New approaches for the asymmetric synthesis of pyrroloisoquinoline and isoquinoline alkaloids

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New approaches for the asymmetric synthesis of pyrroloisoquinoline and isoquinoline alkaloids

by

By Guy Bradwell Streetley

BSc (Hons)

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy at Loughborough University
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Thanks to all the members of the “Chemical Waste” football team for all the good times throughout my PhD.
ABSTRACT

Pyrroloisoquinoline \((n = 1)\) and the pyridoisoquinoline \((n = 2)\) ring systems \((2)\) are found to be the major structural motif of the *erythrina* and the protoberberine group of alkaloids, respectively. We have recognised that suitable bicyclic lactams \((1)\) could act as precursors, in an intramolecular \(N\)-acyliminium ion mediated cyclisation, resulting in a stereoselective approach to the core of the *erythrina* and protoberberine ring systems.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{Me} \\
\text{Me}
\end{array}
\]
\(n = 1, 2\)

\((1)\)

\[
\begin{array}{c}
\text{OH} \\
\text{Ar} \\
\text{N} \\
\text{Me} \\
\text{Me}
\end{array}
\]

\((2)\)

Access to the tetracyclic core of the *erythrina* alkaloids \((3)\) through the application of \(N\)-acyliminium ion chemistry is well established within our group.\(^1\) This has been demonstrated in a formal asymmetric synthesis of both enantiomers of the *erythrina* alkaloid, 3-demethoxyerythratidinone \((4)\),\(^2\) and described in this thesis.

\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]
\((3)\)

\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]
\((4)\)

Our investigations have also involved the manipulation of this methodology toward the synthesis of the *erythrina* alkaloid, \((-\)-erysotrine \((5)\))\(^3\) and the protoberberine alkaloid, \((-\)-xylopinine \((6)\)).\(^4\)

\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]
\((5)\)

\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]
\((6)\)


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<td>NMR</td>
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<td>PCC</td>
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Chapter 1 Introduction
1.1 Erythrina Alkaloids

The *erythrina* family of alkaloids are a well known class of structurally interesting and biologically active natural products. The genus *erythrina* comprises over 110 species of orange and red-flowered trees, shrubs and herbaceous plants, and the majority are found throughout the tropical and subtropical regions of the world. In the flowers, seeds and bark of the genus *erythrina*, there have been found erythrinan alkaloids, some of which possess curare-like and hypnotic activity. These discoveries have resulted in their alkaloidal extracts being used in indigenous folk medicines.

In recent years the study of alkaloids containing the 1*H*-indolo[7*α*,1-*α*] isoquinoline ring systems (1) have been of considerable interest due to their strong curare-like muscle relaxant activity which was observed after oral administration.

\[
\begin{array}{c}
\text{(1)}
\end{array}
\]

This curare-like activity is due to nicotinic cholinergic receptor-blocking properties of this family of alkaloids. The erythrinan skeleton is associated with a number of pharmacological effects including sedative, hypotensive, neuromuscular blocking and CNS depressant properties. *Erythrina* alkaloids possess a unique spirocyclic amine structure and it is this chemical constituent which is responsible for these pharmacological activities. These pharmacological applications are restricted due to the poor selectivity between the different cholinergic sites. However this induces a large array of physiological responses, including paralysis of smooth muscle. Although the pharmacological applications are of interest, the polycondensed carbon framework of *erythrina* alkaloids means that they are an ideal testing ground for new ring-forming methodologies.
### 1.1.1 Structure of *Erythrina* Alkaloids

Most naturally occurring *erythrina* alkaloids possess the tetracyclic framework and substitution pattern shown in structure (2).

![Tetracyclic Framework](image)

(2) $X$ or $Z = O; R = Me$

This structure possesses a tetrahydroisoquinoline system (C and D rings), which is fused to a perhydroindole subunit (A and B rings). These two subunits share a common nitrogen atom and a *spiro* carbon centre.\(^{12-14}\)

The tetracyclic structure of the *erythrina* alkaloids can be classified into two different groups depending on the structure of the D-ring. Those with an aromatic D-ring, e.g. 3-demethoxyerythratidinone (3) and those whose D-ring possess an unsaturated lactone, e.g. cocculolidine\(^15\) (4) and \(\beta\)-erythroidine\(^16\) (5).

![Structures](image)

Cocculolidine (5) was isolated by Wada and co-workers\(^17\) in 1966 from *Cocculus trilobus* DC as an insecticide. The first total synthesis of (±)-cocculolidine (5), a non-aromatic *erythrina* alkaloid, was reported much later by Kitahara and co-workers.\(^15\)
Alkaloids possessing an aromatic D-ring, can be further classified into two different sub-groups based on the structure of A/B-rings: the dienoid type and alkenoid type.\textsuperscript{18,19} The alkenoids, e.g. erythratidine (6), contains one double bond in the A-ring whereas the dienoids, e.g. erysotrine (7), contain two double bonds in the A-ring and/or the B-ring.\textsuperscript{14,19}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{alkaloids.png}
\caption{Structures of Erythrina alkaloids (6) and (7).}
\end{figure}

\subsection*{1.1.2 Biosynthesis of Erythrina Alkaloids}

Many investigations into the biosynthesis of erythrina alkaloids have been reported and many different sequences been hypothesised.\textsuperscript{20-22} The first proposed biosynthetic pathway for the biosynthesis of this unusual class of alkaloids was reported by Barton and Cohen in 1957.\textsuperscript{21} The general belief, at that time, for the biosynthesis of erythrina alkaloids was based upon the tyrosine-derived bisphenethylamine precursor of type (i).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{biosynthesis.png}
\caption{Biosynthesis pathway of Erythrina alkaloids.}
\end{figure}

There are two possible variations on this approach depending on the order of the two coupling processes necessary to form the erythrinan ring system. The first possibility is that the tetraphenol (8), where \(R=H\), could be oxidised to an \(o\)-quinone (9). The subsequent cyclisation of the secondary amine would then generate the indole portion of the skeleton (10). Further oxidative coupling of (10) would then form the \textit{erythrina} skeleton (11), where \(R=H\) (Scheme 1).
The second possibility proceeds via an initial C-C coupling of the phenyl radicals derived from the suitably blocked phenol (12), where R=Me, to give the biphenyl derivative (13).
The oxidation of the intermediate (13) would generate the diphenooquinone (14) and the subsequent cyclisation of the secondary amine would give the required *erythrina* system (Scheme 2).\(^{23}\)

Subsequently, Barton and co-workers\(^{23}\) made an important experimental observation and discovered *erythrina* alkaloids to be formed by skeletal rearrangement from benzylisoquinoline alkaloids. By feeding potential precursors to young *E. crista-galli* plants they identified (S)-norprotosinomenine (15) as a potential precursor for the synthesis of the spirocyclic *erythrina* alkaloids.\(^{23}\) This intermediate is a natural compound that has since been isolated from the *Erythrina variegata* L. (formerly *Erythrina lithosperma* BLUME) fruits by Ghosal and co-workers.\(^{24}\)

Barton and co-workers\(^{23}\) had proposed that a phenolic oxidation of (S)-norprotosinomenine (15) would yield the tetracyclic diene (16).

![Scheme 3](image_url)

Subsequent ring opening and the reduction of the corresponding imine would generate the biphenyl intermediate (16) (Scheme 3). This intermediate could then be converted to the erythrinan skeleton as shown previously in Scheme 2.\(^{25}\)
Franck and Teetz\textsuperscript{26} have, however, since reported that (S)-norreticuline (17), where R = Me, and not (S)-norprotosinomenine (15), as a more reasonable precursor to the biosynthesis of \textit{erythrina} alkaloids. They demonstrated that (S)-norreticuline (17), a positional isomer of (S)-norprotosinomenine (15), would on biomimetic grounds be a more likely precursor in \textit{erythrina} alkaloids biosynthesis.

\begin{align*}
\text{(15)} \\
\text{(17) } R = \text{Me, } R^1 = \text{OH} \\
\text{(18) } R = \text{H, } R^1 = \text{H}
\end{align*}

This observation was supported Maier and Zenk\textsuperscript{27} who fed (S)-norprotosinomenine (15) to \textit{Cocculus laurifolius} plants and discovered that there was no incorporation of (S)-norprotosinomenine (15) into any of the \textit{Cocculus} alkaloids thus confirming that (15) is not a precursor to \textit{erythrina} alkaloids.

Norcoclaurine (18) \((R = \text{H})\) is the precursor to (S)-norreticuline (17) \((R = \text{Me})\) and is believed to be derived from tyrosine. Tyrosine supplies both halves of the \textit{erythrina} alkaloids, with dopamine (19) being incorporated into the isoquinoline unit of (18) only.

\begin{align*}
\text{(19)} \\
\text{(20)}
\end{align*}

The benzyl part of these precursors are derived from 4-hydroxyphenylacetalddehyde (20) which in turn is also derived from tyrosine via \textit{p}-hydroxyphenylpyruvate and subsequent decarboxylation to yield the aldehyde.\textsuperscript{27}
1.2 Protoberberine Alkaloids

The protoberberine alkaloids display a broad diversity of physiological and biological activities and feature predominantly as active components in many traditional medicines especially in China and other Asian countries.\textsuperscript{28}

The biological activity associated with these molecules varies widely but does include: anti-inflammatory, antimicrobial, and antileukemic, as well as antitumor properties.\textsuperscript{28-31}

There are also examples of natural berbine alkaloids which have shown hypotensive activity\textsuperscript{32} and recently the protoberberine alkaloid (±)-tetrahydropalmatine\textsuperscript{33} has been used as an antipsychotic drug which has subsequently increased the interest in this class of compound.\textsuperscript{32}

The protoberberines also play key roles as precursors in the biosynthesis of many isoquinoline alkaloids such as rhoeadine, secoberberine and benzo[c]phenanthridine.\textsuperscript{34}

1.2.1 Structure of Protoberberine Alkaloids

Protoberberine alkaloids are a large class of natural products typically characterised by a tetracyclic ring skeleton with an isoquinoline core.\textsuperscript{30,35} There are approximately 70 known species and their structures are based on two forms: the quaternary protoberberine salts (21) and the tetrahydroprotoberberines (22).

![Structure of Protoberberine Alkaloids](image)

Most naturally occurring protoberberine alkaloids possess the tetracyclic framework shown in structure (23)
The tetracyclic structure of these alkaloids; contain two aromatic rings (the A- and D-ring) and the stereochemistry is in the (S) configuration. These molecules display a wide range of substitution patterns surrounding the ring skeleton especially around the A- and D-rings. Protoberberines commonly bear substituents on the A- and D-rings, at position C(2), C(3), and at C(9), and C(10) (e.g. (S)-Sinactine (24) and (S)-Corypalmine (25)) or at C(10) and C(11) (e.g. (S)-Xylopine (26)). The substituents present are usually a combination of various alkoxy groups, (e.g. methoxy, methylene-dioxy) (24), or hydroxy groups (25).
In addition to this there is also a stereogenic carbon atom present at C(14) and sometimes there are also alkyl or hydroxyl groups at C(13) (e.g. (S)-Ophiocarpine) (27).\textsuperscript{30,36}

1.2.2 Biosynthesis of Protobberine Alkaloids

The biosynthesis of protobberine alkaloids has been studied extensively and as a result protobberine biosynthesis is now fully understood.\textsuperscript{37} Although the initial precursors to the biosynthesis of protobberine alkaloids are very similar to those of the erythrina alkaloids, subtle changes have led to a significant difference in their biosynthetic pathways and these differences will be discussed below.

It is generally known that the key precursor to the biosynthesis of protobberine alkaloids is (S)-reticuline (28) \((R = \text{Me})\).

![Chemical structure of (S)-reticuline (28) and (S)-norcoclaurine (18)](image)

Initial investigations into the biosynthesis of protobberine alkaloids by Battersby and co-workers assumed that norlaudanosoline (29) \((R = \text{H})\) was the universal precursor to (S)-reticuline (28).\textsuperscript{38} This compound was proposed purely on chemical reasoning, though subsequent work has now established (S)-norcoclaurine (18) as the true intermediate to (S)-reticuline (28).\textsuperscript{39} The biosynthetic pathway from tyrosine to (S)-reticuline (28) has been reported and will be discussed below. The synthesis of (S)-norcoclaurine (18) proceeds via an enzyme catalysed condensation of dopamine (19) and 4-hydroxyphenylacetaldehyde (20). The preparation of (19) and (20) has been discussed previously in Chapter 1.2.2 for the biosynthesis of erythrina alkaloids, and will not be discussed further. O-Methylation at C6 gave the key intermediate (S)-coclaurine (30), a known biosynthetic precursor of (S)-reticuline (28). N-Methylation of
(S)-coclaurine (30) followed by hydroxylation at C3' generates intermediate (31). Finally, O-methylation at C4' produces the desired precursor, (S)-reticuline (28), to the protoberberine alkaloids (32).

It is generally believed that the biosynthesis of protoberberine alkaloids proceeds as illustrated in Scheme 4:

![Scheme 4](image)

**Scheme 4**
1.3. \textit{N}-Acyliminium ions

1.3.1 History of \textit{N}-Acyliminium Ions

In the last few decades there have been many advances in classical and modern reagents in terms of their chemo-, regio- and stereoselectivity.\textsuperscript{40} Iminium ions are an important reactive species in organic synthesis for the construction of carbon-carbon and carbon-heteroatom bonds.\textsuperscript{41} The well-known Mannich\textsuperscript{42-45} and Pictet-Spengler\textsuperscript{46,47} reactions have been used in organic chemistry for nearly 100 years as they make effective use of the iminium ion. The iminium ion (Mannich reagent) (33) and more recently the amidoalkylation reagent (\textit{N}-acyliminium ion) (34) are well known, though the latter reagent was initially developed to allow Mannich type condensations with primary amines.\textsuperscript{40}

![Image of chemical structures (33) and (34)]

The \textit{N}-acyliminium ion is a sub-class of iminium ions where the nitrogen atom has been acylated. The electron-attracting properties of the carbonyl group on the nitrogen cause the iminium carbon to be more electron-deficient, thus making the \textit{N}-acyliminium ion a more reactive electrophile than simple \textit{N}-alkyliminium ions. This has led to a new area of versatile electrophilic chemistry known as \textit{\alpha}-amidoalkylation reactions, which are generally expressed as shown in Scheme 5.\textsuperscript{41}

![Image of Scheme 5]

Due to this new intermediate being more reactive it is therefore no surprise that there have been a number of advances in the use of the \textit{N}-acyliminium ion. The main reason
for the continued interest in this area is that previously unreactive nucleophiles, e.g. unactivated benzenoids, now react effectively under N-acyliminium ion conditions. The N-acyliminium ion is a versatile intermediate though the majority of its synthetic applications are of the intermolecular type, however a new dimension in the reactivity and selectivity of this species has now been developed for its intramolecular reactions, especially in the synthesis of alkaloid natural products.40,48-50

The first reported use of N-acyliminium ion cyclisations occurred in the 1950’s where it was mainly used in the synthesis of isoquinoline and indole alkaloids.51-56 An early pioneer in the use of this cyclisation methodology was Belleau’s erythrinan synthesis which afforded the spirocyclic lactam (36) via the N-acyliminium ion (35) (Scheme 6).

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

\[
\begin{align*}
\text{(35)} & \quad \text{N} \\
\text{H} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{(36)} & \quad \text{N} \\
\text{H} & \quad \text{O}
\end{align*}
\]

Scheme 6

1.3.2 Mechanistic aspects

N-Acyliminium ions can be generated as discrete salts, paired with non-nucleophilic anions,40 although this is rare and restricted to physicochemical studies.40,57-60 In synthetic applications, the N-acyliminium ions are almost exclusively produced in situ, due to their limited stability and high reactivity. An N-acyliminium ion is most likely not generated stoichiometrically in the course of the reaction, as it can exist in equilibrium with a covalent adduct (Scheme 7).41

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \\
\text{X} & \quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \\
\text{X} & \quad \text{N}
\end{align*}
\]

Scheme 7

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The proportion of the ionic form and the covalent form may vary significantly depending on the nature of the anion and on experimental conditions.\textsuperscript{41} The mechanism for the formation of the \(N\)-acyliminium ion and its subsequent reaction with a nucleophile is shown in Scheme 8.

\begin{align*}
\text{(37)} & \xrightarrow{\text{Acidic catalyst}} \text{(38)} \\
\text{Scheme 8}
\end{align*}

The \(N\)-acyliminium ion species (38) is generated by acid activation of the precursor (37) with an acidic catalyst. The subsequent irreversible reaction with the nucleophile yields the product (39). Mechanistically this process closely resembles a \(S_N1\)-type reaction.\textsuperscript{40}

Zaugg and Martin have highlighted two extreme kinetic situations. The rate limiting step can be either:

(i) the formation of the \(N\)-acyliminium ion, or

(ii) the reaction of the \(N\)-acyliminium ion with the nucleophile.

The former case suggests that the more stable \(N\)-acyliminium ion leads to a faster reaction whereas in the latter case the opposite is true. In the latter case the reaction of an \(\alpha\)-hydroxymethyl amide with relatively unreactive aromatic nucleophiles requires a strongly acidic media whereas more reactive aromatic nucleophiles only require mildly acidic conditions. In summary, the rate-limiting step is the formation of the \(N\)-acyliminium ion, rather than the electrophilic substitution.\textsuperscript{40}

1.3.3 \(N\)-Acyliminium v's Iminium ions

\(N\)-acyliminium ions are a significant class of electrophile, which are used in carbon-carbon bond forming reactions. Reactions between \(N\)-acyliminium ions and

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nucleophiles (amidoalkylation or Mannich type condensations) are frequently used to introduce substituents at the α-carbon of an amine.\(^6\)

However, in the last two decades it has been established that substitution with electron-attracting groups at the nitrogen makes the Mannich intermediate (40) more reactive, as it enhances its cationic character. Some examples of these modified cations are the \(N\)-acyl derivative (41) and the carbamate (42) which have been widely exploited, although other electronegative substituents such as the amide (43) and \(N\)-tosyl (44) cations have also been investigated. Various cyclic and linear compounds have been distinguished and new variations, e.g. the hydrazonium (45) cations have also been developed, however this depends on the type of \(R^1\), \(R^2\) and \(R^3\) groups’ present.\(^6\)

\[
\begin{align*}
(40) & \text{ } R = H, \text{ alkyl} \\
(41) & \text{ } R = \text{acyl} \\
(42) & \text{ } R = \text{CO}_2\text{R} \\
(43) & \text{ } R = \text{CONR}_2 \\
(44) & \text{ } R = \text{Tos} \\
(45) & \text{ } R = \text{NR}_2
\end{align*}
\]

Due to the presence of an electron withdrawing carbonyl group you would expect the \(N\)-acyliminium ion (41) to be more electron-poor than the Mannich reagent (40), therefore one would expect \(N\)-acyliminium ion to be more reactive than the Mannich reagent. Visual comparison of the \(^{13}\)C NMR spectra of a number of iminium salts (Scheme 9), has highlighted a shift in the imine carbon resonance. For example, substitution of the \(N\)-methyl (46) with an \(N\)-acetyl (47) group resulted in a 5 ppm down-field shift in the imine carbon absorption. The carbamate (48) derived \(N\)-acyliminium ion exhibits an imine carbon absorption at around 190 ppm, thus we can conclude that \(N\)-acyliminium ions are more electrophilic, \(i.e.\) more reactive than iminium ions.\(^{40,59}\)

\[
\begin{align*}
\text{(46)} & \quad \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{SbCl}_6^\circ
\end{array} \\
\text{(47)} & \quad \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{H}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{SbCl}_6^\circ
\end{array} \\
\text{(48)} & \quad \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Et}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{SbCl}_6^\circ
\end{array} \\
\text{Scheme 9}
\end{align*}
\]
To support this further, it is known that, in intermolecular arylations, Mannich reagents only react with strongly activated aromatics (e.g. phenyls),\(^{43}\) whereas the equivalent \(N\)-acyliminiun ions can react quite easily even with extremely poor nucleophiles (e.g. nitrobenzene).\(^ {49,62}\) The difference in reactivity with respect to intramolecular reactions can be illustrated clearly with the olefin cyclisations, used in the synthesis of *erythrina* alkaloids. For example, the \(N\)-acyliminiun ions (50a, 50b) generated from the keto amide (49) gave the cyclised product as expected, however the attempted cyclisation with the equivalent iminium ion (51) resulted in an unidentifiable product.\(^ {63}\)

\[\text{Scheme 10}\]

Other groups have investigated other iminium ion systems, such as (52)\(^ {64}\) and (53)\(^ {65}\) below and have found that these also fail to undergo cyclisation.

\[\text{Scheme 10}\]

The actual difference in reactivity between the \(N\)-acyliminiun ion and the iminium ion is not always that obvious since one also has to consider that the olefin cyclisation reaction is a reversible reaction (Grob fragmentation).\(^ {66}\) The products of the \(N\)-acyliminiun-olefin cyclisation are generally stable to the conditions of their formation. This is due to the fact that the product is an amide and therefore less susceptible to fragmentation in comparison with the product of the iminium-olefin cyclisation, which
is an amine. Therefore, the usefulness of the N-acyliminium ion cyclisations in organic synthesis may be attributed to their irreversibility.40

1.3.4 The Structure of N-acyliminium Ions

As previously stated, in Chapter 1.3.2, in synthetic applications, the N-acyliminium ions are almost exclusively produced in situ, due to their limited stability and high reactivity. However, there are a few examples where the transient N-acyliminium intermediate have been observed in dynamic NMR spectroscopy.

The structure of an N-acyliminium ion intermediate was first reported by Yamamoto and co-workers60 who observed it's formation during their work with the alkoxy carbamate (54). They reported that when the alkoxy carbamate (54), was cooled to -55°C, in the presence of BF₃·OMe₂, they were able to obtain a clean ¹³C NMR spectra of the corresponding N-acyliminium ion intermediate (55) (Scheme 11).

![Scheme 11](image)

Heaney and Taha67 reported a second example where the bis(homoalkyl) hydroxylactam (56) was treated with BF₃·OEt₂, at 25°C, producing the ¹³C NMR spectra of its corresponding N-acyliminium ion (57). They reported that the N-acyliminium ion (57) had reasonable stability for ca. 1h before it cyclised slowly producing the fluoro compound (58). The reason for the unexpected stability is unclear but the NMR data shows a greater electron withdrawing ability of the amide carbonyl in comparison to the carbamate (Scheme 12).
1.3.5 The Stereochemical Outcome of N-acyliminium Ion Cyclisations

The stereochemical outcome of the N-acyliminium ion cyclisations has received a great deal of attention over the years in various synthetic applications and many types of reaction have afforded excellent stereoselectivity. Indeed stereochemical control has become a feature of N-acyliminium ion cyclisations and can be applied to the preparation of a range of enantiomerically enriched compounds containing aromatic, heterocyclic, alkene, alkyne and keto/enol nucleophiles.\(^{40,61,68}\)

However, on most occasions the favoured stereochemistry has arisen from straightforward stereoelectronic reasons, which are similar to the related cationic π-cyclisations.\(^{69-71}\) The most significant control factors are (i) steric approach control of the nucleophile to the iminium species, (ii) steric interactions involving substituents, and, if relevant, (iii) steric interactions in the addition of nucleophiles to the new cyclic carbocation.\(^{41}\) García and co-workers\(^{72}\) have expanded this observation and have reported that the stereoselectivity is due to the steric control caused by substituents already present in the ring (Scheme 13),\(^{16,73-75}\) or along the chain connecting the π-nucleophile, and the nitrogen atom (Scheme 14).\(^{76-78}\)
The synthesis of *erythrina* alkaloids has developed into an important area for stereochemical observations. The “Belleau-type” *N*-acyliminium ion cyclisation shown in Scheme 6 occurs with sole formation of the *cis*-fused perhydroindole system. The stereochemical outcome observed during this reaction can be explained by steric effects. These steric effects arise due to the orthogonal approach of the π-orbital of the arene nucleophile to the plane of the iminium ion.

The alternative “Mondon” cyclisation also proceeds stereoselectively to the *cis*-fused isomer, as illustrated by product (59) (Scheme 15). This observation has been found to be general for a number of different substrates.

Padwa and co-workers have illustrated this fact in a more complex system where the *N*-acyliminium ion precursor is converted exclusively to the tetracyclic lactam (60). In this case, the Lewis acid assisted ring opening of the isomüchnone cycloadducts, undergo rapid proton loss to produce the product (60) (Scheme 16).
The stereocontrol occurs from the preferential addition of the arene nucleophile to the sterically less hindered face of the N-acyliminium ion.

1.3.6 Synthesis of N-acyliminium ions and their precursors

The generation of N-acyliminium ions and the synthesis of their precursors were first reported by Zaugg and Martin in 1965. In subsequent years these methods have been refined and new methods have been added, resulting in five principle methods for the formation of N-acyliminium ions, as illustrated in Scheme 17.

**Scheme 17**

**Route A: N-Acylation of Imines (Schiff Bases)**

The synthesis of imines is easily achieved, in high yields, by the condensation of aldehydes or ketones with primary amines. The acylation of imines, with reactive carboxylic acid derivatives like acid chlorides or anhydrides, was first reported by
James and Judd\textsuperscript{89} when they reacted benzalaniline (61) with benzoyl chloride (Scheme 18).

![Scheme 18](image)

Perhaps the most direct route to N-acyliminium ion species is though acylation of N-alkyl or N-aryl imines. Venkov reported the synthesis of the isoquinoline derivative (65) utilising this methodology. $N$-acylation of the imine (62) with benzyl chloride afforded the intermediate (63). Lewis acid activation of (63) generated the $N$-acyliminium species (64) which underwent an intramolecular cyclisation producing the isoquinoline derivative (65) (Scheme 19).

![Scheme 19](image)
Route B: N-Protonation of N-acylimines

Due to N-acylimines (66) being rather unstable [they tautomerase rapidly to the corresponding enamid (67), Scheme 20], this method for the preparation of N-acyliminium ions is of more mechanistic than synthetic interest.

\[
\begin{align*}
\text{(66)} & \quad \xrightarrow{\text{N-Protonation}} \quad \text{(67)} \\
\text{Scheme 20}
\end{align*}
\]

Würthwein and co-workers\(^\text{59}\) have explored the N-protonation of the imine (68), via Lewis acid activation, and have reported the synthesis of the N-acyliminium ion species (69), as shown in Scheme 21.

\[
\begin{align*}
\text{(68)} & \quad \xrightarrow{\text{HSbCl}_5} \quad \text{(69)} \\
\text{Scheme 21}
\end{align*}
\]

The second example, reported by Krow and co-workers\(^\text{90}\) illustrates that the treatment of the N-acylimine (70) with fluorosulfonic acid-antimony pentafluoride ("magic acid") generates the species (71) via N-protonation (Scheme 22).

\[
\begin{align*}
\text{(70)} & \quad \xrightarrow{\text{FSO}_3\text{H-SbF}_5} \quad \text{(71)} \\
\text{Scheme 22}
\end{align*}
\]
Route C: Electrophilic Addition to Enamides

Lenz\(^{91}\) reported the synthesis of the enamide (73), via the acylation of an imine (72), using either an acid chloride or anhydride, followed by the elimination of HCl. The synthesis of the \(N\)-acyliminium ion (74) was achieved via the protonation of the enamide (Scheme 23).

![Scheme 23]

Route D: Oxidation of Amides

This method revolves around the removal of a hydride from the \(\alpha\)-carbon of an amide, which leads to the formal synthesis of the \(N\)-acyliminium ion. Many research groups have reported that electrochemical methods are the most feasible techniques to perform this type of transformation\(^{92-94}\).

Othman and co-workers\(^{95}\) have reported a noteworthy example where the indolizidine (75) was oxidised with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol and gave the expected methoxy derivative (77) presumably via the \(N\)-acyliminium ion (76) (Scheme 24).
The mechanism for this electrochemical oxidation first involves the removal of an electron from the lone pair of the nitrogen atom to generate the cation radical (78). This is then followed by the removal of a proton and another electron affording the N-acyliminium ion (79) (Scheme 25).

This electrochemical oxidation is conducted in the presence of a nucleophile, in this case methanol, which traps the N-acyliminium ion (79) generated to give α-methoxyalkyl amide (80). This reaction works well for a wide variety of amides and carbamates and has since been reviewed comprehensively (Scheme 25).
Route E: Heterolysis of Amides

Heterolysis of α-substituted amides is the most frequently used method for the formation of synthetically useful N-acyliminium ions. In the vast majority of cases the leaving group (R) is an oxygen substituent, however there are many examples where R is either a halogen, a nitrogen, a sulfur or a phosphorus substituent. The synthesis of the corresponding N-acyliminium ion (82) from α-oxyalkyl amide (81), where R is alkyl or hydrogen, is normally achieved by acid activation with either a Brønsted or Lewis acid (Scheme 26). However in the case where R is an acetyl or methanesulfonyl, no acidic catalysis was required. 40

\[ \text{Scheme 26} \]

1.4 Chiral Non-racemic Lactams in Synthesis

Meyers has extensively employed chiral, non-racemic bicyclic lactams for the synthesis of optically pure alkaloids and carboycles. 96,97 Two general methods have been developed for the construction of the bicyclic lactam system and they both involve a condensation of an optically pure amino alcohol and a dicarbonyl compound. 97

The first method utilises a cyclodehydration process which takes an optically pure alcohol (83) and a γ-keto-acid (84) under Dean Stark conditions in order to generate a lactam such as (85) (Scheme 27).

CA = Chiral Auxiliary

\[ \text{Scheme 27} \]
Meyers and Wanner\textsuperscript{98} have utilised this strategy in their synthesis of the bicyclic lactam (86). In this example they took the chiral auxiliary, (S)-Valinol, and performed a cyclodehydration with levulinic acid generating the bicyclic lactam (86) as a single diastereomer (Scheme 28).

Scheme 28

The second method developed to synthesise these chiral bicyclic lactams is related to the extensive work by Speckamp\textsuperscript{40,61} involving \( N \)-acyliminium species. Condensation of an optically pure amino alcohol (87) with the cyclic anhydride (88) or dicarboxylic acid (89) produced the imide (90), which on the addition of a hydride source generated the ethoxylactam (91). This intermediate was subjected to acidic conditions resulting in ring closure via the \( N \)-acyliminium species (92), furnishing the bicyclic lactam (93) (Scheme 29).\textsuperscript{97,99}

Scheme 29

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1.5 Applications of the Meyers bicyclic lactam substrates in Synthesis

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The use of chiral, nonracemic bicyclic lactams; has provided and continues to provide access to a wide variety of natural and unnatural carbocyclic products in high enantiomeric purity.96

The versatility of the lactam template has led to the development of new methods for the construction of heterocycles. In addition to the cyclopentenone, cyclohexenone (94) and hexahydroindenone (95) systems, products derived from the use of chiral bicyclic lactams now include pyrrolidines (96) and (97), pyrrolidinones (98), piperidines (99) and (100), pyrroloisoquinoline (101) (n = 1), pyridoisoquinoline (101) (n = 2) and tetrahydroisoquinoline (102) (Scheme 30).
These favourable properties make chiral bicyclic lactams highly adaptable templates for asymmetric synthesis.\textsuperscript{96}

1.5.1 Synthesis of tetrahydroisoquinolines

Routes towards the synthesis of naturally occurring tetrahydroisoquinoline alkaloids, such as salsolidine (107) have recently been reviewed extensively in the literature.\textsuperscript{35} Meyers\textsuperscript{100} has reported an asymmetric synthesis of the simple isoquinoline alkaloid, (\textendash\textendash)salsolidine (107). The synthesis of the required chiral bicyclic lactam (104) was achieved by the condensation of the known acid (103) with (S)-phenylglycinol.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{Scheme 31}};
\end{tikzpicture}
\end{center}
Treatment of (104) with sodium bis(methoxyethoxy)aluminium hydride (Red-Al)® generated the ring-opened lactam (105) which upon additional reduction with lithium aluminium hydride gave the N-benzyl substituted isoquinoline (106). Reductive removal of the N-benzyl group, with palladium on charcoal, afforded the natural product, (-)-salsolidine (107) (Scheme 31).

1.5.2 Synthesis of substituted pyrroloisoquinolines

Katritzky noted that there are three major routes towards the synthesis of the pyrroloisoquinoline template (108) (Scheme 32). Route (A) revolves around the formation of the intermediate (109). This intermediate (109) is obtained by a 1,3-dipolar cycloaddition of the nitrones (110) with an electron deficient ethylenes or acetylenes. Reduction of this intermediate (109) would then generate the desired pyrroloisoquinoline template (108) via the formation of the C3-N4 bond. Route (B) revolves around an intramolecular condensation of (111), forming the C3-N4 bond, with the elimination of H2O. 

![Scheme 32](image-url)
Route (C) is synthetically the most important route with regards to the synthesis of the pyrroloisoquinoline template (108). This route revolves around the formation of the C10a-C10b bond via an N-acyliminium ion cyclisation. The N-acyliminium ion species (112) is generated by the protonation of the C-C double bond of an enamide (113a), or by the elimination of a hydroxy group (113b), ethoxy group (113c), or alternatively a phenylthio group (113d).

Katritzky and co-workers have reported the synthesis of the pyrroloisoquinoline (118) via an N-acyliminium ion cyclisation. The pyrroloisoquinoline (118) was prepared via an intermolecular condensation of 3,4-dimethoxyphenethylamine (114) with the furan derivative (115) and benzotriazole in refluxing acetic acid. The expected N-acyliminium ion precursor (116) was not observed as the reaction cyclised directly to the desired product presumably via the N-acyliminium ion intermediate (117) (Scheme 33).

Padwa has recently described the preparation of the bicyclic lactam (101) via a thionium ion promoted Mannich cyclisation. The thioacetal (119) was treated with 2 equiv of dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) in DCM producing the desired product in a one-pot cascade sequence. It is believed that the addition of DMTSF results in a methylthiolation of one of the thiophenyl groups which dissociates...
to generate thionium ion (120). The attack of the amido nitrogen atom onto the cationic centre produced the phenylthio-substituted lactam (121) which cyclised with the addition of further DMTSF to afford the desired bicyclic lactam ring system via the \( N \)-acyliminium ion species (122) (Scheme 34).

![Scheme 34](image)

Li and Yang\textsuperscript{112} have described a novel base-mediated 3,4-dihydroisoquinoline annulation reaction with a \( \alpha \)-bromo-propionate derivative leading to the synthesis of isoquinoline heterocycles. The 3,4-dihydroisoquinoline derivative (123) and the alkylating component, ethyl 3-bromopropionate (124) were reacted with 2 equiv of KO\( \text{B}u \) in dry DMF and this produced the desired 5-membered product in a 75\% yield. It was believed that the initial \( \alpha \)-alkylation intermediate (i) may undergo an intramolecular \( N \)-acylation through an intermediary imino benzylic anion (ii), generated by the deprotonation of (i). Mesomerism of (ii) followed by a \( 5 \)-exo-trig ring closure of the corresponding enaminate led to the product (125) (Scheme 35).
The annulated isoquinoline derivative (125) can be hydrogenated under standard catalytic hydrogenation conditions to the desired pyrroloisoquinoline template (126).

\[
\begin{align*}
\text{(123)} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{N} & \quad \text{CO}_2\text{Et} \\
\text{(124)} & \quad \text{Br} & \quad \text{CO}_2\text{Et} & \quad \text{KO}^\text{tBu} & \quad \text{DMF}, -60^\circ\text{C} \\
\text{(i)} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{OEt} & \quad \text{EtO}^- \\
\text{(ii)} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{EtO}_2\text{C} & \quad \text{OEt} & \quad \text{CO}
\end{align*}
\]

Scheme 35

Kaluza and co-workers\cite{113} have reported a diastereoselective synthesis of highly substituted pyrroloisoquinoline derivatives from \textit{L}-tartaric acid. The key intermediate in their synthesis was the imide (127); synthesised previously by Lee and co-workers\cite{114} from \textit{L}-tartaric acid. Silylation of (127) under standard conditions (TMS-Cl/pyridine) gave the bis-trimethylsilyl ether (128). The subsequent addition of the required Grignard reagent produced the desired hydroxyl lactam (129). Their initial attempts to cyclise to the desired dihydroxypyrroloisoquinoline (130), using TFA in refluxing DCM, were successful but they only isolated the product in trace amounts. In order to improve the synthesis of dihydroxypyrroloisoquinoline (130) they instead prepared the triacetate (131). Treatment of (129) with acetic anhydride (4 equiv) and DMAP, in acetonitrile, produced the triacetate (131) and a small trace of the ring opened by-product. Cyclisation of the crude acetate mixture with BF$_3$Et$_2$O (4 equiv) gave the hexahydropyrroloisoquinoline (132) as a mixture of diastereomers (3:1 ratio). Conversion to the target dihydroxypyrroloisoquinoline (130) was then achieved upon treatment with NaOMe in anhydrous MeOH. Separation, using flash column
chromatography, resulted in a diastereoselective synthesis of both dihydroxy derivatives (Scheme 36).

