95 (1H, dd, J 12.0, 17.2, COC(H)H), 2.33 (1H, dd, J 4.4, 17.2, COCH(H)), 2.50-2.51 (1H, m, NCHCHC(H)), 2.66-2.75 (2H, m, NHCCCH2), 3.30-3.44 (2H, m, CHCH2OH), 4.37 (1H, d, J 9.2, NCHCH), 4.78 (1H, t, J 5.6 OH), 5.16-5.21 (1H, m, CHCH2OH), 6.95-6.99 (1H, m, ArH), 7.05-7.09 (1H, m, ArH), 7.38 (1H, d, J 8.0), 7.40 (1H, d, J 8.0, ArH), 10.46 (1H, s, NH); δC (100MHz; CDCl3) 21.0 (CH2), 24.9 (CH2), 25.4 (CH2), 31.1 (CH2), 32.2 (CH2), 34.5 (CH), 39.1 (CH2), 43.1 (CH), 48.4 (CH), 55.1 (CH), 59.6 (CH2), 106.5 (C), 111.6 (CH), 117.5 (CH), 118.6 (CH),

Chapter 5  Experimental  165
121.0 (CH), 126.5 (C), 133.2 (C), 136.4 (C), 168.8 (NCO); MS (FAB) \( m/z \) 324 [MH\(^+\), 100 \%] (MH\(^+\), 324.1912. \( \text{C}_{20}\text{H}_{24}\text{N}_{2}\text{O}_{2} \) requires 324.1916).
7-Hydroxymethyl-1,3,4,4a'R,5,7'S,8,13,13b'R,13c'S-decahydro-2H-6a,13-diaza-indeno[1,2-c]phenanthren-6-one (204b).

(3S,6aR,10aS,10bR)-3-((1H-Indol-3-yl)methyl)octahydro-2H-oxazolo[2,3-a]isoquinolin-5(3H)-one (202b) (200 mgs, 0.62 mmol) was dissolved in a solution of 2M hydrochloric acid in absolute ethanol (8 ml) and the mixture stirred for a further 18 h at room temperature. After this time the reaction was quenched by addition of saturated aqueous sodium bicarbonate (15 ml) and extracted with ethyl acetate (3 x 20 ml). The organic fraction was dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield a crude yellow solid. Crude 400 MHz 1H-NMR analysis revealed the formation of (204b) exclusively and purification via flash column chromatography over silica with ethyl acetate as eluent gave the target compound as an off-white solid (149 mgs, 75 %).

**Second isomer (204b)** isolated as a white solid; Mp 209-211 °C; [α]D = 27.3 [c = 1.0, CH2Cl2]; νmax (thin film, CH2Cl2)/cm⁻¹ 3426 (OH), 1660 (NCO); δH (400 MHz; CDCl3) 0.90-1.00 (1H, m, COCH2CHC(H)H), 1.23-1.35 (2H, m, NCHCHCH2C(H)H and COCH2CHC(H)C(H)H), 1.52-1.63 (1H, m, COCH2CH), 1.65-1.83 (3H, m NCHCHC(H)H and COCH2CHCH2CH(H) and COCH2CHCH2C(H) and COCH2CHCH2C(H)), 1.90-1.99 (2H, m, NCHCH and NCHCHCH2CH(H) and NCHCHCH2CH(H)), 2.02-2.15 (2H, m, NCHCHCHC(H) and COC(H)H), 2.45-2.51 (2H, m, COCH(H) and NHCCC(H)H), 3.12 (1H, ddd, J 2.4, 6.4, 16.0, NHCCC(H)), 3.61-3.65 (2H, m, CHCH2OH), 4.83 (1H, d, J 5.2, NCHCH), 5.29-5.35 (1H, m, CHCH2OH), 7.07-7.12 (1H, m, ArH), 7.15-7.19 (1H, m, ArH), 7.35 (1H, dd, J 0.8, 8.0), 7.44 (1H, d, J 7.6, ArH), 8.29 (1H, s, NH); δC (100MHz; CDCl3) 21.6 (CH2), 25.4 (CH2), 26.7 (CH2), 29.7 (CH2), 32.3 (CH), 33.6 (CH2), 40.6 (CH2), 43.0 (CH), 50.9 (CH), 53.4 (CH), 61.2 (CH2), 111.1 (CH), 111.2 (C), 118.0 (CH), 119.7 (CH), 122.3

*Chapter 5  Experimental*
(CH), 127.0 (C), 131.4 (C), 136.0 (C), 172.7 (NCO); MS (FAB) m/z 324 [MH$^+$, 33.3 %]

(MH$^+$, 324.1920. C$_{20}$H$_{24}$N$_2$O$_2$ requires 324.1916).
5.4 Development of a Functionalised Dodecahydrobenz[a]indolo[3,2-h]quinolizine Ring System

Methyl 2-(8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)acetate (209a).

1,4-Cyclohexanenedione monoethylene acetal (208) (2.0 g, 12.80 mmol) was dissolved in anhydrous tetrahydrofuran (30 ml) under an inert atmosphere and the solution cooled to −78 °C. Potassium hexamethyldisilazide (KHMDS) (28.2 ml, 14.80 mmol) was added at such a rate that the temperature did not rise above −70 °C and the reaction stirred at this temperature for 1 hour. Methyl bromoacetate (1.32 ml, 14.80 mmol) was added drop-wise to the mixture and after 30 minutes the reaction was allowed to warm to room temperature over 4 hours. The reaction was quenched with addition of water (50 ml) and extracted into ethyl acetate (3 × 75 ml). The organic fractions were combined, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was adsorbed onto silica and purified by flash column chromatography over silica eluting with 1:1 light petroleum:ethyl acetate to give the target compound as a pale yellow oil (2.10 g, 72 %); νmax (thin film, neat)/cm⁻¹ 1715 (C=O), 1174 (C-O); δH (400 MHz; CDCl₃) 1.82 (1H, t, J 13.2, CHC(H)HC), 2.00 (1H, dd, J 4.8, 13.6 COC(H)HCH₂), 2.03-2.14 (2H, m, CHCH(H)C and COCH(H)CH₂), 2.20 (1H, dd, J 6.0, 16.8, CHC(H)HCO), 2.40 (1H, ddd, J 2.4, 4.8, 14.4, COCH₂C(H)H), 2.68-2.77 (2H, m, CHCH(H)CO and COCH₂CH(H)), 3.19-3.24 (1H, m, COCH), 3.68 (3H, s, OCH₃), 4.00-4.09 (4H, m, OCH₂CH₂O); δC (100MHz; CDCl₃) 33.9 (CH₂), 34.6 (CH₂), 37.8 (CH₂), 40.2 (CH₂), 43.1 (CH), 51.7 (CH₃), 64.7 (CH₂), 64.8 (CH₂), 107.1 (C), 172.5 (CO₂Me), 209.6 (CO); MS (FAB) m/z 228 [MH⁺, 71.9 %] (MH⁺, 228.1074. C₁₁H₁₆O₅ requires 228.1076).
1,4-Cyclohexanedione monoethylene acetal (208) (2.0 g, 12.80 mmol) was dissolved in anhydrous tetrahydrofuran (30 ml) under an inert atmosphere and the solution cooled to -78 °C. Potassium hexamethyldisilazide (KHMDS) (29.4 ml, 14.70 mmol) was added at such a rate that the temperature did not rise above -70 °C and the reaction stirred at this temperature for 1 hour. Ethyl bromoacetate (1.63 ml, 14.70 mmol) was added drop-wise to the mixture and after 30 minutes the reaction was allowed to warm to room temperature over 4 hours. The reaction was quenched with addition of water (50 ml) and extracted into ethyl acetate (3 x 75 ml). The organic fractions were combined, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield (209b) as a white solid (2.60 g, 84 %) which required no further purification; Mp 65-67 °C; ν<sub>max</sub> (thin film, CH<sub>2</sub>Cl<sub>2</sub>/cm<sup>-1</sup> 1717 (C=O), 1180 (C-O); δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 1.26 (3H, t, J 7.2, OCH<sub>2</sub>CH<sub>3</sub>), 1.82 (1H, t, J 13.2, CHC(H)HC), 1.95-2.01 (1H, m, COC(H)CH<sub>2</sub>), 2.03-2.14 (2H, m, CHCH(H)C and COCH(H)CH<sub>2</sub>), 2.19 (1H, dd, J 6.0, 16.8, CHC(H)HCO), 2.40 (1H, ddd, J 2.8, 4.8, 14.4, COCH<sub>2</sub>C(H)H), 2.66-2.77 (2H, m, CHCH(H)CO and COCH2CH(H)), 3.16-3.25 (1H, m, COCH), 4.00-4.07 (4H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 4.10-4.16 (2H, m, OCH<sub>2</sub>CH<sub>3</sub>); δ<sub>C</sub> (100MHz; CDCl<sub>3</sub>) 14.2 (CH<sub>3</sub>), 34.0 (CH<sub>2</sub>), 34.6 (CH<sub>2</sub>), 37.8 (CH<sub>2</sub>), 40.0 (CH<sub>2</sub>), 43.1 (CH), 60.5 (CH<sub>2</sub>), 64.7 (CH<sub>2</sub>), 64.8 (CH<sub>2</sub>), 107.4 (C), 172.0 (CO<sub>2</sub>Et), 209.6 (CO); MS (FAB) m/z 242 [MH<sup>+</sup>, 100 %] (MH<sup>+</sup>, 242.1238. C<sub>12</sub>H<sub>15</sub>O<sub>5</sub> requires 242.1233).
Methyl 2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)acetate (217).

To a mixture of methyltriphenylphosphonium bromide (3.52 g, 9.86 mmol) and sodium hydride (395 mgs, 9.86 mmol) under nitrogen was added anhydrous tetrahydrofuran (50 ml) around the sides of the flask. The reaction mixture was stirred vigorously for 45 min to give a bright yellow suspension at which time methyl 2-(8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)acetate (209a) (1.50 g, 6.58 mmol) was added drop-wise as a solution in anhydrous tetrahydrofuran (15 ml). Upon complete addition a deep red colouration was observed and the reaction left to stir vigorously for a further 3 hours. The reaction mixture was cooled to 0 °C and quenched via careful addition of water (100 ml), followed by extraction into ethyl acetate (3 x 75 ml). The combined organics were dried over anhydrous magnesium sulfate, filtered and concentrated under pressure to yield a pale yellow oil. The crude oil was suspended in diethyl ether to precipitate triphenylphosphine oxide and the resulting filtrate evaporated to dryness on the rotary evaporator to furnish the target compound as a colourless oil (1.46 g, 99 %); \( \nu_{\text{max}} \) (thin film, neat)/cm\(^{-1} \) 1738 (CO(O)CH\(_3\)), 1647 (C=O), 1167 (C-O); \( \delta_H \) (400 MHz; CDCl\(_3\)) 1.40-1.46 (1H, m, CHC(H)HC), 1.60-1.66 (1H, m, CH\(_2\)=CCH\(_3\)); 1.76-1.82 (1H, m, CH\(_2\)=CCH\(_2\)CH\(_2\)); 1.88 (1H, ddd, \( J \) 2.4, 4.4, 12.8, CHCH(H)C), 2.31-2.38 (3H, m, CHC(H)HC and CH\(_2\)=CCH\(_2\)CH\(_2\)); 2.65 (1H, dd, \( J \) 7.2, 15.2, CHCH(H)CO); 2.81-2.89 (1H, m, CCH), 3.68 (3H, s, OCH\(_3\)); 3.93-4.00 (4H, m, OCH\(_2\)CH\(_2\)O), 4.62 (1H, s, CC(H)H); 4.77 (1H, s, CCH(H)); \( \delta_C \) (100MHz; CDCl\(_3\)) 32.3 (CH\(_2\)), 36.2 (CH\(_2\)); 36.8 (CH\(_2\)), 37.5 (CH\(_2\)), 41.4 (CH\(_2\)); 51.6 (CH\(_3\)), 64.3 (CH\(_2\)); 64.4 (CH\(_2\)); 106.8 (CH\(_2\)); 108.4 (C), 149.1 (C), 173.1 (CO\(_2\)Me); MS (FAB) \( m/z \) 226 [MH\(^+\), 100 %] (MH\(^+\), 226.1288. C\(_{12}\)H\(_{18}\)O\(_4\) requires 226.1283).
Methyl 2-((7S,SR)-S-formyl-1,4-dioxaspiro[4.5]decan-7-yl)acetate \textit{rac-}(219).

\begin{center}
\includegraphics[width=0.2\textwidth]{methyl_2-(7s,rs)-s-formyl-1,4-dioxaspiro[4.5]decan-7-yl)acetate.png}
\end{center}