Scheme 36

1.5.3 Synthesis of substituted pyridoisoquinolines

Bosch and co-workers\textsuperscript{115} have reported an enantioselective approach to the synthesis of substituted benzo[a]quinolizidine alkaloids utilising a stereoselective cyclocondensation
The cyclocondensation of the racemic oxodiester (134) with dimethoxyphenylalaninol (133a) in refluxing toluene under Dean-Stark conditions gave a mixture of stereoisomeric lactams, from which the enantiopure isomer (135a) was isolated in 60% yield. The subsequent cyclisation of (135a) with BF₃·Et₂O led to the desire benzo[a]quinolizidine (136a) in 40% yield (Scheme 37).

Scheme 37

They also observed that when the reaction was performed instead with the corresponding amimo acid (133b), with the oxodiester (134), they found that the synthesis of the bicyclic lactam (135b) was less efficient (15% yield). However, the corresponding cyclisation with BF₃·Et₂O provided the benzo[a]quinolizidine (136b) in 82% yield (Scheme 37).

Lee and co-workers⁷⁴ have described a chiral synthesis of trans-1-aminobenzo[a]quinolizidine from L-pyroglutamic acid through a stereoselective N-acyliminium ion cyclisation. The amidoester (137) was synthesised in three steps from the commercially available L-pyroglutamic acid.⁷⁴,¹¹⁶ This was converted to the hydroxy...
lactam (138) via the partial reduction of the methyl ester (137) with DIBAL-H producing an aldehyde in situ which was trapped intramolecularly by the amide group generating (138). The hydroxy lactam (138) was then treated with BF₃·Et₂O affording the cyclisation product (139) in 66% yield. The cyclisation product was produced as a single diastereomer due to the diastereoselective attack of the 3,4-demethoxyphenyl ring onto the more accessible side opposite the NHCbz group. The Cbz protecting group was then removed by catalytic hydrogenation over palladium on charcoal in MeOH furnishing the desired product (140) (Scheme 38).

![Scheme 38]

1.6 Applications of N-acyliminium ions

1.6.1 Intramolecular amidoalkylations with aromatic π-nucleophiles

Von Braun and co-workers¹¹⁷ described the first intramolecular amidoalkylations while investigating the ring closure of the sulfonamide glycine derivatives (141). This reaction proceeded via the formation of the corresponding acid chloride followed by the subsequent AlCl₃ – catalysed decarbonylation (Scheme 39).

Introduction - 34 -
The intramolecular reaction of the N-acyliminium ion has received considerable attention in organic chemistry, especially with respect to the synthesis of alkaloid natural products, even though the first intramolecular amidoalkylation did not occur until more than 20 years after the first reported intermolecular amidoalkylations by Tscherniac\textsuperscript{118} and Einhorn\textsuperscript{119} Several isolated examples have occurred since this development, although the major breakthrough in the synthetic application of the intramolecular amidoalkylation occurred in the early 1950's when Belleau\textsuperscript{56} and Mondon\textsuperscript{52,80} applied this reaction to the synthesis of alkaloids.

Einhorn\textsuperscript{119} in 1905 reported the first quenching of an N-acyliminium ion by an electron rich moiety contained within the same molecule (Scheme 40). The intramolecular alkene unit of (142) acts as a $\pi$-nucleophile thus generating the cyclised product (143).

It is therefore no surprise that subsequent intramolecular cyclisation reactions of this type have employed the use of electron rich aromatic rings as $\pi$-nucleophiles. Due the reactive nature of the benzene ring numerous polycyclic ring systems and natural product systems have been accessed \textit{via} intramolecular amidoalkylation with $\pi$-nucleophiles.
1.6.2 Benzenoid π-nucleophiles

The earliest use of benzenoid π-nucleophiles in N-acyliminium ion cyclisations occurred in the 1950’s where the methodology was used in the syntheses of *erythrina* isoquinoline alkaloids by Mondon and Belleau.\(^{52-56,80}\)

*N*-Acyliminium cyclisations have been widely applied to aromatic nucleophiles, and subsequently have been reported and reviewed many times in the literature.\(^{40,41,49,50,61,62,68}\) The increased reactivity of the *N*-acyliminium ion in comparison to the Mannich reagent allows cyclisations to occur even with unactivated benzenoids, which under Mannich reagent conditions would be relatively unreactive.\(^{41}\)

This was demonstrated by Belleau who reported the advantages of the *N*-acyliminium ion variant of the Mannich reagent in the synthesis of the erythrinate (145) (Scheme 41).

As shown in Scheme 41a, the standard iminium ion failed to the cyclise under "various conditions" to the erythrinan skeleton (144) unlike the more reactive *N*-acyliminium ion (Scheme 41b). The Belleau-type\(^{56}\) (Scheme 6 & 41b) and Mondon-type\(^{79,80}\) (Scheme 15) modes of cyclisation differ only by the position of the lactam carbonyl but both
cyclisations solely form the cis-fused perhydroindole configuration. These two routes work smoothly with methoxy-activated or unactivated benzene rings and tolerate various substituents on the aliphatic skeleton.

The benzene ring has been used in many intramolecular additions of \( \pi \)-nucleophiles to \( N \)-acyliminium ion centres especially in the synthesis of isoquinoline and \textit{erythrina} alkaloids. However, many simpler examples, where benzene has acted as a \( \pi \)-nucleophile in \( N \)-acyliminium ion cyclisations, have been reported and will be discussed below.

Allin and co-workers\textsuperscript{7,8} have reported a novel stereoselective approach to the \textit{erythrina} ring system via an asymmetric, intramolecular \( N \)-acyliminium mediated cyclisation. Treatment of the bicyclic lactam (146) with the Lewis acid TiCl\(_4\) ring opens the \( N, O \)-acetal, producing the target pyrroloisoquinoline ring system (147) via the \( N \)-acyliminium ion intermediate (148) (Scheme 42).

![Scheme 42](image)

This methodology has since been developed and applied to the synthesis of more functionalised pyrroloisoquinoline derivatives (149). In the same publication Allin\textsuperscript{8} also demonstrated the efficient removal of the pendant hydroxymethyl auxiliary generating the pyrroloisoquinoline template (150).
This methodology has since been expanded further and has been applied to our formal synthesis of the *erythrina* alkaloid, 3-demethoxyerythratidinone (3), which will be discussed in detail in Chapter 2.1.

Allin and co-workers\(^{120}\) have also reported a two step synthesis of chiral ring-fused isoindolinone derivatives with high levels of diastereoselectivity. Their strategy required the synthesis of diastereoisomerically pure tricyclic lactam (151), prepared from the enantiomerically pure amino alcohol substrate, (S)-phenylalaninol as outlined in Scheme 43.\(^{121}\)

![Scheme 43](image)

Cyclisation to the desired isoindolinone ring system was achieved *via* the Lewis acid induced cyclisation producing the desired product as a mixture of diastereomers. A number of Lewis acids were investigated, however extremely high level of...
diastereoselectivity (≥49:1) were achieved when TMSOTf was used as the Lewis acid activator.

1.6.3 The indole ring as a π-nucleophile

The use of the N-acyliminium ion cyclisations has been applied to the total synthesis of many indole alkaloids. Wawzonek and Marnard\textsuperscript{122} have utilised indole as a π-nucleophile in their preparation of tetrahydro[12H]pyrroloazepinoindoles. In this synthesis the key intermediate is the hydroxylactam (152). Acid activation of this intermediate generates the N-acyliminium ion (153), thus providing access to this tetracyclic product (154), via an intramolecular cyclisation (Scheme 44).

Heaney and co-worker\textsuperscript{123} have reported a scandium and copper triflate mediated N-acyliminium ion cyclisation reaction where they utilised indole as a π-nucleophile. In this case the α-methoxyisoindolone (155) was reacted with 10 mol% of Sc(OTf)\textsubscript{3}, in DCM, producing the β-carboline derivative (156) (Scheme 45).
They have reported that the reaction proceeds via the formation of the N-acyliminium ion intermediate. This group has since developed this methodology and has synthesised other β-carboline derivatives such as (157) and (158).\textsuperscript{124}

Allin and co-workers have reported a number of N-acyliminium ion cyclisations where indole has been used as a π-nucleophile. Their strategy involves the cyclisation of an aromatic substituent onto N-acyliminium intermediates as the key ring-forming step.\textsuperscript{125-127} Their approach required the synthesis of the bicyclic lactam (159) as precursor to the indolizino[8,7-b]indole system (160).
The synthesis of the required indolizino[8,7-b]indole system was achieved by taking the amino alcohol derivative of (S)-tryptophan and reacting it with an appropriate keto-acid, under Dean-Stark conditions in toluene, producing the desired product as a single diastereoisomer (160) (Scheme 46). The expected bicyclic lactam (159) was also isolated though only in 3% yield.\(^{126}\)

This methodology has also allowed access to the six-membered lactam homologue (161) which has been cyclised to the corresponding indolo[2,3-a]quinolizine ring system (162). This result was highly desirable and has opened up access to a wide range of indole targets, including deplancheine (163), geissoschizine (164) and vellosimine (165).

On this occasion the synthesis of the indolo[2,3-a]quinolizine ring system (162) was achieved via the expected bicyclic lactam (161). The synthesis of the lactam was achieved by taking the amino alcohol derivative of (S)-tryptophan and reacting it with methyl 5-oxopentanoate, under Dean-Stark conditions in toluene, producing the bicyclic lactam as a mixture of separable diastereoisomers (161). Treatment with 2M HCl in ethanol cyclised the bicyclic lactam (161) and produced the desired indolo[2,3-a]quinolizine (162) product as a single diastereoisomer (Scheme 47).\(^{125}\)

\[
\begin{align*}
\text{O} & \quad \text{2M HCl} \\
\text{H} & \quad \text{EtOH} \\
\text{N} & \quad \text{H} \\
(161) & \quad \text{OH} \\
& \quad (162)
\end{align*}
\]

Scheme 47

Allin and co-workers have since developed this methodology and have reported the total synthesis of (R) and (S)-deplancheine (163).\(^{127}\) Current work within the Allin group is investigating access to more complex targets such as geissoschizine (164), vellosimine (165) and the highly functionalised template (166) which has been shown to act as a β-turn mimic and display high binding affinity and selectivity for CCK₄ receptors.\(^{126,128}\)
1.6.4 Heterocyclic \( \pi \)-nucleophiles

The use of heterocyclic nucleophiles in \( N \)-acyliminium ion cyclisations generally mirrors the reactions of benzenoid nucleophiles. \( \pi \)-rich heterocycles, e.g. furans, pyrroles and indoles, have similar reactivities to phenyl rings bearing one or two methoxy substituents. The reactivity of \( \pi \)-deficient heterocycles, e.g. pyridine, are however significantly weaker in comparison.\textsuperscript{41}

Furan and Thiophene

There are several examples of \( N \)-acyliminium ion cyclisations with furan or thiophene nucleophiles, though this area is less developed than that of benzenoid nucleophiles. It was found that thiophene nucleophiles are more reactive than phenyl nucleophiles when the \( \alpha \)-position is involved. However, significant regiochemical issues are raised when furans and thiophenes are linked to \( N \)-acyliminium segments by the 3-position.\textsuperscript{41}
Kano and co-workers\textsuperscript{129} have illustrated the ease at which these cyclisations proceed, as shown by the treatment of the thiazolidin-2-one (167) with trifluoroacetic acid producing the corresponding product (168) containing a seven-membered-ring (Scheme 48).

\[
\begin{align*}
\text{(167)} & \xrightarrow{\text{TFA}} \text{(168)} \\
\text{Scheme 48}
\end{align*}
\]

Decroix and co-workers\textsuperscript{95,130} have reported an \(N\)-acyliminium ion cyclisation reaction utilising the thiophene ring in their synthesis of compound (171), a heterocyclic analogue of the isoquinoline alkaloid nuevamine (172). The preparation of the hydroxylactams (170) was achieved from the phthalimide derivative (169) by either reduction, or by the addition of a Grignard reagent onto the imide (\(R = \text{Et, Ph}\)). Subsequent treatment with TFA (or \(\text{SOCl}_2\)) resulted in ring closure and produced the expected indolizidinones (171) in good yields (Scheme 49).

\[
\begin{align*}
\text{(169)} & \xrightarrow{\text{RMgX or NaBH}_4} \text{(170)} \\
\text{Scheme 49}
\end{align*}
\]

Introduction
The use of furan π-nucleophiles in N-acyliminium ion cyclisations has been investigated extensively by Tanis and co-workers. They have reported that products obtained from furan-based N-acyliminium ion cyclisations depend upon a number of factors: the position of the furan tether (2 v's 3-position), the tether length, and the substituent on the furan 5-position. They also observed that furans linked at the 3-position can cyclise to either six- or seven-membered rings, however, furans linked at the 2-positions can only cyclise to the six-membered rings. This reflects the lower nucleophilicity of the furan β-position relative to the α-position.

Tanis and co-workers have envisaged that a number of linearly-fused (173), spirocyclic (174) and bridged aza-cycles (175) could be synthesised by simply altering the placement of the furan tether on the N-acyliminium ion precursor as shown in Scheme 50.

![Scheme 50](image)

This flexibility can provide access to a number of product systems such as (±)-epilupinine (176) and (±)-perhydrohistrionicotoxin (177).
Padwa and co-workers\textsuperscript{132} have also reported an electrophile-induced cyclisation of a tethered furan ring as a novel strategy of synthesising non-aromatic erythroidine alkaloids. Their approach was to take a furanyl substituted hexahydroindolinone (178) and perform an acid induced cyclisation to generate the tetracyclic substituted lactam (179) (Scheme 51).

Pyrroles, Imidazoles and Pyridines

The use of pyrroles as $\pi$-nucleophiles in $N$-acyliminium ion cyclisation reactions has been reported in the literature by a number of different groups.\textsuperscript{77,133-136}

Maryanoff and co-workers\textsuperscript{77} have reported that $N$-substituted pyrroles which are linked to the $N$-acyliminium ion at the $\alpha$-position can cyclise cleanly at the $\beta$-position producing the corresponding pyrrole lactams (180a,b). These lactams were generated by acid induced $N$-acyliminium ion cyclisation of the reduced imide producing the desired lactams as a mixture of diastereomers (ratio 74:26) (Scheme 52).
However, more pyrrole cyclisations have been reported where the $N$-acyliminium ion is linked to the pyrrole nitrogen. This has led to a number of cyclisations at the $\alpha$-position leading to the generation of five-,\textsuperscript{134} six-,\textsuperscript{135} seven-,\textsuperscript{135,136} and even eight-membered rings.\textsuperscript{135} The generation of an eight-membered ring is unusual in $N$-acyliminium ion chemistry and suggest the high reactivity of the pyrrole nucleus may play an important role in this reaction.\textsuperscript{41}

Netchitailo and co-worker\textsuperscript{134} have reported a pyrrole cyclisation which generates a new five-membered ring from the hydroxyisoindole (181) using formic acid (Scheme 53).

Park and co-workers\textsuperscript{137} have reported an $N$-acyliminium ion cyclisation, with an imidazole $\pi$-nucleophile, leading to the total synthesis of the natural products ($\pm$)-glochidine (185) and ($\pm$)-glochidicine (186). The Grignard reaction of the imide (182) with $n$-hexylmagnesium bromide produced a mixture of the hydroxylactam (183) and the ring opened acyclic keto amide (184). The crude mixture was then cyclised in refluxing toluene affording ($\pm$)-glochidine (185). Consequently, refluxing the crude mixture with a catalytic amount of $p$-TSA in xylene yielded ($\pm$)-glochidicine (186) as the sole product (Scheme 54).
As mentioned previously pyridine is an electron-deficient heterocycle, thus one would expect it to be unreactive in $N$-acyliminium ion cyclisations. However, activated pyridine rings with 2-methoxy substitution can cyclise under these $N$-acyliminium ion conditions. Padwa and Brodney$^{138}$ have utilised this method in the synthesis of the tetracyclic product (188). The cyclisation of the activated pyridine ring (187), using $p$-TSA in benzene resulted in the desired product (Scheme 55).$^{138}$
1.7 Synthetic approaches for the construction of *erythrina* alkaloids

Pioneering work by Belleau, Mondon and co-workers and Prelog and co-workers has shown that there are numerous synthetic approaches for the construction of the *erythrina* ring system. These alkaloids have been synthesised in a racemic form by three different methods:

(i) Diels-Alder route,
(ii) intramolecular cyclisation route,
(iii) photochemical route.

If one takes the final step of the bond formation into consideration, the methods for the building up the erythrinan ring system can be loosely classified into seven different reaction types:

(i) C-ring formation with the C5 quaternary centre being formed by intramolecular cyclisation

Early work by Belleau and Mondon has paved the way for many synthetic approaches based around the interception of the C5 centred iminium ion by an aromatic nucleus (189):

Since the work of Belleau the intramolecular cyclisation of an aromatic group to an \( N \)-acyliminium ion compound has been widely investigated, by many groups, and has lead to various modifications of this methodology. Work reported by Mondon has
demonstrated that cyclisations occur more readily when the lactam carbonyl is placed in the potential 5-membered ring instead of the 6-membered ring. The initial approaches have utilised the acylenamine of the endo (5-6) double bond (B), which formed the \( N \)-acyliminium ion (A) after the addition of acid. However, Tsuda and co-workers\(^\text{11}\) have proposed that the protonation of the double bond of the acylenamine, where the double bond was in the exo position would be more favourable than an endo position, due to stereo-electronic reasons. Thus the cyclisation of the acylenamine (C) to the erythrinan skeleton (D) would occur more readily than from the acylenamine (B) (Scheme 56).

\[
\begin{align*}
(B) & \quad \xrightarrow{H^+} \quad (A) & \quad \xrightarrow{H^+} \quad (C) \\
R &= \text{H or substituent} \\
(D) &
\end{align*}
\]

(Scheme 56)

There have been numerous synthetic approaches developed for the synthesis of the erythrina system. The favoured theme for the preparation of the fully substituted carbon centre at the BC ring fusion is based around the trapping of the \( N \)-acyliminium ion intermediate with an electron-rich aryl ring.\(^\text{143,144}\)

Ishibashi and co-workers\(^\text{145}\) have utilised this \( N \)-acyliminium ion methodology to provide a direct synthesis to the natural product (3) via an acid-promoted double cyclisation. The synthesis proceeds via the key intermediate (192) which was generated by the condensation of homoveratrylamine (190) and cyclohexane-1,4-dione.
monoethylene acetal (191) to give the imine (192). N-acylation of (192) with (methylthio)acetic anhydride, followed by the oxidation of the acylenamide with sodium metaperiodate gives the sulfoxide (193). This key intermediate was then converted to the target *erythrina* skeleton (195) via the acid-promoted formation of the *N*-acyliminium ion (194). With the key tetracyclic skeleton (195) in hand, the formation of the natural product (±)-(3), albeit in a racemic form, was then easily achieved in three step procedure as reported by Ishibashi and co-workers \(^{145}\) (Scheme 57).

![Scheme 57](image)

Few reactions can compete with the degree of complexity achieved in a single step by the Diels-Alder cycloaddition; equally the *N*-acyliminium ion plays a similar role, in
forming carbon-carbon bonds, in the synthesis of nitrogen heterocycles. Thus a sequential combination of these two methods would allow a rapid, stereocontrolled synthesis of a variety of natural products.9

Padwa and co-worker9 have developed a new, highly tuneable strategy for the synthesis of erythrina alkaloids which relies on a multi-cascade sequence of reactions. This cascade (or tandem) process is a group of reactions which allows the regio- and stereocontrolled formation of several carbon-carbon bonds (and/or ring systems) in a single operation. In this case, they have developed a noval approach towards the erythrinan skeleton, leading to the synthesis of (±)-erysotramidine, where the spirocyclic ABC ring was formed in a single operation.

The key intermediate in this synthesis is the preparation of the imido sulfoxide (196), possessing both a dienophilic and di-activated aromatic π-tether. This was synthesised from a commercially available allylic bromide using a known procedure.146 The conversion of (196) into (200) initially proceeds via the formation of a α-thio carbocation intermediate generated from the Pummerer reaction of (196). This intermediate was then intercepted by the adjacent imido carbonyl to generate the α-amido substituted furan (197). This intermediate then underwent an intramolecular Diels-Alder cycloaddition across the tethered π-bond to produce the cycloadduct (198). The subsequent formation of N-acyliminium ion intermediate (199) proceeded via the nitrogen-assisted ring opening of the oxabicyclic bridge, which resulted in a 1,2 thioethyl shift and the subsequent elimination of the methoxide ion. The di-activated aromatic tether was then cyclised onto the N-acyliminium ion; producing the tetracyclic amide (200) as a single diastereomer. The enone (200) key precursor can be converted to the natural product (±)-erysotramidine (201), using a combination of methodologies reported by Padwa and co-workers9,147 and Tsuda and co-workers148 (Scheme 58).
(ii) C-ring formation by electrophilic substitution

This methodology for the synthesis of the C-ring, via an electrophilic substitution, has been reported less in the literature;\(^{14,149}\) with only a couple of examples in comparison to the more popular intramolecular cyclisations. Desmaële and co-workers\(^ {14}\) have adopted this methodology and have generated the C-ring by utilising a Pummerer-based cyclisation. The key precursor (203) for the synthesis of the C-ring was achieved in six steps from the commercially available (nitro-methyl)arene derivative (202).\(^ {14}\) With (203) in hand, the formation of the C-ring was then achieved by a three step procedure.
However, the first and most important step was the hetero Michael addition of the lactam anion to phenyl vinyl sulfoxide (204). This was achieved upon treatment with NaHMDS and excess phenyl vinyl sulfoxide (204) in the presence of HMPA. The subsequent cyclisation of the C-ring was then achieved by the next two steps. The treatment of (205) with acetic anhydride under reflux followed by the Lewis acid induced cyclisation of the resulting $\alpha$-acetoxo thioether (206) produced the required tetracyclic phenylthioerythrinan-8-one intermediate (207). The desulfurization of the thioether (207) was achieved using tri-$n$-butyltin hydride and AIBN and produced the desired cis-8-erythrinanone (208) previously reported by Mondon$^{53}$ (Scheme 59). This group has since adapted this methodology and have reported the synthesis of the naturally occurring erythrina alkaloid, (+)-dihydroerythramine (209) (Scheme 116, Chapter 2.5.5).

\[
\begin{align*}
\text{(202)} & \quad + \quad \text{CO}_2\text{Me} \\
\text{CHO} & \quad \text{steps} \\
\text{(203)} & \quad \text{NaHMDS} \\
\text{(204)} & \quad \text{SnCl}_4, \text{DCM} \\
\text{(205)} & \quad \text{AIBN, } n\{(\text{Bu})_3\text{SnH} \\
\text{(206)} & \quad \text{reflux} \\
\text{(207)} & \quad \text{(208)} \\
\text{Scheme 59}
\end{align*}
\]
(iii) A-ring formation by an intramolecular aldol reaction

This methodology requires the synthesis of an intermediate based on the structure (209) (Figure 2). Wasserman and Amici\textsuperscript{150} have utilised this procedure in their synthesis of the \textit{erythrina} alkaloid, 3-demethoxyerythratidinone (3). Their synthesis revolves around the formation of the A-ring \textit{via} an intramolecular aldol reaction of the diketone (215). The key step in their synthesis was the preparation of the tricyclic pyrrolidone carboxylate (212).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure2.png}
\caption{Figure 2}
\end{figure}

The tricyclic intermediate (212) was generated \textit{via} the reaction of 2-(3,4-dimethoxyphenyl)ethylamine (210) with vinyl tricarbonyl ester (211) in the presence of the Lewis acid, POCl\textsubscript{3}. This reaction is of particular interest as the two carbonyls groups at C1 and C3 in (211) play an important activating role in the initial reaction, however they also play a significant role in the conversion of the tricyclic product to the tetracyclic system of the \textit{erythrina} alkaloids.\textsuperscript{150} The reduction of (212) with sodium cyanoborohydride produced a mixture of diastereomers (ca. 1:1); the subsequent benzylation resulted in the formation of a single diastereomer of the corresponding benzyl ether. The reduction of the benzyl ether with LiAlH\textsubscript{4} gave the aldehyde (213). The keto alcohol (214) was then synthesised by a Horner-Emmons reaction with the anion of 2-oxopropylidemethyl phosphonate, followed by the hydrogenation of the \textit{trans}-enone and the corresponding removal of the benzyl protecting group. Reduction, with sodium borohydride, to the diol, followed by a Swern oxidation produced the desired diketone intermediate (215). The subsequent treatment of (215) with NaOH in refluxing MeOH resulted in the intramolecular aldol condensation, along with dehydration, which in turn generated the natural product, (±)-3-demethoxyerythratidinone (3) (Scheme 60).
(iv) A–ring formation from a benzoindolizidine fragment

Prelog,\textsuperscript{139} Stevens\textsuperscript{151} and Tsuda\textsuperscript{152,153} have developed a tetracyclic system via the annulation of the A-ring onto the benzoindolizidine subunit (216).\textsuperscript{14}
This methodology has been utilised by Hosoi\textsuperscript{18,19} and Sano,\textsuperscript{13} who have taken this dioxopyrroline derivative (217) and have converted it to the \textit{erythrina} skeleton \textit{via} an intermolecular Diels-Alder reaction. This group\textsuperscript{13} have since reported the total synthesis of a number of natural products, albeit in a racemic form, including erysotrine (7), erythraline, erysotramidine (201) and 8-oxoerythraline.

Hosoi and co-workers\textsuperscript{19} have taken the key dioxopyrroline intermediate (218), synthesised in three steps from the commercially available homoveratrylamine, using a known procedure reported by Sano and co-workers.\textsuperscript{13} The dioxopyrroline (218) was converted to the tetracyclic intermediate (219) following an intermolecular Diels-Alder reaction with 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene. This was then reduced with LiBH\textsubscript{4} and then hydrolysed, \textit{in situ}, with HCl to isolate the required tetracyclic compound (219). Mesylation and demethoxycarbonylation of the corresponding mesyl derivative with CaCl\textsubscript{2} in DMSO gave the dienone (220). With this key intermediate in hand, this group\textsuperscript{19} have subsequently converted the dienone (220) to the natural product, (\textpm)-erysotrine (7) in a three step procedure (Scheme 61).
In the last few years many methods have been developed where the erythrinane skeleton has been constructed via the formation of the B-ring, starting from the C5 spiro isoquinoline systems such as (221) \(^{5,144,154}\) and (222) \(^{155}\). The most utilised method for the formation of the B-ring has been developed based around skeleton (221). Mariano\(^{144,156}\) and Danishefsky\(^{5}\) have exploited this methodology and this has led to the synthesis of the natural product, (±)-3-demethoxyerythratidinone (3).

A good example of the synthesis of (±)-3-demethoxyerythratidinone (3), using this methodology, was reported by Irie and co-workers.\(^{154}\) This synthesis of the natural product revolves around the use of the intramolecular Wittig reaction. The key intermediate for the synthesis of the B-ring was the amine (224) which was synthesised in several steps from the previously reported spiro-amine (223).\(^{157}\) The amine (224) was then acylated with the phosphonoacetyl chloride to give the phosphonate (225). The B-ring was then generated via an intramolecular Wittig reaction of the amine (225), with KOH in benzene, which produced the desired tetracyclic lactam (226). This intermediate (226) was then converted to the desired natural product, (±)-3-demethoxyerythratidinone (3), in four steps as reported by Irie and co-workers (Scheme 62).\(^{154}\)
(vi) B- and C-ring formation by intramolecular annulation of dibenzazonine

Many effective syntheses have been achieved based on the oxidative phenolic coupling of the bis-(arylethyl)amine subunit (227) and (228)."
Ito and co-workers\(^6\) have utilised this methodology in their synthesis of the natural product, 3-demethoxyerythratidinone (3). Their strategy was based upon the synthesis of the dibenzazonine derivative (232), followed by a phenol oxidation reaction. They took the commercially available 6-bromo-3,4-dimethoxyphenylacetic acid and reacted it with 3-benzyloxyphenethylamine produced the corresponding amide (229). The subsequent removal of the benzyl protecting group, with conc. HCl in ethanol, produced the amide (230). Subsequent irradiation of the amine (230) in methanol, \textit{via} a photochemical reaction (in the presence of sodium hydroxide and a 100W high pressure Mercury lamp) produced the photocyclised phenolic amide (231). Reduction of (231) with NaBH\(_4\) in THF produced the desired phenolic amine (232). With the key precursor (232) in hand, oxidation with PbO\(_2\) produced the desired tetracyclic skeleton of the \textit{erythrina} alkaloids. This was followed by the catalytic hydrogenation of the resulting dienone (233), producing the natural product, (±)-3-demethoxyerythratidinone (3) (Scheme 63).

\begin{center}
\includegraphics[width=\textwidth]{Scheme_63.png}
\end{center}

\textbf{Scheme 63}
(vii) Miscellaneous methods

Apart from the methods discussed above there is also an assortment of miscellaneous methods for the synthesis of the *erythrina* ring system. A classic example will be discussed in detail below:

Livinghouse and co-workers have reported an intramolecular cyclisation of α-keto iminium ylides (238) as a way of constructing the erythrinan skeleton.

They had previously reported the successful utilisation of the intramolecular azomethine ylide [3+2] cycloaddition reaction for the synthesis of physostigmine ring system (234) (Figure 3). Hence their strategy for the synthesis of the erythrinan skeleton was based around the cyclisation of an appropriate substituted arene onto the highly reactive acylnitrilium cation.

![Scheme 64](image-url)
The preparation of the required isonitrile (235) was achieved by the dehydration of the corresponding formamide with POCl₃ in the presence of Et₃N. With the preparation of the isonitrile (235) in hand, the synthesis of the desired 1-acyl-dihydroisoquinolines (237) was then achieved via the cyclisation of the isonitrile (235) with the corresponding acyl chloride (236) in the presence of Ag⁺·OSO₂CF₃. The subsequent alkylation of this intermediate (237) with trimethylsilylmethyl triflate produced the key α-keto iminium ylide (238). Resulting exposure of this dihydroisoquinolinium salt (238) with CsF initiated an intramolecular [3+2] cycloaddition resulting in the formation of the target erythrinan skeleton (239) (Scheme 64).
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1.8 References


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Chapter 2  Results and Discussion
2.1 A formal and total synthesis of both enantiomers of the natural product 3-demethoxyerythratidinone

![Chemical structure of 3-demethoxyerythratidinone](image)

**Data**

\[ \text{C}_{14}\text{H}_{21}\text{NO}_3 \]

m.p. 111-112°C

\([\alpha]_D = +325^\circ\)

2.1.1 Introduction

The seeds of the *Erythrina variegata* L. (formerly *Erythrina lithosperma* BLUME) have previously been known to contain the biosynthetically important alkaloids, \(N\)-norprotosinomenine (15) and erysodienone.\(^1\)\(^2\)\(^3\) (The use of \(N\)-norprotosinomenine (15) in the biosynthesis of *erythrina* alkaloids has been previously discussed in Chapter 1.1.2).

![Chemical structure of N-norprotosinomenine](image)

However, other known *erythrina* alkaloids, e.g. erythraline and erysotrine (7) have also been isolated, but the discovery of two new ketonic alkaloids: erythratidinone (240) and more significantly, 3-demethoxyerythratidinone (3) has led to more interest in these alkaloids.\(^1\)

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The natural product, 3-demethoxyerythratidinone (3) was first isolated in 1973 by Barton and co-workers.\(^1\) Although it is structurally one of the simplest of the \textit{erythrina} alkaloids,\(^4\) its total synthesis, albeit in a racemic form, was not achieved until 1984 by Tsuda and co-workers.\(^5\) This same group, almost a decade later, reported an asymmetric route to the enantiomeric form of the natural product, the so-called '\textit{enantio}(\(-\))\textit{-}3\text{-demethoxyerythratidinone}'.\(^6\) 3-Demethoxyerythratidinone (3) is a well known example of an alkenoid-type \textit{erythrina} alkaloids. As previously stated, in Chapter 1.1.1, the alkenoid-type alkaloids contain one double bond in the A-ring, as shown in structure (3). However, this alkaloid is unique in the \textit{erythrina} genus due to the lack of a 3-methoxy-group. It is generally believed that this alkaloid is biosynthesised from the known \textit{erythrina} base, erythratidinone (240).\(^7\) The general theory is that a late stage modification occurs during the biosynthetic pathway changing the precursor, erythratidinone (240), into this alkaloid. Some plausible routes have been indicated in Scheme 65.\(^1\)

\begin{center}
\textbf{Scheme 65: Biogenesis of 3-demethoxyerythratidinone (3)}
\end{center}
2.1.2 Literature Review

The synthesis of 3-demethoxyerythratidinone (3) has been reported many times in the literature, in a racemic form, however there are only a few examples of non-racemic syntheses of this natural product. Examples of previous racemic and non-racemic syntheses are discussed below.

As discussed previously in Chapter 1.7, the erythrinan skeleton can be constructed via the formation of the B-ring. This methodology was exploited by Danishefsky and Panek who reported their total synthesis of (±)-3-demethoxyerythratidinone (3). Their strategy was based on work previously done in their group where they took a β-oxygen-substituted free radical, which was generated in the presence of an adjacent α,β-unsaturated carbonyl system, and then performed a cyclisation using an intramolecular Giese-type reaction. This process was developed further to incorporate a carbon radical bearing a vicinal nitrogen atom on the connecting chain (Scheme 66a).

\[
\text{In} = \text{radical initiation site} ; \quad X = \text{OAc} ; \quad Y = \text{Sn(Bu)}_3
\]

This method was used to generate the erythrinan skeleton (242), via an internal ‘Michael-like’ free radical cyclisation, as shown in Scheme 67 (Route A). Treatment of (241), synthesised from known starting materials, with \( n\)-Bu\(_3\)SnH in the presence of catalytic AIBN synthesised the key intermediate (242). This represents a formal
synthesis and has previously been converted to the natural product (3) by Tsuda and co-workers. In the same report Danishefsky and Panek also described a similar but more useful method, where they developed a site-specific enol derivative directly from a free radical cyclisation dynamic (Scheme 66b). The advantage gained from using this methodology was that it allowed direct access to the regioselectivity generated by the enolate, thus access to the erythrinan skeleton (244), as shown in Scheme 67 (Route B).

![Diagram of synthetic pathway](image)

Treatment of (241) with tri-n-butyllithiostannane produced the resulting hydroxystannane, which was immediately acetylated with acetic anhydride to afford a

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1:1 mixture of diastereoisomers (243). The subsequent reaction of (243) with \( n\)-Bu\(_3\)SnH in the presence of catalytic AIBN afforded the single diastereoisomer (244). This was then converted in a three step sequence to the natural product, (±)-3-demethoxyerythratidinone (3).

Zard and co-workers\(^8\) have reported a novel Ni / AcOH mediated cyclisation leading to the total synthesis of the natural product, (±)-3-demethoxyerythratidinone (3). Their methodology follows the classic C-ring formation via an intramolecular cyclisation, however, on this occasion they exploited radical chemistry in its construction. In this reaction sequence the key precursor is the trichloroacetamide (245) which was generated in a two steps from the commercially available cyclohexane-1,4-dione monoethylene acetal.\(^8\) However, when this group applied its standard Ni-induced radical cyclisation condition to (245) it failed to produce the desired intermediate (246).

However the same reaction sequence was repeated using the more robust dithioketal derivative (247) prepared from (245) using 1,3-propanedithiol in the presence of BF\(_3\).Et\(_2\)O. On this occasion the desired unsaturated lactam (248) was synthesised in 49% yield. The subsequent acid induced cyclisation of (248) using \( p\)-TSA in refluxing benzene produced the desired compound (249). Finally, the natural product (3) was achieved in a two step sequence: reduction of the amide moiety with LiAlH\(_4\)-AlCl\(_3\) combination and this was followed by the deprotection of the ketone (NCS/AgNO\(_3\)) which occurred with the simultaneous migration of the double bond (Scheme 68).
Ishibashi and co-workers\(^9\) have reported a Mn(III)/Cu(II)-mediated oxidative radical cyclisation of α-(methylthio)acetamides leading to the synthesis of erythrinans. In this particular example they treated the known intermediate (250)\(^10\) with Mn(OAc)\(_3\) in the presence of Cu(OTf)\(_2\) in boiling TFA and this generated the erythrinan derivative (251).\(^10\)

\[\text{Scheme 68} \]

\[\text{Scheme 69} \]
This group, in a previous publication, has already converted derivative (251) to the natural product, (±)-3-demethoxyerythratidinone (3) (Scheme 69).¹⁰

The following is a rare example of an asymmetric synthesis of the natural product (3). As previously stated, Tsuda and co-workers⁶ have reported an asymmetric route to the enantiomeric form of the natural product, the so-called 'enantio'-(-)-3-demethoxyerythratidinone (3).⁶ Their strategy was based around a chiral synthesis of the erythrinan alkaloid via an intramolecular cyclisation.

The synthesis of the enamine-ester (254) was achieved via the condensation of the amino ester (252) with ethyl 5,5-ethylene-2-oxocyclohexanecarboxylate (253).