Methyl 2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)acetate (217) (2.00 g, 8.33 mmol) in anhydrous tetrahydrofuran (30 ml) under nitrogen was treated with borane-dimethylsulfide complex (2M) in tetrahydrofuran (2.50 ml, 5.00 mmol). The mixture was stirred vigorously for 1 hour and then all volatiles were removed under reduced pressure to give a colourless oil. The crude oil was taken up in a minimum amount of dichloromethane and added drop-wise to a solution of pyridinium chlorochromate (4.31 g, 19.99 mmol) in dichloromethane (40 ml). The reaction mixture was then refluxed for 2 hours before being allowed to cool to room temperature and diluted with diethyl ether (50 ml). The organic phases were decanted and filtered through a silica pad and the remaining black solids washed exhaustively with further portions of diethyl ether (5 × 30 ml). All volatiles were removed under reduced pressure to yield a crude oil that was purified by flash column chromatography over silica using 4:1 hexane:ethyl acetate as eluent to yield the target compound as a colourless oil (1.49 g, 70 %); \( \nu_{\text{max}} \) (thin film, neat)/cm\(^{-1} \) 1732 (CHO), 1176 (C-O); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 1.51-1.59 (1H, m, CHOCHCH\(_2\)C(H)H), 1.63-1.80 (3H, m, CHCH\(_2\)C and CHOCHCH\(_2\)CH(H)), 1.84-1.93 (1H, m, CHOCHC(H)H), 2.03-2.09 (1H, m, CHOCHCH(H)), 2.45-2.60 (3H, m, CHOCHCH and CHCH\(_2\)CO), 2.64 (1H, q, J 4.0, CHOCH), 3.67 (1H, s, OCH\(_3\)), 3.91-3.98 (4H, m, OCH\(_2\)CH\(_2\)O), 9.76, (CHO); \( \delta_{\text{C}} \) (100MHz; CDCl\(_3\)) 22.1 (CH\(_2\)), 31.9 (CH\(_2\)), 32.4 (CH), 36.4 (CH\(_2\)), 37.7 (CH\(_2\)), 49.2 (CH), 51.6 (CH\(_3\)), 64.2 (CH\(_2\)), 64.4 (CH\(_2\)), 108.2 (C), 173.0 (CO\(_2\)Me), 203.6 (CHO); MS (FAB) \( m/z \) 242 [MH\(^+\), 28.1 %] (MH\(^+\), 242.1232. C\(_{12}\)H\(_{15}\)O\(_5\) requires 242.1233).
(3'S,6a'S,10a'R,10b'S)-3'-((1H-Indol-3-yl)methyl)octahydrospiro[[1,3]dioxolane-
2,8'-oxazolo[2,3-a]isoquinolin]-5'(6'H)-one (220a)

(5)-2-Amino-3-(1H-indol-3-yl)propan-1-ol (198) (1.12 g mgs, 5.47 mmol) and Methyl 2-
((7S,8R)-8-formyl-1,4-dioxaspiro[4.5]decan-7-yl)acetate rac-(219) (1.40 g, 5.47 mmol) were added to toluene (50 ml) and refluxed under Dean-Stark conditions for 24 hours.
The mixture was allowed to cool to room temperature and the solvent removed under reduced pressure to yield the target compound. Crude 400 MHz 1H-NMR analysis revealed the formation of (220) as a 1:1 mixture of diastereoisomers. These diastereoisomers were purified and separated by flash column chromatography over silica using 4:1 light petroleum:ethyl acetate as eluent (940 mgs, 45 %).

Natural product isomer (220a) isolated as a white solid; Mp 205-207 °C; [α]D = -27.9
[c = 1.0, CH2Cl2]; νmax (thin film, CH2Cl2)/cm⁻¹ 1631 (NC=O), 1229 (C-O); δH (400
MHz; CDCl3) 1.29-1.47 (3H, m, NCHCH and NCHCHC(H)H and COCH2CHC(H)H),
1.51-1.61 (1H, m, NCHCH2C(H)H), 1.77-1.92 (3H, m, COCH2CH and
NCHCH2CH2CHC(H) and COCH2CHCHC(H),) 2.00-2.21 (2H, m, COC(H)H and
NCHCHCH(H)), 2.54 (1H, dd, J 6.0, 18.0, COCH(H)), 2.63 (1H, dd, J 10.4, 13.6,
CHCC(H)), 3.67-3.69 (1H, m, CHOC(H)H), 3.72-3.77 (1H, m, CHCCH(H)), 3.92-3.98
(4H, m, OCH2CH2O), 4.03 (1H, d, J 9.2, CHOC(H)), 4.27-4.33 (1H, m, CHCCH2CH),
4.34 (1H, d, J 8.8, NCH), 7.02 (1H, d, J 1.6, NHCH), 7.10-7.21 (2H, m, ArH), 7.35 (1H,
d, J 8.0, ArH), 7.80 (1H, d, J 7.6, ArH), 8.3 (1H, s, NH); δc (100MHz; CDCl3) 24.8
(CH3), 26.8 (CH2), 32.3 (CH), 33.4 (CH2), 38.7 (CH2), 40.6 (CH2), 42.3 (CH), 56.3 (CH),
64.5 (CH2), 64.5 (CH2), 70.2 (CH2), 92.3 (CH), 108.0 (C), 111.1 (CH), 112.4 (C), 119.3

Chapter 5 Experimental 173
(CH), 119.5 (CH), 122.1 (CH), 122.4 (CH), 127.6 (C), 136.2 (C), 167.2 (NCO); MS (FAB) m/z 382 [MH$^+$, 93.6 %] (MH$^+$, 382.1967. $C_{22}H_{26}N_2O_4$ requires 382.1971).
(S,6a'R,10a'S,10b'R)-3'-((1H-Indol-3-yl)methyl)octahydrospiro[[1,3]dioxolane-2,8'-oxazolo[2,3-α]isoquinolin]-5'(6'H)-one (220).

(S)-2-Amino-3-((1H-indol-3-yl)propan-1-ol (198) (1.12 g mgs, 5.47 mmol) and methyl 2-((7S,8R)-8-formyl-1,4-dioxaspiro[4.5]decan-7-yl)acetate rac-(219) (1.40 g, 5.47 mmol) were added to toluene (50 ml) and refluxed under Dean-Stark conditions for 24 hours. The mixture was allowed to cool to room temperature and the solvent removed under reduced pressure to yield the target compound. Crude 400 MHz ¹H-NMR analysis revealed the formation of (220) as a 1:1 mixture of diastereoisomers. These diastereoisomers were purified and separated by flash column chromatography over silica using 4:1 light petroleum:ethyl acetate as eluent (940 mgs, 45%).

Second isomer (220b) isolated as a white solid; Mp 182-183 °C; [α]D = 19.6 [c = 1.0, CH2Cl2]; v_max(thin film, CH2Cl2)/cm⁻¹ 1631 (N=C=O), 1230 (C-O); δ_H (400 MHz; CDCl3) 1.17-1.42 (3H, m, NCHCH and NCHCHC(H)H and COCH2CHC(H)H), 1.49-1.58 (1H, m, NCHCHCH2C(H)H), 1.76-1.90 (3H, m, COCH2CH and NCHCHCH2CHC(H) and COCH2CHCHC(H)), 1.97-2.00 (2H, m, COC(H)H and NCHCHCHC(H)), 2.60 (1H, dd, J 5.2, 18.0, COC(H)), 2.99 (1H, dd, J 8.8, 14.0, CHCC(H)H), 3.36 (1H, dd, J 3.6, 14.4, CHCC(H)), 3.66 (1H, dd, J 1.6, 7.2, CHOC(H)H), 3.89-3.97 (4H, m, OCH2CH2O), 4.05 (1H, dd, J 7.6, 8.8, CHOCH(H)), 4.22 (1H, d, J 8.0, NCH), 4.56-4.63 (1H, m, CHCCH2CH), 6.99 (1H, d, J 2.0, NHCCH), 7.10-7.21 (2H, m, ArH), 7.35 (1H, d, J 8.0, ArH), 7.69 (1H, d, J 8.0, ArH), 8.43 (1H, s, NH); δ_C (100MHz; CDCl3) 25.5 (CH2), 27.3 (CH2), 31.1 (CH), 33.3 (CH2), 38.5 (CH2), 40.5 (CH2), 41.8 (CH), 54.9 (CH), 64.3 (CH2), 64.4 (CH2), 70.0 (CH2), 91.0 (CH), 107.9 (C), 110.9 (C), 111.1 (CH), 119.0 (CH), 119.5

Chapter 5 Experimental

175
(CH), 122.1 (CH), 122.5 (CH), 127.7 (C), 136.2 (C), 167.9 (NCO); MS (FAB) \textit{ml}z 382 [MH$^+$, 97.1 \%] (MH$^+$, 382.1965. C$_{22}$H$_{26}$N$_2$O$_4$ requires 382.1971).
7-Hydroxymethyl-1,4a'S,5,7'S,8,13,13b'R,13c'R-octahydro-2H,4H-6a,13-diaza-indeno[1,2-c]phenanthrene-3,6-dione (222a).

(3'S,6a'S,10a'R,10b'S)-3'-(1H-indol-3-yl)methyl)octahydrospiro[1,3]dioxolane-2,8'-oxazolo[2,3-a]isoquinolin]-5'(6'H)-one (220a) (500 mgs, 1.31 mmol) was dissolved in a solution of 2M hydrochloric acid in absolute ethanol (15 ml) and the mixture stirred for a further 3 h at 50 °C. After this time the reaction was quenched by addition of saturated aqueous sodium bicarbonate (30 ml) and extracted with ethyl acetate (3 x 40 ml). The organic fraction was dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield a crude yellow solid. Crude 400 MHz ¹H-NMR analysis revealed the formation of (222a) exclusively and purification via flash column chromatography over silica with 95:5 ethyl acetate:methanol as eluent gave the target compound as an off-white solid (248 mgs, 56 %);

Natural product isomer (222a); Mp 202-204 °C; [α]D = 52.0 [c = 0.5, CH3OH]; νmax (thin film, CH2Cl2)/cm⁻¹ 3317 (OH), 1621 (NCO); δH (400 MHz; DMSO) 1.64-1.73 (1H, m, NCHCHC(H)H), 1.90-2.06 (3H, m, NCHCH and COCH2CH and COC(H)H), 2.10-2.31 (4H, m, NCHCHCH2C(H)H and COCH2CHCH2 and COCH(H)), 2.45-2.55 (1H, m, NCHCHCH2CH(H)), 2.61 (2H, dd, J 2.0, 5.6, NHCCCH2), 2.63-2.67 (1H, m, NCHCHCH(H)), 3.19-3.33 (2H, m, CHCH2OH), 4.34 (1H, d, J 8.4, NCHCH), 4.66 (1H, t, J 5.6, OH), 5.04-5.09 (1H, m, CHCH2OH), 6.84-6.88 (1H, m, ArH), 6.94-6.98 (1H, m, ArH), 7.26-7.29 (2H, m, ArH); δC (100MHz; DMSO) 20.9 (CH3), 30.8 (CH2), 35.5 (CH), 39.3 (CH2), 39.9 (CH2), 40.9 (CH), 45.9 (CH2), 48.6 (CH), 54.2 (CH) 59.6 (CH2), 106.7 (C), 111.5 (CH), 117.6 (CH), 118.7 (CH), 121.2 (CH), 126.5 (C), 132.9 (C), 136.5 (C),
168.0 (NCO), 209.0 (CO); MS (FAB) m/z 338 [MH⁺, 69.8 %] (MH⁺, 338.1715. C₂₀H₂₂N₂O₃ requires 338.1709).
7-Hydroxymethyl-1,4a'R,S,7'S,8,13,13b'R,13c'S-octahydro-2H,4H-6a,13-diaza-indeno[1,2-c]phenanthrene-3,6-dione (222b).

(3'S,6a'R,10a'S,10b'R)-3'-(1H-indol-3-yl)methyl)octahydrospiro[1,3]dioxolane-2,8'-oxazolo[2,3-α]isoquinolin]-5'(6'H)-one (220b) (500 mgs, 1.31 mmol) was dissolved in a solution of 2M hydrochloric acid in absolute ethanol (15 ml) and the mixture stirred for a further 18 h at 50 °C. After this time the reaction was quenched by addition of saturated aqueous sodium bicarbonate (30 ml) and extracted with ethyl acetate (3 x 40 ml). The organic fraction was dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield a crude yellow solid. Crude 400 MHz 'H-NMR analysis revealed the formation of (222b) exclusively and purification via flash column chromatography over silica with 95:5 ethyl acetate:methanol as eluent gave the target compound as an off-white solid (256 mgs, 58 %);

Second isomer (186b); Mp 212-213 °C; [α]D = 9.9 [c = 0.5, CH3OH]; νmax (thin film, CH2Cl2)/cm\(^{-1}\) 3311 (OH), 1633 (NCO); δH (400 MHz; CDCl3) 2.00-2.11 (2H, m, COCH2CH and NCHCHC(H)H), 2.30-2.34 (1H, m, NCHCH), 2.39-2.49 (2H, m, NCHCHCH2C(H)H and COCH2CHCH2 and COCH2), 2.63-2.69 (1H, m, NHCCCH(H)H), 3.11 (1H, ddd, J 2.0, 6.4, 16.0, NHCCCH(H)), 3.62-3.72 (2H, m, CH2CH2OH), 5.02 (1H, d, J 5.2, NCHCH), 5.25-5.28 (1H, m, CHCH2OH), 7.08-7.20 (2H, m, ArH), 7.30 (1H, d, J 8.0, ArH), 7.45 (1H, d, J 7.6, ArH), 8.38 (1H, s, NH); δC (100MHz; CDCl3) 21.5 (CH2), 28.2 (CH2), 34.0 (CH), 40.3 (CH2), 41.0 (CH2), 41.6 (CH), 46.7 (CH2), 51.1 (CH), 52.3 (CH), 61.6 (CH2), 111.1 (CH), 111.2 (C), 118.1 (CH), 120.0 (CH), 122.7 (CH), 126.8 (C), 130.0 (C), 136.2 (C),

Chapter 5  Experimental 179
172.0 (NCO), 208.6 (CO); MS (FAB) m/z 338 [MH$^+$, 47.7 %] (MH$^+$, 338.1713.
C$_{20}$H$_{22}$N$_2$O$_3$ requires 338.1709).
7-Formyl-1,4a'S,5,7'S,8,13,13b'R,13c'R-octahydro-2H,4H-6a,13-diaza-indeno[1,2-c]phenanthrene-3,6-dione (223).

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\end{align*}
\]

\(o\text{-Iodoxybenzoic acid (492 mgs, 1.77 mmol) was added to a solution of 7-hydroxymethyl-1,4a'S,5,7'S,8,13,13b'R,13c'R-octahydro-2H,4H-6a,13-diaza-indeno[1,2-c]phenanthrene-3,6-dione (222a) (200 mgs, 0.59 mmol) in ethyl acetate (10 ml) and the reaction heated under reflux for 4 hours. The resulting mixture was allowed to cool to room temperature, filtered through a sinter funnel and evaporated under reduced pressure to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 99:1 ethyl acetate:methanol as eluent to isolate the target compound as a yellow solid (149 mgs, 75%), Mp 165-168 \text{°C}; \text{[\(\alpha\)]}_{D} = 53.1 \text{[c = 0.5, CH}_{2}\text{Cl}_{2}; \text{\nu}_{\text{max}} \text{(thin film, CH}_{2}\text{Cl}_{2})/\text{cm}^{-1} 1732 \text{(CHO)}; \text{\delta}_{\text{H}} \text{(400 MHz; CDCl}_{3}) \text{1.84 (1H, m, NCHCHC(H)H), 1.94-2.02 (1H, m, NCHCH), 2.12 (1H, t, J 12.0, COCH}_{2}\text{CHC(H)H), 2.18-2.30 (2H, m, COCH}_{2}\text{CH and COC(H)H), 2.38-2.47 (1H, m, NCHCHCH}_{2}\text{C(H)H), 2.50-2.56 (2H, m, NCHCHCH}_{2}\text{CHC(H)H and COCH}_{2}\text{CHCH}_{2}\text{CHC(H)H), 2.65-2.71 (1H, m, NCHCHCH}_{2}\text{CHC(H)H), 2.78 (1H, dd, J 4.4, 16.8, COCH}_{2}\text{CHC(H)H), 3.12 (1H, ddd, J 2.4, 6.4, 16.0, NHCCCH}_{2}\text{H), 3.44 (1H, d, J 16.0, NHCCCH}_{2}\text{H), 4.66 (1H, d, J 9.6, NCHCH), 5.97 (1H, dd, J 1.2, 6.0, CHCHO), 7.14-7.24 (2H, m, ArH), 7.33 (1H, d, J 7.6 ArH), 7.56 (1H, d, J 7.6 ArH), 8.18 (1H, s, NH), 9.36 (1H, s, CHO); \text{\delta}_{C} \text{(100MHz; CDCl}_{3}) 20.6 (\text{CH}_{2}), 29.8 (\text{CH}_{2}), 36.9 (\text{CH}), 38.9 (\text{CH}), 39.9 (\text{CH}_{2}), 42.7 (\text{CH}), 46.7 (\text{CH}), 57.3 (\text{CH}), 57.8 (\text{CH}), 108.8 (\text{C}), 111.2 (\text{CH}), 118.4 (\text{CH}), 120.3 (\text{CH}), 123.1 (\text{CH}), 126.0 (\text{C}), 131.5 (\text{C}), 136.4 (\text{C}), 169.1 (\text{NCO}), 119.0 (\text{CHO}), 208.1 (\text{CO}); \text{MS (FAB) } m/z 336 \text{[MH}^{+}, 16.3 \% \text{]} \text{(MH}^{+}, 336.1558. \text{C}_{20}\text{H}_{20}\text{N}_{2}\text{O}_{3} \text{requires 336.1552).}}
\]
5.5 Application of a Claisen/RCM protocol

1,4-bis(Allyloxy)-2,3-dimethylbenzene (268).\textsuperscript{130}

A suspension of 2,3-dimethylhydroquinone (267) (2.50 g, 18.09 mmol), allyl bromide (3.83 ml, 45.23 mmol) and anhydrous potassium carbonate (6.25 g, 45.23 mmol) in acetone (15 ml) was refluxed for 24 hours. The reaction was allowed to cool to room temperature before water (50 ml) and diethyl ether (50 ml) were added. The layers were separated and the aqueous layer extracted with diethyl ether (4 x 50 ml). The combined organic extracts were washed with 1M aqueous sodium hydroxide solution (3 x 100 ml) and water (100 ml), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the crude product as a brown oil. Flash column chromatography on silica, eluting with 10:1 light petroleum:ethyl acetate, yielded bisallyl ether (268) as a white solid (3.63 g, 92 %), Mp 66-68 °C; \nu_{\text{max}} \text{ (thin film, CH}_2\text{Cl}_2)/\text{cm}^{-1} 1647 (C=C), 1101 (C–O); \delta_H \text{ (400MHz; CDCl}_3) 2.18 (6H, s, 2 x ArCH}_3), 4.44 (4H, dt, J 2.0, 5.2, 2 x OCH}_2CH=CH}_2), 5.24 (2H, dq, J 1.6, 10.4, 2 x OCH}_2CH=CH(H)), 5.40 (2H, dq, J 1.6, 17.2, 2 x OCH}_2CH=CH(H)), 6.01-6.10 (2H, m, 2 x OCH}_2CH=CH}_2), 6.61 (2H, s, ArH); \delta_C \text{ (100 MHz; CDCl}_3) 12.2 (2 x CH}_3), 69.7 (2 x CH}_2), 109.5 (2 x CH), 116.7 (2 x CH}_2), 127.2 (2 x (C)), 134.1 (2 x CH), 151.0 (2 x (C)); MS (FAB) m/z 218 [M\textsuperscript{+}, 52.9 %] (M\textsuperscript{+}, 218.1312. C\textsubscript{14}H\textsubscript{18}O\textsubscript{2} requires 218.1307).
2,3-Dimethyl-5,6-diallylhydroquinone (269).\textsuperscript{131}

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{CH} & \quad \text{CH}
\end{align*}
\]

Bis-allyl ether (268) (3.53 g, 16.18 mmol) was refluxed in mesitylene (20 ml) for 24 hours. The solvent was removed under reduced pressure to yield a tarry brown solid. Hexane (50 ml) was added and removed on the rotary evaporator to azeotrope any residual mesitylene. The resulting solid was filter-washed with cold hexane (50 ml) to yield the hydroquinone (269) as a brown solid (2.47 g, 70 %), Mp 93-95 \degree C; \nu_{\text{max}}\ (\text{thin film}, \text{CH}_2\text{Cl}_2)/\text{cm}^{-1} \quad 3404 (\text{OH}), 1635 (\text{C} = \text{C}); \delta_{\text{H}} (400\text{MHz}; \text{CDCl}_3): 2.06 (6\text{H}, \text{s}, 2 \times \text{ArCH}_3), 3.31 (4\text{H}, \text{dt}, J 1.6, 6.0, 2 \times \text{CH}_2\text{CH} = \text{CH}_2), 4.85-4.92 (4\text{H}, \text{m}, 2 \times \text{CH}_2\text{CH} = \text{CH}_2), 5.80-5.90 (2\text{H}, \text{m}, 2 \times \text{CH}_2\text{CH} = \text{CH}_2), 7.40 (2\text{H}, \text{s}, 2 \times \text{ArOH}); \delta_{\text{C}} (100\text{MHz}; \text{DMSO}): 13.04 (2 \times \text{CH}_3), 30.49 (2 \times \text{CH}_2), 114.07 (2 \times \text{CH}_2), 122.36 (2 \times (\text{C})), 123.41 (2 \times (\text{C})), 137.48 (2 \times \text{CH}), 145.71 (2 \times (\text{C})); \text{MS (FAB) } m/z \quad 218 [\text{M}^+ , \text{100 }\%] (\text{M}^+ , 218.1304. \text{C}_{14}\text{H}_{18}\text{O}_2 \text{requires} \ 218.1307).
2,3-Dimethyl-5,6-diallylhydroquinone diacetate (270). Acetic anhydride (5.6 ml, 59.59 mmol) was added slowly to a solution of hydroquinone (269) (5.0 g, 22.92 mmol) and DMAP (0.84 g, 6.88 mmol) in triethylamine (8.0 ml) at 0 °C and the resulting mixture stirred at room temperature for 20 hours. Methanol (20 ml) and diethyl ether (150 ml) were added and the solution washed with 1M aqueous hydrochloric acid solution (100 ml) and saturated aqueous sodium hydrogen carbonate solution (100 ml). The resulting organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a brown oil. Flash column chromatography on silica, eluting with 10:1 light petroleum:ethyl acetate, furnished diacetate (270) as a white solid (6.23 g, 90 %), Mp 97-99 °C; v_max (thin film, CH_2Cl_2)/cm^{-1} 1758 (C=O), 1637 (C=C), 1191 (C-O); δ_H (400MHz; CDCl_3) 2.04 (6H, s, 2 × ArCH_3), 2.30 (6H, s, 2 × OCOCH_3), 3.21-3.33 (4H, br, 2 × CH_2CH=CH_2), 4.92-5.01 (4H, m, 2 × CH_2CH=CH_2), 5.75-5.85 (2H, m, 2 × CH_2CH=CH_2); δ_C (100MHz; CDCl_3): 13.4 (2 × CH_3), 20.7 (2 × CH_3), 31.5 (2 × CH_2), 115.6 (2 × CH_2), 128.7 (2 × (C)), 128.8 (2 × (C)), 135.6 (2 × CH), 146.0 (2 × (C)), 169.1 (2 × (C)); MS (FAB) m/z 302 [MH^+, 29.1 %] (MH^+, 302.1602. C_{18}H_{22}O_4 requires 302.1596).
A catalytic amount of Grubbs 2nd generation catalyst was added to a solution of diacetate (270) (3.15 g, 10.41 mmol) in anhydrous tetrahydrofuran under an inert atmosphere of nitrogen. The completion of the reaction was monitored by TLC analysis and additional catalyst was added if required. After 24 hours stirring the reaction mixture was absorbed on to silica following removal of the reaction solvent and loaded on to a chromatographic column. Flash column chromatography on silica, eluting with 10:1 light petroleum:ethyl acetate, yielded the ring-closed product (153) as a white solid (0.44 g, 89 %), Mp 186-189 °C; νmax (thin film, CH2Cl2)/cm⁻¹ 3024, 974 (C-H alkene), 1747 (C=O), 1200 (C-O); δH (400MHz; CDCl3) 2.05 (6H, s, 2 × ArCH3), 2.34 (6H, s, 2 × OCOCH3), 3.07-3.20 (4H, br, 2 × CH2CH=CH2), 5.81 (2H, t, J 1.2, CH=CH); δC (100MHz; CDCl3): 13.0 (2 × CH3), 20.5 (2 × CH3), 24.4 (2 × CH2), 123.0 (2 × CH), 125.1 (2 × (C)), 127.5 (2 × (C)), 145.0 (2 × (C)), 169.1 (2 × (C)); MS (FAB) m/z 274 [MH⁺, 11.0 %] (MH⁺, 274.1279. C16H18O4 requires 274.1283).
2,3-Dimethyl-5,6,7,8-tetrahydro-1,4-napthalendiol diacetate (276).130