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Treatment of (254) with oxalyl chloride gave the dioxopyrroline (255) as a mixture of diastereomers. This reaction proceeds in two steps: N-acylation to (255) followed by C-acylation to give (256). Asymmetric induction occurs at the second step. The mixture of diastereomers (256) was then reduced with NaBH₄ and then cyclised with BF₃·Et₂O affording the tetracyclic structure of the erythrinan alkaloids (257). With (257) in hand, this group successfully converted it to the enantiomer of the natural product, (-)-3-demethoxyerythratidinone (3) in five steps (Scheme 70).⁶,¹¹

2.2 A Formal Synthesis of (-)-3-demethoxyerythratidinone

Introduction

The total synthesis of (±)-3-demethoxyerythratidinone (3) has been reported many times in the literature,⁴,⁵,⁷-¹⁰,¹²-¹⁵ however asymmetric syntheses of this alkaloid are still very elusive.⁶,¹¹ Thus, we believe that our methodology will provide a novel, highly stereoselective formal asymmetric synthesis of both enantiomers of this natural product.

2.2.1 Retrosynthetic analysis

![Scheme 71](image-url)
The retrosynthetic pathway shown in Scheme 71 utilises a cyclocondensation reaction leading to the synthesis of the tricyclic lactam. Then N-acyliminium ion methodology is required to generate the erythrinan skeleton. Simple manipulation of the ring system would generate the target natural product, 3-demethoxyerythratidinone (3).

2.2.2 Synthesis of the racemic keto-acid

In order to perform our cyclocondensation reaction we were required to synthesise the required keto-acid and β-amino alcohol precursors. Our initial studies focussed on the generation of the required keto-acid (258).

![Chemical Structure](image)

Previous work in the Allin group\textsuperscript{16} had generated the keto acid (260) via the hydrolysis of the commercially available keto-ester (259) using LiOH in THF/H\textsubscript{2}O (Scheme 72).

![Scheme 72](image)

Unfortunately, the keto-ester we required to synthesise our target keto-acid (258) was not commercially available so an alternative route was required. The commercially available mono-protected 1,4-cyclohexanedione monoethylene ketal (261) was alkylated using enolate chemistry, to the keto-ester (262) using methyl bromoacetate and the base KHMDS. The reaction was stirred in dry THF at room temperature for 22 hours, affording (262) in 63% yield (Scheme 73).
Conversion to the corresponding keto-acid (258) was then achieved via subsequent ester hydrolysis. The keto-ester (262) was hydrolysed using LiOH in THF/H₂O, at room temperature, for 22 hours, generating the keto-acid in a good yield of 84% (Scheme 73). The advantage of using LiOH in the hydrolysis step is that it does not de-protect the acetal protecting group.

2.2.3 Synthesis of the chiral β-amino alcohol

The β-amino alcohol component was formed via the reduction of its corresponding amino acid. The commercially available 3-(3,4-dimethoxyphenyl)-L-alanine (263) was reduced to 3-(3,4-dimethoxyphenyl)alaninol (264) using LiBH₄ in the presence of Me₃SiCl in dry THF (Scheme 74). This generated the β-amino alcohol in 97% yield.

The reduction is suggested to proceed via the generation of the BH₃-THF complex shown below. This BH₃-THF complex acts as the reducing agent.

\[
\text{LiBH}_4 + \text{Me}_3\text{SiCl} \xrightarrow{\text{THF}} \text{LiCl} + \text{Me}_3\text{SiH} + \text{BH}_3\text{-THF}
\]
2.2.4 Synthesis of the tricyclic lactam

We now had the keto-acid (258) and the β-amino alcohol (264) in hand, so the next synthetic step was the preparation of the corresponding tricyclic lactam (265). Previous work within the Allin group\textsuperscript{16} had produced the tricyclic lactam (266), an analogue to our required substrate (265).

Our initial attempts to synthesis the required tricyclic lactam (265) followed the methodology used to synthesis the tricyclic lactam (266). The condensation of the keto-acid (258) and the β-amino alcohol (264) under Dean-Stark conditions in refluxing toluene for 144 hours, generated the tricyclic lactam (265) as a single diastereoisomer, and in 55% yield (Scheme 75).

Following the reaction, \textsuperscript{1}H NMR spectroscopy, showed that the reaction had reached completion after only 48 hours as illustrated in Table 1. We discovered that after only 1 hour only starting material was present, with no trace of the desired product (265). After 24 hours the \textsuperscript{1}H NMR spectrum of the crude product showed that the reaction had nearly reached completion with only a small trace of the starting materials still present, however after 48 hours the reaction had reached completion with no trace of the starting materials.
Table 1: Condensation study: followed by $^1$H NMR Spectroscopy.

<table>
<thead>
<tr>
<th>Attempt</th>
<th>Reaction Time</th>
<th>Observation $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 h</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>24 h</td>
<td>(265) + S.M.</td>
</tr>
<tr>
<td>3</td>
<td>48 h</td>
<td>(265)</td>
</tr>
</tbody>
</table>

$^a$Determined by the 250 MHz $^1$H NMR spectrum of the crude product.

With this investigation complete we repeated the reaction with this revised methodology. The condensation under Dean-Stark conditions, for only 48 hours, gave the desired lactam (265) once again as a single diastereoisomer and in an improved yield of 63% (Scheme 74). The increased reaction yield is evidence that the extended reaction time may actually be causing some decomposition of the lactam product (265) during the reaction.

The formation of the single product diastereoisomer of lactam (265) from the racemic keto acid (258) required the epimerization of the stereogenic centre adjacent to the ketone during the reaction. This observation, albeit on other substrates, has been reported by other groups in the preparation of polycyclic lactams for use as $N$-acyliminium ion precursors.$^{16,18,19}$ Ragan and Claffey$^{19}$ have utilised this methodology and have reported the preparation of chiral, non-racemic, tricyclic pyrrolidinones. The condensation of the cyclic keto-acid (267) with the chiral amino alcohol (268) has generated the tricyclic pyrrolidinone (269), with high levels of diastereoselectivity, via the epimerisation of the keto-acid (267) (Scheme 76).

\[ (267) \xrightarrow{\text{R1 R2}} (268) \xrightarrow{\text{H2N OH}} (269) \]

Scheme 76

Results & Discussion
2.2.5 Synthesis of the isoquinoline alcohol

With (265) in hand, we then turned our attention to the proposed asymmetric cyclisation. The $N, O$-acetal carbon of the tricyclic lactam functions as an electrophilic centre when treated with a strong Lewis acid, e.g. TiCl$_4$. The electrophilic nature of this carbon can therefore be exploited by the addition of a nucleophile.$^{20}$

In this case the cyclisation of the tricyclic lactam (265) was achieved by using 3 equiv of TiCl$_4$ as a Lewis acid activator at low temperature in dry DCM to produce the corresponding isoquinoline alcohol derivative (270) in 92% yield and as a 10:1 mixture of product diastereoisomers. Analysis of the $^1$H NMR spectrum showed that the cyclisation had been successful due to the presence of two singlets at 6.60 and 6.66 ppm, representing the two aromatic protons (Scheme 77).

![Scheme 77](image)

Perhaps not surprisingly under such strong Lewis acid conditions, the cyclisation proceeded with the simultaneous deprotection of the ketal protecting group. Reducing the number of equivalents of the Lewis acid used during this reaction did not selectively generate the corresponding cyclisation product with the ketal group intact, but instead produced an inseparable mixture of the protected and unprotected products. Fortunately, the removal of the ketal protecting group at this stage of the reaction sequence was of no disadvantage to our future proposal. The protecting group could be reincorporated at a later stage in this reaction sequence as required.

Our proposed mechanism for the Lewis acid activated cyclisation of the tricyclic lactam (265) to the corresponding isoquinoline derivative (270) is highlighted below (Scheme 78):

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This reaction occurs via the formation of the N-acyliminium ion (271) followed by an intramolecular cyclisation (Scheme 78). This proceeds via the formation of a spirocycle, followed by a subsequent rearrangement generating the required isoquinoline derivative (270).

The $^1$H NMR spectral analysis of the crude product showed the formation of a 10:1 mixture of the product diastereoisomers with the major diastereoisomer (270a) shown below:
Previous work by Allin and co-workers\textsuperscript{16,21} had determined the relative stereochemistry of the related compound (272) prepared by analogous chemistry, by X-ray crystallography (Figure 3).

![Figure 3: X-ray crystal structure of the isoquinoline derivative (272).\textsuperscript{16,21}]

The major diastereoisomer (270a) in this case, was isolated by flash column chromatography and its relative stereochemistry was determined by nOe studies, as we were unable to obtain suitable crystals for X-ray crystallography. The absence of an nOe between the protons at positions 4 and 13a supports the proposed structure indicated. In addition, one would not expect any significant change to occur in the stereochemistry with the introduction of a remote protecting group.

The stereochemical outcome of this cyclisation can be explained with the aid of the conformational model shown below.\textsuperscript{16} The steric influence provided by the angular alkyl substituent $R$ at the iminium carbon atom favours the proposed conformational model A that leads to the observed major diastereoisomer (270a) with overall retention of stereochemistry. On the other hand steric interactions between the angular alkyl group and the benzyl substituent will disfavour conformational model B, which would lead to the minor diastereoisomer (Figure 4).

![Figure 4: Conformational models for acyliminium cyclisations.]

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However, one cannot rule out the possible influence of chelation control caused by a Lewis acid such as TiCl₄. The presence of an asymmetric centre next to the iminium centre may lead to stereocontrol over the formation of a new chiral centre upon cyclisation. If this is the case one can appreciate that the aromatic ring is approaching the planar acyliminium intermediate from the direction of the least steric hindrance (Figure 4).¹⁶,²²

2.2.6 Removal of the hydroxymethyl substituent

It is evident from the structure of (-)-3-demethoxyerythratidinone (3) that a procedure to remove the pendant hydroxymethyl substituent (auxiliary) from the cyclisation product (270) was required (Figure 5).

![Figure 5]

Krafft and co-workers²³ have described a one-step procedure for the removal of the pendant hydroxymethyl substituent. They reported that in the presence of Raney nickel in refluxing toluene, primary alcohols generate deoxygenated compounds that contain one less carbon (Scheme 79).

![Scheme 79]

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The authors proposed that the dehydroxymethylation procedure involved an initial oxidation to the aldehyde followed by an irreversible decarbonylation. For example, the primary alcohol (273) was heated in toluene with Raney nickel and this generated the decarbonylated product (274) in 73% yield (Scheme 79).

This methodology was adapted by Martin and co-worker\textsuperscript{24} who successfully removed the hydroxymethyl group from the bicyclic lactam (275) to generate the intermediate (276), a precursor to the indolizidine alkaloid, pumiliotoxin 521D (277) (Scheme 80).

![Scheme 80](image)

Previous work in the Allin group\textsuperscript{21,25} have applied this methodology on a number of templates (278) and (162), but on both occasions the desired product was not obtained.

![Compounds](image)

Although not strictly used for the removal of pendant hydroxymethyl substituents, there are number of examples in the literature where the equivalent carboxylic acid derivative have been removed via a radical decarbonylation.

Martin and co-workers\textsuperscript{26} have reported an efficient radical decarbonylation of the equivalent carboxylic acid derivative. Their procedure required the formation of the acyl...
selenide derived from (279) by a sequential reaction with isobutyl chloroformate and then sodium phenylselenide. This then underwent radical decarbonylation to afford (280) a precursor to the natural product, (+)-geissoschizine (164) (Scheme 81).

![Scheme 81](image)

Tsuda and co-workers\textsuperscript{6,11,27} have reported a decarboxylation of a similar carboxylic acid derivative (281) utilising the classical Barton radical decarboxylation procedure\textsuperscript{28} (Scheme 82).

![Scheme 82](image)

Using the methodology demonstrated previously by Allin and co-workers,\textsuperscript{16,29-31} we intend to remove the pendant hydroxymethyl substituent (auxiliary) from the tetracyclic product (270) via the application of a three-step procedure.

2.2.7 Oxidation Study

The first step in this sequence was the oxidation of the isoquinoline alcohol derivative (270) to its corresponding aldehyde (282). The first method used in order to achieve this
oxidation applied methodology already developed in the Allin group\textsuperscript{29} for the oxidation of the indolo[2,3-\textit{a}]quinolizidine derivative (162) to its corresponding aldehyde (283). The oxidation of (162) using IBX generated the aldehyde (283) as a single diastereoisomer and in 69\% yield (Scheme 83).

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics{image1.png}};
  \node (b) at (3.5,0) {\includegraphics{image2.png}};
  \node (c) at (0,-1.5) {\includegraphics{image3.png}};
  \node (d) at (3.5,-1.5) {\includegraphics{image4.png}};
  \node (e) at (1.75,-0.75) {IBX, DMSO};
  \node (f) at (1.75,0) {20 h, 69\%};
\end{tikzpicture}
\end{center}

\textbf{Scheme 83}

The use of 2-iodoxybenzoic acid (IBX) (285) in DMSO as a mild oxidant, has been reported by Frigerio and co-worker\textsuperscript{32,33} for the successful conversion of alcohols to aldehydes or ketones.\textsuperscript{34}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics{image5.png}};
  \node (b) at (3.5,0) {\includegraphics{image6.png}};
\end{tikzpicture}
\end{center}

\begin{center}
\textbf{IBX} \hspace{5cm} \textbf{DMP}
\end{center}

IBX is the precursor to Dess-Martin periodinane (DMP) (286) and is readily prepared from the inexpensive, commercially available 2-iodobenzoic acid (284) and potassium bromate using a preparative procedure reported by Dess and Martin\textsuperscript{35,36} (Scheme 84).

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\includegraphics{image7.png}};
  \node (b) at (3.5,0) {\includegraphics{image8.png}};
  \node (c) at (0,-1.5) {\includegraphics{image9.png}};
  \node (d) at (3.5,-1.5) {\includegraphics{image10.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 84}

When we reacted our substrate (270) with IBX (1.1 eq) in DMSO for 20 hours, we successfully generated the required aldehyde (282) as a single diastereoisomer, and in a

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48% yield (Scheme 85). $^1$H NMR spectroscopy of the product supported our findings that the alcohol had been oxidised to the corresponding aldehyde (282), due to the presence of CHO peak at ~9.83 ppm. However, attempts to improve the yield by increasing the equivalents of IBX proved to be unsuccessful. Although the yields were consistently low the main problem however, was the co-eluting IBX by-products also present. Attempts to remove these co-eluting IBX by-products by flash column chromatography, proved to be unsuccessful.

Frigerio and co-workers$^{32}$ have proposed a mechanism for the oxidation of alcohols such as (287) using IBX to the corresponding aldehyde (288) (Scheme 86).

The low yield of 48% and the purification problems were unsatisfactory at this stage of the synthesis, so we decided an alternative method was required for this oxidation.
So, in order to improve this reaction we decided to use the related oxidising agent, Dess-Martin periodinane (286)\textsuperscript{35} due to its superior solubility (Scheme 84). The isoquinoline alcohol derivative (270) and the oxidising agent Dess-Martin periodinane were stirred in dry DCM for 24 hours and produced the required aldehyde (282) in 93% yield (Scheme 87). The \textsuperscript{1}H NMR spectrum of the product suggested that the aldehyde (282) had been synthesised, as the same CHO peak at ~9.83 ppm was present.

2.2.8 Decarbonylation Study

With the synthesis of the aldehyde in hand, the next step for the removal pendant hydroxymethyl substituent (auxiliary) was achieved via the decarbonylation of the aldehyde (282).

Tsuji and Ohno\textsuperscript{37} have reported that metallic palladium is a useful catalyst for the decarbonylation of aldehydes and acyl halides. However, they discovered that the decarbonylation reaction could only be applied to aldehydes if the temperature was at least 200°C.\textsuperscript{38} So in order for the decarbonylation reaction to be useful in organic chemistry, an alternative catalyst was required, so that the reaction could be carried out smoothly under mild conditions.

Tsuji and Ohno\textsuperscript{39} and Walborsky\textsuperscript{40} have reported that various aldehydes such as (289) can be decarbonylated under mild conditions upon treatment with the well known rhodium complex chlorotris(triphenylphosphine)rhodium (Wilkinson’s catalyst) (290) (Scheme 88).
The by-product of this reaction, rhodium bis(triphenylphosphine) carbonyl chloride (291), was also found to be extremely useful for the decarbonylation of aldehydes and acyl halides under mild conditions in homogeneous systems. This complex, (291), was readily prepared in solution by the reaction of Wilkinson's catalyst (290) with carbon monoxide at room temperature and at atmospheric pressure. Tsuji and Ohno have also observed that at higher temperatures complex (291) can perform decarbonylations catalytically.

The proposed mechanism for the decarbonylation of aldehydes with the rhodium complex (291) is illustrated in Scheme 89. The initial step is the oxidative addition of (291) to the aldehyde (RCHO) to form complex (292).

When heated in the absence of carbon monoxide, one mole of carbon monoxide is lost to produce the acyl complex (293). Complex (293) is then converted to complex (294).

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via an acyl-alkyl rearrangement. Finally, a reductive elimination of complex (294) regenerates the catalyst (291) with the formation of the desired decarbonylated product (RH).

Doughty and Pignolet\(^{41}\) have reported the decarbonation of aldehydes with cationic complexes of chelating diphosphine ligands. These complexes, \([\text{Rh(dppe)}_2]\text{Cl (dppe} = 1,3\text{-bis(diphenylphosphino)ethane})\) and \([\text{Rh(dppp)}_2]\text{Cl (dppp} = 1,3\text{-bis(diphenylphosphino)propane})\) (295), were prepared by reacting \(\text{RhCl(CO)(PPh}_3)_2\) (291) with an excess of the diphosphine ligand in toluene (Scheme 90).

\[
\begin{array}{cccc}
\text{RhCl(CO)(PPh}_3)_2 & \xrightarrow{\text{dppp}} & [\text{Rh(dppp)}_2]\text{Cl} \\
(291) & \text{Toluene} & (293) \\
\end{array}
\]

\text{Scheme 90}

The decreased electron density of these complexes in comparison to \(\text{RhCl(CO)(PPh}_3)_2\) (291) have resulted in these complexes binding carbon monoxide less strongly due to a decrease in the Rh-CO \(\pi\) back-bonding. The catalytic activity of these rhodium (I) complexes with chelated diphosphine ligands is enhanced, in comparison to the well known Wilkinson’s catalyst, thus decarbonylations can occur at a considerably lower temperature and with long-term catalyst stability.

Meyer and Kruse\(^{42}\) have utilised this methodology and have applied it in their synthesis of Uhle’s ketone (297). In this publication they reported that they generated the active catalyst \([\text{Rh(dppe)}_2]\text{Cl in situ}\).

\[
\begin{array}{ccc}
\text{CHO} & \xrightarrow{\text{Rh(PPh}_3)_2(\text{CO})\text{Cl (dppe, xylene}}} & \text{(296)} \\
(297) & & \\
\end{array}
\]

\text{Scheme 91}

Results & Discussion
The reaction proceeds readily in xylene at 140°C, using 1-5 mole % of the rhodium catalyst \( \text{RhCl(CO)(PPh}_3)_2 \) (291), and produced the desired decarbonylated product (296) in a near quantitative yield (Scheme 91).

Allin and co-workers\(^{30,31} \) have utilised the methodology developed by Meyer and Kruse\(^{42} \) and have applied it to the synthesis of the pyrroloisoquinoline ring system. The decarbonylation of the aldehyde (298) using the active catalyst \([\text{Rh(dppe})_2\text{Cl}] \) developed in situ was refluxed in \( p \)-xylene, but unfortunately the reaction only generated the enamide (299) with no sign of the desired decarbonylated product (300). The formation of the enamide has been previously observed by Tsuji and Ohno\(^{39} \) and occurs due to the \( \beta \)-elimination of the aldehyde. This is accompanied by the evolution of hydrogen gas and forms the alkene instead of the alkane. However, the desired product (300) was formed in 89% yield by catalytic hydrogenation of the enamide (299) (Scheme 92).

We have since applied this methodology to our more complex system and our findings will be discussed in detail below. Our initial investigation was conducted using 5 mol% of the catalyst \( \text{RhCl(CO)(PPh}_3)_2 \) (291) and 12.5 mol% of 1,3-bis(diphenylphosphino) propane ligand in anhydrous \( p \)-xylene. The aldehyde (282) was refluxed under these conditions for 240 hours producing, once again, the corresponding enamide (301) and a mixture of by-products (Scheme 93). Purification via flash column chromatography enabled us to isolate the enamide in 18% yield, unfortunately it also co-eluted with an inseparable phosphorus by-product (Table 2: Entry 1). Analysis of the \( ^1 \text{H} \) NMR spectrum clearly showed that we had synthesised the enamide (301) due to the presence of two sets of doublets at \( \sim 6.10 \) and 7.29 ppm. No trace of the desired decarbonylated
product (302) was isolated, but some recovered starting material was obtained. Unfortunately, the $^1$H NMR spectrum of the recovered starting material had shown that the aldehyde had degraded during the reaction process. Reducing the reaction time from 240 hours to 120 hours had no significant effect on the yield of the enamide (301), with again no trace of the desired amidoketone product (302) (Table 2: Entry 2).

![Scheme 93](image)

Numerous attempts using these conditions only produced the enamide (301) in low yield with no trace of the desired decarbonylated product (302). So, alternative reaction conditions were required to achieve our aim.

A colleague$^{43}$ was simultaneously investigating the decarbonylation reaction on the indolizino[8,7-b]indole derivative (303) below. Variables such as time, solvent, quantity of catalyst and the relative proportion of the diphosphine ligand were investigated.

![Scheme 93](image)

As a result of this investigation an alternative procedure was ascertained for this decarbonylation reaction. The solvent $p$-xylene (137-138°C) was replaced with the
higher boiling mesitylene (163-165°C) and 10 mol% of the catalyst (291) was used without the diphosphine ligand 1,3-bis(diphenyl-phosphino)propane (dppp).

Table 2: Decarbonylation Study

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>dppp (mol%)</th>
<th>Solvent</th>
<th>Reaction time (h)</th>
<th>Product (302)</th>
<th>Enamide (301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>12.5</td>
<td>xylene</td>
<td>240</td>
<td>-</td>
<td>18%</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>12.5</td>
<td>xylene</td>
<td>120</td>
<td>-</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>-</td>
<td>mesitylene</td>
<td>120</td>
<td>Trace</td>
<td>38%</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>25</td>
<td>mesitylene</td>
<td>120</td>
<td>6%</td>
<td>55%</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>25</td>
<td>mesitylene</td>
<td>120</td>
<td>~6%</td>
<td>48%</td>
</tr>
</tbody>
</table>

We applied this revised methodology on our substrate and refluxed the aldehyde (282) in mesitylene with 10 mol% of the catalyst. This generated the enamide (301) (+ phosphorus by-products) in an improved yield of 38% but more significantly we successfully managed to synthesise a trace amount of the desired amidoketone (302) directly from the aldehyde (282) (Scheme 94) (Table 2: Entry 3). Analysis of the $^1$H NMR spectrum showed two single aromatic protons at 6.58 and 6.87 ppm, with no trace of either the aldehyde (282) or the enamide (301).

![Scheme 94](image)

This result supported the observation made by Tsuji and Ohno$^{39}$ who reported that increasing the reaction temperature led to an improvement in the reactivity of the
rhodium catalyst RhCl(CO)(PPh$_3$)$_2$ (291). In order to be thorough we decided to repeat the reaction with the addition of 25 mol% of 1,3-bis(diphenylphosphino)propane ligand. Much to our surprise we had a significant improvement in the yield of the enamide (301) (55%), and although still very low, we did achieve 6% yield of the desired decarbonylated product (302) (Table 2: Entry 4). Numerous attempts using these conditions led to no improvement in the synthesis of the enamide (301) or more importantly the decarbonylated product (302).

The final step in the auxiliary removal sequence could be achieved via a catalytic hydrogenation of the crude mixture from the previous step. Upon treatment with hydrogen in the presence of 10 mol% of palladium on charcoal we successfully obtained the desired amidoketone (302) in 79% yield (Scheme 94).$^{16}$

More recently, Allin and co-workers$^{44}$ have reported an alternative procedure for this decarbonylation sequence. Due to the excessive reaction time generally required for our substrates, using our decarbonylation protocol, a more facile approach was developed utilising a decarboxylation strategy. The idea was to oxidise the aldehyde (304) to its corresponding carboxylic acid derivative (305) before converting it to the equivalent acyl selenide derivative (306). This was then followed by a tin-mediated deacylation affording the desired indolo[2,3-a]quinolizine template (307) (Scheme 95).
2.2.9 Re-introduction of the ketal protection

The next step in the synthesis was the re-introduction of the ketal protecting group. This was achieved by refluxing (302) with ethylene glycol and p-TSA in toluene, affording the desired product (308) in 70% yield (Scheme 96). Since compound (308) is a known intermediate, this now represents a formal total asymmetric synthesis of 3-demethoxyerythratidinone (3).²²

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

MeO \quad \text{OMe}

(302) (308)

Scheme 96

In summary, we have successfully prepared the protected imidoketone (308) in a six-step sequence as shown in Scheme 97, in an enantiomerically pure form. Although, we can not make a comparison to a natural compound in order to compare optical purity, we are confident that no degradation has occurred during the synthesis due to the fact that we have synthesised this intermediate as a single diastereomer. With any degradation one would expect to see the formation of a mixture of diastereomers. This intermediate (308) has previously been synthesised by Tsuda and co-workers,⁵ albeit in a racemic form, and has been converted to the natural product, 3-demethoxyerythratidinone (3) by a four-step sequence (Scheme 103).
Scheme 97
2.3 A Formal Synthesis of (+)-3-demethoxyerythratidinone

![Chemical structure of 3-demethoxyerythratidinone (3)](image)

**Introduction**

Using the methodology described in Chapter 2.2, we decided to synthesise the opposite enantiomer of the natural product, 3-demethoxyerythratidinone (3), in order to demonstrate the versatility of our methodology. This was achieved by changing the (L)-amino alcohol for the corresponding (D)-amino alcohol precursor and then following an identical reaction sequence.

2.3.1 Synthesis of the chiral β-amino alcohol

The synthesis of the required β-amino alcohol precursor was achieved via the application of a two step procedure. The commercially available N-acetyl-3-(3,4-dimethoxyphenyl)-D-alanine (309) was hydrolysed with 1M HCl to generate the corresponding α-amino acid (310) in 95% yield.\(^5\) With the α-amino acid, 3-(3,4-dimethoxyphenyl)-D-alanine (310) in hand, we simply reduced the acid using the methodology described previously. Reducing the α-amino acid using LiBH\(_4\) and Me\(_3\)SiCl in dry THF generated β-amino alcohol, 3-(3,4-dimethoxyphenyl)-D-alaninol (311) in 94% yield (Scheme 98).\(^7\)
2.3.2 Synthesis of the lactam

The preparation of the corresponding tricyclic lactam (312), with opposite optical rotation, was achieved using the methodology described previously for the synthesis of the tricyclic lactam (265) (Scheme 75). The condensation of β-amino alcohol (309) with keto-acid (258) (Scheme 73), in refluxing toluene under Dean-Stark conditions for 48 hours, gave the desired tricyclic lactam (312) in 60% yield (Scheme 99). Visual comparison of the $^1$H NMR spectra showed that the tricyclic lactam (312) was virtually identical to tricyclic lactam (265) and as observed previously, for the opposite enantiomer, the tricyclic lactam (312) was once again produced as a single diastereoisomer. The optical rotation of this intermediate (312) was +56.1 compared to -55.7 for lactam (265).

2.3.3 Synthesis of the isoquinoline alcohol

With the synthesis of the tricyclic lactam (312) in hand, the subsequent asymmetric cyclisation to produce the corresponding isoquinoline alcohol (313) was achieved in 91% yield (Scheme 99).
As described in Chapter 2.2.5, the asymmetric cyclisation of the tricyclic lactam (312) to the corresponding isoquinoline alcohol derivative (313) was achieved using 3 equiv of the Lewis acid TiCl₄ in dry DCM (Scheme 99). The optical rotation of this intermediate (313) was +60.8 compared to -53.4 for the isoquinoline alcohol (270). The concentration of the sample may account for the slight discrepancy between the two optical rotation values. As reported for the opposite enantiomer, the ketal protecting group, once again, was removed during this synthetic step. But, as before, this posed no significant disadvantage to our future proposal, as it could be reincorporated at a later stage in the reaction sequence as required.

2.3.4 Removal of the hydroxymethyl substituent

The next step in our synthetic sequence was the removal of the pendant hydroxymethyl substituent from the cyclisation product (313). This was achieved by the application of the same three-step procedure described previously for the opposite enantiomer.¹⁶,³⁰,³¹
(i) Oxidation

As described previously, the initial step in the decarbonylation sequence was the oxidation of the isoquinoline alcohol derivative (313) to its corresponding aldehyde (314) (Scheme 100).

![Scheme 100](image)

This was achieved by oxidising the primary alcohol (313) with the oxidising agent Dess-Martin periodinane, in dry DCM, for 20 hours to afford the aldehyde (314) in 91% yield. The $^1$H NMR spectrum of this product verified the synthesis of the aldehyde, as there was clearly a CHO peak at $\sim9.8$ ppm representing the aldehyde proton. Visual comparison of the $^1$H NMR spectra with the previously synthesised aldehyde (282) supported our observation as both spectra were virtually identical. The optical rotation of this intermediate (314) was $+13.2$ compared to $-10.2$ for the aldehyde (282).

(ii) Decarbonylation

With the aldehyde in hand, the next step for the removal of the pendant hydroxymethyl substituent was achieved via the decarbonylation of the aldehyde (314). Using the best conditions developed for the previous enantiomer, we refluxed the aldehyde (314) in mesitylene in the presence of 10 mol% of the rhodium catalyst, Rh($PPh_3$)$_2$COCl, and 25 mol% of 1,3-bis(diphenylphosphino)propane ligand, dppp, for 96 hours. This produced a mixture of the enamide (315) in 29% yield; and more importantly we synthesised the desired amidoketone (316) in a significantly improved yield (29%) (Scheme 101). This result was a surprise as we used the same conditions as for the opposite enantiomer.
(Table 2: Entry 5) where we only achieved 6% yield of the desired amidoketone (302). This tells us that the quality and condition of the catalyst plays an important role in the synthesis of the amidoketone (316) in comparison to the enamide (315) as in this particular case we had a fresh batch of the rhodium catalyst.

(iii) Hydrogenation

The final step in the auxiliary removal sequence could be achieved by catalytic hydrogenation of the crude mixture from the previous step. Upon treatment with hydrogen in the presence of 10 mol% of palladium on charcoal we successfully furnished the desired amidoketone (316) in 70% yield (Scheme 101). Visual comparison with the $^1$H NMR spectrum of (301) showed that the hydrogenation had been successful with no trace of the enamide (315). The optical rotation of this intermediate was $+39.6$ compared to $-36.9$ for the amidoketone (302).

\[
\begin{align*}
\text{RhCl}(&\text{CO})(\text{PPh}_3)_2 \text{dppp} + \text{Mesitylene} \\
\rightarrow &\text{EtOH, 70\%} \\
\text{(314)} &\rightarrow (29\%) \text{(315)} + (29\%) \text{(316)}
\end{align*}
\]

Scheme 101

2.3.5 Re-introduction of the ketal protection

Next, we focussed on the re-introduction of the ketal protecting group onto the amidoketone (316). This was achieved by reacting the amidoketone (316) with ethylene glycol and p-TSA, under Dean-Stark conditions, for 16 hours to produce the protected
ketone (317) in 80% yield (Scheme 102). Compound (317) gave an optical rotation of +21.7, compared to the opposite enantiomer (308) with a value of -26.1, thus we have successfully synthesised this compound in both enantiomeric forms. Since compound (317) is a known intermediate, this now represents a formal total synthesis of the epimeric natural product (3).

\[
\text{Scheme 102}
\]

In summary, we have successfully synthesised the opposite enantiomer of the protected amidoketone (308), in a six-step sequence following the same synthetic sequence shown in Scheme 97, in an enantiomerically pure form. As previously stated, this intermediate (317) has previously been synthesised by Tsuda and co-worker, albeit in a racemic form, and has subsequently been converted to the natural product, 3-demethoxyerythratidinone (3) by a four-step sequence (Scheme 103).

2.4 Conversion to the natural product, 3-demethoxyerythratidinone (3)

We have now achieved a formal total asymmetric synthesis of both enantiomers of the natural product, 3-demethoxyerythratidinone (3).22 Tsuda and co-workers in 1984 described five different synthetic routes to the synthesis of this natural product. The two reaction sequences illustrated, in Schemes 103 and 104, show the routes that could be taken for both enantiomers of the protected imidoketone (308) and (317), in order to convert them both to their equivalent natural products.
Treatment of the racemic protected imidoketones (308) & (317) with LDA and phenylselenenyl chloride afforded the intermediate (318). Oxidative elimination of the phenylselenenyl group introduced an α, β-unsaturation as illustrated in (319). Reduction of the lactam carbonyl (319) followed by acid hydrolysis of the resulting amine (320) produced, with simultaneous migration of the double bond, the *erythrina* alkaloid (3) in 77% yield (Scheme 103).5

Treatment of the protected imidoketone (308) & (317) with LiAlH₄ afforded the amine (321). This was followed by acid hydrolysis which removed the ketal protecting group generating the ketone (322). Treatment of (322) with LDA followed by phenylsulfenylation with (PhS)₂ resulted in a mixture of mono-(323a) and (323b) and di-(323c) phenylsulfides. This inseparable mixture of (323a) and (323b) was oxidised with m-CPBA and the resulting sulfoxides were heated at reflux in carbon tetrachloride affording the (3) and (324) (Scheme 104).5

Results & Discussion
Results & Discussion

Scheme 104

(308) & (317) → (321) → (322) → (323a) R¹ = H, R² = SPh
(323b) R¹ = SPh, R² = H
(323c) R¹ = R² = SPh
2.5 Routes towards the total synthesis of natural products, (-)-erysotrine and (-)-erythraline, and other related alkaloids

Introduction

Due to the success of our methodology on the formal asymmetric synthesis of both enantiomers of the natural product, 3-demethoxyerythratidinone (3) (Chapter 2.1 and 2.2) we decided to continue our work on the synthesis of related erythrina alkaloids. We will therefore describe our progress and application of our methodology towards the synthesis of the more complex erythrina alkaloids, in particular (-)-erysotrine (7) and (-)-erythraline (325).

2.5.1 Retrosynthetic analysis

\[ \text{RI} = \text{R2} = \text{Me} \ (7) \]
\[ \text{RI} + \text{R2} = \text{CH}_2 \ (325) \]

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The retrosynthetic pathway shown in Scheme 105 utilises a cyclocondensation reaction leading to the synthesis of the tricyclic lactam. N-Acyliminium ion methodology is then applied to generate the erythrinan skeleton. Simple manipulation of the ring system would generate the target natural products, (-)-erysotrine (7) and (-)-erythraline (325).

2.5.2 Attempted synthesis of the racemic keto-acid

In order to perform our cyclocondensation reaction we were required to synthesise the required keto-acid and β-amino alcohol precursors. Our initial studies focussed on the generation of the required keto-acid.

Our first approach was to adapt our previous methodology and synthesise a keto-acid derivative (326) based on our success with keto-acid (258). On this occasion we were required to synthesise the 1,3- instead of the 1,4-mono-protected di-ketone in order to get the protected ketone in the correct orientation for our desired products.

The initial step in the synthesis of the required keto-acid (326) was the preparation of the corresponding mono-protected di-ketone (328). Takagi and co-workers have previously reported the preparation of the required mono-protected di-ketone from the commercially available 1,3-cyclohexanedione (327), using ethylene glycol (1 equiv) and p-TSA, refluxed in toluene under Dean-Stark conditions for 4.5 hours. We repeated these reaction conditions and successfully generated the desired product, 1,3-cyclohexanedione monoethylene ketal (328), however in an unsatisfactory 9% yield (Scheme 106).\(^{46,47}\) Unfortunately, we also synthesised the equivalent diethylene ketal (329) in 17% yield, but we were able to re-isolate a significant amount of starting material.
Our attempts to improve the yield of the mono-protected ketone (328) using different equivalents of ethylene glycol were unsuccessful (Table 3). In each case the $^1$H NMR spectrum of the crude product showed a significant amount of the di-protected ketone, as well as starting material. There was no specific control towards the mono-protected di-ketone, in comparison to the di-protected ketone.

Table 3: Mono-protection study of 1,3-cyclohexanediene (327)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ethylene glycol (equiv)</th>
<th>Mono-protected ketone (328)</th>
<th>Di-protected ketone (329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>9%</td>
<td>17%</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>0.75</td>
<td>11%</td>
<td>7%</td>
</tr>
</tbody>
</table>

With the poor selectivity and yields observed above, we decided that a different approach was required in order to synthesise the required mono-protected di-ketone (328).

Batty and Crich,48 have reported the synthesis of a similarly mono-protected di-ketone substrate (332) via a two step procedure (Scheme 107). This group took the substrate, 2-methylcyclohexane-1,3-dione (330) and using excess ethylene glycol prepared the di-protected ketal (331). They then performed a controlled hydrolysis of one of the ketal protecting groups, using 15% $\text{H}_2\text{SO}_4$ and silica gel to produce the monoethylene ketal (332).
Using this methodology we took our di-ketone substrate (327) and added 4 equivalents of ethylene glycol, in the presence of $p$-TSA, and refluxed under Dean-Stark conditions for 16 hours, to produce the desired 1,3-cyclohexanone diethylene ketal (329) in 78% yield (Scheme 108).

Without further purification, the diethylene ketal (329) was then dissolved in DCM and 15% H$_2$SO$_4$ and silica gel were added. The mixture was then stirred for 2.5 hours at room temperature and this produced the desired mono-protected di-ketone (328) in 75% yield (Scheme 108).

With the synthesis of the (328) in hand; we then focused our attention on its conversion to the required keto-ester (333). Using methodology described in Chapter 2.2.2, we hoped to synthesise the required keto-ester (333) using the same enolate chemistry. Although there are two possible outcomes for this reaction, at positions (i) and (ii), we believed the alkylation might be directed toward position (i) rather than position (ii) due to the steric hindrance generated by the ketal protecting group (Figure 4).
With this hypothesis in hand, we attempted the alkylation using the standard conditions discussed previously in Chapter 2.2.2. The first attempt at the alkylation using KHMDS (1.1 equiv) stirred in dry THF, at -78 °C, for 20 hours produced a mixture of compounds (Scheme 109). Unfortunately, further analysis of the \(^1\)H NMR spectrum of the crude product showed that there was no trace of the desired product (333). After purification, using flash column chromatography, and further characterisation we discovered that the alkylation had occurred at the undesired, and believed to be most hindered, position (Position (ii), Figure 4).

Subsequent attempts at this alkylation using excess KHMDS (up to 1.5 equiv) did not produce the desired product (333). Under these conditions the \(^1\)H NMR spectrum showed a mixture of unidentifiable products. Reducing the amount of KHMDS (down to 0.75 equiv) did produce a mono-alkylated product, unfortunately the \(^1\)H NMR spectrum showed that the alkylation had again occurred at the unwanted position (ii) instead of position (i) as required.

As a result of these observations, we were now unable to synthesise the proposed keto-acid (326), so we decided that an alternative approach was necessary to synthesise the required keto-acid. Our aim was to try and block position (ii) (Figure 4), thus directing the alkylation to the required position. To do this we needed to generate a new template.
(Figure 5) where position (ii) is blocked, thus preventing the alkylation occurring at that position.

2.5.3 Synthesis of the racemic keto-acid

Our new approach was to synthesise a new template (Figure 5) where position (ii) is, effectively, blocked by a double bond. We hoped that the subsequent alkylation would now occur at the desired position (Position (i)), (Figure 5).

![Figure 5]

R = H (334), Cl (335), OMe (336), OEt (337)

Four easily accessible substrate variations were considered based on this template. The first two substrates: 2-cyclohexen-1-one (334) and 3-ethoxy-2-cyclohexen-1-one (337) were commercially available, whereas the remaining two substrates: 3-chloro-2-cyclohexen-1-one (335) and 3-methoxy-2-cyclohexen-1-one (336) were easily synthesised from known literature procedures from commercially available 1,3-cyclohexanediione (327). These substrates were chosen as they all had slightly different properties. Substrates (336) and (337) were chosen as the R substituent (R = OMe & OEt) could be easily hydrolysed regenerating the ketone functionality when required. It was hoped that the electron-withdrawing properties of substrate (335) would direct the subsequent alkylation towards the required position away from position (ii) (Figure 5). Substrate (334) was chosen as it was the basic template with no R substituent, but the double bond gave us the option to add the required substituents at a later stage in the reaction sequence.

Using methodology developed by Chandrasekhar and Reddy, commercially available 1,3-cyclohexanediione (327) was refluxed with trimethyl orthoformate, methanol and p-
TSA (cat.) in toluene for 80 minutes. The desired product 3-methoxy-2-cyclohexen-1-one (336) was obtained in 86% yield with no further purification necessary (Scheme 110).

\[
\begin{array}{c}
\text{(327)} \\
\xrightarrow{\text{CH(OCH}_3)_2, p\text{-TSA, MeOH, Toluene}} \\
\text{MeO} - \\
\text{(336)} \\
\text{86%} \\
\end{array}
\]

Scheme 110

Clark and Heathcock\(^5\) prepared 3-chloro-2-cyclohexen-1-one (335) from the commercially available 1,3-cyclohexanedione (327). They dissolved (327) in chloroform and then added oxalyl chloride slowly due to a vigorous evolution of gas. The reaction mixture was stirred at room temperature for 10 minutes, before being refluxed for an additional 13 minutes to generate the required product (335) in 68% yield (Scheme 111).

\[
\begin{array}{c}
\text{(327)} \\
\xrightarrow{(\text{COCI})_2, \text{CHCl}_3} \\
\text{Cl} - \\
\text{(335)} \\
\text{68%} \\
\end{array}
\]

Scheme 111

With (334)–(337) in hand, we then attempted the alkylation using our standard conditions discussed previously in Chapter 2.2.2.\(^{21}\)

Our initial attempt at this alkylation using KHMDS (1.1equiv) and 3-methoxy-2-cyclohexen-1-one (336) as the substrate, in dry THF at -78 °C for 20 hours, generated a mixture of starting material and a trace amount of the desired keto-ester (338) (Table 4: Entry 1) (Scheme 112). Purification via flash column chromatography enabled us to isolate the desired product (338) and analysis of \(^1\)H NMR spectrum indicated that we had synthesised the desired keto-ester (338), as it clearly showed still the presence of a

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single proton at ~5.38 ppm representing the double bond, thus indicating the alkylation had occurred at the correct position.

Attempts at improving these alkylation conditions, using a co-solvent such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), were unsuccessful as on both occasions only starting materials were recovered (Table 4: Entry 2 & 6).

This alkylation reaction was attempted with a number of different bases, as shown in Table 4, however changing the base from KHMDS to NaHMDS or LiHMDS only had a negative affect on the required alkylation (Table 4: Entry 3 & 4). On both occasions only starting materials were isolated with no trace of the desired product (338).

Table 4: Attempted alkylations with (336), using a range of different bases.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Equivalents</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS</td>
<td>1.1</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>KHMDS &amp; DMPU</td>
<td>1.1</td>
<td>S.M.</td>
</tr>
<tr>
<td>3</td>
<td>NaHMDS</td>
<td>1.1</td>
<td>S.M.</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>1.1</td>
<td>S.M.</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>1.1</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>LDA &amp; DMPU</td>
<td>1.1</td>
<td>S.M.</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>1.5</td>
<td>30%</td>
</tr>
<tr>
<td>8</td>
<td>LDA</td>
<td>1.8</td>
<td>58%</td>
</tr>
</tbody>
</table>

With no real success achieved with the alternative bases used we decided to apply the well known base lithium diisopropylamine (LDA). This reaction was initially attempted using LDA (1.1 equiv) stirred in dry THF, at -78 °C, for 24 hours and...
produced a trace amount of the desired keto-ester (338) (Table 4: Entry 5). Again we had successfully synthesised our desired product (338), but as previously, the yield was still extremely poor.

However, we decided to repeat the reaction again, this time using more equivalents of LDA. We performed the alkylation using LDA (1.5 equiv) under the same reaction conditions and isolated the keto-ester (338) in an improved 30% yield. Unfortunately, as observed previously, there was still a significant amount of starting material still present (Table 4: Entry 7).

As shown in Table 4: Entry 8, we eventually managed to convert our substrate, 3-methoxy-2-cyclohexen-1-one (336) to its equivalent keto-ester (338) in 58% yield using 1.8 equivalents of LDA stirred in dry THF at -78 °C for 24 hours. The 1H NMR spectrum of the crude product showed the desired product (338) had been synthesised with only a trace of starting material still present (Scheme 112).51

With these conditions in hand, we applied this methodology and successfully synthesised the other three keto-esters (339)-(341), where R = H, Cl, OEt, in yields of 52, 48, 59%, respectively (Scheme 113).

With all four keto-esters (338)-(341) in hand, the next step in our reaction sequence was to convert them to the required keto-acid.

The synthesis of the required keto-acids was achieved via subsequent ester hydrolysis utilising the same methodology discussed previously in Chapter 2.2.2. The keto-esters (338)-(341) were hydrolysed using LiOH in THF/H2O, at room temperature for 22 hours, generating the keto-acids (R = OMe (342), OEt (343), Cl (344) in overall yields

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of 79, 84 and 81%, respectively. Unfortunately, the synthesis of the required keto-acid (345), where \( R = H \), was unsuccessful. The \(^1\)H NMR spectrum of the crude product showed that we had generated the required keto-acid along with some unknown by-products. Attempts at purification via flash column chromatography resulted in the decomposition of the desired product (Scheme 114).

\[
\begin{align*}
\text{Scheme 114} \\
\text{R} &= \text{OMe (342), OEt (343), Cl (344), H (345)}
\end{align*}
\]

### 2.6 Towards the total synthesis of the natural product, (-)-erythraline, and other related alkaloids

Introduction

The application of our methodology for the synthesis of more complex erythrina alkaloids, in particular (-)-erythraline (325) and its derivative, dihydroerythramine (or tetrahydroerythraline) (346) is described below. These alkaloids were isolated from the seeds of a number of erythrina plants including *Erythrina latissima*, *Erythrina fusca Lour* and even from the previously mentioned *Erythrina variegata* L. (formerly *Erythrina lithosperma* BLUME) (Chapter 2.2.1).
2.6.1 Literature Review

The synthesis of (-)-erythraline (323) and other related alkaloids including dihydroerythramine (or tetrahydroerythraline) (346) and erythrocarine (347) have been reported only a few times in the literature, albeit in a racemic form, however there are no examples of a non-racemic synthesis of these natural products to the best of our knowledge. Examples of previous racemic approaches to these natural products are discussed below.

Mori and co-workers\textsuperscript{52} have reported the total synthesis of the related alkaloid erythrocarine (347) utilising a nickel-mediated alkylative carboxylation and a ring closing metathesis (RCM) of a diyne as the key steps. The synthesis of the alkyne (349) was achieved in four steps from the commercially available 6-bromopiperonal (348) as reported by Mori and co-workers.\textsuperscript{52} Carboxylation to the alkyne was achieved using a nickel complex and was followed by the addition of an alkynylzinc reagent. The reaction mixture was then hydrolysed before being treated with diazomethane, generating the desired ester (350). Deprotection of the Boc group followed by Michael addition and deprotection of the silyl group afforded the bicyclic ester (351). Allylation of the secondary amine was followed by a Swern oxidation of the reduced ester (352). The addition of vinylmagnesium bromide afforded a diastereomeric mixture of products and the resulting alcohol was protected with an acetyl group to give the precursor (353). Treatment of (353) with HCl produced the diyne hydrochloride which, in the presence of 10 mol% of Grubbs first-generation catalyst, produced the tetracyclic compound (354) in a 1:1 ratio of diastereomers. Finally, treatment with \( \text{K}_2\text{CO}_3 \) in MeOH removed the acetyl group generating the natural product erythrocarine (347) (Scheme 115).
Desmaële and co-workers\textsuperscript{53} reported the synthesis of the (±)-dihydroerythramine (346) using methodology that generates the required C-ring by utilising a Pummerer-based cyclisation. The key precursor (355) for the synthesis of the C-ring \textit{via} this Pummerer-based cyclisation was achieved in four steps from the commercially available (nitro-
methyl)arene derivative (202). With (355) in hand, the formation of the C-ring was then achieved by a three step procedure. The first step investigated was the two-carbon elongation required at the nitrogen atom of the lactam (355).

Scheme 116
This elongation was achieved via a hetero Michael addition of the lactam anion to phenyl vinyl sulfoxide (204) upon treatment with NaHMDS. The subsequent Pummerer cyclisation of the C-ring was then achieved by treating sulfoxide (356) with TMSOTf in the presence of i-Pr₂NEt. The crude product was then subjected to desilylation with n-Bu₄NF producing the required tetracyclic thioether (357). The desulfurization of the thioether (357) was achieved using tri-n-butyltin hydride and AIBN to produce the desired 3-methylene-erythrinan-8-one (358). With the erythrinan system complete, attention turned to the functionalization of the A ring. Oxidative cleavage of the exocyclic double bond was achieved using the Lemieux-Johnson oxidation conditions, producing the required ketone (359). Luche reduction of the carbonyl produced the desired alcohol (360) as a mixture of diastereomers (3:1). Methylation of the resulting hydroxyl group generated the key precursor hexahydrocryptamidine (361) and finally, reduction of the carbonyl group with AlH₃ gave the desired natural product, (±)-dihydroerythramine (346) (Scheme 116).

Sano and co-workers⁵⁴ have reported a regiospecific and stereoselective synthesis of the erythrinan skeleton utilising an intermolecular Diels-Alder reaction. The key intermediate is the dioxopyrroline (362), synthesised in three steps from a commercially available arylethylamine, using a known procedure reported by Sano and co-workers.⁵⁴ With the dioxopyrroline derivative (362) in hand, the synthesis of the desired tetracyclic erythrinian skeleton (364) was then achieved via a three step procedure. The first step was an intermolecular Diels-Alder reaction with the activated butadiene, 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (363). The resulting intermediate was then reduced with LiBH₄ and then hydrolysed in situ, with HCl to isolate the required tetracyclic compound (364). Mesylation of the enone (364) and the subsequent demethoxycarbonylation of the corresponding mesyl derivative with MgCl₂ in DMSO gave the dienone (365). Reduction with NaBH₄ gave the corresponding alcohol (359) as a mixture of diastereomers. Methylation of (366) with methyl iodide in the presence of Et₄NBr and KOH generated the (±)-8-oxoerythraline (367). Finally reduction with a LiAlH₄-AlCl₃ combination afforded the natural product, (±)-erythraline (325) (Scheme 117).
2.6.2 Synthesis of the enantiopure β-amino alcohol substrate

With the synthesis of the required keto-acid (342) in hand, as discussed previously in Chapter 2.5.3, we turned our attention to the preparation of the required β-amino alcohol. In this case, in order to access the target natural products (-)-erythraline (325) and its derivative, dihydroerythramine (346), we needed to synthesise the methylenedioxy phenyl-L-α1aninol (368).
Unfortunately, this β-amino alcohol (368) and its corresponding amino acid parent are not commercially available, which was a surprise due to the number of natural products containing the methylenedioxy ring system. However, Ollero and co-workers\textsuperscript{55} have synthesised a protected amino ester (372), containing the methylenedioxy ring system, generated from the commercially available \textit{L}-DOPA (369) using a three step procedure. Due to the insolubility of \textit{L}-DOPA (369) it was first converted to its equivalent methyl ester before being subjected to further protections. The phenols were protected as tert-butyldimethylsilyl (TBDMS) ethers, generating the amino ester (370).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme_118}
\caption{Scheme 118}
\end{figure}

The amino group was then protected with 9-phenylfluoren-9-yl bromide (PfBr), affording the protected amino ester (371). The methylenedioxy group was then introduced in a one-step procedure using \textit{CH}_2\textit{Cl}_2 and CsF in DMF and this occurred with the simultaneous deprotection of the silyl groups generating the desired compound (372) (Scheme 118).

In the same publication, Ollero and co-workers\textsuperscript{55} have also synthesised the desired (\textit{R})-amino acid (376) via the use of a chiral auxiliary. Deprotonation of the oxazinone (373) with NaHMDS followed by the alkylation of the substituted benzylic bromide (374) afforded the alkylation adduct (375). The alkylated oxazinone was then hydrolysed with
a mixture of MeOH and 3M HCl (6:1) and then hydrogenated with Pd(OH)$_2$/C generating the optically pure amino acid (R)-(376) (Scheme 119).

Using this methodology we could generate the opposite (S)-enantiomer of the amino acid (376) by using the (S)-oxazinone. With the amino acid (376) in hand, we could then reduce it using LiAlH$_4$, producing the desired β-amino alcohol (368). However, we decided that this methodology was impractical and instead chose to synthesise the β-amino alcohol derivative (368) by adapting the methodology described in Scheme 118, as L-DOPA (369) is a cheaper and more accessible starting material.

The first step in our synthesis was to esterify the commercially available substrate dihydroxyphenyl-L-alanine (L-DOPA) (369) in order to improve its solubility and stability.$^{56}$ This was achieved by dissolving L-DOPA in MeOH and then adding thionyl chloride dropwise generating the methyl ester hydrochloride salt in a quantitative yield. The next step was to protect the phenolic groups with a TBDMS ether protecting group. This was achieved by using the protecting group TBDMSCl, activated in the presence of imidazole, to generate the desired amino ester (370) in 60% yield.$^{55}$ With compound (370) in hand, the amino group was then Boc-protected with di-tert-butyl dicarbonate andEt$_3$N to produce the N-Boc-protected amino ester (377) in 67% yield. With the protecting groups in place the next step was the formation of the methylenedioxy ring.
system using BrCH₂Cl and CsF. The formation of the methylenedioxy ring proceeds via the simultaneous deprotection of the silyl protecting groups producing the desired amino ester (378) in 91% yield. Analysis of the ¹H NMR spectrum confirmed the formation of the methylenedioxy ring with a two proton peak at ~5.94 ppm. With the synthesis of the methylenedioxy ring complete, the next step was the removal of the N-Boc protection using TFA in dry DCM to produce the corresponding amino ester (379) in 69% yield. The final step in this sequence was the reduction of the amino ester (379) to the target β-amino alcohol (368) using excess NaBH₄ in absolute ethanol (Scheme 120).

Unfortunately, the ¹H NMR spectrum of the crude product showed that we had synthesised the desired product (368), along with some unknown by-products. Attempts at purification using flash column chromatography were unsuccessful, and we were unable to isolate the product (368) from the unknown by-products (Scheme 120).
Unfortunately due to time constraints, and a change in our synthetic target, we decided not to repeat this work.

2.6.3 Future work: Our proposed synthesis of (-)-erythraline, and other related alkaloids

With the keto-acid (342) (Chapter 2.5.3) and β-amino alcohol (368) in hand, our proposal shown in Scheme 121 was to prepare the corresponding tricyclic lactam (380) using our standard condensation conditions. We would then perform an intramolecular cyclisation generating the tetracyclic erythrinal skeleton (381). Simple manipulation of this skeleton using known literature methodology would lead to the synthesis of a number of natural products, including (-)-erythraline (325).

![Scheme 121](image)

Unfortunately, work done on an alternative synthetic target leading to the synthesis of erysotrine (7) and erysotramidine (201) and described in detail in Chapter 2.7.2 had shown that the standard condensation of the keto-acid (342) with a similar amino alcohol derivative did not produce the expected tricyclic lactam, but instead performed a ‘Michael-like’ addition of the amine. Details of this work will be discussed in Chapter 2.7.2.
However, due to time constraints we were unable to amend this methodology with substrate (368), and our work towards the total synthesis of the natural products (-)-erythraline (325) and dihydroerthramine (346) was abandoned at this stage. Instead we decided to concentrate our attention on the synthesis of the similar natural products erysotrine (7) and erysotramidine (201) as the amino alcohol derivative required for this synthesis was more readily accessible and thus more practical with the limited time available.

2.7 Towards the total synthesis of the natural product (-)-erysotrine, and other related alkaloids

(-)-Erysotrine (7) and its 8-oxo-derivative, (-)-erysotramidine (201) have been isolated from the seeds of a number of erythrina plants including *Erythrina latissima*, *Erythrina fusca* Lour and also from the previously mentioned *Erythrina variegata* L. (formerly *Erythrina lithosperma* BLUME) (Chapter 2.2.1).
2.7.1 Literature Review

The synthesis of erysotrine (7) and other related alkaloids, including erysotramidine (201) and erythravine (382), have been reported many times in the literature, albeit in racemic form, however there are only a few examples of non-racemic syntheses of these natural products. Examples of previous racemic and non-racemic syntheses of these natural products are discussed below.

Padwa and co-workers\textsuperscript{57} have reported that an intramolecular electrophilic aromatic substitution reaction of hexahydroindolinones allows for the rapid construction of the tetracyclic erythrinan skeleton. In this specific case, Padwa and co-workers have synthesised the bicyclic lactam (384) \textit{via} condensation of 3,4-demethoxyphenethylamine and keto-ester (383) in the presence of trifluoroacetic acid (TFA). The formation of the \(\alpha,\beta\)-unsaturated ene-amide (384) occurred with the simultaneous acid catalysed elimination of the phenylsulfonyl group. With the bicyclic lactam (384) in hand, the next step was the smooth cyclisation to the desired erythrinan skeleton (386) and this was achieved upon treatment with NBS in acetonitrile. This reaction proceeded \textit{via} the formation of the \(N\)-acyliminium ion intermediate (385). Treatment of (386) with DBU in refluxing xylene resulted in the formation of the \(\alpha,\beta,\gamma,\delta\)-unsaturated diene-amide (387). This product was believed to have been formed by an initial dehydrobromination, followed by the isomerisation of the \(\pi\)-bond into the thermodynamically more stable position. The stereoselective allylic oxidation of (387) with SeO\(_2\) in the presence of formic acid gave a 1:1 mixture of the formate (388) and the alcohol (389) as a single diastereoisomer. The formate (388) was then converted to the alcohol (389) upon treatment with acetyl chloride in ethanol.\textsuperscript{58} The final step in the synthesis of (±)-erysotramidine (201) is the \(O\)-methylation of the alcohol using KOH/MeI in THF using methodology previously reported by Tsuda and co-workers (Scheme 122).\textsuperscript{59-61}
Tsuda and co-workers have reported the first asymmetric synthesis of (+)-erysotrine (7) from an L-DOPA derivative utilizing an asymmetric Diels-Alder reaction under super high pressure. The key intermediate in this synthesis is the chiral dienophile, dioxopyrroline (391), prepared in three steps from (S)-3,4-dimethoxyphenylalanine methyl ester hydrochloride (390). With (390) in hand, the subsequent Diels-Alder reaction with 1-methoxy-3-trimethylsilyloxybutadiene (5 equiv) (392) in DCM at 130°C (10 kbar pressure) produced the desired erythrinan skeleton (393). The next step was the protection of the ketone with ethylene glycol and p-TSA in benzene, followed by the reduction of the corresponding intermediate with sodium borohydride in methanol producing the required alcohol (394). Alkaline hydrolysis of the methyl ester followed.
by the application of the classical Barton decarboxylation protocol on the corresponding carboxylic acid produced the target intermediate (395).

Results & Discussion
Acid hydrolysis of (395) generated the enone (396) with simultaneous deprotection of the ketone moiety. Mesylation of (396) followed by decarbomethoxylation with CaCl2/DMSO gave the dienone (397). This intermediate is a known compound, albeit in a racemic form, and has previously been converted to the natural product erysotrine (7) by Tsuda and co-workers (Scheme 123).

Fukumoto and co-workers\textsuperscript{64} have reported the first total synthesis of the \textit{erythrina} alkaloid (±)-erythravine (382) utilising the tandem ring closing metathesis (RCM) protocol.

\textbf{Scheme 124}

Results & Discussion
The diester (398) was synthesised in three steps from the commercially available 3,4-dimethoxyphenethylamine (114), as reported by Fukumoto and co-workers. The reduction of (398) with LiAlH₄ followed by selective silylation gave the TBDPS-ether (399). Swern oxidation of (399) and the subsequent reaction of the resulting aldehyde with the Bestmann’s reagent afforded the enyne (400). Subsequent steps included desilylation, Swern Oxidation, and Grignard reaction using vinylmagnesium bromide, generating the required dienyne (401) as a 1:1 epimeric mixture. The resulting alcohol (401) was then converted to the corresponding acetate (402) upon treatment with acetic anhydride. The acetate (402) was then reacted with 10 mol% of Grubb’s first generation catalyst, refluxed in DCM, producing the required tetracyclic intermediate, which upon treatment with K₂CO₃ in methanol furnished the desired natural product, (±)-erythravine (382) (Scheme 124).

2.7.2 Synthesis of the tricyclic lactam leading to an attempted synthesis of erysotrine

Continuing our progress towards the synthesis of erysotrine (7) and other related alkaloids including erysotramidine (201), we will now discuss the synthesis of the tricyclic lactam (403). With the keto-acid (342) (Chapter 2.5.3) and β-amino alcohol (264) (Chapter 2.2.3) precursors in hand, the next step in this synthesis was the cyclocondensation of these two intermediates, using our standard methodology.

The preparation of the tricyclic lactam (403) was initially attempted by refluxing the keto-acid (342) and the β-amino alcohol (264) in toluene, under Dean-Stark conditions, for 48 hours (Scheme 125).
We hoped that under these reaction conditions we would generate the lactam as usual, but this would occur with the simultaneous hydrolysis of the vinyl ether, generating the desired ketone (403). Unfortunately, the initial analysis of the $^1$H NMR spectrum of the crude product showed that the desired lactam (403) had not been synthesised due to the presence of a single proton peak at $\sim 5.60$ ppm, representing the double bond. We initially believed that we had synthesised the tricyclic lactam (404) due to the presence of the third methoxy peak.

![Image](404)

However, LCMS analysis of the crude product highlighted three major molecular weights (MW): 184, 345 and 539. Unfortunately, there was no peak representing the desired MW: 358 required for the tricyclic lactam (404). The MW: 184 represented the keto-acid (342) starting material, however MW: 345 interested us as it had the same molecular weight as the desired tricyclic lactam (403). We now believe that we generated the enamide (405), as this would have the same molecular weight as (403). This observation is supported by the $^1$H NMR spectrum, as the single proton peak at $\sim 5.60$ ppm was broader than expected, suggesting we had synthesised a conjugated ketone, and furthermore, the additional methoxy peak was later identified as keto-acid starting material (342). Attempted purification, using flash column chromatography, enabled us to isolate a trace amount of the enamide (405) and a number of other by-products including starting material (only the keto-acid (342)). Unfortunately, we were unable to isolate the enamide (405) cleanly as it co-eluted with an unknown by-product, therefore we were unable to fully characterise.

![Image](406)

$\text{Ar} = \text{C}_9\text{H}_9(\text{OMe})_2$
However, MW: 538 intrigued us as it suggested that there was a competing reaction occurring during the condensation. The proposed structure representing this molecular weight is the lactam (406) above. Unfortunately, we have no evidence to support this claim as we were unable to isolate this product (406) using flash column chromatography, as the product was unstable and decomposed on the column.

What we think is happening is that during our standard condensation reaction some of the β-amino alcohol substrate is instead attacking the conjugated double bond, performing a 'Michael-like' addition. Although we have no physical evidence for the formation of this product (406) (or similar product), we are not surprised that such a product could be formed due to the conjugation present in the keto-acid derivative (342). Further evidence, for this theory is supported by the fact that we only managed to re-isolate some of the keto-acid (342) with no trace of the β-amino alcohol (264). This would be expected if the β-amino alcohol was simultaneously attacking with the keto-acid from two different directions as the keto-acid would not be consumed during the reaction.

This reaction was repeated a few times using the keto-acid (343) (Scheme 126), but once again, we were only able to isolate a trace amount of the enamide (405).

![Scheme 126](image)

Increasing the number of equivalents of the β-amino alcohol used in this reaction was also tried in an attempt to consume the excess keto-acid, but this had no effect on the overall yield of the enamide (405). Something was competing with the formation of the enamide (405) and we assumed it was something to do with the conjugated double bond. So, in order to prevent this competing side reaction we decided to try and remove the double bond from our keto-acid substrate (342).
This was attempted using methodology by Schultz and co-workers,\(^6\) who used lithium metal and liquid ammonia to remove a double bond from a similar vinyl ether substrate (407) (Scheme 127).

![Scheme 127](image)

We applied this methodology in an attempt to produce the desired keto-acid substrate (409) where the double bond had been removed (Scheme 128). The keto-ester (338), synthesised in two steps from the commercially available 1,3-cyclohexanone (327) (Chapter 2.5.2), was treated with lithium metal and liquid ammonia in dry THF at \(-78^\circ\text{C}\) (Scheme 128).

![Scheme 128](image)

The \(^1\text{H}\) NMR spectrum of the crude isolated compound showed that the single proton at \(~5.38\ \text{ppm}\) representing the double bond had been removed, but unfortunately, the reaction conditions were too harsh and the resulting keto-ester (408) had totally decomposed and was no longer recognisable.
As a consequence of this observation we decided an alternative route was required in order to synthesise the desired erythrinan skeleton necessary to achieve our target synthesis of the natural products, erysotrine (7) and erysotramidine (201).

2.7.3 An alternative synthesis of (-)-Erysotrine, and related alkaloids

Lete and co-workers\textsuperscript{67} have reported the synthesis of the pyrroloisoquinolone (410) where they have utilised an amide coupling reaction, followed by a BF\textsubscript{3}.Et\textsubscript{2}O induced N-acyliminium ion cyclisation as shown in Scheme 129.

Our aim was to adapt this methodology in order to produce our target tetracyclic ring system of the erythrina alkaloids.

2.7.4 Alternative retrosynthetic analysis of erysotrine

The retrosynthetic pathway shown in Scheme 130 utilises an amide coupling reaction followed by a Lewis Acid induced N-acyliminium ion cyclisation leading to the
formation of the erythrinan skeleton. Simple manipulation of this ring system would generate the target natural products, (-)-erysotrine (7) and (-)-erysotramidine (201).

![Scheme 130]

2.7.5 Synthesis of the protected β-amino alcohol

Since the synthesis of the keto-acid precursor (342) has been discussed previously, we will therefore only describe the synthesis of the β-amino alcohol derivative (411). The first step in this synthesis was the Boc-protection of the commercially available 3-(3,4-dimethoxyphenyl)-L-alanine (263). This was achieved in 80% yield using triethylamine and di-tert-butyl dicarbonate, stirred in a mixture of water and 1,4-dioxane at 0 °C. With the N-Boc amino acid (412) in hand, we then performed a reduction of the acid, with LiBH₄ and Me₃SiCl in dry THF, in order to generate the required N-Boc amino alcohol (413). Unfortunately, the ¹H NMR spectrum showed that an intramolecular cyclisation had occurred forming the oxazolidinone (414), as there was no peak at ~1.43 ppm presenting the tert-butyloxoy group of the Boc-protection (Scheme 131).
The acid is reduced to the alcohol as expected but the lithium metal coordinates to the alcohol and the Boc group causing the alcohol to cyclise, thus producing the oxazolidinone (414).

In order to synthesise the TBDMS-protected amino alcohol (411), an alternative procedure was required in order to generate the amino alcohol derivative (413). We needed to first synthesise the N-Boc amino ester (415), before reducing it with NaBH₄. The first step was the preparation of the α-amino ester hydrochloride salt, from the commercially available α-amino acid (263), using thionyl chloride and methanol, and this produced the α-amino ester in a quantitative yield. With the amino ester in hand, we next wanted to protect the amino group. As described above, the amino group was Boc-protected with di-tert-butyl dicarbonate and triethylamine and this produced the N-Boc amino ester (415) in 58% yield. The amino ester (415) was then reduced with NaBH₄ (4 equiv), stirred in absolute ethanol, and this produced the desired N-Boc amino alcohol (413) in 81% yield, with no trace of the unwanted oxazolidinone (414). TBDMS-protection of the N-Boc-amino alcohol (413) with tert-butyl(dimethyl)silyl chloride (TBDMSCl), in the presence of imidazole, produced the TBDMS-protected amino alcohol (416) in 75% yield (Scheme 132).

Results & Discussion
The final step in this reaction sequence, in order to generate the desired substrate (411), was the removal of the N-Boc protection. This was attempted with excess trifluoroacetic acid (TFA) in dry DCM, but unfortunately, the $^1$H NMR spectrum of the crude product showed that we had not synthesised the target substrate (411), but had once again synthesised the oxazolidinone (414) by-product. The TFA had deprotected the silyl ether causing it to cyclise onto the Boc protecting group producing the oxazolidinone ring (Scheme 133).

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{(263)} & \quad \text{(415)}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{HN} & \quad \text{HN} \\
\text{(416)} & \quad \text{(413)}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{OH} & \quad \text{OH} \\
\text{(411)} & \quad \text{(416)}
\end{align*}
\]

In order to prevent the silyl ether cyclising onto the Boc protecting group we decided to change the silyl protecting group to tert-butyldiphenylsilyl chloride (TBDPSCI). We hoped that the two phenyl rings would increase the steric bulk of the protecting group, thus preventing it from cyclising onto the Boc group.

We took the N-Boc-amino alcohol (413) and using TBDPSCI, in the presence of imidazole, we successfully synthesised the TBDPS-protected alcohol (417) in 60%
yield. With the TBDPS-protected amino alcohol (417) in hand, the final step was the removal of the N-Boc protection, using as before TFA in dry DCM. The $^1$H NMR spectrum of the isolated product showed that the de-protection had been successful. The target intermediate (418) was synthesised in 63% yield, with no visible trace of the oxazolidinone (414) by-product (Scheme 134).

2.7.6 Synthesis of the bicyclic amide

With the keto-acid (342) and the protected $\beta$-amino alcohol (418) precursors in hand, the next step in our synthesis was the amide coupling reaction required in order to generate the bicyclic amide (419), the key precursor to the desired erythrinan skeleton. In order to test this methodology, we decided to attempt this reaction first with the more readily accessible keto-acid (421).
The commercially available keto-ester (420) was easily converted to the required keto-acid (421) in 94% yield, using our standard hydrolysis conditions (LiOH in THF/H₂O) (Scheme 135).^{16}

Using methodology reported by Taylor and co-workers,^{68} the synthesis of the bicyclic amide (422) was achieved by coupling the keto-acid (421) with the TBDPS-protected β-amino alcohol (418) using EDCI, HOABt and NMM at -15 °C. This synthesised the key intermediate (422) in 67% yield and the analysis of the ¹H NMR spectrum of the crude product showed a mixture of product diastereoisomers (~1:1). We repeated this reaction with HOBt instead of HOABt and we successfully synthesised the desired product (422) in 98% yield, again as a mixture of product diastereoisomers (~1:1). We are confident we have synthesised the intermediate (422), since the ¹H NMR spectrum showed a multiplet at ~6.01 ppm representing the NH proton of the amide coupling (Scheme 136).

Attempts at separating the diastereomers using flash column chromatography, were unsuccessful, so we decided to cyclise the diastereomeric mixture without separation. The bicyclic amide (422) was treated with BF₃.Et₂O (3 equiv) and refluxed in dry DCM for 4 days generating a mixture of the desired product (270) and starting material. This reaction was repeated using a larger excess of BF₃.Et₂O (20-30 equiv), under the same reaction conditions, and we successfully generated the target tetracyclic core of the
erythrina alkaloids (270) in 61% yield, presumably via the formation of the N-acyliminium ion intermediate (423). Analysis of the \textsuperscript{1}H NMR spectrum of the crude product showed that we synthesised the desired product (270) as a mixture of product diastereomers (2.5:1) (Scheme 137).

Allin and co-workers\textsuperscript{16} have previously synthesised this intermediate (270), as a 10:1 mixture of product diastereomers, using our standard cyclocondensation and Lewis acid mediated cyclisation methodology (Scheme 138). The structure of this intermediate (270) was confirmed by X-ray crystallography, as shown previously in Figure 3, Chapter 2.2.5.\textsuperscript{16}

Direct comparison of the \textsuperscript{1}H NMR spectrum clearly showed that the two compounds were the same, thus leaving us in no doubt that we had successfully synthesised the target ring system, although, the diastereomeric ratio on this occasion was not as high as the previous synthesis of this product (270) (Scheme 138). Though disappointed with the diastereomeric ratio, we were encouraged by this result and decided to continue with this approach and applied this methodology to our substituted keto-acid substrate (342) (Chapter 2.5.3), in order to provide access to the erythrinan skeleton of the natural products, erysotrine (7) and erysotramidine (201).
The synthesis of the bicyclic amide (419) was achieved by coupling the keto-acid (342) with the TBDPS-protected β-amino alcohol (418) using the same methodology described previously (EDCI, HOABt and NMM at -15°C). We successfully synthesised the key intermediate (419) in 81% yield and analysis of the \(^1\)H NMR spectrum of the crude product showed a mixture of product diastereoisomers (~1:1). We repeated this reaction with HOBt instead of HOABt and successfully synthesised the desired product (419) in 89% yield, again as a mixture of product diastereoisomers (~1:1). As observed previously for substrate (422), the \(^1\)H NMR spectrum shows a peak at ~6.20 ppm representing the NH proton, thus we are confident that we have synthesised intermediate (419) (Scheme 139).
As observed previously for substrate (422), attempts to separate the diastereomers, using flash column chromatography, were unsuccessful so we decided to cyclise the diastereomeric mixture without separation.

2.7.7 Attempted synthesis of the tetracyclic core of the target erythrina alkaloid

With the bicyclic amide (419) in hand, we then applied the same cyclisation methodology in an attempt to synthesise the equivalent tetracyclic core of the target erythrina alkaloid. However, upon treatment with BF₃·Et₂O (20-30 equiv) under reflux in dry DCM for 4 days, we unfortunately did not generate the desired tetracyclic intermediate (424) (Scheme 140).