Pd/C (0.074 g, 10 % w/w) was added to a solution of diacetate adduct (271) (0.74 g, 2.70 mmol) in absolute ethanol (30 ml). The resulting suspension was stirred at atmospheric pressure under hydrogen at room temperature for 24 hours. The solution was filtered through Celite and the filtrate washed with ethyl acetate (50 ml). The solvent was removed under reduced pressure, to yield the product as a white solid (0.73 g, 99 %), Mp 194-196 °C; \( \nu_{\text{max}} \) (thin film, CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 1748 (C=O), 1199 (C-O); \( \delta_H \) (400MHz; CDCl\(_3\)) 1.54-1.87 (4H, br, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)), 2.04 (6H, s, 2 x ArCH\(_3\)), 2.33 (6H, s, 2 x OCOCH\(_3\)), 2.51-2.77 (4H, br, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)); \( \delta_C \) (100MHz; CDCl\(_3\)) 12.9 (2 x CH\(_3\)), 20.5 (2 x CH\(_3\)), 22.0 (2 x CH\(_2\)), 23.5 (2 x CH\(_2\)), 126.8 (2 x (C)), 127.9 (2 x (C)), 145.3 (2 x (C)), 169.2 (2 x (C)); MS (FAB) m/z 276 [MH\(^+\), 46.6 %] (MH\(^+\), 276.1438. C\(_{16}\)H\(_{20}\)O\(_4\) requires 276.1440).
To a saturated solution of chromium (VI) oxide (1.81 g, 18.10 mmol) in 80 % acetic acid (10 ml) was added 2,3-dimethyl-5,6,7,8-tetrahydro-1,4-napthalendiol diacetate (276) (0.50 g, 1.81 mmol) portionwise. The resulting mixture was heated to 50 °C for a further 20 hours with stirring. After this time the mixture was added to ice water (20 ml) with continuous stirring and a precipitate began to form. The aqueous mixture was maintained at 0 °C for a further 18 hours to yield a larger volume of a white precipitate which was collected via filtration. The precipitate was dissolved in ethyl acetate, dried over anhydrous magnesium sulphate, filtered and concentrated to give the bis-oxidised product as a white solid (286 mg, 55 %), Mp 205-207 °C; \( \nu_{\text{max}} \) (thin film, \( \text{CH}_2\text{Cl}_2 \))/cm\(^{-1} \) 1761 (C=O(O)), 1695 (C=O), 1200 (C-O); \( \delta_H \) (400MHz; \( \text{CDCl}_3 \)) 2.23 (6H, s, 2 x ArCH\(_3\)), 2.43 (6H, s, 2 x OCOCH\(_3\)), 2.99 (4H, br, C=OCH\(_2\)CH\(_2\)C=O); \( \delta_C \) (100MHz; \( \text{CDCl}_3 \)) 13.6 (2 x CH\(_3\)), 20.1 (2 x CH\(_3\)), 39.1 (2 x CH\(_2\)), 125.3 (2 x (C)), 139.4 (2 x (C)), 144.9 (2 x (C)), 169.2 (2 x (C)) 194.2 (2 x C=O); MS (El) m/z 304 [M\(^+\), 5.1 %] (M\(^+\), 304.0943. C\(_{16}\)H\(_{16}\)O\(_6\) requires 304.0947).

(274); \( \nu_{\text{max}} \) (thin film, \( \text{CH}_2\text{Cl}_2 \))/cm\(^{-1} \) 3382 (OH), 1260 (C-O); \( \delta_H \) (400MHz; \( \text{CDCl}_3 \)) 2.09 (6H, s, 2 x ArCH\(_3\)), 2.45 (6H, s, 2 x OCOCH\(_3\)), 7.33 (2H, CCHCHC).
1,4-Dimethoxy-2,3-dimethyl-5,6-diallyhydroquinone (282).

Finely ground potassium hydroxide (0.64 g, 11.46 mmol) was added portion wise to a solution of 2,3-dimethyl-5,6-diallyhydroquinone (269) (1.0 g, 4.58 mmol) in dimethylformamide at 0 °C and stirred for 10 minutes. After this time methyl iodide (0.71 ml, 11.46 mmol) was added drop wise and the solution was then allowed to stir at room temperature for 4 hours. The mixture was then added to ice water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated to yield a dark brown oil. The crude oil was adsorbed onto silica and purified by column chromatography using 5:1 light petroleum:ethyl acetate as eluent. The product was isolated as a light brown oil (1.10 g, 98 %), \( \nu_{\text{max}} \) (thin film, \( \text{CH}_2\text{Cl}_2 \)) \( \text{cm}^{-1} \): 1636 (C=C), 1242 (C-O); \( \delta_H \) (400MHz; CDCl\(_3\)): 2.19 (6H, s, 2 x \( \text{ArCH}_3 \)), 3.41 (4H, dt, \( J = 2.0, 5.6, 2 \times \text{CCH}_2\text{CH}=\text{CH}_2 \)), 3.66 (6H, s, 2 x \( \text{OCH}_3 \)), 4.90 (2H, dq, \( J = 1.6, 16.8, 2 \times \text{CCH}_2\text{CH}=\text{CH}(\text{H}) \)), 4.99 (2H, dq, \( J = 1.6, 10.0, 2 \times \text{CCH}_2\text{CH}=\text{CH}(\text{H}) \)), 5.92-6.01 (2H, m, 2 \times \( \text{CCH}_2\text{CH}=\text{CH}_2 \)); \( \delta_C \) (100MHz; CDCl\(_3\)): 12.1 (2 \( \times \text{CH}_3 \)), 30.8 (2 \( \times \text{CH}_2 \)), 60.9 (2 \( \times \text{CH}_3 \)), 114.7 (2 \( \times \text{CH}_2 \)), 129.1 (2 \( \times \) (C)), 129.5 (2 \( \times \) (C)), 137.6 (2 \( \times \text{CH} \)), 153.2 (2 \( \times \) (C)); MS (FAB) \( m/z \): 246 [M\(^+\), 100 %] (M\(^+\), 246.1620. \( \text{C}_{16}\text{H}_{22}\text{O}_2 \) requires 246.1620).
A catalytic amount of Grubbs 2nd generation catalyst was added to a solution of 1,4-dimethoxy-2,3-dimethyl-5,6-diallylhydroquinone (282) (2.0 g, 8.12 mmol) in anhydrous toluene under an inert atmosphere of nitrogen. The completion of the reaction was monitored by TLC analysis and additional catalyst was added if required. After 18 hours stirring the reaction mixture was absorbed onto silica and purified by flash column chromatography with 6:1 light petroleum:ethyl acetate as eluent. The target compound was isolated as a light brown oil (957 mg, 54 %), \( \nu_{\text{max}} \) (thin film, \( \text{CH}_2\text{Cl}_2 \))/cm\(^{-1}\) 1628 (C=C), 1241 (C-O); \( \delta_{\text{H}} \) (400MHz; \( \text{CDCl}_3 \)) 2.11 (6H, s, 2 \( \times \text{ArCH}_3 \)), 3.27 (4H, d, \( J_{1.2} \), 2 \( \times \text{CCH}_2\text{CH} \)), 3.60 (6H, s, 2 \( \times \text{OCH}_3 \)), 5.84 (2H, t, \( J_{1.2} \), 2 \( \times \text{CCH}_2\text{CH} \)); \( \delta_{\text{C}} \) (100MHz; \( \text{CDCl}_3 \)) 12.5 (2 \( \times \text{CH}_3 \)), 24.3 (2 \( \times \text{CH}_2 \)), 60.9 (2 \( \times \text{CH}_3 \)), 124.0 (2 \( \times \text{CH} \)), 125.7 (2 \( \times (\text{C}) \)), 128.0 (2 \( \times (\text{C}) \)), 152.0 (2 \( \times (\text{C}) \)); MS (FAB) \( m/z \) 218 [\( \text{M}^+ \), 90.0 %] (\( \text{M}^+ \), 218.1312. \( \text{C}_{14}\text{H}_{16}\text{O}_2 \) requires 218.1307).
1,4-Dibenzoyl-2,3-dimethyl-5,6-diallylhydroquinone (285).

To a stirred solution of 2,3-dimethyl-5,6-diallylhydroquinone (269) (1.0 g, 4.58 mmol) in dichloromethane (15 ml) was added triethylamine (1.92 ml, 13.74 mmol) dropwise at room temperature. The reaction mixture was stirred for 15 minutes at room temperature and then cooled to 0 °C whereupon benzoyl chloride (1.17 ml, 10.08 mmol) was added dropwise. The resulting mixture was stirred for a further 5 hours after which time triethylamine hydrochloride salt precipitated out. Diethyl ether (50 ml) was added and the suspension filtered, dried over anhydrous magnesium sulfate and concentrated to yield a crude white solid. Recrystallisation from diethyl ether yielded the purified product as a crystalline white solid (1.87 g, 96 %), Mp 169-171 °C; ν\textsubscript{max} (thin film, CH\textsubscript{2}Cl\textsubscript{2})/cm\textsuperscript{-1} 1731 (C=O), 1639 (C=C), 1268 (C-O); δ\textsubscript{H} (400MHz; CDCl\textsubscript{3}) 2.12 (6H, s, 2 × ArCH\textsubscript{3}), 3.27 (2H, dd, J 5.2, 15.2, 2 × CCH(H)CH=CH\textsubscript{2}), 3.44 (2H, dd, J 5.6, 15.6, 2 × CCH(H)CH=CH\textsubscript{2}), 4.88-4.98 (4H, br, 2 × CCH\textsubscript{2}CH=CH\textsubscript{2}), 5.80-5.87 (2H, m, 2 × CCH\textsubscript{2}CH=CH\textsubscript{2}), 7.53 (4H, t, J 7.6, ArH), 7.66 (2H, t, J 7.6, ArH), 8.24 (4H, dd, J 1.2, 8.4, ArH); δ\textsubscript{C} (100MHz; CDCl\textsubscript{3}) 13.6 (2 × CH\textsubscript{3}), 31.7 (2 × CH\textsubscript{2}), 115.8 (2 × CH\textsubscript{2}), 128.7 (4 × CH), 129.0 (2 × (C)), 129.1 (2 × (C)), 129.3 (2 × (C)), 130.2 (4 × CH), 133.7 (2 × CH), 135.6 (2 × CH), 146.2 (2 × (C)), 164.8 (2 × (C)); MS (FAB) m/z 426 [MH\textsuperscript{+}, 15.7 %] (MH\textsuperscript{+}, 426.1916. C\textsubscript{28}H\textsubscript{26}O\textsubscript{4} requires 426.1909).
1,4-Dibenzoyl-2,3-dimethyl-5,8-dihydronaphthalene (286).

A catalytic amount of Grubbs 2nd generation catalyst was added to a solution of 1,4-dimethoxy-2,3-dibenzoyl-5,6-diallylhydroquinone (285) (1.53 g, 3.59 mmol) in anhydrous toluene under an inert atmosphere of nitrogen. The completion of the reaction was monitored by TLC analysis and additional catalyst was added if required. After 24 hours a white precipitate was filtered, dissolved in ethyl acetate and dried over anhydrous magnesium sulfate. The solvent was removed on the rotary evaporator to give the crude target compound which was recrystallised from diethyl ether to yield a white solid (1.17 g, 82 %), Mp 226-228 °C; \( \nu_{\text{max}} \) (thin film, CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 1732 (C=O), 1649 (C=C), 1266 (C-O); \( \delta_1 \) (400MHz; CDCl\(_3\)) 2.13 (6H, s, 2 \times ArCH\(_3\)), 3.22 (4H, br, 2 \times CCH\(_2\)CH), 5.78 (2H, s, 2 \times CCH\(_2\)CH), 7.55 (4H, t, 7.6, ArH), 7.67 (2H, t, 7.6, ArH), 8.26 (4H, dd, 1.6, 8.4, ArH); \( \delta_C \) (100MHz; CDCl\(_3\)) 13.0 (2 \times CH\(_3\)), 24.5 (2 \times CH\(_2\)), 123.0 (2 \times CH), 125.4 (2 \times (C)), 127.8 (2 \times (C)), 128.7 (4 \times CH), 129.2 (2 \times (C)) 130.2 (4 \times CH), 133.7 (2 \times CH), 145.1 (2 \times (C)), 164.7 (2 \times (C)); MS (FAB) \( m/z \) 398 [MH\(^+\), 3.3 %] (MH\(^+\), 398.1611. C\(_{26}\)H\(_{22}\)O\(_4\) requires 398.1596).
1,4-Dibenzoyl-2,3-dimethyl-5,6,7,8-tetrahydronaphthalene (287)

Pd/C (127 mgs, 10 % w/w) was added to a solution of 1,4-dibenzoyl-2,3-dimethyl-5,8-dihydronaphthalene (286) (1.27 g, 3.17 mmol) in ethyl acetate (30 ml). The resulting suspension was stirred at atmospheric pressure under hydrogen at room temperature for 24 hours. The solution was filtered through Celite and the filtrate washed with ethyl acetate (2 x 50 ml). The solvent was removed on the rotary evaporator to furnish the product (287) as a white solid (1.19 g, 93 %), Mp 229-231 °C; νmax (thin film, CH2Cl2)/cm⁻¹ 1731 (C=O), 1260 (C-O); δH (400MHz; CDCl3) 1.58-1.83 (4H, br, CH2CH2CH2CH2), 2.12 (6H, s, 2 x ArCH3), 2.38-2.79 (4H, br, CH2CH2CH2CH2), 7.53 (4H, t, J 7.6, ArH), 7.65 (2H, t, J 7.2, ArH), 8.26 (4H, dd, J 1.6, 8.4, ArH); δC (100MHz; CDCl3): 13.1 (2 x CH3), 22.0 (2 x CH2), 23.7 (2 x CH2), 127.2 (2 x (C)), 128.3 (2 x (C)), 128.7 (4 x CH), 129.3 (2 x (C)) 130.2 (4 x CH), 133.7 (2 x CH), 145.5 (2 x (C)), 164.7 (2 x (C)); MS (FAB) m/z 400 [MH⁺, 4.0 %] (MH⁺, 400.1759. C26H24O4 requires 400.1753).
1,4-Dimethoxyethoxymethyl-2,3-dimethyl-5,6-diallylhydroquinone (290).

Anhydrous tetrahydrofuran (30 ml) was added to sodium hydride (770 mgs, 19.25 mmol) under nitrogen and the suspension cooled to 0 °C. 2,3-Dimethyl-5,6-diallylhydroquinone (269) (2.00 g, 9.17 mmol) was added portion-wise and the reaction left to stir for 5 minutes. After this time methoxyethoxymethyl chloride (2.20 ml, 19.25 mmol) was added drop-wise and the mixture allowed to warm to room temperature over 2 hours. The reaction was quenched with the addition of ice water (30 ml) and ethyl acetate (50 ml) added. The aqueous layer was extracted with further portions of ethyl acetate (2 x 50 ml) and the combined organic fractions combined, dried over anhydrous magnesium sulfate and volatiles removed under reduced pressure. The crude product was purified via flash column chromatography eluting with 4:1 light petroleum:ethyl acetate to give the target compound as a light brown oil (3.33 g, 92 %), \( \nu_{\text{max}} \) (thin film, CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 1635 (C=C), 1116 (C-O); \( \delta_H \) (400MHz; CDCl\(_3\)); 2.20 (6H, s, 2 x ArCH\(_3\)), 3.39 (6H, s, 2 x OCH\(_3\)), 3.42-3.46 (4H, br, 2 x CCH\(_2\)CH=CH\(_2\)), 3.58-3.61 (4H, m, 2 x OCH\(_2\)OCH\(_2\)CH\(_2\)O), 3.92-3.94 (4H, m, 2 x OCH\(_2\)OCH\(_2\)CH\(_2\)O), 4.82-4.88 (2H, br, 2 x CCH\(_2\)CH=CH\(_2\)), 4.96-4.99 (2H, br, 2 x CCH\(_2\)CH=CH\(_2\)), 4.98 (4H, s, 2 x OCH\(_2\)OCH\(_2\)CH\(_2\)O), 5.90-6.00 (2H, m, 2 x CCH\(_2\)CH=CH\(_2\)); \( \delta_C \) (100MHz; CDCl\(_3\)): 13.6 (2 x CH\(_3\)), 31.0 (2 x CH\(_2\)), 59.0 (2 x CH\(_3\)), 69.1 (2 x CH\(_2\)), 71.7 (2 x CH\(_2\)), 98.7 (2 x CH\(_3\)), 114.8 (2 x CH\(_2\)) 129.3 (2 x (C)), 129.7 (2 x (C)), 137.3 (2 x CH), 150.9 (2 x (C)); MS (FAB) \( m/z \) 394 [M\(^+\), 100 %] (M\(^+\), 394.2359. C\(_{22}\)H\(_{34}\)O\(_6\) requires 394.2355).
A catalytic amount of Grubbs 2nd generation catalyst was added to a solution of 1,4-dimethoxyethoxymethyl-2,3-dimethyl-5,6-diallylhydroquinone (290) (2.60 g, 6.59 mmol) in anhydrous toluene under an inert atmosphere of nitrogen. The completion of the reaction was monitored by TLC analysis and additional catalyst was added if required. After 24 hours stirring the reaction mixture was adsorbed onto silica and purified by flash column chromatography with 6:1 light petroleum:ethyl acetate. The target compound was isolated as a white solid (990 mgs, 41 %), Mp 53-55 °C; $\nu_{\text{max}}$ (thin film, CH$_2$Cl$_2$)/cm$^{-1}$ 1595 (C=C), 1111 (C-O); $\delta_{\text{H}}$ (400MHz; CDCl$_3$); 2.18 (6H, s, 2 x ArCH$_3$), 3.34-3.36 (4H, br, 2 x CCH$_2$CH=CH$_2$), 3.40 (6H, s, 2 x OCH$_3$), 3.59-3.63 (4H, m, 2 x OCH$_2$OCH$_2$CH$_2$O), 3.94-3.96 (4H, m, 2 x OCH$_2$OCH$_2$CH$_2$O), 4.98 (4H, s, 2 x OCH$_2$OCH$_2$CH$_2$O), 5.88 (2H, t, $J = 1.2$, CH=CH); $\delta_{\text{C}}$ (100MHz; CDCl$_3$): 13.5 (2 x CH$_3$), 25.1 (2 x CH$_2$), 59.1 (2 x CH$_3$), 69.2 (2 x CH$_2$), 71.8 (2 x CH$_2$), 98.2 (2 x CH$_3$), 124.0 (2 x CH), 126.2 (2 x (C)), 128.1 (2 x (C)), 150.0 (2 x (C)); MS (FAB) m/z 366 [$M^+$, 19.2 %] ($M^+$, 366.2048. C$_{20}$H$_{30}$O$_6$ requires 366.2042).
1,4-Dimethoxyethoxymethyl-2,3-dimethyl-5,6,7,8-tetrahydronaphthalene (292).

Pd/C (100 mgs, 10 % w/w) was added to a solution of 1,4-dimethoxyethoxymethyl-2,3-dimethyl-5,8-dihydronaphthalene (291) (1.0 g, 2.73 mmol) in ethyl acetate (25 ml). The resulting suspension was stirred at atmospheric pressure under hydrogen at room temperature for 19 hours. After this time the solution was filtered through Celite and the filtrate washed with ethyl acetate (2 × 30 ml). Volatiles were removed under reduced pressure to yield the crude target which was adsorbed onto silica and purified by flash column chromatography eluting with 10:1 light petroleum:ethyl acetate. The target compound was isolated as a crystalline white solid (975 mgs, 97 %), Mp 56-58 °C; $\nu_{max}$ (thin film, CH$_2$Cl$_2$)/cm$^{-1}$ 1113 (C-O); $\delta_H$ (400MHz; CDCl$_3$); 1.69-1.75 (4H, br, CH$_2$CH$_2$CH$_2$CH$_2$), 2.17 (6H, s, 2 × ArCH$_3$), 2.69-2.75 (4H, br, CH$_2$CH$_2$CH$_2$CH$_2$) 3.40 (6H, s, 2 × OCH$_3$), 3.60-3.62 (4H, m, 2 × OCH$_2$OCH$_2$CH$_2$O), 3.94-3.96 (4H, m, 2 × OCH$_2$OCH$_2$CH$_2$O), 4.97 (4H, s, 2 × OCH$_2$OCH$_2$CH$_2$O); $\delta_C$ (100MHz; CDCl$_3$) 13.4 (2 × CH$_3$), 22.6 (2 × CH$_2$), 24.4 (2 × CH$_2$), 59.1 (2 × CH$_3$), 69.1 (2 × CH$_2$), 71.8 (2 × CH$_2$), 98.0 (2 × CH$_2$), 127.6 (2 × (C)), 128.9 (2 × (C)), 150.3 (2 × (C)); MS (FAB) $m/z$ 368 [M$^+$, 46.5 %] (M$^+$, 368.2204. C$_{20}$H$_{32}$O$_6$ requires 366.2199).
5-Methoxy-1,4-naphthoquinone (294).\textsuperscript{146}

To a stirred solution of juglone (235) (1.75 g, 10.05 mmol) and silver (I) oxide (3.49 g, 15.07 mmol) in anhydrous dichloromethane (30 ml) was added methyl iodide (1.25 ml, 20.10 mmol) under nitrogen. The reaction mixture was stirred for 22 hours and then filtered through Celite and the cake washed with dichloromethane (2 x 25 ml). The filtrate was evaporated to dryness on the rotary evaporator and then recrystallized from ethanol to yield target (294) as a red solid (1.87 g, 99 %), Mp 186-188 °C, Lit: Mp 186-187 °C; \( \nu_{\text{max}} \) (thin film, CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 1650 (C=C), 1018 (C-O); \( \delta_H \) (400MHz; CDCl\(_3\)); 4.02 (3H, s, OCH\(_3\)), 6.88 (2H, s, COCHCHCO), 7.33 (1H, dd, J 1.6, 8.4, CH\(_3\)OCCH), 7.70 (1H, t, J 7.6, CH\(_3\)OCCHCH), 7.74 (1H, dd, J 1.6, 7.6, CH\(_3\)OCCHCHCH\(_2\) ); \( \delta_C \) (100MHz; CDCl\(_3\)) 56.5 (CH\(_3\)), 117.9 (CH), 119.2 (CH), 119.7 (C), 134.0 (C), 135.0 (CH), 136.2 (CH), 140.9 (CH), 159.6 (C), 184.4 (C), 185.2 (C); MS (FAB) \( m/z \) 188 [MH\(^+\), 55.2 %] (MH\(^+\), 188.0548. C\(_{11}\)H\(_8\)O\(_3\) requires 188.0552).
5-Methoxy-1,4-naphthalenediol (295).146

To a solution of sodium dithionite (13.76 g, 79.06 mmol) in water (75 ml) was added a solution of 5-methoxy-1,4-naphthoquinone (294) (1.75 g, 9.30 mmol) in ethyl acetate (50 ml). The resulting two phase solution was stirred for 1.5 hours, the organic layer separated, and the aqueous phase extracted with further portions of ethyl acetate (2 x 75 ml). The combined organics were washed with water (3 x 100 ml), dried over anhydrous magnesium sulfate and reduced under pressure. The product was obtained as a light-brown solid and required no further purification (1.54 g, 87 %), Mp 207-209 °C, Lit: Mp >100 °C (dec.); νmax (thin film, ) CH2Cl2/cm⁻¹ 3433 (OH), 1633 (C=O), 1017 (C-O); δH (400MHz; MeOD); 3.97 (3H, s, OCH3), 6.62 (1H, d, J 8.0, COCHCHCO), 6.74 (1H, d, J 8.0, COCHCHCO), 6.83 (1H, d, J 7.6, CH3OCCH), 7.26 (1H, t, J 7.6, CH3OCCHCH), 7.76 (1H, dd, J 0.8, 8.4, CH3OCCHCHCH); δC (100MHz; MeOD) 56.6 (CH3), 105.7 (CH), 110.4 (CH), 110.8 (CH), 116.6 (C), 117.0 (CH), 125.8 (CH), 128.5 (C), 146.6 (C), 148.2 (C), 157.3 (C); MS (FAB) m/z 190 [M⁺, 100 %] (M⁺, 190.0633. C11H10O3 requires 190.0630).
A solution of 5-methoxy-1,4-naphthalenediol (295) (1.25 g, 6.57 mmol), potassium carbonate (4.54 g, 32.85 mmol) and allyl bromide (3.34 ml, 39.44 mmol) in acetone (50 ml) was heated at reflux for 24 hours. The reaction mixture was filtered and evaporated to dryness. The resulting solid was dissolved in ethyl acetate (30 ml), washed with brine (3 x 30 ml), dried over anhydrous magnesium sulfate and the solvent removed under pressure. The crude brown oil was used without further purification.