Analysis of the ¹H NMR spectrum of the crude reaction product showed that there were three aromatic protons present. If the desired product had been synthesised one would expect two singlets, in the ¹H NMR spectrum, representing the two aromatic protons. Therefore, we can conclude that the aryl ring failed to cyclise and as a result we did not generate the desired erythrinan skeleton. However, the signal representing the NH proton at ~6.2 ppm is no longer present in the ¹H NMR spectrum suggesting maybe a partial cyclisation had occurred. Further characterisation and analysis has identified the isolated compound as the tricyclic lactam (404) below:
The reaction proceeds as expected forming the N-acyliminium ion intermediate (425), but instead of the aryl ring cyclising to generate the desired tetracyclic product (424) as expected. We believe that the conjugated vinyl ether donates electron density, stabilising the N-acyliminium ion (425), thus generating the corresponding enamide (426). Next, the alcohol from the hydroxymethyl substituent then performs an intramolecular cyclisation forming the isolated tricyclic lactam (404) (Scheme 141).

In order to prevent the formation of the tricyclic lactam (404) we decided that it was necessary to hydrolyse the vinyl ether to its equivalent ketone (403). This will eliminate the unwanted side reaction and thus will allow us to perform our standard intramolecular N-acyliminium ion cyclisation methodology. Using a procedure developed by Cook and co-workers we treated the tricyclic lactam (404) with 2M HCl in THF/H₂O, heated at 55°C, for 20 hours (Scheme 142).
Unfortunately, the expected ketone (403) was not isolated but instead we believe that we have generated the enamide product (405) in 62% yield.

![Chemical Structure](image)

The reaction proceeded as might be expected, with the vinyl ether being hydrolysed to form the corresponding ketone. Unfortunately, during the reaction, the N, O-acetal is simultaneously ring-opened to form the enamide (405), rather than the desired tricyclic lactam (403) (Scheme 143).

![Scheme 143](image)

We believe that we have synthesised enamide (405) due to the fact that the $^1$H NMR spectrum displays a single proton peak at ~5.30 ppm corresponding to the alkenic proton of the double bond. It also clearly shows that there are only two methoxy peaks, which indicates that the hydrolysis has been successful. This is supported by the IR
spectrum that shows two peaks at 1598 and 1731 cm\(^{-1}\) representing the conjugated ketone. The presence of an OH peak at 3416 cm\(^{-1}\) also supports the observation that the reaction proceeded with the ring-opening the \(N, O\)-acetal.

Due to the limited time available we decided to attempt several cyclisations of the enamide (405) as a substrate in order to try and synthesise the desired tetracyclic product (427) (Scheme 144). Attempts at this cyclisation using a Lewis Acid (or a Brønsted acid) were performed as shown below in Table 5.

![Scheme 144](image)

However, all attempts to induce the cyclisation of the enamide (405) failed to deliver the desired product (427) and on each occasion only starting material was re-isolated. The expected \(N\)-acyliminium ion intermediate (428) provides a possible explanation why the cyclisation failed to generate the desired product (427). The enol is unstable and under acidic conditions will readily hydrolyse to produce the corresponding ketone. This would simultaneously stabilise the \(N\)-acyliminium ion, thus regenerating the enamide (405) (Scheme 144).
Table 5: Attempted cyclisation of tricyclic lactam (405)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid/ Brønsted Acid</th>
<th>Solvent</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TiCl₄</td>
<td>DCM</td>
<td>S.M.</td>
</tr>
<tr>
<td>2</td>
<td>HCl (2M)</td>
<td>EtOH</td>
<td>S.M.</td>
</tr>
<tr>
<td>3</td>
<td>BF₃·Et₂O</td>
<td>DCM</td>
<td>S.M.</td>
</tr>
</tbody>
</table>

2.7.8 Future Work

Although we have failed to synthesise tricyclic lactam (403) or the desired tetracyclic products (424) and (427), we are confident that the proposed enamide (405) can be cyclised to generate the erythrinan skeleton (427) stereoselectively, using our standard N-acyliminium ion cyclisation methodology. Previous work by Allin and co-workers⁷⁰,⁷¹ have cyclised a related enamide substrate (429) and have synthesised the desired xylopinine derivative (430), utilising a two step sequence, as shown in Scheme 145.

Scheme 145

With the erythrinan skeleton (427) in hand, removal of the pendant hydroxymethyl substituent can be achieved using our recently developed radical decarboxylation
protocol, which will generate the key intermediate (431). The introduction of α,β-unsaturation can be achieved using standard literature procedures generating the known compound (432). Intermediate (432) has been converted by others to the natural products, erysotrine (7) and erysotramidine (201) (Scheme 146).27,57,61,63

![Scheme 146](image-url)

**Results & Discussion**
2.8 Towards the synthesis of the natural product, (-)-Xylopinine

![Structure of (-)-Xylopinine (26)](image)

**Data**

\[
\begin{align*}
C_{21}H_{25}NO_4 \\
m.p. 173-176^\circ C \\
[\alpha]_D = -266^\circ
\end{align*}
\]

**Introduction**

Xylopinine (26) is a typical member of the protoberberines, a large family of naturally occurring alkaloids characterised by a tetracyclic ring skeleton and an isoquinoline core.\(^7\) This tetrahydroprotoberberine alkaloid contains a tertiary amine moiety, and a stereogenic center at the C (14) position.\(^7\) This alkaloid has two fused phenyl rings and also has additional functionality present, provided by the four methoxy groups located on the A- and D-phenyl rings.

Investigation of *Xylophia decreta*, a member of the Annonaceae family, by Schmutz\(^7\) led to the isolation of the protoberberine alkaloid, (-)-xylopinine (26). The absolute configuration of this alkaloid was determined to be \(14R\) by Corrodi and Hardegger.\(^7\)

Xylopinine (26) has also been reported to exhibit sedative effects, along with moderately strong and relatively long lasting adrenergic \(\alpha\)-blocking properties. The physiological effects observed from these \(\alpha\)-blocking properties include the lowering of blood pressure. There are various other biological properties attributed to this family of alkaloids including antimicrobial, antileukemic, antitumor and anti-inflammatory activity which has resulted in a number of synthetic applications being reported in the literature.\(^7\)
2.8.1 Literature review

The synthesis of xylopinine (26) have been reported many times in the literature, albeit in a racemic form, however there are only a handful of examples of a non-racemic synthesis of this natural product. Examples of the asymmetric synthesis of this natural product will be discussed below.

Munchhof and Meyers have reported the total synthesis of this natural product (26) utilising the classical Pictet-Spengler cyclisation reaction.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{(S)-phenylglycinol} & \quad \text{MeO} \\
\text{(433)} & \quad \text{MeO}
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{H}_2 / \text{Pd-C} & \quad \text{MeO} \\
\text{Red-Al} & \quad \text{MeO}
\end{align*}
\]

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

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

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

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

Scheme 147
The key intermediate (434) was prepared by the condensation of the known keto-acid (433) with (S)-phenylglycinol under Dean-Stark conditions, producing the bicyclic lactam as a single diastereomer. Treatment of (434) with Red-Al ring opens the N,O-acetal generating the isoquinoline (435), with no reduction of the lactam. The subsequent LiAlH₄ reduction of (435) and debenzylation with H₂/Pd-C, afforded the isoquinoline (436). Following formalin-formic acid treatment, the Pictet-Spengler cyclisation ensued to give the desire product, (-)-xylopinine (26) (Scheme 147).

Davis and Mohanty⁷² have reported the asymmetric synthesis of the naturally occurring (S)-(−)-xylopinine (26) from a readily available sulfinimine derived cyclic imine.

\[
\begin{align*}
\text{MeO} & \quad \text{OTBDMS} \\
\text{MeO} & \quad + \\
\text{MeO} & \quad \text{p-Tolyl} \\
(438) & \quad \text{LDA} \\
\text{MeO} & \quad \text{CN} \\
(437) & \\
\text{MeO} & \quad \text{N} \\
(441) & \quad \text{TsCl, Py} \\
\text{MeO} & \quad \text{OH} \\
(440) & \quad \text{NaH} \\
\text{MeO} & \quad \text{LiAlH}_4 \\
\text{MeO} & \quad \text{xylopinine (26)} \\
\end{align*}
\]
The key step in this synthesis is the formation of the chiral sulfinamide (439) generated by the reaction of the laterally lithiated nitrile of (437) with the o-tert-butyldimethylsilyl-protected sulfinimine (438). The chiral sulfinamide (438) was synthesized in five steps from commercially available 3,4-dimethoxyphenethanol as reported by Davis and Mohanty. Treatment of (439) in aqueous MeOH with 4 equiv of LiOH generated the isoquinoline alcohol (440). The alcohol was then converted into the tosylate and treated with NaH to give the 8-oxo-xylopinine (441). Subsequent treatment with LiAlH₄ generated the natural product, (S)-(−)-xylopinine (26) (Scheme 148).

Comins and co-workers have reported a chiral auxiliary mediated Pictet-Spengler reaction leading towards the total asymmetric synthesis of (−)-xylopinine (26).

The key intermediate is the chiral carbamate (442) synthesised from 3,4-dimethoxyphenethylamine and the chiral auxiliary, (+)-trans-2-(α-cumyl)cyclohexanol. The Pictet-Spengler reaction of (443) and the carbamate (442) was performed using

Results & Discussion
trifluoroacetic acid (5 equiv) in DCM, and this generated the required benzylisooquinoline (444). The benzyloisoquinoline (444) was then cyclised upon treatment with $t$-BuLi and potassium tert-amylate in THF, generating the desired precursor 8-oxo-berberine (441). With the 8-oxo-berberine (441) in hand, the final step of the synthesis was the reduction of the lactam carbonyl with Red-Al, utilising methodology by Lenz,\(^80\) generating the natural product, (-)-xylopinine (26) (Scheme 149).

2.8.2 Retrosynthetic analysis

The retrosynthetic pathway shown in Scheme 150 utilises a cyclocondensation reaction leading to the synthesis of a tricyclic lactam. $N$-Acyliminium ion methodology is then required to generate the protoberberine skeleton. Simple manipulation of the ring system would then afford the target natural product, xylopinine (26).
2.8.3 Towards the total synthesis of (-)-xylopinine – preliminary results

Allin and co-workers have reported the stereoselective synthesis of isoquinoline derivatives from bicyclic lactam templates. They recognised that a suitable substituted bicyclic lactam could be used as a precursor in a stereoselective synthesis of the tricyclic tetrahydroisoquinoline ring system, seen as a sub-unit (BCD rings) of the protoberberine alkaloids, e.g. xylopinine (26) and its derivatives.

\[
\begin{align*}
\text{X} & = \text{H}_2, \text{xylopinine (26)} \\
\text{X} & = \text{O}, \text{known precursor}
\end{align*}
\]

The synthesis of the required bicyclic lactam (447) was achieved by condensation of commercially available (S)-phenylalaninol (446) with methyl 5-oxopentanoate (445), refluxed in toluene under Dean-Stark conditions, affording a 4:1 mixture of separable diastereoisomers (447a) and (447b). The subsequent N-acyliminium ion cyclisation was then achieved upon treatment with TiCl$_4$, stirred in DCM at -10°C, producing the corresponding cyclised product (448) as a single product diastereoisomer (Scheme 151).

\[
\begin{align*}
\text{(445)} & \quad + \quad \text{(446)} \\
\text{Toluene} & \quad \rightarrow \\
\text{(447a)} & \quad + \quad \text{(447b)} \\
\text{TiCl}_4 & \quad \downarrow \\
\text{DCM} & \quad \rightarrow \\
\text{(448)} & \quad \text{Scheme 151}
\end{align*}
\]
This methodology was applied to the equivalent methoxy-substituted substrate (449) and has generated the tetrahydroisoquinoline (450) as a single diastereomer (Scheme 152).

Scheme 152

2.8.4 Current Progress: Synthesis of the lactol precursor

The two key precursors for our proposed synthesis of the natural product, xylopinine (26), are the β-amino alcohol (264) and the appropriate aldehyde (451) or its corresponding lactol (452) (Scheme 153). The synthesis of the β-amino alcohol (264) has been discussed above, in Chapter 2.2.3, and therefore we will now only discuss the preparation of the required lactol precursor (452).

Scheme 153

The synthesis of the required lactol precursor (452) was achieved in five steps from the commercially available substrate, homoveratric acid (453). The first step in this sequence was the reduction of the homoveratric acid (453), using LiBH₄ and Me₃SiCl in THF, to produce the corresponding homoveratryl alcohol (454) in 97% yield. The subsequent ring closure was then achieved upon treatment with p-formaldehyde and trifluoroacetic acid (TFA)₈₈ affording the isochromene (455) in 83% yield. The next step was the oxidation of the isochromene (455) using KMnO₄ and the phase transfer catalyst TEBAC, refluxed in DCM, affording the corresponding isochromenone (456) in 89% yield. The subsequent ring opening of the lactone (456), using KOH, resulted
in the generation of the hydroxy intermediate\(^9\) (457) which, was then oxidised without purification to the desired lactol (452) (Scheme 154).

\[
\begin{align*}
&\text{MeO} \quad \text{MeO} \\
&\text{MeO} \quad \text{MeO} \\
\text{(453)} &\quad \xrightarrow{\text{Me}_3\text{SiCl} / \text{LiBH}_4} \quad \text{THF} \\
&\quad 97\% \\
&\text{MeO} \quad \text{MeO} \\
\text{(454)} &\quad \xrightarrow{(\text{CH}_2\text{O})_n} \quad \text{TFA} \\
&\quad 83\%
\end{align*}
\]

Previous work in the Allin group,\(^7\) on a similar hydroxy intermediate (459) (Scheme 155), had tested a number of different oxidising agents as shown in Table 6. They discovered that the best oxidising agent for this step was Dess-Martin periodinane (Entry 4) (Chapter 2.2.7), as this generated the lactol (460) in 70% yield. As can be seen, the other oxidants PCC, PDC and IBX (Entry 1-3) generally synthesised the lactol (460) in poor yields and in the case of PCC only the lactone (458) was re-isolated. As can be appreciated, the relactonisation of the hydroxy intermediate to the equivalent lactone (458) is an inevitable problem due to the fact that relactonisation would lead to the formation of the more stable six-membered ring.

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Table 6: Oxidation study-preparation of the lactol (452)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Lactol (452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PCC</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>PDC</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>IBX</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>DMP</td>
<td>70%</td>
</tr>
</tbody>
</table>

With this knowledge in hand, we took the hydroxy intermediate (457) and performed the oxidation with Dess-Martin periodinane (1-1.5 equiv) in dry DCM and successfully synthesised the required lactol (452), although the yields obtained were consistently low (18-55%) (Scheme 154).

We also attempted this reaction with stabilised IBX (SIBX), a derivative of IBX and Dess-Martin periodinane.92,93 SIBX is a non-explosive oxidising agent composed from a mixture of IBX (49%), benzoic acid (22%) and isophthalic acid (29%). We took the hydroxy intermediate (457) and performed the oxidation with SIBX (1-3 equiv) in dry DCM and successfully synthesised the desired lactol (452), although the maximum yield obtained was only 38% (Scheme 154), (Table 7).

Table 7: Synthesis of the lactol (452) using SIBX

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents</th>
<th>Lactol (452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>38%</td>
</tr>
</tbody>
</table>
As mentioned above, the major problem was that the hydroxy intermediate (457) reverting back to the lactone (456). As a result, we decided that an alternative procedure was required which did not involving the generation of the hydroxy intermediate (457), thus eliminating the possibility of relactonisation occurring.

### 2.8.5 An alternative synthesis of the lactol precursor

Due to the poor yields obtained for the final step in the lactol (452) synthesis shown in Scheme 154; we decided that an alternative procedure was required to produce the lactol (452) (Scheme 156). Sinhababu and Borchardt have reported the synthesis of the phthalaldehydic acid (462) from the commercially available o-bromobenzaldehyde derivative (461).\textsuperscript{94} One could then perform a Wittig reaction with Ph$_3$P$^+$(Cl)$^-\text{CH}_2\text{OMe}$, to generate vinyl ether (463), which would be followed by the subsequent hydrolysis of the vinyl ether to generate the desired lactol (452).

![Scheme 156](image)

Our initial attempts at synthesising the desired phthalaldehydic acid (462), using the methodology reported by Sinhababu and Borchardt, were unsuccessful. Unfortunately, due to time constraints we were unable to repeat this chemistry, but we are confident
that a slight adjustment of our procedure will enable us to synthesise the key intermediate (462). Once this has been achieved, we would then apply the Wittig conditions described above, in order to generate the desired lactol (452). These conditions have previously been applied to a similar substrate (464) and have successfully generated the desired lactol (460), in good yields, though problems still remain regarding the removal of the phosphorus by-products (Scheme 157).

2.8.6 Synthesis of the tricyclic lactam

With the lactol (452) and the β-amino alcohol (264) in hand, we performed our standard condensation reaction, refluxing in toluene under Dean-Stark conditions, to produce the desired tricyclic lactam (465) in 57% yield (Scheme 158).
We then performed our standard Lewis acid mediated cyclisation in an attempt to generate the desired protoberberine skeleton (466). The tricyclic lactam (465) was treated with TiCl₄ (3 equiv) in dry DCM at -78°C, but unfortunately we were unable to determine from the ¹H NMR spectrum whether or not we had successfully synthesised the desired product (466). Analysis of the ¹H NMR spectrum did show however, that we had not synthesised the possible by-product, the enamide (467).

Previous work by Allin and co-workers⁷⁰ had observed that during their attempted cyclisation of a similar tricyclic lactam (468), they synthesised the enamide (429) instead of the desired tetracyclic product. Presumably the N, O-acetal ring was opened as expected, forming the N-acyliminium ion intermediate (469).

![Scheme 159](image-url)
Instead of the aryl ring cyclising to form the desired product, the $N$-acyliminium ion was quenched through $\beta$-elimination to yield the enamide (429) (Scheme 159). This proceeds in a manner similar to the E2 elimination mechanism.

### 3.8.7 Future Work

We are confident that once we have synthesised intermediate (466) we will be able to convert it to the natural product, (-)-xylopine (26) using literature methodology. Our recently developed radical decarboxylation protocol$^{44}$ will generate the known intermediate, 8-oxo-xylopine (441). Intermediate (441) has previously been converted to the desired natural product (26), by Davis$^{72}$ and Comins,$^{75}$ via Red-Al reduction (Scheme 160).

![Scheme 160](image)
2.9 Conclusions

In summary, a facile and highly stereoselective approach has been developed for the formation of the tetracyclic template of the *erythrina* alkaloids, from readily available non-racemic substrates. The stereoselective synthesis of the *N*-acyliminium ion precursors of the *erythrina* (Scheme 161) and protoberberine (Scheme 162) alkaloids, has been achieved through the condensation of a racemic keto-acid (or lactol) and an appropriate chiral β-amino alcohol.

- Stereoselective synthesis of the oxazolo[3,2-i]indole-5,8-dione template:

![Scheme 161](image)

- Stereoselective synthesis of the oxazolo[3,2-b]isoquinoline-5-one template:

![Scheme 162](image)

In our work towards natural product targets the key ring-forming step involves the cyclisation of a pendant aryl substituent onto an *N*-acyliminium ion intermediate generating the tetracyclic core of the *erythrina* alkaloids (Scheme 163). Key developments include:

Results & Discussion - 162 -
- Stereoselective cyclisation generating the indolo[1-α]isoquinoline-3,6-dione template:

![Scheme 163](image)

- A potential precursor for the asymmetric synthesis of the tetracyclic core of the protoberberine alkaloids:

![Scheme 164](image)

The potential for application of our novel methodology in target synthesis has been demonstrated by the removal of the hydroxymethyl substituent, generating the core of the *erythrina* alkaloids (Scheme 165).

- Removal of the pendant hydroxymethyl substituent from the indolo[1-α]isoquinoline-3,6-dione template:

![Scheme 165](image)
We have demonstrated the versatility of this methodology and have achieved the asymmetric synthesis of both enantiomers of the natural product (Scheme 166).

- Formal asymmetric synthesis of both enantiomers of the *erythrina* alkaloid, 3-demethoxyerythratidinone:

![Scheme 166](image)

An alternative synthesis of the *erythrina* alkaloid skeleton has been investigated where the key ring-forming step involves the cyclisation of an aryl substituent of an amide precursor. Key advances include:

- The synthesis of the bicyclic amide precursor of the *erythrina* alkaloids:

![Scheme 167](image)

- Asymmetric synthesis of the indolo[1-α]isoquinolin-6-one template:

![Scheme 168](image)

Results & Discussion - 164 -
• The synthesis of a functionalised amide precursor of the *erythrina* alkaloids:

![Scheme 169]

• Access to a potential precursor for the asymmetric synthesis of the indolo[1-a] isoquinoline-2,6-dione template:

![Scheme 170]

Future work will focus on extending the methodology described to other, more complex *erythrina* and protoberberine alkaloid targets.
Chapter 3 Experimental
3.1 General Information

3.1.1 Solvents

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

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Ethanol (&lt;99.8%)</td>
<td>Used as purchased from Fisher Scientific, UK.</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>Used as purchased from Fisher Scientific, UK.</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>Distilled from phosphorus pentoxide.</td>
</tr>
<tr>
<td>N,N-Dimethylformamide (&lt;99.8%)</td>
<td>Used as purchased from Aldrich Chemical Co. Ltd.</td>
</tr>
<tr>
<td>Dimethylsulfoxide (&lt;99.9%)</td>
<td>Used as purchased from Aldrich Chemical Co. Ltd.</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>Distilled from calcium chloride.</td>
</tr>
<tr>
<td>Hexane</td>
<td>Used as purchased from Fisher Scientific, UK.</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>Used as purchased from Fisher Scientific, UK.</td>
</tr>
<tr>
<td>Light petroleum ether (40-60°C):</td>
<td>Distilled from calcium chloride.</td>
</tr>
<tr>
<td>Mesitylene (98%)</td>
<td>Used as purchased from Aldrich Chemical Co.Ltd.</td>
</tr>
<tr>
<td>Methanol</td>
<td>Used as purchased from Fisher Scientific, UK.</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>Distilled from sodium and benzophenone.</td>
</tr>
<tr>
<td>Toluene</td>
<td>Used as purchased from Fisher Scientific, UK.</td>
</tr>
<tr>
<td>p-Xylene (&gt;99%)</td>
<td>Used as purchased from Aldrich Chemical Co. Ltd.</td>
</tr>
</tbody>
</table>

3.1.2 Reagents

Reagent chemicals were purchased from Acros (Fisher) Chemicals Ltd., Aldrich Chemical Company Ltd., Lancaster Chemical Synthesis Ltd., Merck Chemicals Ltd. and Strem Chemical UK.
3.1.3 Chromatographic Procedures

Analytical thin layer chromatography (TLC) was conducted using aluminium backed plates coated with 0.2 mm silica gel (Merck Kiesegel 60 F254). Plates were visualised under UV light (254 nm) or by staining with potassium permanganate, iodine or phosphomolybdic acid.

Flash column chromatography was conducted using silica gel (Merck Kiesgel 60 H). Samples were applied as saturated solutions in an appropriate solvent or pre-adsorbed onto the minimum quantity of silica. Pressure was applied to the column by the use of hand bellows.

3.1.4 Spectra

Infra-red spectroscopy (IR) was recorded on a Paragon 1000 Perkin-Elmer Fourier Transform Spectrophotometer (with internal calibration) in the range of 4000-600 cm\(^{-1}\). Samples were either dissolved in an appropriate solvent and run as a thin film on sodium chloride plates or in the form of potassium bromide disc.

\(^1\)H and \(^13\)C Nuclear magnetic resonance (NMR) spectra were recorded using either a Bruker AC-250 or DPX-400 Spectrometer. All NMR samples were prepared in deuterated solvents with all values quoted in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. Multiplicities were recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), quartets (q), double of doublets (dd) and multiplets (m). Coupling constants (\(J\) values) are reported in Hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the \(^1\)H NMR spectrum.
3.1.5 Mass Spectrometry

Mass spectra (high/low resolution) and accurate mass were recorded using a Jeol SX102 mass spectrometer using electron impact (EI) or fast atom bombardment (FAB) ionisation techniques.

3.1.6 Other Data

Melting points were determined using an Electrothermal 9100 melting point apparatus and are uncorrected.

Elemental analyses were conducted on a Perkin-Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance.

Optical rotations were performed using an Optical Activity AA-2001 Automatic Polarimeter using a 0.25 dm cell.

X-ray data was collected using a Bruker SMART 1000 CCD diffractometer with graphite monochromated Mo-Kα radiation operating at low temperature (150K).

Yields (unless stated otherwise) are quoted for isolated pure products.
3.2 Formal asymmetric synthesis of (-)-3-demethoxyetheradidinone

Methyl-2-(8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoate (262)

1,4-Cyclohexanedione monoethylene ketal (261) (2.00 g, 12.8 mmol) was dissolved in dry THF (20 ml) and the solution was cooled to $-78^\circ$C. KHMD (28.1 ml of a 0.5 M solution in toluene, 14.1 mmol) was added and the solution was stirred at $-78^\circ$C for 1 h. Methyl bromoacetate (1.30 ml, 14.08 mmol) was added carefully to the mixture and stirred for an additional 1 h. The mixture was then warmed to room temperature and stirred for an additional 20 h. The residue was quenched with 2M HCl and extracted with diethyl ether (3 x 25 ml). The organic extracts were dried with anhydrous Na$_2$SO$_4$ and the solvent was removed by evaporation under reduced pressure yielding a yellow oil. The residue obtained was purified by flash column chromatography on silica gel using a mixture of diethyl ether and hexanes (2:1) as eluent affording methyl-2-(8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoate (262) (1.83 g, 63%) as a colourless oil. $\nu_{\text{max}}$ (DCM)/cm$^{-1}$ 2890 (OMe), 1734 (CO$_2$Me), 1718 (CO); $\delta_H$ (400 MHz; CDCl$_3$) 1.78 (1H, t, J 13.1, CH(CH)CHCO), 1.97-2.12 (3H, m, (CH(H)CHCO and CH$_2$CH$_2$CO), 2.18 (1H, dd, J 16.7, 6.0, CHCH(H)CO$_2$Me), 2.36 (1H, ddd, J 14.3, 5.0, 2.7, CH$_2$CH(H)CO), 2.69-2.76 (2H, m, CH$_2$CH(H)CO and CHCH(H)CO$_2$Me), 3.17-3.23 (1H, m, CH$_2$CHCO), 3.67 (3H, s, CH$_3$O), 4.00-4.08 (4H, m, 2 x CH$_2$O); $\delta_C$ (100 MHz; CDCl$_3$) 33.67 (CH$_2$), 34.52 (CH$_2$), 37.78 (CH$_2$), 40.19 (CH$_2$), 43.06 (CH), 51.60 (CH$_3$O), 64.25 (CH$_2$O), 64.62 (CH$_3$O), 107.05 (C-ketal), 172.43 (CO$_2$CH$_3$), 209.38 (CO); MS (El) m/z 228 [M$^+$, 8.3%]; (Found: M$^+$, 228.0993. C$_{11}$H$_{16}$O$_5$ requires 228.0998).
Methyl-2-(8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoate (262) (1.53 g, 7.10 mmol) was dissolved in a mixture of THF (70 ml) and water (30 ml). Lithium hydroxide (0.30 g, 7.10 mmol) was added and the mixture was stirred at room temperature for 20 h. The mixture was then concentrated, re-suspended in water (50 ml) and acidified to pH 3 using 1M HCl. The aqueous layer was then extracted with ethyl acetate (3 x 25 ml), dried with anhydrous MgSO₄ and the solvent was removed by evaporation under reduced pressure affording 2-(8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoic acid (258) (1.24 g, 84%) as a colourless solid. Further purification was not necessary. Mp 128-129; ν max (DCM)/cm⁻¹ 3195 (OH), 1717 (CO); δH (400 MHz; CDCl₃) 1.78 (1H, t, J 13.6, CH(H)CHCO), 1.97-2.15 (3H, m, (CH(H)CHCO and CH₂CH₂CO), 2.18-2.29 (1H, m, CHCH(H)CO₂H), 2.35-2.45 (1H, m, CH₂CH(H)CO), 2.66-2.81 (2H, m, CH₂CH(H)CO and CHCH(H)CO₂H), 3.13-3.23 (1H, m, CH₂CHCO), 3.99-4.05 (4H, m, 2x CH₂O); δC (100 MHz; CDCl₃) 33.81 (CH₂CHCO), 34.35 (CH₂CH₂CO), 37.63 (CH₂CH₂CO), 39.97 (CH₂CO₂H), 42.82 (CH), 64.54 (CH₂O), 64.78 (CH₂O), 107.05 (C-ketal), 177.41 (CO₂H), 209.71 (CO); MS (EI) m/z 214 [M⁺, 4.7%]; (Found: M⁺, 214.0837. C₁₀H₁₄O₅ requires 214.0841).
(2S)-2-Amino-3-[3,4-dimethoxyphenyl]propan-1-ol (264)\(^{2,3}\)

![Chemical structure](attachment:image)

A solution of chlorotrimethylsilane (4.50 ml, 35.5 mmol) was added under a nitrogen atmosphere to a solution of lithium borohydride (8.88 ml of a 2M solution in THF, 17.8 mmol) in THF (25 ml) over a period of 2 min. 3-(3,4-Dimethoxyphenyl)-L-alanine (263) (2.00 g, 8.88 mmol) was added portionwise over 5 min, and then left to stir at room temperature for 24 h. Methanol (30 ml) was added slowly to the solution and the solvent was then removed by evaporation under reduced pressure. The residue was then treated with 20% aqueous potassium hydroxide solution and extracted with DCM (3 x 20 ml). The organic extracts were dried with anhydrous Na\(_2\)SO\(_4\) and the solvent was removed by evaporation under reduced pressure affording (2S)-2-amino-3-[3,4-dimethoxyphenyl]propan-1-ol (264) (1.82 g, 97%) as a colourless solid. Mp 81-83°C; Lit: Mp 78-79°C;\(^{2,3}\) \([\alpha]_D = -22.5 \ (c = 1.28, \text{EtOH});\) \([\alpha]_D = -21.5 \ (c = 8.0, \text{EtOH});\)\(^{3}\) \(\nu_{\text{max}} (\text{DCM})/\text{cm}^{-1}:\) 3353 (OH), 2934 (sp\(^3\) CH), 2838 (OMe), 1515 (CO); \(\delta_H (400 \ \text{MHz; \ CDCl}_3)\) 2.44 (1H, dd, \(J = 13.6, 8.7, \text{CH(H)CHNH}_2\)), 2.72 (1H, dd, \(J = 13.6, 5.2, \text{CH(H)CHNH}_2\)), 3.09-3.13 (1H, m, NH\(_2\)CH), 3.37 (1H, dd, \(J = 10.6, 7.1, \text{CH(H)OH}\)), 3.62 (1H, dd, \(J = 10.6, 3.9, \text{CH(H)OH}\)), 3.86 (3H, s, CH\(_3\)O), 3.87 (3H, s, CH\(_3\)O), 6.72-6.75 (2H, m, ArH), 6.80-6.82 (1H, m, ArH); \(\delta_C (100 \ \text{MHz; \ CDCl}_3)\) 40.50 (CH\(_2\)CHNH\(_2\)), 54.25 (NH\(_2\)CH), 55.92 (CH\(_3\)O), 55.98 (CH\(_3\)O), 66.46 (CH\(_2\)OH), 111.48 (ArCH), 112.45 (ArCH), 121.21 (ArCH), 131.26 (ArC), 147.75 (ArC-OCH\(_3\)), 149.09 (ArC-OCH\(_3\)); MS (EI) m/z 211 [M\(^+\), 15.1%]; (Found: M\(^+\), 211.1211. C\(_{11}\)H\(_{17}\)O\(_3\) requires 211.1208).
(3S,6aS,10aR)-3-(3,4-Dimethoxy)phenylmethyl-8-(1,3-dioxolane)perhydro[1,3]oxazolo[2,3-1]indol-5-one (265)

Method A

(2S)-2-Amino-3-[3,4-dimethoxyphenyl]propan-1-ol (264) (1.10 g, 5.00 mmol) and 2-(8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoic acid (258) (1.10 g, 5.00 mmol) was dissolved in toluene (150 ml) and refluxed under Dean-Stark conditions for 144 h. The solution was then allowed to cool and the solvent was removed by evaporation under reduced pressure. The resulting yellow oil was then purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes (4:1) as eluent affording (3S,6aS,10aR)-3-(3,4-dimethoxy)phenylmethyl-8-(1,3-dioxolane)perhydro[1,3]oxazolo[2,3-1]indol-5-one (265) (1.00 g, 51%) as a colourless solid.

Method B

(2S)-2-Amino-3-[3,4-dimethoxyphenyl]propan-1-ol (264) (1.10 g, 5.00 mmol) and 2-(8-oxo-1,4-dioxaspiro[4,5]dec-7-yl)ethanoic acid (258) (1.10 g, 5.00 mmol) was dissolved in toluene (150 ml) and refluxed under Dean-Stark conditions for 48 h. The solution was then allowed to cool and the solvent was removed by evaporation under reduced pressure. The resulting yellow oil was then purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes (4:1) as eluent affording (3S,6aS,10aR)-3-(3,4-dimethoxy)phenylmethyl-8-(1,3-dioxolane)perhydro[1,3]oxazolo[2,3-1]indol-5-one (265) (1.23 g, 63%) as a colourless solid.

Mp 98-99°C; [a]D = + 56.1 (c = 1.14, CHCl3); v max (DCM)/cm⁻¹ 1717 (CO), 1653 (lactam); δH (250 MHz; CDCl3) 1.68-2.05 (6H, m, NCCCH₃CH₂, NCCCH₂CH₂ and

Experimental
CH₂CHCH₂CO, 2.39-2.53 (2H, m, CH₂CHCH₂CO and CHCHCH(H)CO), 2.66 (1H, dd, J 13.9, 9.3, CH(H)Ar), 2.90-3.07 (2H, m, CH₂CHCH(H)CO and CH(H)Ar) 3.86 (3H, s, CH₃O), 3.87 (3H, s, CH₃O), 3.91-3.97 (5H, m, 2 x CH₂O and CH(H)O), 4.01-4.08 (1H, m, CH(H)O), 4.24-4.30 (1H, m, NCHCH₂O), 6.70-6.77 (3H, m, ArH); δc (100 MHz; CDCl₃) 30.44 (CH₂), 30.84 (CH₂), 33.71 (CH₂), 39.33 (CHCH₂CO), 39.91 (CH₂Ar), 41.56 (CHCH₂CO), 55.30 (NCHCH₂O), 55.83 (CH₃O), 55.88 (CH₂O), 63.92 (CH₂O), 64.37 (CH₂O), 71.58 (NCHCH₂O), 98.97 (NCCH₂CH₂), 107.88 (C-ketal), 111.28 (ArCH), 112.54 (ArCH), 121.31 (ArCH), 129.56 (ArC), 147.83 (ArC-OCH₃), 148.93 (ArC-OCH₃), 176.28 (CO); MS (El) m/z 389 [M⁺, 59.3%]; (Found: M⁺, 389.1842. C₂₁H₂₇NO₃ requires 389.1838).
(4S,9bS,13aS)-4-(Hydroxymethyl)-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (270)

(3S,6aS,10aS)-3-(3,4-Dimethoxy)phenylmethyl-8-(1,3-dioxolane)perhydro[1,3]oxazolo[2,3-1]indol-5-one (265) (1.23 g, 3.16 mmol) was dissolved in dry DCM (40 ml) under a nitrogen atmosphere and the reaction mixture was cooled to –78°C. TiCl₄ (1.04 ml, 9.48 mmol) was added drop wise by syringe and the mixture was stirred at –78°C for 10 min. After this time, the solution was allowed to reach room temperature before being stirred for an additional 20 h. The mixture was then quenched with saturated ammonium chloride solution (60 ml), extracted with DCM (3 x 25 ml), dried over anhydrous MgSO₄ and the solvent was removed by evaporation under reduced pressure affording a yellow solid. The solid was purified by flash column chromatography on silica gel using a mixture of 5% methanol in DCM as eluent affording (4S,9bS,13aS)-4-(hydroxymethyl)-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (270) (1.00 g, 92%) as a colourless solid. Mp 215-217°C; [\(\alpha\)]D = - 53.4 (c = 1.22, CHCl₃); \(\nu\) max (DCM)/cm⁻¹ 3444 (OH), 1717 (CO), 1645 (lactam); \(\delta\) H (400 MHz; CDCl₃) 2.24 (1H, dd, J 24.4, 7.1, CHCH(H)CO), 2.30-2.45 (4H, m, NCCH₂CH₂ and NCCH₂CH₂), 2.61 (2H, ddd, J 16.4, 8.7, 3.9, CHCH(H)CO and NCHCH(H)Ar), 2.70 (1H, dd, J 18.0, 10.9, CHCH(H)CO), 2.96 (1H, dd, J 16.1, 6.0, CHCH(H)CO), 3.09-3.11 (1H, m, CH₂CO), 3.31 (1H, dd, J 16.4, 12.0, NCHCH(H)Ar), 3.63-3.66 (1H, m, NCHCH₂OH), 3.87 (3H, s, CH₃O), 3.88 (3H, s, CH₃O), 4.01-4.16 (2H, m, CH₂OH), 4.85 (1H, dd, J 9.6, 4.8, OH), 6.60 (1H, s, ArH), 6.66 (1H, s, ArH). \(\delta\) C (100 MHz; CDCl₃) 30.25 (NCHCH₂Ar), 33.42 (NCCH₂CH₂), 35.21 (NCCH₂CH₂), 37.87 (CHCH₂CO), 38.23 (CHCH₂CO), 43.47 (CHCH₂CO), 53.91 (NCHCH₂OH), 56.00 (CH₃O), 56.41 (CH₃O), 62.18 (CH₂OH), 65.94 (NCCH₂CH₂), 107.28 (ArCH), 111.71 (ArCH), 125.91 (ArC), 133.66 (ArC), 148.23 (Ar-C-CH₂),
148.72 (ArC-\text{OCH}_3), 173.90 (\text{NCO}), 209.72 (\text{CO}); MS (El) m/z 345 [M^+, \text{6.5\%}];
(Found: \text{M}^+, 345.1581. \text{C}_{11}\text{H}_{16}\text{O}_5 \text{requires} 345.1576).
(4S,9bS,13aS)-7,8-Dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2H-indolo [7a,1-a] isoquinoline-4-carbaldehyde (282)⁴,⁵

**IBX oxidation**

(4S,9bS,13aS)-4-(Hydroxymethyl)-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (270) (0.40 g, 1.16 mmol) and IBX (0.36 g, 1.28 mmol) was dissolved in DMSO (5 ml) and the solution was stirred at room temperature for 20 h. The DMSO was removed by evaporation under reduced pressure producing a dark orange solid. The solid was then dissolved in ethyl acetate and filtered through celite. The solution was washed with ethyl acetate (150 ml), extracted in water (3 x 50 ml) and dried with anhydrous MgSO₄. The excess solvent was removed by evaporation under reduced pressure affording (4S,9bS,13aS)-7,8-dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-4-carbaldehyde (282) (0.11 g, 48%) as a yellow solid.