Anhydrous tetrahydrofuran (15 ml) was added to sodium hydride (153 mgs, 3.82 mmol) under nitrogen and the suspension cooled to 0 °C. The crude 4-Allyloxy-8-methoxy-1-naphthaleneol (296) (800 mgs, 3.47 mmol) was added via syringe and the reaction left to stir for 10 minutes. After this time allyl bromide (0.32 ml, 3.82 mmol) was added dropwise and the mixture allowed to warm to room temperature over 18 hours. The reaction was quenched with the addition of ice water (20 ml) and ethyl acetate (30 ml) added. The aqueous layer was extracted with further portions of ethyl acetate (2 x 30 ml) and the combined organic fractions combined, dried over anhydrous magnesium sulfate and volatiles removed under reduced pressure. The crude brown solid was recrystallised from diethyl ether to yield colourless block-like crystals (643 mgs, 67 %), Mp 201-203 °C; νmax (thin film, CH2Cl2)/cm−1 1633 (C=C), 1017 (C-O); δH (400MHz; CDCl3) 3.95 (3H, s, 2 x OCH3), 4.55 (2H, dt, J 1.6, 4.8, OCH2CH=CH2 ), 4.63 (2H, dt, J 1.6, 5.2, OCH2CH=CH2), 5.28-5.30 (1H, m, OCH2CH=CH(H)), 5.31-5.32 (1H, m, OCH2CH=CH(H)), 5.49 (1H, dq, J 1.6, 17.2, OCH2CH=CH(H)), 5.57 (1H, dq, J 2.0, 17.2, OCH2CH=CH(H)), 6.10-6.21 (2H, m, 2 x OCH2CH=CH2), 6.71 (1H, d, J 8.4, COCHCHCO), 6.78 (1H, d, J 8.4, COCHCHCO), 6.89 (1H, dd, J 0.8, 8.0, CH3OCCH), 7.38 (1H, t, J 8.4, CH3OCCHCH), 7.91 (1H, dd, J 0.8, 8.4, CH3OCCHCHCH); δc (100
MHz; CDCl$_3$) 56.2 (CH$_3$), 69.4 (CH$_2$), 71.9 (CH$_2$), 105.8 (CH), 107.0 (CH), 109.8 (CH), 114.7 (CH), 116.5 (CH$_2$), 117.2 (CH$_2$), 119.1 (C), 125.9 (CH), 129.1 (C), 133.6 (CH), 134.1 (CH), 148.9 (C), 149.8 (C), 156.7 (C); MS (FAB) m/z 270 [M$^+$, 100 %] (M$^+$, 270.1256. C$_{17}$H$_{16}$O$_3$ requires 270.1256).
5.6 Application of a mixed Claisen/ortho-Fries strategy

5-Benzyloxy-1,4-naphthoquinone (307).\textsuperscript{153}

Silver (I) oxide (5.85 g, 25.26 mmol) was added to a stirred solution of juglone (235) (1.1 g, 6.32 mmol) and benzyl bromide (1.54 ml, 18.96 mmol) in chloroform (20 ml). After 2 hours the solution was filtered through a Celite pad to remove silver salts and the solvent was removed at reduced pressure. The oily residue was purified by flash column chromatography over silica using 10:1 hexane:ethyl acetate as the eluent to afford (307) as fine orange needles (1.20 g, 72 %), Mp 111-112 °C, Lit: Mp 113 °C; \( \nu_{\text{max}} \) (thin film, CH\textsubscript{2}Cl\textsubscript{2})/cm\textsuperscript{-1} 1659 (C=O), 1163 (C-O); \( \delta_H \) (400MHz; CDCl\textsubscript{3}); 5.27 (2H, s, OCH\textsubscript{2}Ph), 6.86 (2H, s, COCHCHCO), 7.30-7.35 (2H, m, CH\textsubscript{2}OCCH and CH\textsubscript{2}CCHCHCH), 7.40 (2H, t, \( J \) 7.6, 2 \( \times \) CH\textsubscript{2}CCHCH), 7.57-7.64 (3H, m, 2 \( \times \) CH\textsubscript{2}CCH and CH\textsubscript{2}OCCHCHCH), 7.71 (1H, dd, \( J \) 0.8, 7.6, CH\textsubscript{2}OCCHCHCH); \( \delta_C \) (100MHz; CDCl\textsubscript{3}) 70.9 (CH\textsubscript{2}), 119.5 (CH), 119.6 (CH), 120.2 (C), 126.7 (2 \( \times \) CH), 128.0 (CH), 128.7 (2 \( \times \) CH), 134.1 (C), 134.9 (CH), 136.0 (C), 136.2 (CH), 140.9 (CH), 158.5 (C), 184.2 (C), 185.2 (C); MS (FAB) \( m/z \) 264 [M\textsuperscript{+}, 44.8 %] (M\textsuperscript{+}, 264.0868. C\textsubscript{17}H\textsubscript{12}O\textsubscript{3} requires 264.0865).

\begin{center}
\includegraphics[width=2cm]{5.6.png}
\end{center}
5-Benzylxy-1,4-naphthalenediol (302)

5-Benzylxy-1,4-naphthoquinone (2.12 g, 11.27 mmol) (307) was dissolved in ethyl acetate (100 ml) and added to a separating funnel containing an aqueous solution of sodium dithionite (16.67 g, 95.77 mmol, in 100 ml). After several minutes of vigorous shaking, the organic layer was isolated and washed with water (2 x 50 ml). The organic layer was then dried over anhydrous magnesium sulfate and concentrated to give the target hydroquinone as a light-brown foam, which required no further purification (1.90 g, 89 %), Mp 157-159 °C; \( \nu_{\text{max}} \) (thin film, \( \text{CH}_2\text{Cl}_2 \)/cm\(^{-1} \) 3386 (OH), 1606 (C=C), 1262 (C-O); \( \delta_\text{H} \) (400MHz; \( \text{CDCl}_3 \)); 5.27 (2H, s, OCH\(_2\)Ph), 6.69 (1H, d, \( J = 8.4 \), COCHCHCO), 6.76 (1H, d, \( J = 8.4 \), COCHCHCO), 6.92 (1H, d, \( J = 7.6 \), CH\(_2\)OCCH), 7.33 (1H, t, \( J = 8.4 \), CH\(_2\)OCCH), 7.39-7.45 (5H, m, 2 \( \times \) CH\(_2\)CCH and 2 \( \times \) CH\(_2\)CCHCH and CH\(_2\)CCHCHCH), 7.79 (1H, dd, \( J = 1.2, 8.8 \), CH\(_2\)OCCHCHCH); \( \delta_\text{C} \) (100MHz; \( \text{CDCl}_3 \)) 71.6 (CH\(_2\)), 106.1 (CH), 109.4 (CH), 110.8 (CH), 115.6 (C), 115.9 (CH), 125.2 (CH), 126.8 (C), 128 (2 \( \times \) CH), 128.9 (CH), 129 (2 \( \times \) CH), 135.2 (C), 143.7 (C), 148.2 (C), 155.2 (C); MS (FAB) \( m/z \) 266 [M\(^+\), 100 %] (M\(^+\), 264.0941. C\(_{17}\)H\(_{14}\)O\(_3\) requires 266.0943).
4-(Allyloxy)-8-(benzyloxy)naphthalen-1-ol (308).

A solution of 5-benzyloxy-1,4-naphthalenediol (302) (1.0 g, 3.76 mmol), potassium carbonate (571 mgs, 4.13 mmol) and allyl bromide (0.35 ml, 4.13 mmol) in acetone (20 ml) was heated at reflux for 24 hours. The reaction mixture was filtered and evaporated to dryness. The resulting solid was dissolved in ethyl acetate (30 ml), washed with brine (3 × 30 ml), dried over anhydrous magnesium sulfate and the solvent removed under pressure. The dark brown solid required no further purification (954 mgs, 83 %), Mp 116-118 °C; ν_{max} (thin film, CH₂Cl₂)/cm⁻¹ 3411 (OH), 1630 (C=C), 1292 (C-O); δ_{H} (400MHz; CDCl₃); 4.63 (2H, dt, J 1.6, 5.2, OCH₂CH=CH₂), 5.26 (2H, s, OCH₂Ph) 5.30 (1H, dq, J 1.6, 10.4, OCH₂CH=CH(H)), 5.48 (1H, dq, J 1.6, 17.2, OCH₂CH=C(H)H) 6.10-6.20 (1H, m, OCH₂CH=CH₂), 6.76 (2H, q, J 8.8, COCH₂CHCO), 6.92 (1H, d, J 7.6, CH₂OCCH), 7.32 (1H, t, J 8.2, CH₂OCCHCH), 7.39-7.49 (5H, m, 2 × CH₂CCH and 2 × CH₂CCHCH and CH₂CCHCHCH), 7.92 (1H, dd, J 0.8, 8.4, CH₂OCCHCHCH), 9.02 (1H, s, COH); δ_{C} (100MHz; CDCl₃) 69.7 (CH₂), 71.7 (CH₂), 106.2 (CH), 108.1 (CH), 109.1 (CH), 115.7 (C), 116.3 (CH), 117.2 (CH₂), 125.2 (CH), 128.0 (2 × CH), 128.3 (C), 128.8 (CH), 129.1 (2 × CH), 133.7 (CH), 135.3 (C), 147.0 (C), 148.1 (C), 155.1 (C); MS (FAB) m/z 306 [M⁺, 86.3 %] (M⁺, 306.1256. C₂₀H₁₈O₃ requires 306.1256).

Chapter 5 Experimental 202
4-(Allyloxy)-8-(benzyloxy)naphthalen-1-yl dimethylcarbamate (303).

To a well stirred solution of sodium hydride (993 mgs, 24.83 mmol) in anhydrous tetrahydrofuran (20 ml) was added 4-(allyloxy)-8-(benzyloxy)naphthalen-1-ol (3.80g, 12.41 mmol) (308) in anhydrous tetrahydrofuran (20 ml) drop-wise at room temperature. After stirring the reaction mixture for 2 hours, N,N-dimethylcarbamoyl chloride (2.28 ml, 24.83 mmol) was added and stirring continued for another 8 hours. The reaction was quenched via careful addition of water (10 ml) and then a further 50 ml added. The resulting carbamate was extracted with ethyl acetate (3 x 75 ml) and the combined organic fractions dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude was purified by flash column chromatography over silica eluting with hexane:ethyl acetate 3:1 to furnish (303) as a yellow solid (4.62 g, 99 %), Mp 101-102 °C; νmax (thin film, CH2Cl2)/cm⁻¹ 1645 (C=C), 1265 (C-O); δH (400MHz; CDCl3); 2.55 (3H, s, CONCH3), 2.72 (3H, s, CONCH3), 4.67 (2H, dt, J 1.6, 5.2, CCH2CH=CH2) 5.08 (2H, s, OCH2Ph), 5.32 (1H, dq, J 1.2, 10.4, CCH2CH=CH(H)), 5.50 (1H, dq, J 1.6, 17.2, CCH2CH=C(H)H), 6.10-6.20 (1H, m, CCH2CH=CH2), 6.75 (1H, d, J 8.4, COCHCHCO), 6.93 (2H, m, COCHCHCO and CH2OCCH), 7.33 (1H, t, J 8.0, CH2OCCHCHCH), 7.35-7.48 (5H, m, 2 × CH2CCH and 2 × CH2CCHCH and CH2CCHCHCHCH), 7.93 (1H, dd, J 0.8, 8.4, CH2OCCHCHCH); δC (100MHz; CDCl3) 35.7 (CH3), 36.4 (CH3), 69.3 (CH2), 70.8 (CH2), 105.4 (CH), 107.7 (CH), 115.1 (CH), 117.4 (CH2), 119.3 (CH), 120.6 (C), 125.6 (CH), 128.1 (CH), 128.5 (C), 128.6 (2 × CH), 128.7 (2 × CH), 133.3 (CH), 136.8 (C), 140.8 (C), 151.8 (C), 154.7 (C), 155.8 (NCO); MS (FAB) m/z 377 [M⁺, 45.7 %] (M⁺, 377.1631. C23H23NO4 requires 377.1627).
3- Allyl-8-(benzyloxy)-4-hydroxynaphthalen-1-yl dimethylcarbamate (309)

![Chemical Structure]

4-(Allyloxy)-8-(benzyloxy)naphthalen-1-yl dimethylcarbamate (303) (1.0 g, 2.65 mmol) was refluxed in mesitylene (10 ml) for 24 hours. The solvent was removed under reduced pressure to yield a tarry brown solid. Hexane (30 ml) was added and removed on the rotary evaporator to azeotrope any residual mesitylene. The resulting solid was filter-washed with cold hexane (30 ml) to yield the hydroquinone (309) as a dark brown solid (793 mgs, 79 %), Mp 89-91 °C; \( \nu_{\text{max}} \) (thin film, CH\(_2\)Cl\(_2\))/cm\(^{-1}\) 3416 (OH), 1634 (C=C), 1262 (C-O); \( \delta_{\text{H}} \) (400MHz; CDCl\(_3\)); 2.58 (3H, s, CONCH\(_3\)), 2.75 (3H, s, CONCH\(_3\)), 3.26 (2H, d, J 6.4, CCH\(_2\)CH=CH\(_2\)), 5.10 (2H, s, OCH\(_2\)Ph) 5.11-5.12 (1H, m, CCH\(_2\)CH=CH(H)), 5.15 (1H, q, J 2.0 , CCH\(_2\)CH=C(H)H), 5.90-5.97 (1H, m, CCH\(_2\)CH=CH\(_2\)), 6.14 (1H, s, COH), 6.74 (1H, s, COCCCHCO), 6.82 (1H, d, J 7.6, CH\(_2\)OCCH), 7.20 (1H, t, J 8.4, CH\(_2\)OCCHCH), 7.36-7.49 (5H, m, 2 x CH\(_2\)CCCH and 2 x CH\(_2\)CCHCH and CH\(_2\)CCHCHCH), 7.65 (1H, d, J 8.4, CH\(_2\)OCCHCHCH); \( \delta_{\text{C}} \) (100MHz; CDCl\(_3\)) 34.3 (CH\(_2\)), 35.7 (CH\(_3\)), 36.4 (CH\(_3\)), 70.7 (CH\(_2\)), 106.5 (CH\(_2\)), 115.0 (CH), 116.2 (CH\(_2\)), 119.1 (CH), 120.1 (C), 121.5 (CH), 125.0 (CH), 126.9 (CH), 128.0 (CH), 128.2 (C), 128.5 (2 x CH), 129.2 (C), 136.2 (CH), 137.0 (C), 139.6 (C), 147.0 (C), 154.4 (C), 156.3 (NCO); MS (FAB) \( m/z \) 377 [M\(^+\), 36.1 %] (M\(^+\), 377.1621. C\(_{23}\)H\(_{23}\)NO\(_4\) requires 377.1627).
3-Allyl-8-(benzyloxy)-4-methoxynaphthalen-1-yl dimethylcarbamate (310).