**Dess-Martin periodinane oxidation**

(4S,9bS,13aS)-4-(Hydroxymethyl)-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (270) (1.15 g, 3.33 mmol) in dry DCM (30 ml), under a nitrogen atmosphere, was added dropwise via cannula to a solution of Dess-Martin periodinane (1.55 g, 3.67 mmol) in dry DCM (30 ml) also under a N₂ atmosphere. The solution was then stirred at room temperature for 20 h. After this time, the excess solvent was removed by evaporation under reduced pressure producing a dark yellow solid. The solid was purified by flash column chromatography on silica gel

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using 100% ethyl acetate as an eluent affording (4S,9bS,13aS)-7,8-dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7α,1-a]isoquinoline-4-carbaldehyde (282) (1.06 g, 93%) as a yellow solid.

Mp 167-169; [α]D = -10.2 (c = 1.08, CHCl3); νmax (DCM)/cm⁻¹ 1715 (CO), 1685 (lactam); δH (250 MHz; CDCl3) 2.23-2.50 (5H, m, CHCH(H)CO, NCCH2CH2 and NCCH2CH2), 2.60-2.86 (2H, m, CHCH(H)CO and NCHCH(H)Ar), 2.93-3.21 (4H, m, NCHCH(H)Ar, CHCH2CO and CHCH2CO), 3.87 (3H, s, CH3O), 3.88 (3H, s, CH3O), 3.90-4.04 (1H, m, NCHCHO), 6.65 (1H, s, ArH), 6.70 (1H, s, ArH), 9.84 (1H, s, CHO); δC (100 MHz; CDCl3) 27.35 (NCHCH2Ar), 33.42 (NCCH2CH2), 35.37 (NCCH2CH2), 36.76 (CHCH2CO), 38.84 (CHCH2CO), 43.53 (CHCH2CO), 55.91 (CH3O), 56.30 (CH3O), 57.74 (NCH2CH2), 63.62 (NCCH2CH2), 107.13 (ArCH), 112.03 (ArCH), 124.15 (ArC), 133.34 (ArC), 148.45 (ArC-OCH3), 148.67 (ArC-OCH3), 177.09 (NCO), 196.46 (CHO), 209.57 (CO); MS (EI) m/z 343 [M⁺, 15.5%]; (Found: M⁺, 343.1424. C11H16O5 requires 343.1420).
(9bS,13aS)-7,8-Dimethoxy-1,10,11,12,13,13\a-hexahydro-2H-indole[7a,1-a]
isoquinoline-2,12-dione (301) (+ phosphorus by-products)

Using RhCl(CO)(PPh\textsubscript{3})\textsubscript{2} and dppp refluxed in xylene

Method A

[Bis(triphenylphosphine)]rhodium(I) carbonyl chloride (25 mg, 0.04 mmol) was added to anhydrous p-xylene (15 ml) under a nitrogen atmosphere. The mixture was then stirred at 80°C for 15 min. 1,3-Bis(diphenylphosphino)propane (38 mg, 0.91 mmol) was added, and the mixture was stirred at 80°C for a further 30 min. (4S,9bS,13aS)-7,8-Dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13\a-octahydro-2H-indolo[7a,1-a]isoquinoline-4-carbaldehyde (282) (0.25 g, 0.73 mmol) in anhydrous p-xylene (5 ml) was added and the mixture was heated at reflux for 240 h. The excess p-xylene was removed by evaporation under reduced pressure producing a black oil. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (3:1) as eluent affording (9bS,13aS)-7,8-dimethoxy-1,10,11,12,13,13\a-hexahydro-2H-indole[7a,1-a]isoquinoline-2,12-dione (301) (40 mg, 18%) as a yellow oil and co-eluting phosphorus by-products.

Method B

[Bis(triphenylphosphine)]rhodium(I) carbonyl chloride (50 mg, 0.07 mmol) was added to anhydrous p-xylene (15 ml) under a nitrogen atmosphere. The mixture was then stirred at 80°C for 15 min. 1,3-Bis(diphenylphosphino)propane (75 mg, 0.18 mmol) was
added, and the mixture was stirred at 80°C for a further 30 min. (4S,9bS,13aS)-7,8-Dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-4-carbaldehyde (282) (0.50 g, 1.46 mmol) in anhydrous p-xylene (15 ml) was added and the mixture was heated at reflux for 120 h. The excess p-xylene was removed by evaporation under reduced pressure producing a black oil. The residue was purified by flash column chromatography using a mixture of ethyl acetate and hexane (3:1) as eluent affording (9bS,13aS)-7,8-dimethoxy-1,10,11,12,13,13a-hexahydro-2H-indole[7a,1-a]isoquinoline-2,12-dione (301) (90 mg, 20%) as a yellow oil and co-eluting phosphorus by-products.

Using RhCl(CO)(PPh3)_2 refluxed in mesitylene

[Bis(triphenylphosphine)]rhodium(I) carbonyl chloride (40 mg, 0.06 mmol) was added to mesitylene (20 ml) under a nitrogen atmosphere. The mixture was then stirred at 80°C for 20 min. (4S,9bS,13aS)-7,8-Dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-4-carbaldehyde (282) (0.20 g, 0.58 mmol) was added and the mixture was heated at reflux for 120 h. The excess mesitylene was removed by evaporation under reduced pressure producing a dark green oil. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (3:1) as eluent affording (9bS,13aS)-7,8-dimethoxy-1,10,11,12,13,13a-hexahydro-2H-indole[7a,1-a]isoquinoline-2,12-dione (301) (70 mg, 38%) and the co-eluting phosphorus by-products as a yellow oil and a trace of the amidoketone (302) (~1 mg, 6%).

Using RhCl(CO)(PPh3)_2 and dppp refluxed in mesitylene

[Bis(triphenylphosphine)]rhodium(I) carbonyl chloride (40 mg, 0.06 mmol) was added to mesitylene (20 ml) under a nitrogen atmosphere. The mixture was stirred at 80°C for 20 min. 1,3-Bis(diphenylphosphino)propane (16 mg, 0.15 mmol) was added, and the mixture was stirred at 80°C for a further 30 min. (4S,9bS,13aS)-7,8-Dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-4-carbaldehyde
(282) (0.20 g, 0.58 mmol) was added and the mixture was heated at reflux for 120 h. The excess mesitylene was removed by evaporation under reduced pressure producing a dark green oil. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (3:1) as eluent affording (9bS,13aS)-7,8-dimethoxy-1,10,11,12,13,13a-hexahydro-2H-indole[7a,1-a]isoquinoline-2,12-dione (301) (100 mg, 55%) and the co-eluting phosphorus by-products as a yellow oil, and the amidoketone (302) (10 mg, 6%).

\( \nu_{\text{max}} \text{(DCM)/cm}^{-1} 1719 \) (CO), 1686 (lactam); \( \delta_{\text{H}} \) (400 MHz; CDCl\(_3\)) 1.87-1.94 (1H, m, NCCH(H)CH\(_2\)), 2.23-2.36 (4H, m, NCCH(H)CH\(_2\), NCCH\(_2\)CH\(_2\) and CHCH(H)CO), 2.72 (1H, dd, J 16.5, 3.6, CHCH(H)CO), 2.84 (1H, dd, J 18.2, 10.6, CHCH(H)CO), 2.97 (1H, dd, J 16.5, 6.0, CHCH(H)CO), 3.36-3.38 (1H, m, CHCH\(_2\)CO), 3.89 (3H, s, CH\(_3\)O), 3.90 (3H, s, CH\(_3\)O), 6.10 (1H, d, J 7.5, ArCH=CHN), 6.68 (1H, s, ArH), 6.71 (1H, s, ArH), 6.85 (1H, d, J 7.5, ArCH=CHN); \( \delta_{\text{C}} \) (100 MHz; CDCl\(_3\)) 31.18 (NCCH\(_2\)CH\(_2\)), 33.85 (NCCH\(_2\)CH\(_2\)), 36.07 (CHCH\(_2\)CO), 37.69 (CHCH\(_2\)CO), 43.02 (CHCH\(_2\)CO), 56.97 (CH\(_3\)O), 56.43 (CH\(_3\)O), 62.33 (NCCH\(_2\)CH\(_2\)), 106.43 (ArCH), 109.32 (ArCH), 113.09 (CH=CH), 119.63 (CH=CH), 123.52 (ArC), 129.73 (ArC), 148.76 (ArC-OCH\(_3\)), 149.02 (ArC-OCH\(_3\)), 170.82 (NCO), 209.80 (CO); MS (EI) m/z 313 [M\(^+\), 13.3%]; (Found: M\(^+\), 313.1309. C\(_{11}\)H\(_{16}\)O\(_5\) requires 313.1314).
(9bS,13aS)-7,8-Dimethoxy-1,4,5,10,11,12,13,13α-octahydro-2H-indolo[7a,1-α]
isoquinoline-2,12-dione (302)

(9bS,13aS)-7,8-Dimethoxy-1,10,11,12,13,13α-hexahydro-2H-indole[7a,1-α]
isoquinoline-2,12-dione (301) (+ phosphorus by-products) (230 mg, 0.73 mmol) and a
catalytic amount of 10% palladium on charcoal was dissolved in absolute ethanol (25
ml). A 3-way tap was fitted; the sample was then de-gassed by the vacuum and then
purged with H₂ gas. This was repeated 3 times before the mixture was left to stir at room
temperature for a further 20 h. The mixture was then filtered through celite, washed
with DCM (3 x 20 ml) and dried with anhydrous MgSO₄. The excess solvent was then
by evaporation under reduced pressure producing a dark yellow oil. The residue was
purified by flash column chromatography on silica gel using 100% ethyl acetate as the
eluent affording (9bS, 13aS)-7,8-dimethoxy-1,4,5,10,11,12,13,13α-octahydro-2H-indolo
[7a,1-α] isoquinoline-2,12-dione (302) (100 mg, 43%) as a yellow oil. [α]D = -36.9 (c =
1.16, CHCl₃); νmax (DCM)/cm⁻¹ 1717 (CO), 1677 (lactam); δH (400 MHz; CDCl₃) 2.12
(1H, dd, J 17.4, 7.2, CHCH(H)CO), 2.25-2.43 (4H, m, NCCH₂CH₂ and NCCH₂CH₂),
2.61-2.77 (3H, m, CHCH(H)CO, NCH₂CH(H)Ar and CHCH(H)CO), 2.97-3.10 (4H, m,
NCH₂CH(H)Ar, NCH(H)CH₂Ar, CHCH(H)CO and CHCH₂CO), 3.87 (3H, s,
CH₂O), 3.88 (3H, s, CH₂O), 4.36-4.41 (1H, m, NCH(H)CH₂Ar), 6.58 (1H, s, ArH), 6.69 (1H, s,
ArH); δC (100 MHz; CDCl₃) 27.58 (NCH₂CH₂Ar), 33.54 (NCH₂CH₂), 34.75
(NCH₂CH₂Ar), 35.25 (NCCH₂CH₂), 37.49 (CHCH₂CO), 37.80 (CHCH₂CO), 43.26
(CHCH₂CO), 55.93 (CH₃O), 56.35 (CH₃O), 62.47 (NCH₂CH₂), 107.32 (ArCH),
111.80 (ArCH), 125.54 (ArC), 134.35 (ArC), 148.41 (ArC-OC₃H), 148.34 (ArC-
OCH₃), 172.12 (NCO), 210.03 (CO); MS (EI) m/z 315 [M⁺, 33.5%]; (Found: M⁺,
(9bS,13aS)-12,12-Ethylenedioxy-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a] isoquinoline-2-dione (308)

(9bS,13aS)-7,8-Dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a] isoquinoline-2,12-dione (302) (50 mg, 0.16 mmol) and p-TSA (5 mg) was dissolved in toluene (50 ml). Ethylene glycol (0.26 ml, 0.48 mmol) was then added to this stirring solution and the reaction mixture was refluxed, under Dean-Stark conditions, for 20 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (25 ml), extracted with ethyl acetate (3 x 25 ml) and dried with anhydrous MgSO₄. The excess solvent was then removed by evaporation under reduced pressure affording (9bS,13aS)-12,12-ethylenedioxy-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a] isoquinoline-2-dione (308) (40 mg, 70%) as a yellow oil. \([\alpha]_D = -26.1 (c = 1.15, \text{CHCl}_3); v_{\text{max}}(\text{DCM})/\text{cm}^{-1} 2852 (\text{OMe}), 1677 (\text{lactam}), 1514 (\text{C-O}); \delta_{\text{H}} (400 \text{ MHz}; \text{CDCl}_3) 1.70-175 (2\text{H}, \text{m}, \text{NCCH}_2\text{CH}_2), 1.83 (1\text{H}, \text{dd}, J 14.4, 3.2, CH(H)CHCH_2\text{CO}), 1.98-2.15 (3\text{H}, \text{m}, CH(H)CHCH_2\text{CO} \text{ and NCCH}_2\text{CH}_2), 2.35-2.52 (2\text{H}, \text{m}, \text{CH}_2\text{CHCH}_2\text{CO}), 2.60 (1\text{H}, \text{ddd}, J 16.4, 5.2, 2.4, \text{NCH}_2\text{CH(H)Ar}), 2.77-2.80 (1\text{H}, \text{m}, \text{CH}_2\text{CHCH}_2\text{CO}), 2.98-3.07 (1\text{H}, \text{m}, \text{NCH}_2\text{CH(H)Ar}), 3.17-3.24 (1\text{H}, \text{m}, \text{NCH(H)CH}_2\text{Ar}), 3.85 (3\text{H}, \text{s}, \text{CH}_3), 3.88 (3\text{H}, \text{s}, \text{CH}_3), 3.93-3.98 (4\text{H}, \text{m}, \text{OCH}_2\text{CH}_2), 4.16-4.22 (1\text{H}, \text{m}, \text{NCH(H)CH}_2\text{Ar}), 6.56 (1\text{H}, \text{s}, \text{ArH}), 6.79 (1\text{H}, \text{s}, \text{ArH}); \delta_{\text{C}} (100 \text{ MHz}; \text{CDCl}_3) 26.87 (\text{ArCH}_2\text{CH}_2\text{N}), 30.26 (\text{NCCH}_2\text{CH}_2), 33.49 (\text{NCCH}_2\text{CH}_2), 34.96 (\text{ArCH}_2\text{CH}_2\text{N}), 36.74 (\text{CH}_2\text{CHCH}_2\text{CO}), 37.19 (\text{CH}_2\text{CHCH}_2\text{CO}), 37.31 (\text{CH}_2\text{CHCH}_2\text{CO}), 55.85 (\text{OCH}_3), 56.21 (\text{OCH}_3), 62.27 (\text{NCCH}_2\text{CH}_2), 64.09 (\text{OCH}_2\text{CH}_2), 64.44 (\text{OCH}_2\text{CH}_2), 107.72 (\text{C-ketal}), 108.02 (\text{ArCH}), 111.85 (\text{ArCH}), 125.95 (\text{ArC}), 133.95 (\text{ArC}), 147.56 (\text{ArC-OCH}_3), 148.02 (\text{ArC-OCH}_3), 175.10 (\text{NCO}); \text{MS (EI)} m/z 359 [M^+, 5.2%]; (Found: M^+, 359.1739. C_{20}H_{33}NO_5 \text{ requires 359.1733}).
3.3 Formal asymmetric synthesis of (+)-3-demethoxyerthratidinone

(2R)-2-Amino-3-(3,4-dimethoxyphenyl)-D-propionic acid \( (310)^6 \)

Pure \( N\)-acetyl-3-(3,4-dimethoxyphenyl)-\( D\)-alanine \( (309) \) (3.00 g, 11.2 mmol) was dissolved in (1M) \( HCl \) (15 ml) and the mixture was heated at refluxed for 20 h. The excess \( HCl \) was then removed by evaporation under reduced pressure. The residue was then dissolved in 95% ethanol (40 ml) and then concentrated aqueous ammonia was added dropwise until the solution was pH 6. The solid was then filtered and washed with ethanol (100 ml). The excess ethanol was then removed by evaporation under reduced pressure affording \( (2R)-2\text{-amino-3-(3,4-dimethoxyphenyl)-D-propionic acid} \) \( (310) \) (2.26 g, 95 %) as a colourless solid. No further purification was necessary. Mp 254-257°C; \([\alpha]_D = -4.8 \) (c = 1.09, \( HCl \)); \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\) 3196 (\( \text{CO}_2\text{H} \)), 2837 (\( \text{OCH}_3 \)), 1606 (\( \text{NH}_2 \)); \( \delta_H \) (250 MHz; DCl) 3.15-3.36 (2H, m, \( \text{CH(H)CHNH}_2 \) and \( \text{CH(H)CHNH}_2 \)), 3.79 (3H, s, \( \text{CH}_3\text{O} \)), 3.80 (3H, s, \( \text{CH}_3\text{O} \)), 4.48 (1H, t, \( J = 7.2 \), \( \text{CH}_2\text{CHNH}_2 \)), 6.84-6.95 (3H, m, \( \text{ArH} \)); \( \delta_C \) (100 MHz; DCl) 37.63 (\( \text{CH}_2\text{CHNH}_2 \)), 65.55 (\( \text{CHOH} \)), 167.56 (\( \text{CO}_2\text{H} \)); MS (El) \( m/z \) 225 [\( \text{M}^+ \), 5.1%]; (Found: \( \text{M}^+ \), 225.0997. \( \text{C}_{11}\text{H}_{15}\text{O}_4 \) requires 225.1001).
A solution of chlorotrimethylsilane (4.50 ml, 35.5 mmol) was added under a nitrogen atmosphere to a solution of lithium borohydride (8.88 ml of a 2M solution in THF, 17.8 mmol) in THF (25 ml) over a period of 2 min. 3-(3,4-Dimethoxyphenyl)-D-alanine (310) (2.00 g, 8.88 mmol) was added portionwise over 5 min, and then left to stir at room temperature for 24 h. Methanol (30 ml) was added slowly to the solution and the solvent was then removed by evaporation under reduced pressure. The residue was then treated with 20% aqueous potassium hydroxide solution and extracted with DCM (3 x 20 ml). The organic extracts were dried with anhydrous Na₂SO₄ and the solvent was removed by evaporation under reduced pressure affording (2R)-2-amino-3-[3,4-dimethoxyphenyl]propan-1-ol (311) (1.77 g, 94%) as a colourless solid. Mp 82-83; Lit: Mp 78-79°C; [α]D = + 21.7 (c = 1.27, EtOH); ν max (DCM)/cm⁻¹ 3385 (OH), 2938 (sp³ CH), 2838 (OMe), 1517 (C-O); δH (400 MHz; CDCl₃) 2.44 (1H, dd, J 13.6, 8.8, CH(H)CHNH₂), 2.73 (1H, dd, J 13.6, 5.2, CH(H)CHNH₂), 3.09-3.13 (1H, m, NH₂CH), 3.42 (1H, dd, J 10.4, 7.2, CH(H)OH), 3.63 (1H, dd, J 10.8, 4.0, CH(H)OH), 3.87 (3H, s, CH₃O), 3.88 (3H, s, CH₃O), 6.72-6.75 (2H, m, ArH), 6.81-6.83 (1H, m, ArH); δC (100 MHz; CDCl₃) 40.49 (CH₂CHNH₂), 54.21 (NH₂CH), 55.87 (CH₃O), 55.93 (CH₃O), 66.44 (CH₂OH), 111.31 (ArCH), 112.27 (ArCH), 121.15 (ArCH), 131.19 (ArC), 147.64 (ArC-OCH₃), 148.98 (ArC-OCH₃); MS (El) m/z 211 [M⁺, 1.2%]; (Found: M⁺, 211.1134. C₁₁H₁₆O₃ requires 211.1130).
(3R,6aR,10aR)-3-(3,4-Dimethoxy)phenylmethyl-8-(1,3-dioxolane)perhydro[1,3]oxazolo[2,3-1]indol-5-one (312)

(2R)-2-Amino-3-[3,4-dimethoxyphenyl]propan-1-ol (311) (0.41 g, 1.94 mmol) and 2-8-oxo-1,4-dioxaspiro[4,5]dec-7-yl]ethanoic acid (258) (0.41 g, 1.94 mmol) was dissolved in toluene (150ml) and refluxed under Dean-Stark conditions for 48 h. The solution was then allowed to cool and the solvent was removed by evaporation under reduced pressure. The resulting yellow oil was then purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes (4:1) as eluent affording (3R,6aR,10aR)-3-(3,4-dimethoxy)phenylmethyl-8-(1,3-dioxolane)perhydro[1,3]oxazolo[2,3-1]indol-5-one (312) (0.45 g, 60%) as a colourless solid. Mp 98-99°C; [α]D = -55.7 (c = 1.13, CHCl3); νmax (DCM)/cm⁻¹ 1717 (CO), 1653 (lactam); OH (400 MHz; CDCl3) 1.72-2.04 (6H, m, NCCH2CH2, NCCH2CH2 and CH2CHCH2CO), 2.40-2.50 (2H, m, CH2CHCH2CO and CHCHCH(H)CO), 2.75 (1H, dd, J 13.9, 9.1, CH(H)Ar), 2.93-3.04 (1H, m, CH2CHCH(H)CO and CH(H)Ar), 3.85 (3H, s, CH3O), 3.87 (3H, s, CH3O), 3.91-3.96 (5H, m, 2 x CH2O and CH(H)O), 4.03-4.10 (1H, m, CH(H)O), 4.24-4.30 (1H, m, NCHCH2O), 6.73-6.81 (3H, m, ArH); δC (100 MHz; CDCl3) 30.45 (CH2), 30.84 (CH2), 33.71 (CH2), 39.33 (CHCH2CO), 39.91 (CH2Ar), 41.56 (CHCH2CO), 55.30 (NCHCH2O), 55.83 (CH3O), 55.88 (CH3O), 63.92 (CH2O), 64.37 (CH2O), 71.59 (NCHCH2O), 98.97 (NCCH2CH2), 107.88 (C-ketal), 111.28 (ArCH), 112.54 (ArCH), 121.31 (ArCH), 129.56 (ArC), 147.83 (ArC-OCH3), 148.93 (ArC-OCH3), 176.28 (CO); MS (EI) m/z 389 [M⁺, 59.5%]; (Found: M⁺, 389.1842. C21H27N03 requires 389.1838).
(4R,9bR,13aR)-4-(Hydroxymethyl)-7,8-dimethoxy)-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (313)

(3R,6aR,10aR)-3-(3,4-Dimethoxy)phenylmethyl-8-(1,3-dioxolane)perhydro[1,3]oxazolo[2,3-1]indol-5-one (312) (1.10 g, 2.83 mmol) was dissolved in dry DCM (50 ml) under a nitrogen atmosphere and the reaction mixture was cooled to −78°C. TiCl₄ (0.93 ml, 8.48 mmol) was added drop wise by syringe and the mixture was stirred at −78°C for 10 min. After this time, the solution was allowed to reach room temperature before being stirred for an additional 20 h. The mixture was then quenched with saturated ammonium chloride solution (60 ml), extracted with DCM (3 x 25 ml), dried over anhydrous MgSO₄ and the solvent was removed by evaporation under reduced pressure affording a yellow solid. The solid was purified by flash column chromatography on silica gel using a mixture of 5% methanol in DCM as the eluent affording (4R,9bR,13aR)-4-(hydroxymethyl)-7,8-dimethoxy)-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a] isoquinoline-2,12-dione (313) (0.75 g, 77%) as a colourless solid. Mp 215-217°C; [α]D = +60.8 (c = 1.06, CHCl₃); ν max (DCM)/cm⁻¹ 3415 (OH), 1712 (CO), 1666 (lactam); δH (400 MHz; CDCl₃) 2.24 (1H, dd, J 18.0, 7.0, CHCH(H)CO), 2.29-2.44 (4H, m, NCCH₂CH₂ and NCCH₂CH₂), 2.58 (1H, ddd, J 16.5, 9.4, 3.8, CHCH(H)CO and NCHCH(H)Ar), 2.96 (1H, dd, J 16.1, 6.1, CHCH(H)CO), 3.09-3.11 (1H, m, CHCH₂CO), 3.31 (1H, dd, J 16.5, 12.0, NCHCH(H)Ar), 3.63-3.66 (1H, m, NCHCH₂OH), 3.87 (3H, s, CH₃O), 3.88 (3H, s, CH₃O), 4.00-4.13 (2H, m, CH₂OH), 4.86 (1H, dd, J 9.7, 5.4, OH), 6.60 (1H, s, ArH), 6.66 (1H, s, ArH). δC (100 MHz; CDCl₃) 30.21 (NCHCH₂A), 33.34 (NCCH₂CH₂), 35.18 (NCCH₂CH₂), 37.80 (CHCH₂CO), 38.20 (CHCH₂CO), 43.44 (CHCH₂CO), 53.85 (NCHCH₂OH), 55.96 (CH₃O), 56.32 (CH₃O), 62.11 (CH₂OH), 65.94 (NCCH₂CH₂), 107.00 (ArCH), 111.71 (ArCH), 125.91 (ArC), 133.66 (ArC), 147.64 (CH₃CO), 156.38 (ArC), 168.72 (CO), 170.84 (CO), 171.24 (CO), 193.64 (CO), 194.07 (CO), 194.11 (CO)
148.24 (ArC-OCH₃), 148.57 (ArC-OCH₃), 173.89 (NCO), 209.72 (CO); MS (El) m/z 345 [M⁺, 15.9%]; (Found: M⁺, 345.1581. C₁₉H₂₃NOS requires 345.1576).
(4R,9bR,13aR)-7,8-Dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-4-carbaldehyde (314)

(4S,9bS,13aS)-4-(Hydroxymethyl)-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (313) (0.74 g, 2.14 mmol) in dry DCM (30 ml), under a nitrogen atmosphere, was added dropwise via cannula to a solution of Dess-Martin periodinane (1.00 g, 2.36 mmol) in dry DCM (30 ml) also under a N2 atmosphere. The solution was then stirred at room temperature for 20 h. After this time, the excess solvent was removed by evaporation under reduced pressure producing a dark yellow solid. The solid was purified by flash column chromatography on silica gel using 100% ethyl acetate as an eluent affording (4R,9bR,13aR)-7,8-dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-4-carbaldehyde (314) (0.67 g, 91%) as a yellow solid. Mp 168-170°C; [α]D = + 13.2 (c = 1.06, CHCl3); ν max (DCM)/cm⁻¹ 1716 (CO), 1683 (lactam); δH (400 MHz; CDCl3) 2.25 (1H, dd, J 17.8, 7.4, CHCH(H)CO), 2.34-2.38 (2H, m, NCCH2CH2), 2.45-2.49 (2H, m, NCCH2CH2), 2.61 (1H, dd, J 16.0, 3.7, CHCH(H)CO), 2.67 (1H, dd, J 17.8, 10.1, NCHCH(H)Ar), 3.00-3.22 (4H, m, NCHCH(H)Ar, CHCH2CO and CHCH2CO), 3.87 (3H, s, CH3O), 3.89 (3H, s, CH3O), 4.01-4.04 (1H, m, NCHCH2OH), 6.66 (1H, s, ArH), 6.71 (1H, s, ArH), 9.83 (1H, s, CHO); δC (100 MHz; CDCl3) 27.35 (NCH2CH2), 33.42 (NCCH2CH2), 35.37 (NCCH2CH2), 36.84 (CHCH2CO), 38.83 (CHCH2CO), 43.21 (CHCH2CO), 55.98 (CH3O), 56.30 (CH3O), 57.74 (NCH2CH2), 63.62 (NCCH2CH2), 107.13 (ArCH), 112.03 (ArCH), 124.15 (ArC), 133.34 (ArC), 148.45 (ArC-OCH3), 148.67 (ArC-OCH3), 174.76 (NCO), 196.46 (CHO), 209.57 (CO); MS (El) m/z 343 [M⁺, 11.8%]; (Found: M⁺, 343.1414. C19H21NO5 requires 343.1420).
(9bR,13aR)-7,8-Dimethoxy-1,10,11,12,13,13a-hexahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (315)

[Bis(triphenylphosphine)]rhodium(I) carbonyl chloride (135 mg, 0.20 mmol) was added to mesitylene (50 ml) under a nitrogen atmosphere. The mixture was stirred at 80°C for 20 min. 1,3-Bis(diphenylphosphino)propane (201 mg, 0.49 mmol) was added, and the mixture was stirred at 80°C for a further 30 min. (4R,9bR,13aR)-7,8-Dimethoxy-2,12-dioxo-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-4-carbaldehyde (314) (0.67 g, 1.95 mmol) was added and the mixture was heated at reflux for 96 h. The excess mesitylene was then removed by evaporation under reduced pressure producing a dark green oil. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (3:1) as eluent affording (9bR,13aR)-7,8-dimethoxy-1,10,11,12,13,13a-hexahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (315) (180 mg, 29%) and the co-eluting phosphorus by-products as a yellow oil, and the amidoketone (316) (180 mg, 29%). v_max (DCM)/cm⁻¹ 1719 (CO), 1686 (lactam); δ_H (400 MHz; CDCl₃) 1.87-1.94 (1H, m, NCCCH(H)CH₂), 2.23-2.36 (4H, m, NCCCH(H)CH₂, NCCCH₂CH₂ and CHCH(H)CO), 2.72 (1H, dd, J 16.5, 3.6, CHCH(H)CO), 2.84 (1H, dd, J 18.2, 10.6, CHCH(H)CO), 2.97 (1H, dd, J 16.5, 6.0, CHCH(H)CO), 3.36-3.38 (1H, m, CHCH₂CO), 3.89 (3H, s, CH₃O), 5.69 (JH, d, J 7.5, ArCH=CHN), 6.68 (1H, s, ArH), 6.71 (1H, s, ArH), 6.85 (1H, d, J 7.5, ArCH=CHN); δ_C (100 MHz; CDCl₃) 31.18 (NCCH₂CH₂), 33.85 (NCCH₂CH₂), 36.07 (CHCH₂CO), 37.69 (CHCH₂CO), 43.02 (CHCH₂CO), 56.97 (CH₃O), 56.43 (CH₃O), 62.33 (NCCH₂CH₂), 106.43 (ArCH), 109.32 (ArCH), 113.09 (CH=CH), 119.63 (CH=CH), 123.52 (ArC), 129.73 (ArC), 148.76 (ArC-OCH₃), 149.02 (ArC-OCH₃), 170.82 (NCO), 209.80 (CO).
(9bR,13aR)-7,8-Dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (316)

(9bR,13aR)-7,8-Dimethoxy-1,10,11,12,13,13a-hexahydro-2H-indole[7a,1-a]isoquinoline-2,12-dione (315) (+ phosphorus by-products) (180 mg, 0.57 mmol) and a catalytic amount of 10% palladium on charcoal was dissolved in absolute ethanol (25 ml). A 3-way tap was fitted; the sample was then de-gassed by the vacuum and then purged with H₂ gas. This was repeated 3 times before the mixture was left to stir at room temperature for a further 20 h. The mixture was then filtered through celite, washed with DCM (3 x 20 ml) and dried with anhydrous MgSO₄. The excess solvent was then by evaporation under reduced pressure producing a dark yellow oil. The residue was purified by flash column chromatography on silica gel using 100% ethyl acetate as the eluent affording (9bR,13aR)-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a]isoquinoline-2,12-dione (316) (90 mg, 50 %) as a yellow oil. [α]D = +39.6 (c = 1.13, CHCl₃); ν max (DCM)/cm⁻¹ 2850 (OMe), 1715 (CO), 1685 (lactam); δH (400 MHz; CDCl₃) 2.13 (1H, dd, J 17.4, 7.2, CHCH(H)CO), 2.25-2.46 (4H, m, NCCH₂CH₂ and NCCH₂CH₂), 2.61-2.77 (3H, m, CHCH(H)CO, NCH₂CH(H)Ar and CHCH(H)CO), 2.98-3.06 (4H, m, NCH₂CH(H)Ar, NCH₂CH(H)Ar and CHCH(H)CO), 3.87 (3H, s, CH₃O), 3.88 (3H, s, CH₃O), 4.36-4.41 (1H, m, NCH(H)CH₂Ar), 6.58 (1H, s, ArH), 6.69 (1H, s, ArH); δC (100 MHz; CDCl₃) 27.59 (NCH₂CH₂Ar), 33.52 (NCCH₂CH₂), 34.75 (NCH₂CH₂Ar), 35.25 (NCCH₂CH₂), 37.47 (CHCH₂CO), 37.81 (CHCH₂CO), 43.26 (CHCH₂CO), 55.92 (CH₃O), 56.30 (CH₃O), 62.47 (NCCH₂CH₂), 107.13 (ArCH), 111.67 (ArCH), 125.49 (ArC), 134.33 (ArC), 148.27 (ArC-CH₃), 148.41 (ArC-CH₃) 172.12 (NCO), 210.16 (CO); MS (EI) m/z 315 [M⁺, 12.4%]; (Found: M⁺, 315.1466. C₁₈H₂₁NO₄ requires 315.1471).
(9bR,13aR)-12,12-Ethylenedioxy-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a] isoquinoline-2-dione (317)

(9bR,13aR)-7,8-Dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a] isoquinoline-2,12-dione (316) (0.24 mg, 0.76 mmol) and p-TSA (5 mg) was dissolved in toluene (50 ml). Ethylene glycol (0.14 ml, 2.28 mmol) was then added to this stirring solution and the reaction mixture was refluxed, under Dean-Stark conditions, for 20 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution (25 ml), extracted with ethyl acetate (3 x 25 ml) and dried with anhydrous MgSO₄. The excess solvent was then removed by evaporation under reduced pressure affording (9bR,13aR)-12,12-ethylenedioxy-7,8-dimethoxy-1,4,5,10,11,12,13,13a-octahydro-2H-indolo[7a,1-a] isoquinoline-2-dione (317) (0.22 g, 80%) as a yellow oil. [α]₀ = + 21.7 (c = 1.33, CHCl₃); ν max (DCM)/cm⁻¹ 2852 (OMe), 1673 (lactam), 1514 (C-O); δH (400 MHz; CDCl₃) 1.70-1.75 (2H, m, NCCH₂CH₂), 1.83 (1H, dd, J 14.4, 6.8, CH(H)CHCH₂CO), 1.99-2.17 (3H, m, CH(H)CHCH₂CO and NCCH₂CH₂), 2.34-2.51 (2H, m, CH₂CHCH₂CO), 2.60 (1H, ddd, J 16.3, 5.4, 2.2, NCH₂CH(H)Ar), 2.76-2.80 (1H, m, CH₂CHCH₂CO), 3.00-3.05 (1H, m, NCH₂CH(H)Ar), 3.17-3.24 (1H, m, NCH(H)CH₂Ar), 3.85 (3H, s, CH₃O), 3.88 (3H, s, CH₃O), 3.93-4.02 (4H, m, OCH₂CH₂O), 4.13-4.22 (1H, m, NCH(H)CH₂Ar), 6.56 (1H, s, ArH), 6.79 (1H, s, ArH); δC (100 MHz; CDCl₃) 26.86 (ArCH₂CH₂N), 30.45 (NCCH₂CH₂), 33.49 (NCCH₂CH₂), 34.94 (ArCH₂CH₂N), 36.75 (CH₂CHCH₂CO), 37.19 (CH₂CHCH₂CO), 37.30 (CH₂CHCH₂CO), 55.85 (OCH₃), 56.22 (OCH₃), 62.25 (NCCH₂CH₂), 64.09 (OCH₂CH₂O), 64.43 (OCH₂CH₂O), 107.77 (C-acetal), 108.02 (ArCH), 111.89 (ArCH), 125.97 (ArC), 133.98 (ArC), 147.57 (ArC-CH₃), 148.03 (ArC-CH₃), 175.07 (NCO); MS (EI) m/z 359 [M⁺, 2.1%]; (Found: M⁺, 359.1730. C₂₀H₂₃NO₅ requires 359.1733).

Experimental
3.4 Towards the keto-acid precursor of (-)-erysotrine and (-)-erythraline

1,3-Cyclohexanedione monoethylene ketal (328)

Method A

Ethylene glycol (2.49 ml, 44.6 mmol) was added to a stirring mixture of Cyclohexane-1,3-dione (327) (5.00 g, 44.6 mmol) and p-TSA (85 mg, 0.45 mmol) in toluene (60 ml). The reaction mixture was then refluxed under Dean-Stark conditions for 4.5 h. After this time, the reaction was quenched with saturated aqueous sodium bicarbonate solution (40 ml) and extracted with ethyl acetate (3 x 40 ml). The organic extracts were dried with anhydrous MgSO₄ and the excess solvent was removed by evaporation under reduced pressure to yield a yellow solid. The solid was then purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (1:1) as eluent affording 1,3-cyclohexanediolone monoethylene ketal (328) (0.59 g, 9%) as a clear oil.

Method B

1,3-Cyclohexanedione diethylene ketal (329) (146 mg, 0.73 mmol) was dissolved in DCM (20 ml) before being treated with silica gel (0.30 g) and 15% sulphuric acid (0.20 ml). The reaction mixture was then stirred at room temperature for 2.5 h. After this time, the reaction mixture was then filtered, and the filtrate was washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried with anhydrous MgSO₄ and the excess solvent was removed by evaporation under reduced pressure to yield a yellow oil. The residue was then purified by flash column chromatography on
silica gel using a mixture of ethyl acetate and hexane (1:1) as eluent affording 1,3-
cyclohexanedione monoethylene ketal (328) (85 mg, 75%) as a clear oil.

\[ \nu_{\text{max}} \text{(DCM)/cm}^{-1} = 1717 \text{ (CO)}; \delta_{\text{H}} \text{(400 MHz; CDCl}_3\text{) } 1.83-1.91 \text{ (4H, m, CH}_2\text{CH}_2\text{CH}_2\text{-acetal and CH}_2\text{CH}_2\text{CH}_2\text{-ketal), 2.31 (2H, t, J 6.0, CH}_2\text{CH}_2\text{CH}_2\text{CO), 2.58 (COCH}_2\text{-ketal), 3.92-3.98 (4H, m, OCH}_2\text{CH}_2\text{O); } \delta_{\text{C}} \text{(100 MHz; CDCl}_3\text{) } 20.06 \text{ (CH}_2\text{CH}_2\text{CH}_2\text{-acetal), 34.06 (CH}_2\text{CH}_2\text{CH}_2\text{-ketal), 40.14 (CH}_2\text{CH}_2\text{CH}_2\text{CO), 51.56 (COCH}_2\text{-ketal), 64.58 (OCH}_2\text{CH}_2\text{O), 109.88 (CO-ketal), 207.37 (CO).} \]
Ethylene glycol (9.95 ml, 0.18 mol) was added to a stirring mixture of Cyclohexane-1,3-dione (327) (5.00 g, 44.6 mmol) and p-TSA (85 mg, 0.45 mmol) in toluene (90 ml). The reaction mixture was then refluxed under Dean-Stark conditions for 16 h. After this time, the reaction was quenched with saturated aqueous sodium bicarbonate solution (25 ml) and extracted with ethyl acetate (3 x 25 ml). The organic extracts were dried with anhydrous MgSO₄ and the excess solvent was removed by evaporation under reduced pressure to yield a yellow solid. The solid was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (1:1) as eluent affording 3-cyclohexanedione diethylene ketal (329) (7.02 g, 78%) as a white solid. Mp 38-41°C; \(\nu_{\text{max}}\) (DCM)/cm⁻¹ 1656 (C=O); \(\delta_H\) (400 MHz; CDCl₃) 1.61-1.77 (6H, m, CH₂CH₂CH₂C-ketal, CH₂CH₂CH₂C-ketal and CH₂CH₂CH₂C-ketal), 1.93 (2H, s, CH₂C-ketal), 3.93 (4H, s, OCH₂CH₂O), 3.97 (4H, s, OCH₂CH₂O); \(\delta_C\) (100 MHz; CDCl₃) 19.81 (CH₂CH₂C-ketal), 34.03 (2 x CH₂CH₂C-ketal), 43.68 (CH₂C-ketal), 64.40 (2 x OCH₂CH₂O), 109.05 (2 x C-ketal); MS (EI) m/z 200 [M⁺, 8.3%]; (Found: 200.1052, C₁₀H₁₆O₄ requires 200.1049).
Attempted preparation: Methyl-2-(7-oxo-1,4-dioxaspiro[4.5]dec-8-yl)ethanoate (333)

Method A

1,3-Cyclohexanedione monoethylene ketal (328) (210 mg, 1.23 mmol) was dissolved in dry THF (20 ml) and the solution was cooled to −78°C. KHMDS (2.72 ml of a 0.5 M solution in toluene, 1.36 mmol) was then added and the solution was stirred at −78°C for 1 h. Methyl bromoacetate (0.13 ml, 1.36 mmol) was then added carefully to the reaction mixture and the reaction was left to stir for an additional 1 h. The mixture was then allowed to warm to room temperature before being stirred for a further 20 h. After this time, the residue was quenched with 2M HCl and extracted with diethyl ether (3 x 25 ml). The organic extracts were dried with anhydrous Na2SO4 and the excess solvent was removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (3:2) as eluent affording a light yellow oil. δH (250 MHz; CDCl3): The 1H NMR spectrum of the crude product showed a mixture of unknown products and traces of starting material.

Method B

1,3-Cyclohexanedione monoethylene ketal (328) (0.51 g, 3.31 mmol) was dissolved in dry THF (20 ml) and the solution was cooled to −78°C. KHMDS (4.96 ml of a 0.5 M solution in toluene, 2.48 mmol) was added and the solution was stirred at −78°C for 1 h. Methyl bromoacetate (0.56 ml, 3.64 mmol) was then added carefully to the reaction mixture and the reaction was left to stir for an additional 1 h. The mixture was then allowed to warm to room temperature before being stirred for a further 20 h. After this
time, the residue was quenched with 2M HCl and extracted with diethyl ether (3 x 25 ml). The organic extracts were dried with anhydrous Na₂SO₄ and the excess solvent was removed by evaporation under reduced pressure affording a light yellow oil. δ_H (250 MHz; CDCl₃): The ¹H NMR spectrum of the crude product showed a mixture of unknown alkylated products and starting material.

Method C

1,3-Cyclohexanedione monoethylene ketal (328) (0.52 g, 3.33 mmol) was dissolved in dry THF (20 ml) and the solution was cooled to -78°C. KHMDS (6.00 ml of a 0.5 M solution in toluene, 3.00 mmol) was then added and the solution was stirred at -78°C for 1 h. Methyl bromoacetate (0.56 ml, 3.64 mmol) was then added carefully to the reaction mixture and the reaction was left to stir for an additional 1 h. The mixture was then allowed to warm to room temperature before being stirred for a further 20 h. After this time, the residue was quenched with 2M HCl and extracted with diethyl ether (3 x 25 ml). The organic extracts were dried with anhydrous Na₂SO₄ and the excess solvent was removed by evaporation under reduced pressure affording a light yellow oil. δ_H (250 MHz; CDCl₃): The ¹H NMR spectrum of the crude product showed a mixture of unknown alkylated products and starting material.
3-Methoxy-2-cyclohexen-1-one (336)$^{10}$

A mixture of Cyclohexane-1,3-dione (327) (2.00 g, 17.8 mmol), p-TSA (42 mg), methanol (10 ml) and trimethyl orthoformate (1.96 ml, 17.8 mmol) was heated at reflux in toluene (30 ml) for 80 min. The reaction mixture was allowed to cool before being washed with a 10% aqueous NaOH solution (2 x 20 ml) and brine (20 ml). The solution was then dried with anhydrous MgSO$_4$ and the excess solvent was removed by evaporation under reduced pressure affording 3-methoxy-2-cyclohexen-1-one (336) (1.94 g, 86%) as a yellow oil. No further purification was necessary. $\nu_{\text{max}}$ (DCM)/cm$^{-1}$ 2945 (OMe), 1665 (CO), 1603 (C=C); $\delta_{\text{H}}$ (400 MHz; CDCl$_3$) 1.96-2.03 (2H, m, CH$_2$CH$_2$CH$_2$), 2.33 (2H, t, J 5.1, CH=CCH$_2$), 2.41 (2H, t, J 6.4, COCH$_2$), 3.71 (3H, s, OCH$_3$), 5.37 (1H, s, CH=); $\delta_{\text{C}}$ (100 MHz; CDCl$_3$) 21.41 (CH$_2$), 28.83 (CH$_2$), 36.76 (CH$_2$), 55.64 (CH$_3$O), 102.61 (CH=), 178.76 (CH=C(OCH$_3$)), 199.64 (CO); MS (EI) m/z 126 [M$^+$, 68.7%]; (Found: M$^+$ 126.0682. C$_7$H$_{10}$O$_2$ requires 126.0681).
3-Chloro-2-cyclohexen-1-one (335)\textsuperscript{11}

To a suspension of Cyclohexane-1,3-dione (327) (2.00 g, 17.8 mmol) in chloroform (10 ml) was added slowly oxalyl chloride (3.77 ml, 35.7 mmol). The addition was accompanied by vigorous evolution of gas. After stirring at room temperature for 10 min, the slurry was then refluxed for 13 min to give a dark yellow solution. The excess solvent was then removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:4) as eluent affording 3-chloro-2-cyclohexen-1-one (335) (1.61 g, 68%) as a yellow oil. \( \nu_{\text{max}} \) (DCM)/cm\(^{-1}\) 1683 (CO), 1606 (C=C); \( \delta_h \) (400 MHz; CDCl\(_3\)) 2.07-2.13 (2H, m, CH\(_2\)CH\(_2\)CH\(_2\)CO), 2.38-2.42 (2H, m, CH\(_2\)CH\(_2\)CH\(_2\)CO), 2.68 (2H, dt, \( J \) 6.1, 1.5, CH\(_2\)CH\(_2\)CH\(_2\)CO), 6.21 (1H, t, \( J \) 1.6, COH=); \( \delta_c \) (100 MHz; CDCl\(_3\)) 22.37 (CH\(_2\)), 34.05 (CH\(_2\)), 36.51 (CH\(_2\)), 128.18 (CH=), 158.61(CH=C(Cl)), 196.78 (CO); MS (EI) m/z 130 [M\(^+\), 45.7%]; (Found: M\(^+\), 130.0184. C\(_6\)H\(_7\)ClO requires 130.0185).
Methyl 2-[4-(methoxy)-2-oxocyclohex-3-enyl]ethanoate (338)\textsuperscript{12}

\begin{center}
\includegraphics[width=0.5\textwidth]{structure}
\end{center}

Method A

3-Methoxy-2-cyclohexen-1-one (336) (0.85 g, 6.74 mmol) was dissolved in dry THF (20 ml) and the solution was cooled to \(-78^\circ\)C. KHMDS (14.82 ml of a 0.5 M solution in toluene, 7.41 mmol) was added and the solution was stirred at \(-78^\circ\)C for 1 h. Methyl bromoacetate (0.69 ml, 7.41 mmol) was then added carefully to the reaction mixture and the reaction was left to stir for an additional 1 h. The mixture was then allowed to warm to room temperature before being stirred for a further 20 h. After this time, the residue was quenched with 2M HCl and extracted with diethyl ether (3 x 25 ml). The organic extracts were dried with anhydrous Na\textsubscript{2}SO\textsubscript{4} and the excess solvent was removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (2:3) as eluent affording a light yellow oil. \(\delta\textsubscript{H} (250\text{ MHz}; \text{CDCl}_3)\): The \(^1\text{H}\) NMR spectrum of the crude product showed a mixture of starting material and a small trace of the desired product (338).

Method B

3-Methoxy-2-cyclohexen-1-one (336) (0.50 g, 3.96 mmol) was dissolved in dry THF (20 ml) and the solution was cooled to \(-78^\circ\)C. NaHMDS (0.79 ml, 4.36 mmol) was added and the solution was stirred at \(-78^\circ\)C for 1 h. Methyl bromoacetate (0.41 ml, 4.36 mmol) was added carefully to the reaction mixture and the reaction was left to stir for an additional 1 h. The mixture was then allowed to warm to room temperature before being stirred for a further 20 h. After this time, the residue was quenched with 2M HCl and extracted with diethyl ether (3 x 25 ml). The organic extracts were dried with anhydrous Na\textsubscript{2}SO\textsubscript{4} and the excess solvent was removed by evaporation under reduced pressure.
The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (1:4) as eluent affording a light yellow oil. δ_H (250 MHz; CDCl₃): The ¹H NMR spectrum of the crude product showed starting material with no trace of the desired product (338).

**Method C**

3-Methoxy-2-cyclohexen-1-one (336) (0.50 g, 3.96 mmol) was dissolved in dry THF (20 ml) and the solution was cooled to -78°C. LiHMDS (0.74 ml, 3.96 mmol) was added and the solution was stirred at -78°C for 1 h. Methyl bromoacetate (0.41 ml, 4.36 mmol) was added carefully to the reaction mixture and the reaction was left to stir for an additional 1 h. The mixture was then allowed to warm to room temperature before being stirred for a further 20 h. After this time, the residue was quenched with saturated aqueous ammonium chloride solution (40 ml) and extracted with diethyl ether (3 x 25 ml). The organic extracts were dried with anhydrous Na₂SO₄ and the excess solvent was removed by evaporation under reduced pressure affording a yellow oil. δ_H (250 MHz; CDCl₃): The ¹H NMR spectrum of the crude product showed starting material with no trace of the desired product (338).

**Method D**

To a stirred solution of diisopropylamine (2.59 ml, 18.31 mmol) in dry THF (10 ml), under a N₂ atmosphere, was added n-butyllithium (2.5 M solution in hexanes) (7.32 ml, 18.3 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min before being cooled to -78 °C. A solution of 3-Methoxy-2-cyclohexen-1-one (336) (2.10 g, 16.7 mmol) in dry THF (15 ml) was then added via cannula and the resulting mixture was stirred for an additional 1 h at -78 °C. Methyl bromoacetate (1.85 ml, 20.0 mmol) was then added dropwise via syringe and the reaction mixture was then allowed to warm slowly to room temperature over a period of 24 h. After this time, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (40 ml) and extracted in ethyl acetate (3 x 50 ml). The combined organic extracts were washed
with saturated aqueous ammonium chloride solution (100 ml), dried with anhydrous MgSO₄ and the excess solvent was then removed by evaporation under reduced pressure affording a yellow oil. δ_H (250 MHz; CDCl₃): The ¹H NMR spectrum of the crude product showed mainly starting material, however there was a small trace of the desired product (338).

Method E

To a stirred solution of diisopropylamine (5.03 ml, 35.7 mmol) in dry THF (10 ml), under a N₂ atmosphere, was added n-butyllithium (2.5 M solution in hexanes) (14.3 ml, 35.7 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min before being cooled to −78 °C. A solution of 3-Methoxy-2-cyclohexen-1-one (336) (3.00 g, 23.8 mmol) in dry THF (15 ml) was then added via cannula and the resulting mixture was stirred for an additional 1 h at −78 °C. Methyl bromoacetate (2.64 ml, 28.5 mmol) was then added dropwise via syringe and the reaction mixture was then allowed to warm slowly to room temperature over a period of 24 h. After this time, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (40 ml) and extracted in ethyl acetate (3 x 50 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride solution (100 ml), dried with anhydrous MgSO₄ and the excess solvent was then removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using 5% diethyl ether in light petroleum (bp 40-60°C) as eluent affording methyl 2-[4-(methoxy)-2-oxocyclohex-3-enyl]ethanoate (338) (1.41 g, 30%) as a yellow oil.

Method F

To a stirred solution of diisopropylamine (3.52 ml, 25.0 mmol) in dry THF (10 ml), under a N₂ atmosphere, was added n-butyllithium (2.5 M solution in hexanes) (3.52 ml, 25.0 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min before being cooled to −78 °C. A solution of 3-Methoxy-2-cyclohexen-1-one (336) (1.75 g, 13.9 mmol) in dry THF (15 ml) was then added via cannula and the resulting mixture
was stirred for an additional 1 h at -78 °C. Methyl bromoacetate (1.41 ml, 15.3 mmol) was then added dropwise via syringe and the reaction mixture was then allowed to warm slowly to room temperature over a period of 24 h. After this time, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (40 ml) and extracted in ethyl acetate (3 x 50 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride solution (100 ml), dried with anhydrous MgSO4 and the excess solvent was then removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using 5% diethyl ether in light petroleum (bp 40-60°C) as eluent affording 2-[4-(methoxy)-2-oxocyclohex-3-enyl] ethanoate (338) (1.59 g, 58%) as a yellow oil.

v max (DCM)/cm⁻¹ 2947 (OMe), 1734 (CO₂Me), 1653 (CO), 1609 (C=C); δH (400 MHz; CDCl₃) 1.75 (1H, m, CH₂CH(H)CHCO), 2.08-2.13 (1H, m, CH₂CH(H)CHCO), 2.28 (1H, dd, J 16.4, 7.7, CHCH(H)CO₂CH₃), 2.37 (1H, ddd, J 17.6, 5.0, 2.8, CH(H)CH₂CHCO), 2.54-2.63 (1H, m, CH(H)CH₂CHCO), 2.70-2.78 (1H, m, CHCH₂CO₂CH₃), 2.91 (1H, dd, J 16.4, 5.2, CHCH(H)CO₂CH₃), 3.69 (3H, s, CH₃O), 3.70 (3H, s, CH₃O), 3.70 (3H, s, CH₃O), 5.38 (1H, s, C(OCH₃)=CHCO); δC (100 MHz; CDCl₃) 27.14 (CH₂), 28.85 (CH₂), 34.48 (CH₂), 42.32 (CH₂CHCO), 51.70 (CH₃O), 55.79 (CH₃O), 101.68 (CH=), 173.20 (CO₂CH₃), 177.90 (CH=C(OCH₃)), 198.79 (CO); MS (EI) m/z 198 [M⁺, 10.3%]; (Found: M⁺, 198.0891. C₁₀H₁₄O₄ requires 198.0892).
Methyl 2-[4-(chloro)-2-oxocyclohex-3-enyl]ethanoate (340)

![Methyl 2-[4-(chloro)-2-oxocyclohex-3-enyl]ethanoate](image)

To a stirred solution of diisopropylamine (1.94 ml, 13.8 mmol) in dry THF (10 ml), under a N₂ atmosphere, was added n-butyllithium (2.5 M solution in hexanes) (5.54 ml, 13.8 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min before being cooled to −78 °C. A solution of 3-Chloro-2-cyclohexen-1-one (335) (1.00 g, 7.66 mmol) in dry THF (15 ml) was then added via cannula and the resulting mixture was stirred for an additional 1 h at −78 °C. Methyl bromoacetate (0.78 ml, 8.42 mmol) was then added dropwise via syringe and the reaction mixture was then allowed to warm slowly to room temperature over a period of 24 h. After this time, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (40 ml) and extracted in ethyl acetate (3 x 50 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride solution (100 ml), dried with anhydrous MgSO₄ and the excess solvent was then removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using 10% diethyl ether in light petroleum (bp 40-60°C) as eluent affording methyl 2-[4-(chloro)-2-oxocyclohex-3-enyl]ethanoate (340) (0.74 g, 48%) as a yellow oil. v_max (DCM)/cm⁻¹ 2950 (OMe), 1734 (CO₂Me), 1675 (CO), 1613 (C=C); δ_H (400 MHz; CDCl₃) 1.89 (1H, m, CH₂CH(H)CH₂CO), 2.15-2.21 (1H, m, CH₂CH(H)CH₂CO), 2.30 (1H, dd, J 16.4, 6.7, CHCH(H)CO₂CH₃), 2.64 (1H, ddd, J 18.7, 5.2, 2.6, CH(H)CH₂CHCO), 2.78-2.93 (3H, m, CH(H)CH₂CHCO, CH₂CO₂CH₃ and CHCH(H)CO₂CH₃), 3.70 (3H, s, CH₃O), 6.22 (1H, d, J 2.5, CH=), δ_C (100 MHz; CDCl₃) 27.65 (CH₂), 33.34 (CH₂), 33.58 (CH₂), 41.70 (CH₂CHCO), 51.42 (CH₃O), 127.26 (C=), 157.57 (C=), 172.10 (CO₂CH₃), 196.10 (CO); MS (EI) m/z 201 [(M − H)⁺, 8.3%]; (Found: M⁺ - H, 201.0323. C₉H₁₁ClO₃ requires 201.0319).

Experimental
Methyl 2-[4-(ethoxy)-2-oxocyclohex-3-enyl]ethanoate (341)

To a stirred solution of diisopropylamine (1.81 ml, 12.8 mmol) in dry THF (10 ml), under a N₂ atmosphere, was added n-butyllithium (2.5 M solution in hexanes) (5.14 ml, 12.8 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min before being cooled to -78 °C. A solution of 3-Ethoxy-2-cyclohexen-1-one (337) (1.00 g, 7.13 mmol) in dry THF (15 ml) was then added via cannula and the resulting mixture was stirred for an additional 1 h at -78 °C. Methyl bromoacetate (0.73 ml, 7.85 mmol) was then added dropwise via syringe and the reaction mixture was then allowed to warm slowly to room temperature over a period of 24 h. After this time, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (40 ml) and extracted in ethyl acetate (3 x 50 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride solution (100 ml), dried with anhydrous MgSO₄ and the excess solvent was then removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using 5% diethyl ether in light petroleum (bp 40-60°C) as eluent affording methyl 2-[4-(ethoxy)-2-oxocyclohex-3-enyl]ethanoate (341) (0.89 g, 59%) as a yellow oil. v max (DCM)/cm⁻¹ 2947 (OMe), 1736 (CO₂Me), 1659 (CO), 1613 (C=C); δ H (400 MHz; CDCl₃) 1.35 (3H, t, J 6.8, OCH₂CH₃), 1.74 (1H, m, CH₂CH(H)CHCO), 2.07-2.14 (1H, m, CH₂CH(H)CHCO), 2.27 (1H, dd, J 16.4, 7.6, CHCH(H)CO₂CH₃), 2.37 (1H, ddd, J 17.6, 5.2, 2.8, CH(CH₂)CHCH₂CO₂CH₃), 2.54-2.63 (1H, m, CH(CH₂)CHCH₂CHCO), 2.70-2.77 (1H, m, CHCH₂CO₂CH₃), 2.90 (1H, dd, J 16.4, 5.2, CHCH(H)CO₂CH₃), 3.70 (3H, s, CH₃O), 3.85-3.97 (2H, m, OCH₂CH₃), 5.35 (1H, d, J 1.2, C(OCH₂CH₃)=CHCO); δC (100 MHz; CDCl₃) 14.10 (CH₃), 27.31 (CH₂), 29.25 (CH₂), 34.67 (CH₂), 42.24 (CH₂CHCO), 51.65 (CH₂O), 64.34 (OCH₂CH₃), 101.63 (CH=), 173.20 (CO₂CH₃), 177.16 (CH=C(OCH₂CH₃)), 198.92 (CO); MS (EI) m/z 212 [M⁺, 27.2%]; (Found: M⁺, 212.1050. C₁₁H₁₆O₄ requires 212.1049).
Methyl 2-(2-oxocyclohex-3-enyl)ethanoate (339)

To a stirred solution of diisopropylamine (2.64 ml, 18.7 mmol) in dry THF (10 ml), under a N₂ atmosphere, was added n-butyllithium (2.5 M solution in hexanes) (2.64 ml, 18.7 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 15 min before being cooled to −78 °C. A solution of 2-Cyclohexen-1-one (334) (1.00 g, 10.4 mmol) in dry THF (15 ml) was then added via cannula and the resulting mixture was stirred for an additional 1 h at −78 °C. Methyl bromoacetate (1.06 ml, 11.4 mmol) was then added dropwise via syringe and the reaction mixture was then allowed to warm slowly to room temperature over a period of 24 h. After this time, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (40 ml) and extracted in ethyl acetate (3 x 50 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride solution (100 ml), dried with anhydrous MgSO₄ and the excess solvent was then removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using 5% diethyl ether in light petroleum (bp 40-60°C) as eluent affording methyl 2-(2-oxocyclohex-3-enyl)ethanoate (339) (0.91 g, 52%) as a yellow oil.  νmax (DCM)/cm⁻¹ 2950 (OMe), 1732 (CO₂Me), 1674 (CO), 1620 (C=O); δH (400 MHz; CDCl₃) 1.79-1.85 (1H, m, CH₂CH(H)CHCO), 2.11-2.15 (1H, m, CH₂CH(H)CHCO), 2.26-2.32 (1H, m, CH₂CH(H)CH₂), 2.37-2.49 (2H, m, CH₂CH₂CHCO), 2.83-2.93 (2H, m, CH₂CH₂CH₂CO₂CH₃ and CH₂CH(H)CH₂CO₂CH₃), 3.70 (3H, s, CH₃O), 6.00 (1H, ddd, J 10.1, 2.7, 1.1, CH₂CH=CHCO), 6.95-7.00 (1H, m, CH₂CH=CHCO); δC (100 MHz; CDCl₃) 25.94 (CH₂), 28.66 (CH₂), 34.28 (CH₂), 43.61 (CH₂CH₂CO₂CH₃), 21.70 (CH₃O), 129.15 (CH₂CH=CHCO), 150.12 (CH₂CH=CHCO), 172.95 (CO₂CH₃), 199.49 (CO); MS (EI) m/z 168 [M⁺, 5.3%]; (Found: M⁺, 168.0788. C₉H₁₂O₃ requires 168.0787).
Methyl 2-[4-(methoxy)-2-oxocyclohex-3-enyl]ethanoate (338) (0.73 g, 3.68 mmol) was dissolved in a mixture of THF (30 ml) and water (13 ml). Lithium hydroxide (0.17 g, 4.05 mmol) was added and the mixture was stirred at room temperature for 20 h. The mixture was then concentrated, re-suspended in water (30 ml) and acidified to pH 3 using 1M HCl. The aqueous layer was then extracted with ethyl acetate (3 x 20 ml), dried with anhydrous MgSO4 and the excess solvent was then removed by evaporation under reduced pressure affording 2-[4-(methoxy)-2-oxocyclohex-3-enyl]ethanoic acid (342) (0.54 g, 79%) as a yellow solid. Further purification was not necessary. Mp 132-135°C; ν max (DCM)/cm⁻¹ 2945 (OH), 1717 (CO2H), 1601 (CO); δH (400 MHz; CDCl3) 1.77 (1H, m, CH2CH(H)CHCO), 2.10-2.16 (1H, m, CH2CH(H)CHCO), 2.33 (1H, dd, J 16.1, 5.8, CHCH(H)CO2H), 2.40 (1H, ddd, J 17.8, 5.0, 2.7, CH(H)CH2CHCO), 2.55-2.64 (1H, m, CH(H)CH2CHCO), 2.69-2.77 (1H, m, CHCH2CO2H), 2.91 (1H, dd, J 16.1, 6.9, CHCH(H)CO2H), 3.73 (3H, s, CH3O), 5.43 (1H, d, J 1.4, C(OCH3)=CHCO); δC (100 MHz; CDCl3) 27.67 (CH2), 28.90 (CH2), 35.63 (CH2), 42.01 (CH2CHCO), 56.06 (CH3O), 101.55 (CH=), 175.61 (CH=C(OCH3)), 179.27 (CO2H), 200.44 (CO); MS (El) m/z 184 [M⁺, 16.7%]; (Found: M⁺, 184.0733. C9H12O4 requires 184.0736).
Methyl 2-[4-(ethoxy)-2-oxocyclohex-3-enyl]ethanoate (341) (1.53 g, 7.10 mmol) was dissolved in a mixture of THF (70 ml) and water (30 ml). Lithium hydroxide (0.30 g, 7.10 mmol) was added and the mixture was stirred at room temperature for 20 h. The mixture was then concentrated, re-suspended in water (50 ml) and acidified to pH 3 using 1M HCl. The aqueous layer was then extracted with ethyl acetate (3 x 20 ml), dried with anhydrous MgSO₄ and the excess solvent was then removed by evaporation under reduced pressure affording 2-[4-(ethoxy)-2-oxocyclohex-3-enyl]ethanoic acid (343) (1.24 g, 84%) as a yellow solid. Further purification was not necessary. Mp 138-139°C; δ max (DCM)/cm⁻¹ 2984 (OH), 1731 (CO₂H), 1596 (CO); δH (400 MHz; CDCl₃) 1.36 (3H, t, J 7.0, OCH₂CH₃), 1.76 (1H, m, CH₂CH(H)CHCO), 2.10-2.15 (1H, m, CH₂CH(H)CHCO), 2.32 (1H, dd, J 16.2, 6.3, CHCH(H)CO₂H), 2.39 (1H, ddd, J 17.7, 5.0, 2.7, CH(H)CH₂CHCO), 2.55-2.59 (1H, m, CH(H)CH₂CHCO), 2.71-2.75 (1H, m, CHCH₂CO₂H), 2.92 (1H, dd, J 16.2, 6.5, CHCH(H)CO₂H), 3.88-3.97 (2H, m, OCH₂CH₃), 5.41 (1H, d, J 1.6, C(OCH₂CH₃)=CHCO); δC (100 MHz; CDCl₃) 14.11 (CH₃), 27.50 (CH₂), 29.12 (CH₂), 35.47 (CH₂), 41.98 (CH₂CHCO), 64.72 (OCH₂CH₃), 101.87 (CH=), 176.79 (CH=C(OCH₂CH₃)), 178.38 (CO₂H), 200.31 (CO); MS (EI) m/z 198 [M⁺, 25.0%]; (Found: M⁺, 198.0891. C₁₀H₁₄O₄ requires 198.0892).
Methyl 2-[4-(chloro)-2-oxocyclohex-3-enyl]ethanoate (340) (0.43 g, 2.12 mmol) was dissolved in a mixture of THF (30 ml) and water (13 ml). Lithium hydroxide (0.10 g, 2.33 mmol) was added and the mixture was stirred at room temperature for 20 h. The mixture was then concentrated, re-suspended in water (50 ml) and acidified to pH 3 using 1M HCl. The aqueous layer was then extracted with ethyl acetate (3 x 20 ml), dried with anhydrous MgSO4 and the excess solvent was then removed by evaporation under reduced pressure affording 2-[4-(chloro)-2-oxocyclohex-3-enyl]ethanoic acid (344) (0.32 g, 81%) as a yellow oil. Further purification was not necessary. ν\text{max} (DCM)/cm⁻¹ 3065 (OH), 1708 (CO₂H), 1674 (CO), 1620 (C=O); δ\text{H} (400 MHz; CDCl₃) 1.89 (1H, m, CH₂CH(H)CHCO), 2.18-2.23 (1H, m, CH₂CH(H)CHCO), 2.34 (1H, dd, J 16.8, 7.0, CHCH(H)CO₂H), 2.64-2.71 (1H, ddd, J 21.3, 5.1, 2.4, CH(H)CH₂CHCO), 2.77-2.92 (2H, m, CH(H)CH₂CHCO and CHCH₂CO₂H), 2.89 (1H, dd, J 16.8, 5.5, CHCH(H)CO₂H), 6.25 (1H, d, J 2.5, C(Cl)=CHCO); δ\text{C} (100 MHz; CDCl₃) 28.44 (CH₂), 34.30 (CH₂), 34.44 (CH₂), 42.40 (CH), 128.05 (CH=), 158.75 (CH=C(Cl)), 178.12 (CO₂H), 197.06 (CO); MS (El) m/z 188 [M⁺, 0.7%]; (Found: M⁺, 188.0233. C₈H₉ClO₃ requires 188.0240).
Attempted preparation: 2-(2-Oxocyclohex-3-enyl)ethanoic acid (345)

Methyl 2-[2-oxocyclohex-3-enyl]ethanoate (339) (0.43 g, 2.12 mmol) was dissolved in a mixture of THF (30 ml) and water (13 ml). Lithium hydroxide (0.10 g, 2.33 mmol) was added and the mixture was stirred at room temperature for 20 h. The mixture was then concentrated, re-suspended in water (50 ml) and acidified to pH 3 using 1M HCl. The aqueous layer was then extracted with ethyl acetate (3 x 20 ml), dried with anhydrous MgSO₄ and the excess solvent was then removed by evaporation under reduced pressure affording a yellow oil. δ_H (400 MHz; CDCl₃): The ¹H NMR spectrum of the crude product showed possible traces of the desired product (345) and starting material. Attempts at purification resulted in decomposition.
3.5 Towards the amino alcohol precursor of (-)-erythraline

Methyl (S)-2-amino-3-(3,4-dihydroxyphenyl)propanoate hydrochloride¹³,¹⁴

![Chemical structure of methyl (S)-2-amino-3-(3,4-dihydroxyphenyl)propanoate hydrochloride]

L-DOPA (369) (2.00 g, 10.4 mmol) was dissolved in methanol (40 ml) and cooled in an ice bath (0 °C). Thionyl chloride (1.11 ml, 15.2 mmol) was added dropwise to the solution with gentle stirring. The solution was then dried with anhydrous Na₂SO₄ and filtered. The filtrate was evaporated to dryness under reduced pressure affording methyl (S)-2-amino-3-(3,4-dihydroxyphenyl)propanoate hydrochloride (2.51 g, 100%) as a colourless solid. No further purification was necessary. (DCM)/cm⁻¹ 3355 (OH), 2978 (OMe), 1690 (CO); δH (400 MHz; MeOD) 2.87-3.03 (2H, m, CH₂CHCO₂CH₃), 3.65 (3H, s, CH₃O), 3.93-3.97 (1H, m, CH₂CHCO₂CH₃), 4.04-4.07 (2H, m, NH₂CHCO₂CH₃), 6.42-6.69 (3H, m, ArH); δC (100 MHz; MeOD) 35.25 (CH₂), 52.73 (OCH₃), 53.64 (CH), 115.97 (ArCH), 117.17 (ArCH), 120.49 (ArCH), 125.46 (ArC), 144.72 (ArC-OH), 145.33 (ArC-OH), 170.47 (CO₂CH₃).
Methyl (2S)-2-amino-3-[3,4-bis(tert-butyldimethylsilyloxy)phenyl]propanoate
(370)$^{13,14}$

Imidazole (4.12 g, 60.5 mmol) was added to a cold solution (0 °C) of L-DOPA methyl ester hydrochloride (1.00 g, 4.04 mmol) and TBDMSI (2.13 g, 14.1 mmol) in anhydrous DMF (10 ml). After stirring at this temperature for 3.5 h and with the addition of saturated NaHCO$_3$ solution, the mixture was extracted with DCM (3 x 50 ml). The organic layers were then washed with water, dried over anhydrous Na$_2$SO$_4$ and the excess solvent was removed by evaporation under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexanes (1:4) affording methyl (2S)-2-amino-3-[3,4-bis(tert-butyldimethylsilyloxy)phenyl]propanoate (370) as a yellow oil. (1.07 g, 60%) $[\alpha]_D^\circ = +2.1$ (c = 1.06, CHCl$_3$); $\nu_{\text{max}}$(DCM)/cm$^{-1}$ 3380 (NH$_2$), 2856 (OMe), 1741 (CO); $\delta$$_H$(400 MHz; CDCl$_3$) 0.21 (12H, s, 2 x OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 0.98 (18H, s, 2 x OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 2.74 (1H, dd, J 13.6, 7.6, $CH$(H)Ar), 2.96 (1H, dd, J 8.8, 5.6, $CH$(H)Ar), 3.66 (1H, t, J 5.2, $NH$_2$CH$_2$Ar ) 3.70 (3H, s, CH$_3$O), 6.56-6.76 (3H, m, ArH); $\delta$$_C$(100 MHz; CDCl$_3$) -4.09 (4 x CH$_3$), 18.41 (2 x C(CH$_3$)$_3$), 25.91 (6 x CH$_3$), 40.33 (CH$_2$), 51.94 (OCH$_3$), 55.82 (CH), 121.01 (ArCH), 122.21 (ArCH), 122.67 (ArCH), 130.02 (ArC), 145.79 (ArC), 146.71 (ArC), 175.41 (CO$_2$CH$_3$); MS (El) m/z 439 [M$^+$, 4.7%]; (Found: M$^+$, 439.2580. C$_{22}$H$_{41}$NO$_3$Si$_2$ requires 439.2574).
Methyl (2S)-3-(3,4-di[(1-(1,1-dimethylethyl)-1,1-dimethylsilyl)oxy]phenyl)-2-((1,1-dimethylethyl)oxy)carbonyl)amino)propanoate (377)