\[
\begin{align*}
\text{OMe} & \\
\text{O} & \\
\text{Bn} & \\
\text{N} & \\
\end{align*}
\]

Finely ground potassium hydroxide (65 mgs, 1.17 mmol) was added portion wise to a solution of 3-allyl-8-(benzyloxy)-4-hydroxynaphthalen-1-yl dimethylcarbamate (309) (400 mgs, 1.06 mmol) in dimethylformamide (10 ml) at 0 °C and stirred for 10 minutes. After this time methyl iodide (0.1 ml, 1.17 mmol) was added drop-wise and the solution was then allowed to stir at room temperature for 4 hours. The mixture was then added to ice water (50 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated to yield a dark brown oil. The crude oil was adsorbed onto silica and purified by column chromatography using 1:1 light petroleum:ethyl acetate as eluent. The product was isolated as a dark brown solid (373 mgs, 90 %), Mp 79-81 °C; \( \nu_{\text{max}} \) (thin film, \( \text{CH}_2\text{Cl}_2 \)) cm\(^{-1} \), 1635 (C=C), 1261 (C-O); \( \delta_{\text{H}} \) (400MHz; \( \text{CDCl}_3 \)), 2.57 (3H, s, CONCH\(_3\)), 2.72 (3H, s, CONCH\(_3\)), 3.55 (2H, dt, \( J 1.2, 6.0 \), CCH\(_2\)CH=CH\(_2\)), 3.87 (3H, s, COCH\(_3\)), 5.10 (2H, s, OCH\(_2\)Ph), 5.09-5.11 (1H, m, CCH\(_2\)CH=C\( \text{H}(\text{H}) \)), 5.13(H, q, \( J 2.0 \), CCH\(_2\)CH=C(H)H), 5.95-6.05 (1H, m, CCH\(_2\)CH=CH\(_2\)), 6.67 (1H, d, \( J 8.0 \), CHOCCCH), 6.91 (1H, s, COCCCH\(_2\)), 7.33-7.48 (6H, m, CH\(_2\)OCCH\(_2\)H, 2 × CH\(_2\)CH, 2 × CH\(_2\)CCH\(_2\)and CH\(_2\)CCH\(_2\)HCH\(_2\)) C, 7.69 (1H, d, \( J 8.4 \), CH\(_2\)OCCHCH\(_2\)H); \( \delta_{\text{C}} \) (100MHz; \( \text{CDCl}_3 \)) 33.6 (CH\(_3\)), 35.6 (CH\(_3\)), 36.3 (CH\(_3\)), 62.0 (CH\(_3\)), 70.8 (CH\(_2\)), 106.7 (CH), 115.0 (CH), 116.4 (CH\(_2\)), 119.8 (C), 121.6 (CH), 126.3 (CH), 128.1 (CH), 128.5 (2 × CH), 128.6 (C), 128.6 (2 × CH), 131.2 (C), 136.6 (C), 136.8 (CH), 143.4 (C), 150.8 (C), 155.2 (C), 155.5 (NCO); MS (FAB) \( m/z \) 391 [M\(^+\), 35.7 %] (M\(^+\), 391.1789. \( \text{C}_{24}\text{H}_{25}\text{NO}_4 \) requires 391.1784).
A solution of 4-(allyloxy)-8-(benzyloxy)naphthalen-1-yl dimethylcarbamate (303) (400 mgs, 1.06 mmol) in anhydrous tetrahydrofuran (10 ml) was added to a stirred solution of sec-butyllithium (1.4 M solution in hexanes) (0.84 ml, 1.17 mmol) and tetramethyleneethylenediamine (0.18 ml, 1.17 mmol) in anhydrous tetrahydrofuran under an inert atmosphere at -78 °C. After 2 hours of stirring at -78 °C the reaction was allowed to attain room temperature and then quenched with careful addition of saturated aqueous ammonium chloride solution (20 ml). The resulting mixture was extracted with ethyl acetate (3 x 30 ml) and the combined organics dried over anhydrous magnesium sulfate and then volatiles removed on the rotary evaporator. The crude brown oil was purified via flash column chromatography over silica using hexane:ethyl acetate 1:1 as eluent to yield the target (187) as a yellow solid (204 mgs, 51 %), Mp 86-88 °C; νmax (thin film, CH2Cl2/cm⁻¹) 3367 (OH), 1633 (C=C); δH (400MHz; CDCl3); 2.88-3.03 (6H, br, 2 x CONCH3), 4.56 (2H, dt, J 1.2, 5.2, CCH2CH=CH2), 5.18 (2H, s, OCH2Ph), 5.24 (1H, dd, J 1.2, 10.4 CCH2CH=CH(H)), 5.41 (1H, dq, J 1.6, 17.2, CCH2CH=C(H)H), 6.02-6.11 (1H, m, CCH2CH=CH2), 6.66 (1H, s, COCCHCO), 6.91 (1H, d, J 7.6, CH2OCCH), 7.28-7.42 (6H, m, CH2OCCHCH, 2 x CH2CCH, 2 x CH2CCHCH and CH2CCHCHCH), 7.85 (1H, dd, J 0.8, 8.8 CH2OCCHCHCH), 9.26 (1H, s, COH); δC (100MHz; CDCl3) 34.9 (CH3), 38.1 (CH3), 69.5 (CH2), 71.8 (CH2), 106.1 (CH), 107.0 (CH), 115.5 (C), 116.3 (CH), 117.1 (C), 117.4 (CH2), 126.1 (CH), 128.2 (2 x CH), 128.7 (C), 128.9 (CH), 129.1 (2 x CH), 133.3 (CH), 134.9 (C), 144.1 (C), 147.0 (C), 155.6 (C), 169.7 (NCO); MS (FAB) m/z 377 [MH⁺, 74.9 %] (MH⁺, 377.1698. C23H23N04 requires 377.1705).
CHAPTER SIX:

APPENDIX
6.0  X-Ray Crystallography Data

(3S,6aR,10aS,10bR)-3-((1H-Indol-3-yl)methyl)octahydro-2H-oxazolo[2,3-a]isoquinolin-5(3H)-one (202b).

![Chemical Structure](image)

Table 1. Crystal data and structure refinement for (202b).

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<tr>
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<tr>
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</tr>
<tr>
<td>Space group</td>
<td>P2(1)2(1)2(1)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
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</tr>
<tr>
<td>Volume</td>
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</table>

Appendix

207
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for (202b). U(eq) is defined as one third of the trace of the orthogonalized U{ij} tensor.

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<th>y</th>
<th>z</th>
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<td>-749(1)</td>
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Appendix
Table 3. Bond lengths [Å] and angles [°] for (202b).

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<th>Angle (°)</th>
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<td>1.531(3)</td>
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Appendix
N(4)-C(3)-C(2) 112.56(16)
N(4)-C(3)-C(12) 101.87(14)
C(2)-C(3)-C(12) 112.34(17)
C(5)-N(4)-C(10B) 127.75(17)
C(5)-N(4)-C(3) 122.30(16)
C(10B)-N(4)-C(3) 108.47(14)
O(1)-C(5)-N(4) 121.45(18)
O(1)-C(5)-C(6) 122.37(16)
N(4)-C(5)-C(6) 116.17(17)
C(5)-C(6)-C(6A) 115.77(16)
C(6)-C(6A)-C(7) 111.08(15)
C(6)-C(6A)-C(10A) 110.39(15)
C(7)-C(6A)-C(10A) 110.47(16)
C(8)-C(7)-C(6A) 112.08(18)
C(9)-C(8)-C(7) 110.88(17)
C(8)-C(9)-C(10) 110.41(17)
C(9)-C(10)-C(10A) 111.39(16)
C(10B)-C(10A)-C(10) 110.71(15)
C(10B)-C(10A)-C(6A) 108.67(15)
C(10)-C(10A)-C(6A) 111.26(15)
O(11)-C(10B)-N(4) 103.28(14)
O(11)-C(10B)-C(10A) 111.24(15)
N(4)-C(10B)-C(10A) 113.76(15)
C(10B)-O(11)-C(12) 108.22(14)
O(11)-C(12)-C(3) 106.41(15)
C(1)-C(13)-N(1) 110.22(18)
C(14)-N(1)-C(13) 108.56(17)
N(1)-C(14)-C(15) 129.85(18)
N(1)-C(14)-C(19) 107.87(17)
C(15)-C(14)-C(19) 122.24(18)
C(16)-C(15)-C(14) 117.20(19)
C(15)-C(16)-C(17) 121.39(19)
C(18)-C(17)-C(16) 121.42(19)
C(17)-C(18)-C(19) 118.62(19)
C(18)-C(19)-C(14) 119.12(18)
C(18)-C(19)-C(1) 134.03(18)
C(14)-C(19)-C(1) 106.81(17)
Table 4. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) for (202b). The anisotropic displacement factor exponent takes the form: 

$$-2\pi^2 [h^2 a^* a^* U_{11} + \ldots + 2hk a^* b^* U_{12}]$$

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Appendix

211
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^{-3}) for (202b).

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Table 6. Hydrogen bonds for (202b) [Å and °].

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Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,-y+2,z-1/2
Complementary routes for the stereoselective synthesis of functionalized benzoquinolizidine targets

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Michael J. McKenzie, c Mercedes Amat, b Oriol Bassas, b
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Available online 27 June 2006

Abstract—We report new and complementary routes for the highly stereoselective construction of functionalized benzoquinolizidine targets from readily available, non-racemic chiral templates. The methods developed allow us to predetermine relative product stereochemistries by judicious choice of substrate sub-structure, and provide ready access to alternative stereoisomers.

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The benzo[α]quinolizidine ring system is of considerable interest and significance since this heterocyclic template is found within a range of pharmacologically interesting alkaloids. For example, (−)-protoemetinol 1, isolated by Battersby from Alangium lamarckii, is structurally related to psychotrine 2 and O-methylpsychotrine 3, and indeed 1 has formed the basis of synthetic approaches to these more functionalized derivatives. 2 Alangine, 4, a recently isolated natural product also from A. lamarckii differs stereochemically from compounds 1-3 in that it has trans relative stereochemistry at positions 2 and 11b. 3 Compounds 2 and 3 are known to be potent inhibitors of HIV-1 reverse transcriptase, and such biological significance earmarks the development of new asymmetric routes for accessing functionalized benzo[α]quinolizidine targets as an important task. 4

Over recent years our research teams have, independently, developed a new approach for the stereoselective synthesis of heterocyclic ring systems that involves the cyclization of a pendent aromatic substituent onto an N-acyliminium intermediate as the key ring-forming step. 5 We now wish to report the development of complementary routes for the highly stereoselective synthesis of functionalized benzo[α]quinolizidine targets that allow at will, the efficient preparation of targets with a...
range of relative product sterechemistries through judicious choice of substrate structure and reaction protocol.

We envisaged one route to the chosen functionalized targets through application of conjugate addition chemistry to an α,β-unsaturated tetrahydroisoquinoline substrate, since in related work on an indolo[2,3-a]quinolizine skeleton the use of appropriate nucleophilic reagents in conjugate addition reactions has proved to be very successful, proceeding with good yield and with exclusive diastereoselectivity.5,6

In an attempt to influence the approach of the attacking nucleophile we generated template 6 through TBDPS-protection of the hydroxyl group of 5 before introducing unsaturation (Scheme 1). Substrate 5 was obtained as a single diastereoisomer on Lewis acid induced cyclization of the corresponding bicyclic lactam precursor, as previously reported by our group.8 Our aim here was to shield the 'upper' face of the heterocycle to encourage attack from below, and hence produce the desired cis product stereochemistry (relative to the H-atoms at stereocentres 2 and 11b).

The results of conjugate addition studies on template 6 are highlighted in Scheme 2, with product 7 isolated in 70% yield as a single diastereoisomer, and product 8 in 55% yield but as a 1:1 mixture of diastereoisomers. The relative stereochemistry of 7 was confirmed by nOe studies, and found to have trans relative stereochemistry with respect to the H-atoms at the chiral centres.9

One possible explanation for the observed stereochemical outcome of the conjugate addition reactions to unsaturated lactam 6 could be, as highlighted in Figure 1, an axial attack of the vinyl cuprate, under stereoelectronic control, to give the kinetic product 7. However, the conjugate addition of the enolate of ethyl 1,3-dithiolane-2-carboxylate may be reversible, affording the 1:1 mixture of isomers 8a (2,11b trans, kinetic):8b (2,11b cis, thermodynamic) under the reaction conditions (−78 °C to 25 °C, 24 h).

In an attempt to determine the effect, if any, of the hydroxymethyl substituent on the stereoselectivity of the conjugate addition process, we decided to examine the reaction of substrate 13, having removed the hydroxyethyl substituent by the route highlighted in Scheme 3.

With α,β-unsaturated amide 13 in hand, we turned our attention to the proposed functionalization of the α-position of the unsaturated lactam through conjugate addition chemistry using the more successful vinyl nucleophile (Scheme 4).

Product 14 was isolated in good yield (67%), and we were pleased to observe the formation of a single diastereoisomer by examination of the crude reaction mixture by 250 MHz 1H NMR spectroscopy. The relative stereochemistry of 14 was confirmed by nOe studies, and again found to have the H-atoms at the chiral centres showing trans relative stereochemistry.9 We also attempted the addition reaction with the lithiated dithiolane nucleophile, but in this case we only obtained an intractable product mixture.

Axial attack

Figure 1.

Scheme 1. Reagents and conditions: (i) imidazole (3 equiv), DMAP (cat.), TBDPSCI (2 equiv), DCM, rt, 24 h, (97%); (ii) LDA, PhSeBr, THF, −78 °C to rt, 24 h; then NaIO₄, NaHCO₃, MeOH, H₂O, rt, 18 h (42%, two steps).

Scheme 2. Reagents and conditions: (i) vinylmagnesium bromide (10 equiv), CuCN (7.5 equiv), TMSCI (7.5 equiv), THF, −78 °C to rt, 24 h; (ii) LDA (2 equiv), ethyl 1,3-dithiolane-2-carboxylate (1.2 equiv), THF, −78 °C to rt, 24 h.
Clearly the (protected) hydroxymethyl group of substrate 6 plays no major role in determining the approach of the nucleophile, with the inherent conformation of the parent heterocyclic template being responsible for the stereochemical induction, with the nucleophile approaching from the least hindered (convex) face of the ring system. In summary, products 7 and 14 are formed as single diastereoisomers and with trans relative stereochemistry at positions 2 and 11b, as required for alkaloids such as alangine, 4.

An alternative route for the introduction of substituents onto the lactam ring would involve the incorporation of functionality at an earlier stage in the sequence. The development of synthetic routes to prochiral or racemic glutarates,10 such as 15, and the subsequent use of these oxo diesters in stereoselective cyclocondensation reactions with chiral amino alcohols has previously been demonstrated.5b In this current approach, cyclocondensation of the appropriate substrates leads to the formation of functionalized bicyclic lactams 16a and 16b in a process that involves the discrimination of two enantiotopic acetate chains (Scheme 5).

Lactams 16a,b were separable, and their relative stereochemistry was established by X-ray crystallography. N-Acyliminium ion precursor 16a, on treatment with TiCl₄ in DCM at reflux for 3 days, gave 17 in 36% yield as a single product diastereoisomer (Scheme 6). X-ray crystallography11 confirmed the relative stereochemistry of this product to be as shown in Scheme 6, with the H-atoms at the chiral centres now having cis relative stereochemistry, as required in benzo[a]quinolizidine targets, such as 1-3.

Removal of the hydroxymethyl moiety from 17 by an analogous route to that described in Scheme 3 gave the desired functionalized benzo[a]quinolizidine target 18.

In conclusion, we have developed new and highly stereoselective routes to functionalized benzo[a]quinolizidine targets, both in the 2,11b-cis and -trans series. The relative stereochemistry of the products can be influenced through appropriate selection of synthetic approach, allowing complementary routes to diastereoisomerically...
substituted products 14 and 18 as single diastereoisomers. The absolute stereochemistry of such products can, if required, be tuned by the choice of appropriate enantiomer of the β-aminolcohol starting material.

Acknowledgements

The Loughborough group thanks the EPSRC and Charnwood Molecular for an industrial CASE award to L.J.D. for a postdoctoral grant to M.M.M.S. and the Education and Science (Spain) for a fellowship to O.B., and the Fundación para una Ciencia e Tecnología (Portugal) for a postdoctoral grant to M.M.M.S.

References and notes


9. For compounds 7 and 14, a positive NOE effect was observed between the proton at position 11β and a proton of the newly added vinyl substituent. No positive NOE effect was observed between the proton substituents at positions 11β and 2.
11. X-ray data for 17: Data collected at 150 K on a Bruker SMART 1000 diffractometer; solution by direct methods and refinement by full-matrix least-squares on F2 using all the data. Non-hydrogen atoms refined with anisotropic atomic displacement parameters; hydrogen atoms inserted at calculated positions using a riding model, except for the alcohol proton which was located and refined with a fixed atomic displacement parameter. Crystal dimensions 0.36 × 0.24 × 0.22 mm3, monoclinic, P21/n, a = 5.1398(4), b = 11.7652(8), c = 14.524(1) Å, β = 94.27(4)° and V = 875.8(1) Å3, Z = 2. ρcalcd = 1.378 M g/cm3. 7592 Refl., 2156 independent (Rint = 0.0212), μ = 0.102 mm−1, F(000) = 388, 238 least-squares parameters, R1 = 0.0303, wR = 0.0777 (2σ data). CCDC 297432 contains supplementary crystallographic data in cif format. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk).

12. Data for selected compounds: Compound 14: [a]D 2 +43.0 (c 1.0, CHCl3); δH (400 MHz; CDCl3) 2.02–2.08 (1H, m), 2.30–2.37 (1H, m), 2.54 (2H, t, J = 4), 2.63 (1H, dt, J = 2.8, 15.2), 2.67–2.73 (1H, m), 2.79–2.85 (1H, m), 2.91–2.90 (1H, m), 3.86 (3H, s), 3.87 (3H, s), 4.63–4.66 (1H, m), 4.83–4.88 (1H, m), 5.12–5.18 (2H, m), 5.91–6.00 (1H, m), 6.62 (1H, s), 6.64 (1H, s); δC (100 MHz; CDCl3) 28.5, 33.1, 34.8, 36.3, 40.1, 53.5, 55.9, 56.1, 107.8, 111.7, 115.4, 127.6, 129.0, 139.4, 146.8, 146.9, 169.0 (Found (EI): M+ 333.1576). C13H23NO5 requires 333.1576.


Appendix
Towards a total synthesis of the manadomanzamine alkaloids: the first asymmetric construction of the pentacyclic indole core

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Available online 10 May 2007

Abstract—We report a highly diastereoselective approach for the synthesis of the pentacyclic indole core of the manadomanzamine alkaloid skeleton, with complete control over the relative and absolute stereochistries at the three contiguous stereocentres at ring positions 1, 10, and 24, from a readily available chiral template.

In 2003 Hamann and co-workers reported the isolation of two novel marine alkaloids, manadomanzamine A and B, from the Indonesian sponge Acanthostrongylophora sp.1 These compounds were found to exhibit strong activity against Mycobacterium tuberculosis (Mtb) with MIC values of 1.9 and 1.5 μg/mL, respectively. In addition these alkaloids show activities against HIV-1 and AIDS opportunistic infections. The recent increasing occurrence and threat of tuberculosis has renewed interest in the development of anti-tuberculosis agents, since the WHO estimates that currently one-third of the world’s population is infected with TB, with 3.1 million deaths occurring per annum. Further, such a lead compound with activity against both HIV-1 and AIDS opportunistic infections is of significant value. A plausible biosynthetic pathway to the manadomanzamines has been proposed from the more common manzamine alkaloids.1 To date no total synthesis of the manadomanzamines has been reported, and indeed a general and stereoselective approach to simpler core analogues, including 1, a dodecahydrobenz[a]indolo[3,2-f]quinolizine, is still lacking. This pentacyclic ring system, sometimes referred to as an ‘inside yohimbane’, has previously been prepared in racemic fashion by Morrison et al.,2 and has been observed as a by-product in approaches to racemic yohimbine and reserpine by Martin.3 Our research group, and others, have had considerable success in recent years in the development of asymmetric routes to several important heterocyclic templates, based on the development of highly diastereoselective N-acyliminium cyclization strategies.4 Our own recent applications of this methodology in natural
product synthesis have included targets from the erythrina group of alkaloids and several indole alkaloids. In this Letter we report a highly diastereoselective construction of the manadomanzamine core, 1, with complete stereocontrol at ring positions 1, 10, and 24.

Our retrosynthetic analysis of the pentacyclic target 1, presented in Scheme 1, led back to the use of (S)-tryptophanol 3, as both a source of indole and as the chiral auxiliary in the proposed N-acyliminium cyclization.

The bifunctional substrate 2 was prepared by an homologation reaction through Wittig functionalization of commercially available ketone 4, followed by hydrolysis of the resulting enol ether (Scheme 2). Compound 2 is isolated as a mixture of the cis and trans isomers (ca. 1:3, respectively), with the trans isomer predominating.

Aldehyde 2, a racemate, was subjected to the standard cyclocondensation reaction with (S)-tryptophanol. The use of racemic multi-functional aldehyde substrates in stereoselective condensation reactions has been much explored by Bosch and Amat. In our hands, the condensation of racemic cis/trans-2 with (S)-tryptophanol under Dean-Stark conditions in toluene for 24 h gave a 1:1 mixture of two readily separable diastereoisomers 5a,b in 69% overall yield (Scheme 3). Presumably the dynamic kinetic resolution that is well known for such substrates under cyclocondensation conditions occurs here to give the preferred trans orientation in 2.

The relative stereochemistry of 5a was determined by NOE studies on the isolated compound and that of isomer 5b by X-ray crystallographic analysis. Whereas diastereoisomer 5a has the correct relative and absolute
stereochemistry required for the C-10 and C-24 positions of the manadomanzamine natural products, isomers such as 5b may prove useful in future analogue generation studies. The stereochemistry at the noted C-1 position is of no significance at this stage, as this corresponding aminal centre will form a planar iminium carbon atom in subsequent reaction steps. The stereochemical outcome of the cyclocondensation reaction shown in Scheme 3 can be rationalized by considering the formation of the aminal intermediates from each enantiomer of the aldehyde substrate 2, formed en route to the lactam products Sa,b, as highlighted in Scheme 3.

The preferred aminal conformations 6a,b allow a favored trans-decalin-like arrangement of the reactive intermediate, with an all-equatorial substituent pattern,6 prior to irreversible lactamization, with the H-atom at the aminal carbon centre preferred in an axial arrangement, leading only to minimal diaxial interactions in these conformations.

With individual asymmetric building blocks 5a and 5b in hand, we turned our attention to the proposed N-acyl-iminium cyclization step. These asymmetric building blocks were separately subjected to acid-induced cyclization reactions promoted by 2 M HCl in EtOH at room temperature for 18 h. Under these conditions, substrate 5a underwent clean cyclization in 73% yield to a single diastereoisomer of the desired product 8a (Scheme 4). NOE experiments subsequently established that the pentacyclic product 8a was generated with the correct relative and absolute stereochemistries at ring positions 1, 10 and 24 as required for the manadomanzamine natural product skeleton.8 Such highly diastereoselective cyclization reactions of the indolyl nucleus onto N-acyliminium intermediates are now well established,4a,d,e,g and the usual rationalization of the observed stereochemical induction holds true in this particular case. The stereocontrol arises from a preferred conformation, 7a, having minimal A(1,3) strain between the H-atom at the stereogenic centre of the tryptophanol moiety and the lactam carbonyl group in the transition state.9 Cyclization of the indolyl nucleus thus takes place from a pro-equatorial orientation, leading to a seemingly preferred axial orientation of all three H-substituents at positions C-1, 10 and 24 in compound 8b, matching the natural product stereochemistry at these three contiguous asymmetric centres.

In the case of lactam substrate 5b, as outlined in Scheme 5, cyclization proceeded in comparable (75%) yield to give a single product diastereoisomer, which was subsequently determined (NOE) to have the relative stereochemistry shown in structure 8b.10 Again the stereocontrol arises through the preferred conformation 7b, minimizing the A(1,3) strain between the H-atom at the stereogenic centre of the tryptophanol moiety and the lactam carbonyl group, despite the fact that the transition state must lead to a pro-axial attack onto the iminium species by the indolyl nucleus.

In summary, we report the first highly asymmetric synthesis of the pentacyclic core of the manadomanzamine alkaloids in only two linear synthetic steps from readily available reagents. Our route allows the controlled formation of the correct relative and absolute stereochemistries at the three contiguous chiral centres at positions C-1, C-10, and C-24 of the heterocyclic skeleton. Although not described in this Letter, we have established and reported several routes for removal of the hydroxymethyl auxiliary group from similar heterocyclic templates.4d Our current work is devoted to the development of this synthetic route to allow access to more highly functionalized intermediates and thus to a total synthesis of the manadomanzamines and their synthetic analogues, and will be reported in due course.

Appendix
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References and notes
5. In this Letter, we refer to the manadomanzamine numbering scheme when referring to the corresponding dodecahydrobenzo[a]jandolo[3,2-a]quinolizidine positions simply for ease of comparison.
7. For compound 8a, in summary, the protons at ring positions 1 and 24 give a positive NOE, to each other, but neither gives an NOE to the proton at ring position 10.
8. For compound 8a, in summary, the protons at ring positions 1 and 24 give a positive NOE, to each other, but neither gives an NOE to the proton at ring position 10. The hydroxymethyl group (CH2) gives a positive NOE to the proton at ring position 1.
10. For compound 8b, in summary, the protons at ring positions 1 and 10 give a positive NOE, to each other, but neither gives an NOE to the proton at ring position 24. The hydroxymethyl group (CH2) gives a positive NOE to the proton at ring position 1.

Appendix