To a stirring solution of methyl (2S)-2-Amino-3-[3,4-bis(tert-butyldimethylsilyloxy)phenyl]propanoate (370) (0.70 g, 1.59 mmol) and di-tert-butyl dicarbonate (0.38 g, 1.75 mmol) in DCM (40 ml) was added triethylamine (0.22 ml, 1.59 mmol) at room temperature. The reaction mixture was then allowed to stir at this temperature for a further 24 h. After this time, the reaction mixture was diluted with diethyl ether (50 ml), washed with 10% hydrochloric acid and extracted with saturated aqueous NaHCO₃ solution. The organic extracts were then dried with anhydrous MgSO₄ and the solvent was removed by evaporation under reduced pressure. The residue was then purified by flash column chromatography on silica gel using a mixture of ethyl acetate and hexane (1:4) to afford methyl (2S)-3-(3,4-di[(1-(1,1-dimethylethyl)-1,1-dimethylsilyl)oxy]phenyl)-2-((1,1-dimethylethyl)oxy)carbonyl)amino)propanoate (377) (0.58 g, 67%) as a yellow oil. [α]D = +8.6 (c = 1.12, DCM); Lit: [α]D = +5.0 (c = 1.0, DCM); ν max (DCM)/cm⁻¹ 3441 (NCO), 2857 (OMe), 1748 (CO); δH (400 MHz; CDCl₃) 0.17-0.20 (12H, m, 2 x OSi(CH₃)₂C(CH₃)₃), 0.97 (9H, s, OSi(CH₃)₂C(CH₃)₃), 0.99 (9H, s, OSi(CH₃)₂C(CH₃)₃), 1.43 (9H, s, NHCO₂C(CH₃)₃), 2.94 (2H, d, J 5.7, CH₂Ar), 3.69 (3H, s, CH₃O), 4.50-4.55 (1H, m, NHCHCO₂CH₃), 4.94 (1H, d, J 7.9, -NHCHCO₂CH₃), 6.53 (1H, dd, J 8.1, 2.1, ArH), 6.61 (1H, d, J 2.2, ArH), 6.72 (1H, d, J 8.1, ArH); δC (100 MHz; CDCl₃) -3.99 (4 x CH₃), 18.44 (2 x C), 25.94 (2 x C(CH₃)₃), 28.32 (3 x CH₃), 37.53 (CH₂), 52.12 (OCH₃), 54.37 (CH), 85.16 (C), 121.05 (ArCH), 122.20 (2 x ArCH), 128.90 (ArC), 145.97 (ArC-O), 146.76 (ArC-O), 155.07 (NHCO₂(CH₃)₃), 172.37 (CO₂CH₃); MS (El) m/z 539 [M⁺, 11.0%]; (Found: M⁺, 539.3102 C₂₇H₄₆NO₆Si₂ requires 539.3198).
Methyl (2S)-3-(1,3-benzodioxol-5-yl)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)propanoate (378)

Bromochloromethane (1.97 ml, 29.3 mmol) was added to a stirring solution of cesium fluoride (7.13 g, 47.0 mmol) and Methyl (2S)-3-(3,4-di{[1-(1,1-dimethylethyl)-1,1-dimethylsilyl]oxy}phenyl)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)propanoate (377) (6.33 g, 11.7 mmol) in anhydrous DMF (30 ml) under an nitrogen atmosphere. The mixture was heated at 110°C for 2.5 h. Upon cooling, the mixture was diluted with DCM and filtered. The filtrate, along with the DCM washings of the residue was washed with H₂O (6 x 50 ml), dried with anhydrous MgSO₄ and the solvent was removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:5) to afford methyl (2S)-3-(1,3-benzodioxol-5-yl)-2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)propanoate (378) (3.46 g, 91%) as a yellow oil. [α]D⁰ = +26.2 (c = 1.14, CHCl₃); νmax (DCM)/cm⁻¹ 3383 (NCO), 2930 (OMe), 1743 (CO), 1714 (CO); δH (400 MHz; CDCl₃) 1.43 (9H, s, NHC02C(CH₃)₃), 2.95-3.06 (2H, m, CH₂Ar), 3.73 (3H, s, CH₃O), 4.51-4.55 (1H, m, -NHC02CH₂CH₃), 4.98 (1H, d, J 7.6, -NHCHCO₂CH₃), 5.93 (2H, q, J 2.8, -OCH₂O-), 6.55-5.61 (2H, m, ArH), 6.72 (1H, d, J 8.0, ArH); δC (100 MHz; CDCl₃) 28.30 (3 x CF3), 38.00 (CH₂), 52.26 (OCH₃), 54.51 (CH), 79.97 (C), 100.96 (CH₂), 108.32 (ArCH), 109.60 (ArCH), 122.39 (ArCH), 129.58 (ArC), 146.62 (ArC-O), 147.71 (ArC-O), 155.08 (NHCO₂(CH₃)₃), 172.28 (CO₂CH₃); MS (El) m/z 323 [M⁺, 3.7%]; (Found: M⁺ 323.1365 C₁₆H₂₁N0₆ requires 323.1369).
Methyl (2S)-2-amino-3-(1,3-benzodioxol-5-yl)propanoate (379)

To a stirring solution of methyl (2S)-3-(1,3-Benzodioxol-5-yl)-2-(((1,1-dimethylethyl)oxy)carbonyl)amino)propanoate (378) (3.46 g, 10.7 mmol) in DCM (30 ml) was added TFA (16.5 ml, 0.21 mol). The reaction mixture was stirred at room temperature for a further 3 h. After this time, saturated NaHCO₃ was added until the effervescence subsided. The two layers were separated and the aqueous layer was extracted with DCM (3 x 25 ml). The combined organic layers were dried with anhydrous MgSO₄ and the solvent was removed by evaporation under reduced pressure affording methyl (2S)-2-amino-3-(1,3-benzodioxol-5-yl)propanoate (379) (1.65 g, 69%) as a yellow oil. [α]D = +25.4 (c = 1.12, CHCl₃); νₘₐₓ (DCM)/cm⁻¹ 3383 (NH₂), 2950 (OMe), 1737 (CO); δH (400 MHz; CDCl₃) 2.76 (1H, dd, J 13.6, 7.6, CH(H)Ar), 2.98 (1H, dd, J 13.6, 4.8, CH(H)Ar), 3.67 (1H, m, NH₂CHCO₂CH₃), 3.73 (3H, s, CH₃O), 5.94 (2H, s, -OCH₂O-), 6.63-6.76 (3H, m, ArH); δC (100 MHz; CDCl₃) 40.70 (CH₂), 52.03 (OCH₃), 55.90 (CH), 100.94 (CH₂), 108.32 (ArCH), 109.50 (ArCH), 122.33 (ArCH), 130.79 (ArC), 146.47 (ArC-O), 147.75 (ArC-O), 175.43 (CO₂CH₃); MS (FAB) m/z 224 [(M + 1)⁺, 4.2%]; (Found: M⁺+1, 224.0925. C₁₁H₁₃NO₄ requires 224.0923).
Attempted preparation: (S)-2-Amino-3-(1,3-benzodioxol-6-yl)propan-1-ol (368)$^{15}$

To a stirring solution of Methyl (2S)-2-amino-3-(1,3-benzodioxol-5-yl)propanoate (379) (1.64 g, 7.35 mmol) in absolute ethanol (40 ml) at 0°C was added sodium borohydride (2.78 g, 73.5 mmol) portion wise over a period of 2 min. The solution was allowed to warm to room temperature overnight, before being re-cooled back down to 0°C. The reaction mixture was then quenched with successive additions of conc. HCl (2 ml) and water (15 ml). The excess ethanol was then removed by evaporation under reduced pressure and the resulting residue was taken up in ethyl acetate (40 ml), extracted with brine (40 ml) and dried with anhydrous MgSO$_4$. The solvent was then removed by evaporation under reduced pressure affording (S)-2-amino-3-(1,3-benzodioxol-6-yl)propan-1-ol (368) (1.16 g, 81%) as a yellow oil. Lit: Mp 87-97°C;$^{15}$ $\delta_H$ (250 MHz; CDCl$_3$): The $^1$H NMR spectrum of the crude product showed that the β-amino alcohol had been synthesised, unfortunately a number of impurities were also present. Attempts at purification were unsuccessful.
3.6 Towards the amino alcohol precursor of (-)-erysotrine

(S)-2-[(1,1-Dimethylethoxyxycarbonyl)amino]-3-(3,4-dimethoxyphenyl)propanoic acid (413)

3-(3,4-Dimethoxyphenyl)-L-alanine (263) (0.50 g, 2.22 mmol) was dissolved in H2O (20 ml) and triethylamine (0.37 ml, 2.66 mmol) was added at 0°C. To this solution was added di-tert-butyl dicarbonate (0.51 g, 2.33 mmol) as a solution in 1,4-dioxane (20 ml). The solution was then allowed to stir overnight whilst attaining ambient temperature. After this time, the excess 1,4-dioxane was removed by evaporation under reduced pressure yielding an aqueous residue. This aqueous residue was then acidified with 1M HCl to ca. pH 2-3, extracted with ethyl acetate (3 x 50 ml), washed with saturated NaHCO3 solution (1 x 50 ml) and brine (1 x 50 ml). The organic fractions were then dried with anhydrous Na2SO4 and the solvent was removed by evaporation under reduced pressure. The residue was then purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (2:1) as the eluent affording (S)-2-[(1,1-dimethylethoxyxycarbonyl)amino]-3-(3,4-dimethoxyphenyl) propanoic acid (413) (0.58 g, 80%) as an colourless solid. Mp 265-267°C; [α]D = -28.2 (c = 1.25, CHCl3); (Found: C, 58.96; H, 7.37; N, 4.78. C16H23NO6 requires C, 59.06; H, 7.13; N, 4.31 %); ν max (DCM)/cm⁻¹ 3332 (OH), 2836 (OMe), 1715 (CO), 1516 (C-O);

1H (400 MHz; CDCl3) 1.31 (3H, s, NHCO2C(CH3)2), 1.42 (6H, s, NHCO2C(CH3)3), 2.99 (2H, br dd, J 14.1, 5.6, ArCH2CHCO2H), 3.85 (3H, s, CH3O), 3.86 (3H, s, CH3O), 4.56 (1H, m, ArCH2CHCO2H), 4.95 (1H, d, J 8.0, NHCO2C(CH3)3), 6.71-6.73 (2H, m, ArH), 6.79-6.81 (1H, m, ArH); δC (100 MHz; CDCl3) 28.00 (CH3), 28.29 (2 x CH3), 37.33 (CH2), 54.36 (CH), 55.78 (OCH3), 55.85 (OCH3), 80.33 (C(CH3)3), 111.20 (ArCH), 112.35 (ArCH), 121.43 (ArCH), 128.16 (ArC), 148.09 (ArC-OCH3), 148.85 (ArC-OCH3), 155.38 (NCO), 176.57 (CO2H); MS (EI) m/z 325 [M⁺, 3.4%]; (Found: M⁺, 325.1529. C16H23NO6 requires 325.1525).
3-(3,4-Dimethoxyphenyl)-L-alanine (263) (2.00 g, 8.88 mmol) was dissolved in methanol (10 ml) and cooled in an ice bath (0°C). Thionyl chloride (0.97 ml, 13.3 mmol) was added dropwise to the solution with gentle stirring. The solution was then dried with anhydrous Na$_2$SO$_4$ and filtered. The filtrate was evaporated to dryness under reduced pressure affording (S)-methyl-2-amino-3-(3,4-dimethoxyphenyl)propanoate hydrochloride (2.40 g, 98%) as a colourless gum. No further purification was necessary. 

(DCM)/cm$^{-1}$ 2938 (OMe), 1714 (CO), 1516 (NH$_2$); $\delta$$_H$ (400 MHz; MeOD) 3.09-3.25 (2H, m, CH$_2$CHCO$_2$CH$_3$), 3.35 (3H, s, CH$_3$O), 3.82 (3H, s, CH$_3$O), 3.84 (3H, s, CH$_3$O), 4.23-4.27 (1H, m, CH$_2$CHCO$_2$CH$_3$), 4.31-4.34 (2H, m, NH$_2$CHCO$_2$CH$_3$), 6.79-6.88 (3H, m, ArH); $\delta$$_C$ (100 MHz; MeOD) 36.87 (CH$_2$), 53.65 (CH), 55.19 (OCH$_3$), 56.45 (OCH$_3$), 56.48 (OCH$_3$), 113.32 (ArCH), 114.04 (ArCH), 123.09 (ArCH), 127.98 (ArC), 150.19 (ArC-OCH$_3$), 150.80 (ArC-OCH$_3$), 171.31 (CO$_2$CH$_3$); MS (EI) m/z 239 [M$^+$, 2.3%]; (Found: M$^+$, 239.1156. C$_{12}$H$_{17}$NO$_4$ requires 239.1158).
**tert-Butyl (S)-1-(methoxycarbonyl)-2-(3,4-dimethoxyphenyl)ethylcarbamate (416)**

(S)-Methyl 2-amino-3-(3,4-dimethoxyphenyl)propanoate hydrochloride (2.45 g, 10.2 mmol) was dissolved in H₂O (40 ml) and triethylamine (1.71 ml, 12.3 mmol) was added at 0°C. To this solution was added di-tert-butyl dicarbonate (2.35 g, 10.8 mmol) as a solution in 1,4-dioxane (40 ml). The solution was then allowed to stir overnight whilst attaining ambient temperature. After this time, the excess 1,4-dioxane was removed by evaporation under reduced pressure yielding an aqueous residue. This aqueous residue was then acidified with 1M HCl to ca. pH 2-3, extracted with ethyl acetate (3 x 50 ml), washed with saturated NaHCO₃ solution (1 x 50 ml) and brine (1 x 50 ml). The organic fractions were then dried with anhydrous Na₂SO₄ and the solvent was removed by evaporation under reduced pressure yielding a colourless solid. The solid was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:4) as the eluent affording tert-butyl (S)-1-(methoxycarbonyl)-2-(3,4-dimethoxyphenyl)ethylcarbamate (416) (1.93 g, 58%) as a clear oil. [α]D = -65.6 (c = 1.28, CHCl₃); νmax (DCM)/cm⁻¹ 3362 (NH), 2834 (OMe), 1743 (CO₂Bu), 1700 (CO₂Me); δH (400 MHz; CDCl₃) 1.43 (9H, s, NHC02C(CH₃)₃), 2.98-3.09 (2H, m, ArCH₂CHC0₂CH₃), 3.72 (3H, s, CH₃O), 3.85 (3H, s, CH₃O), 4.54 (1H, m, ArCH₂CHC0₂CH₃), 4.99 (1H, d, J = 7.9, NHC02C(CH₃)₃), 6.64-6.80 (3H, m, ArH); δC (100 MHz; CDCl₃) 28.31 (3 x CH₃), 37.87 (CH₂), 52.23 (OCH₃), 54.49 (CH), 55.78 (OCH₃), 55.84 (OCH₃), 79.95 (C(CH₃)₃), 111.16 (ArCH), 112.31 (ArCH), 121.35 (ArCH), 128.39 (ArC), 148.05 (ArC-OCH₃), 148.81 (ArC-OCH₃), 155.09 (NCO), 172.45 (CO₂CH₃); MS (FAB) m/z 339 [M⁺, 47.1%]; (Found: M⁺, 339.1686. C₁₇H₂₅NO₆ requires 339.1682).
Method A

Chlorotrimethylsilane (1.98 ml, 4.50 mmol) was added under nitrogen atmosphere to a stirring solution of lithium borohydride (5.10 ml of a 2M solution in THF, 2.25 mmol) in THF (15 ml) over a period of 2 min. (S)-2-[(1,1-Dimethylethoxy carbonyl)amino]-3-(3,4-dimethoxyphenyl)propanoic acid (413) (0.35 g, 1.12 mmol) was added portionwise over a period of 5 min and the reaction mixture was allowed to stir at room temperature for a further 24 h. After this time, methanol (30 ml) was added slowly to the reaction mixture and the excess solvent was removed by evaporation under reduced pressure. The residue was then dissolved in 10% potassium hydroxide solution (40 ml); extracted with DCM (3 x 30 ml) and dried with anhydrous MgSO$_4$. The excess solvent was then removed by evaporation under reduced pressure to yield a clear oil. $\delta_H$ (250 MHz; CDCl$_3$): The $^1$H NMR spectrum of the crude product indicated that we had not generated the desired product (414), but had instead synthesised the corresponding oxazolidinone (415).

Method B

To a stirring solution of tert-Butyl (S)-1-(methoxycarbonyl)-2-(3,4-dimethoxyphenyl) ethyl carbamate (416) (2.27 g, 7.00 mmol) in absolute ethanol (50 ml) at 0°C was added sodium borohydride (2.65 ml, 70.0 mmol) portion wise over a period of 2 min. The solution was allowed to warm to room temperature overnight, before being re-cooled back down to 0°C. The reaction mixture was then quenched with successive additions of conc. HCl (2 ml) and water (15 ml). The excess ethanol was then removed by
evaporation under reduced pressure and the resulting residue was taken up in ethyl acetate (40 ml), extracted with brine (40 ml) and dried with anhydrous MgSO₄. The excess solvent was then removed by evaporation under reduced pressure yielding an off white solid. The solid was purified by flash column chromatography on silica gel using 100% ethyl acetate as the eluent affording (S)-2-[(1,1-dimethylethyl)oxycarbonyl] amino]-3-(3,4-dimethoxyphenyl)propan-1-ol (414) (1.77 g, 81%) as a colourless solid.

Mp 92-93°C; [α]D = -16.9 (c = 1.28, MeOH); (Found: C, 61.51; H, 8.07; N, 4.46. C₁₆H₂₅NO₅ requires C, 61.72; H, 8.09; N, 4.50 %); ν max (DCM)/cm⁻¹ 3355 (OH), 2932 (OMe), 1700 (CO), 1521 (C-O); δH (400 MHz; CDCl₃) 1.42 (9H, s, NHCO₂C(CH₃)₃), 2.78 (2H, d, J 7.6, ArCH₂CHCH₂OH), 3.54 (1H, dd, J 11.2, 5.6, ArCH₂CHCH(H)OH), 3.65 (1H, dd, J 11.2, 3.6, ArCH₂CHCH(H)OH), 3.81-3.88 (1H, m, ArCH₂CHCH₂OH), 3.85 (3H, s, CH₃O), 3.87 (3H, s, CH₃O), 4.74-4.75 (1H, m, NHCO₂C(CH₃)₃), 6.74-6.82 (3H, m, ArH); δC (100 MHz; CDCl₃) 28.36 (3 x CH₃), 36.98 (CH₂), 53.71 (CH), 55.85 (OCH₃), 55.90 (OCH₃), 64.45 (CH₂), 79.75 (C(CH₃)₃), 111.22 (ArCH), 112.23 (ArCH), 121.26 (ArCH), 130.23 (ArC), 147.71 (ArC-CH), 148.93 (ArC-CH₃), 156.19 (NCO); MS (EI) m/z 311 [M⁺, 4.7%]; (Found: M⁺, 311.1736. C₁₆H₂₅NO₅ requires 311.1733).
Imidazole (0.82 g, 12.0 mmol) was added to a cold solution (0°C) of (S)-2-[(1,1-Dimethylethyl)oxy]carbonyl]amino]-3-(3,4-dimethoxyphenyl)propan-1-ol (414) (0.50 g, 1.61 mmol) and TBDMSI (0.48 g, 3.21 mmol) in dry DCM (20 ml). After stirring at this temperature for 16 h, the reaction was quenched with the addition of saturated NaHCO₃ solution and extracted with DCM (3 x 50 ml). The organic layers were then washed with water, dried over anhydrous Na₂SO₄ and the excess solvent was removed by evaporation under reduced pressure. The residue was then purified by flash column chromatography on silica gel using 100% ethyl acetate as the eluent affording (2S)-1-[(1,1-Dimethylethyl)-1,1-dimethylsilyl]oxy)-2-[(1,1-dimethylethyl)oxy)carbonyl]amino]-3-(3,4-dimethoxyphenyl)propanoate (417) (0.51 g, 75%) as a clear oil. [α]D = -24.3 (c = 1.35, CHCl₃); νmax (DCM)/cm⁻¹ 3367 (NH), 2952 (ArH), 2855 (OMe), 1712 (CO), 1515 (C-O); δH (400 MHz; CDCl₃) 0.10 (6H, s, OSi(CH₃)₂C(CH₃)₃), 0.92 (6H, s, OSi(CH₃)₂C(CH₃)₃), 1.43 (9H, s, NHCO₂C(CH₃)₃), 2.76-2.78 (2H, m, ArCH₂CHCH₂), 3.50-3.52 (2H, m, ArCH₂CHCH₂), 3.86 (3H, s, CH₃O), 3.87 (3H, s, CH₃O), 4.74-4.75 (1H, m, ArCH₂CHCH₂), 6.76-6.80 (3H, m, ArH); δC (100 MHz; CDCl₃) -3.58 (2 x CH₃), 18.28 (C(CH₃)₂), 25.90 (3 x CH₃), 28.41 (3 x CH₃), 36.78 (CH₂), 52.93 (CH), 55.77 (OCH₃), 55.87 (OCH₃), 62.71 (CH₂), 79.19 (C(CH₃)₃), 111.05 (ArCH), 112.40 (ArCH), 121.44 (ArCH), 130.86 (ArC), 147.45 (ArC-OCH₃), 148.73 (ArC-OCH₃), 156.41 (NCO); MS (El) m/z 425 [M⁺, 5.6%]; (Found: M⁺, 425.2594. C₂₂H₃₉NO₅Si requires 425.2598).
(2S)-1-[(1,1-Dimethylethyl)-1,1-dimethylsilyloxy]-2-amino-3-(3,4-dimethoxyphenyl)propanoate (412)

![Chemical structure](image)

To a stirring solution of (2S)-1-[(1,1-Dimethylethyl)-1,1-dimethylsilyloxy]-2-[(1,1-dimethylethyl)oxy]carbonylamino]-3-(3,4-dimethoxyphenyl)propanoate (417) (0.50 g, 1.17 mmol) in dry DCM (25 ml) was added trifluoroacetic acid (2.68 ml, 23.5 mmol). The mixture was stirred at room temperature for 80 min and after this time saturated NaHCO₃ solution was added until the effervescence had subsided. The layers were separated and the aqueous layer was extracted with DCM (3 x 25 ml). The combined organic layers were dried with anhydrous MgSO₄ and the excess solvent was removed by evaporation under reduced pressure affording a yellow oil. $\delta^1H$ (250 MHz; CDCl₃): The $^1H$ NMR spectrum of the crude product showed that the desired product (412) has not been generated, but instead we had synthesised again the corresponding oxazolidinone (415).
Imidazole (0.82 g, 12.04 mmol) was added to a cold solution (0°C) of (S)-2-[(1,1-Dimethyl[ethyl]oxy)carbonyl]amino]-3-(3,4-dimethoxyphenyl)propan-1-ol (414) (0.50 g, 1.61 mmol) and TBDPSCI (0.84 ml, 3.21 mmol) in dry DCM (20ml). After stirring at this temperature for 3.5 h, and with the addition of saturated NaHCO₃ solution, the mixture was extracted with DCM (3 x 50ml). The organic layers were then washed with water, dried over anhydrous Na₂SO₄ and the excess solvent was removed by evaporation under reduced pressure. The residue was then purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (3:2) as the eluent affording (2S)-1-[(1,1-dimethyl[ethyl]-oxy)-2-[ (1,1-dimethyl[ethyl]oxy)carbonyl]amino]-3-(3,4-dimethoxyphenyl)propanoate (418) (0.52 g, 60%) as a clear oil. [α]D = - 22.9 (c = 1.24, CHCl₃); ν max (DCM)/cm⁻¹: 3365 (NH), 2930 (ArH), 2856 (OMe), 1718 (CO), 1517 (C-O); OH (400 MHz; CDCl₃) 1.11 (9H, s, OSi(C₆H₅)₂C(CH₃)₃), 1.43 (9H, s, NHCO₂C(CH₃)₃), 2.86 (2H, d, J 7.0, ArCH₂CHCH₂), 3.57-3.63 (2H, m, ArCH₂CHCH₂), 3.79 (3H, s, CH₃O), 3.83 (3H, s, CH₃O), 3.92-3.96 (1H, m, ArCH₂CHCH₂), 4.78 (1H, d, J 8.8, NHCO₂C(CH₃)₃), 6.70-6.75 (3H, m, ArH), 7.34-7.43 (6H, m, OSi(C₆H₅)₂C(CH₃)₃), 7.63-7.66 (4H, m, OSi(C₆H₅)₂C(CH₃)₃); δC (100 MHz; CDCl₃) 19.42 (C(CH₃)₃), 26.66 (3 x CH₃), 28.48 (3 x CH₃), 37.16 (CH₂), 53.04 (CH), 55.77 (OCH₃), 55.91 (OCH₃), 64.09 (CH₂), 79.13 (OC(CH₃)₃), 111.22 (ArCH), 112.49 (ArCH), 121.50 (ArCH), 127.80 (PhCH), 129.85 (PhCH), 130.74 (ArC), 133.30 (PhC), 135.59 (PhCH), 147.57 (ArC-OCH₃), 148.85 (ArC-OCH₃), 155.37 (NCO); MS (FAB) m/z 549 [M⁺, 1.3%]; (Found: M⁺, 549.2920. C₃₂H₄₅NO₅Si requires 549.2911).
(2S)-1-[(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy)-2-amino-3-(3,4-dimethoxyphenyl)propanoate (419)\textsuperscript{16}

To a stirring solution of (2S)-1-[(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy)-2-[(1,1-dimethylethyl)oxy]carbonyl]amino]-3-(3,4-dimethoxyphenyl)propanoate (418) (0.20 g, 0.36 mmol) in dry DCM (10 ml) was added trifluoroacetic acid (0.56 ml, 7.28 mmol) and the reaction mixture was stirred at room temperature for 3 h. After this time, saturated NaHCO\textsubscript{3} solution was added until the effervescence had subsided. The mixture was then extracted with DCM (3 x 25 ml), dried with anhydrous MgSO\textsubscript{4} and the excess solvent was removed by evaporation under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:4) as the eluent affording (2S)-1-[(1,1-dimethylethyl)-1,1-diphenylsilyl]oxy)-2-amino-3-(3,4-dimethoxyphenyl)propanoate (419) (0.10 g, 63%) as a clear oil. $[\alpha]$\textsubscript{D} = -18.1 (c = 1.32, CHCl\textsubscript{3}); $\nu_{\text{max}}$ (DCM)/cm\textsuperscript{-1} 3373 (NH\textsubscript{2}), 2930 (ArH), 2855 (OMe), 1515 (C-O); $\delta_{\text{H}}$ (400 MHz; CDCl\textsubscript{3}) 1.09 (9H, s, OSi(C\textsubscript{6}H\textsubscript{5})\textsubscript{2}C(CH\textsubscript{3})\textsubscript{3}), 2.45 (1H, dd, J 13.6, 8.4, CH(\text{H})CHNH\textsubscript{2}), 2.72 (1H, dd, J 13.2, 5.2, CH(\text{H})CHNH\textsubscript{2}), 3.11-3.15 (1H, m, CH\textsubscript{2}CHNH\textsubscript{2}), 3.52 (1H, dd, J 10.0, 6.8, CH\textsubscript{2}CH(\text{H})OH), 3.63 (1H, dd, J 9.6, 4.4, CH\textsubscript{2}CH(\text{H})OH), 3.82 (3H, s, CH\textsubscript{3}O), 3.84 (3H, s, CH\textsubscript{3}O), 6.70-6.78 (3H, m, ArH), 7.35-7.43 (6H, m, OSi(C\textsubscript{6}H\textsubscript{5})\textsubscript{2}C(CH\textsubscript{3})\textsubscript{3}), 7.66-7.69 (4H, m, OSi(C\textsubscript{6}H\textsubscript{5})\textsubscript{2}C(CH\textsubscript{3})\textsubscript{3}); $\delta_{\text{C}}$ (100 MHz; CDCl\textsubscript{3}) 19.49 (C(CH\textsubscript{3})\textsubscript{3}), 26.80 (3 x CH\textsubscript{3}), 39.92 (CH\textsubscript{2}), 54.47 (CH\textsubscript{3}), 55.80 (OCH\textsubscript{3}), 55.92 (OCH\textsubscript{3}), 68.35 (CH\textsubscript{2}), 111.22 (ArCH), 112.35 (ArCH), 121.22 (ArCH), 127.77 (PhCH), 129.51 (PhCH), 131.57 (ArC), 133.53 (2 x PhC), 135.63 (PhCH), 147.46 (ArC-OCH\textsubscript{3}), 148.83 (ArC-OCH\textsubscript{3}). MS (El) m/z 449 [M\textsuperscript{+}, 0.6%]; (Found: M\textsuperscript{+}, 449.2381. C\textsubscript{27}H\textsubscript{35}NO\textsubscript{3}Si requires 449.2386).
3.7 Towards the asymmetric synthesis of (-)-erysotrine

2-(2-Oxocyclohexyl)ethanoic acid (422)\(^1\)

![Chemical structure](image)

Ethyl-2-cyclohexanone acetate (421) (0.50 g, 2.70 mmol) was dissolved in a mixture of THF (18 ml) and water (8 ml). Lithium hydroxide (0.17 g, 4.07 mmol) was added and the mixture was stirred at room temperature for 20 h. The reaction was concentrated, resuspended in water (30 ml) and acidified to pH 3 with 1M HCl. The aqueous layer was then extracted with ethyl acetate (3 x 20 ml), dried with anhydrous MgSO\(_4\) and the excess solvent was then removed by evaporation under reduced pressure affording 2-(2-oxocyclohexyl)ethanoic acid (422) (0.40 g, 94%) as a colourless oil. No further purification was necessary. \(\nu_{\text{max}}\) (DCM)/\(\text{cm}^{-1}\) 3200 (OH), 1709 (CO); \(\delta_H\) (400 MHz; CDCl\(_3\)) 1.37-1.48 (1H, m, \(\text{CH(H)}\text{CHCO}\)), 1.59-1.79 (2H, m, \(\text{CH(H)}\text{CH}_{2}\text{CHCO}\) and \(\text{CH}_{2}\text{CH(H)}\text{CH}_{2}\text{CO}\)), 1.86-1.93 (1H, m, \(\text{CH(H)}\text{CH}_{2}\text{CHCO}\)), 2.08-2.24 (3H, m, \(\text{CH}_{2}\text{CH(H)}\text{CH}_{2}\text{CO}\), \(\text{CH(H)}\text{CHCO}\) & \(\text{CHCH(H)}\text{CO}_{2}\text{H}\)), 2.33-2.48 (2H, m, \(\text{CH}_{2}\text{CH}_{2}\text{CO}\)), 2.79-2.89 (2H, m, \(\text{CHCH(H)}\text{CO}_{2}\text{H}\) & \(\text{CH}_{2}\text{CHCO}\)); \(\delta_C\) (100 MHz; CDCl\(_3\)) 25.16 (CH\(_2\)), 27.77 (CH\(_2\)), 33.82 (CH\(_2\)), 34.28 (CH\(_2\)), 41.78 (CH\(_2\)), 46.90 (CH), 178.48 (CO\(_2\)H), 211.14 (CO); MS (EI) m/z 156 [M\(^+\), 24.7%]; (Found: M\(^+\), 156.0785. C\(_8\)H\(_{12}\)O\(_3\) requires 156.0787).
Method A

2-(2-Oxocyclohexyl)ethanoic acid (422) (0.18 g, 1.18 mmol) was dissolved in dry DCM (30 ml), under a N₂ atmosphere, and cooled to –15°C. HOABt (0.16 g, 1.18 mmol) and EDCI (0.23 g, 1.18 mmol) was then added and the reaction was stirred at –15°C for a further 20 min. N-methylmorpholine (0.13 ml, 1.18 mmol) and (2S)-1-[(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy)-2-amino-3-(3,4-dimethoxyphenyl)propanoate (419) (0.53 g, 1.18 mmol) was then added and the reaction was stirred at –15°C for an additional 3 h. After this time, the reaction was quenched with ice cold (1M) HCl and the reaction was extracted in DCM (3 x 30 ml). The organic extracts were washed with saturated NaHCO₃, dried with anhydrous MgSO₄ and the solvent was removed by evaporation under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:3) as the eluent affording N-(S)-1-[(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy)-3-(3,4-dimethoxyphenyl)propan-2-yl)-2-(2-oxocyclohexyl)acetamide (423) (0.46 g, 67%) as a yellow oil.

Method B

2-(2-Oxocyclohexyl)ethanoic acid (422) (0.35 g, 2.22 mmol) was dissolved in dry DCM (40 ml), under a N₂ atmosphere, and cooled to –15°C. HOABt (0.30 g, 2.22 mmol) and EDCI (0.23 g, 2.22 mmol) was then added and the reaction was stirred at –15°C for a further 20 min. N-methylmorpholine (0.24 ml, 2.22 mmol) and (2S)-1-[(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy)-3-(3,4-dimethoxyphenyl)propan-2-yl)-2-(2-oxocyclohexyl)acetamide (423) (0.46 g, 67%) as a yellow oil.
ethyl)-1,1-diphenylsilyl]oxy)-2-amino-3-(3,4-dimethoxyphenyl)propanoate (419) (1.00 g, 2.22 mmol) was then added and the reaction was stirred at -15°C for an additional 3 h. After this time, the reaction was quenched with ice cold (1M) HCl and the reaction was extracted in DCM (3 x 30 ml). The organic extracts were washed with saturated NaHCO₃, dried with anhydrous MgSO₄ and the solvent was removed by evaporation under reduced pressure affording N-(S)-1-[(1,1-dimethylethyl)-1,1-diphenylsilyl]oxy)-3-(3,4-dimethoxyphenyl)propan-2-yl)-2-(2-oxocyclohexyl)acetamide (423) (1.28 g, 98%) as a yellow oil.

\[ \alpha_d = +26.3 \ (c = 1.28, \ CHCl_3) \ ]; \ \nu_{\max} (\text{DCM})/\text{cm}^{-1} 3314 (\text{NCO}), 2931 (\text{ArH}), 2856 (\text{OMe}), 1707 (\text{CO}), 1654 (\text{NCO}), 1515 (\text{C-O}); \ \delta_H (\text{400 MHz; CDCl}_3) 1.09 (9H, s, OSi(C₆H₅)₂C(CH₃)₃), 1.17-1.34 (2H, m, CH₂CH(H)CH₂CO and CH(H)CH₂CH₂CO), 1.56-1.71 (2H, m, CH₂CH₂CH₂CO), 1.79-2.13 (3H, m, NHCOCH(H)CH₂CO, CH₂CH(H)CH₂CO and CH(H)CH₂CH₂CO), 2.30-2.40 (2H, m, CH₂CH₂CH₂CO), 2.53 (1H, ddd, \ J = 14.4, 6.4, 2.4, NHCOCH(H)CH₂CO), 2.76-2.88 (3H, m, NHCOCH₂CHCO and ArCH₂CHCH₂), 3.57-3.64 (2H, m, ArCH₂CHCH₂), 3.80 (3H, s, CH₃O), 3.84 (3H, s, CH₃O), 4.18-4.24 (1H, m, ArCH₂CHCH₂), 5.98 (1H, m, NHCOCH₂CHCO), 6.67-6.76 (3H, m, ArH), 7.35-7.45 (6H, m, OSi(C₆H₅)₂C(CH₃)₃), 7.61-7.65 (4H, m, OSi(C₆H₅)₂C(CH₃)₃); \ \delta_C (\text{100 MHz; CDCl}_3) 19.38 (C(CH₃)₃), 26.96 (3 x CH₃), 28.01 (CH₂), 34.03 (CH₂), 34.64 (CH₂), 36.72 (CH₂), 36.94 (CH₂), 42.03 (CH₂), 47.82 (CH), 51.60 (CH), 55.78 (OCH₃), 55.86 (OCH₃), 63.88 (CH₂), 111.02 (ArCH), 112.43 (ArCH), 121.43 (ArCH), 127.83 (PhCH), 129.88 (PhCH), 130.62 (ArC), 133.26 (2 x PhC), 135.57 (PhCH), 147.50 (ArC-OCH₃), 148.78 (ArC-OCH₃), 171.20 (NCO), 212.27 (CO); MS (FAB) m/z 588 [(M⁺ + 1), 11.4%]; (Found: M⁺ + 1, 588.3161. C₃₅H₄₆NO₅Si requires 588.3165).
(13bS)-1,2,3,4,4a,5,8,9-Octahydro-8-(hydroxymethyl)-11,12-dimethoxyindolo[1-a]isoquinolin-6-one (270)\textsuperscript{1,16}

\[ \text{MeO} \]
\[ \text{MeO} \]

\[ \text{OH} \]

\[ \text{N-(S)-1-[(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy)-3-(3,4-dimethoxyphenyl)propan-2-yl)-2-(2-oxocyclohexyl)acetamide (423) } \]

(50 mg, 0.09 mmol) was dissolved in dry DCM (10 ml) and BF\textsubscript{3}.Et\textsubscript{2}O (0.03 ml, 0.26 mmol) was added drop wise via syringe. The reaction mixture was heated at reflux for 96 h. After this time, the reaction was quenched with saturated NaHCO\textsubscript{3} solution, extracted with ethyl acetate (3 x 25 ml) and dried anhydrous MgSO\textsubscript{4}. The excess solvent was removed by evaporation under reduced pressure affording (13bS)-1,2,3,4,4a,5,8,9-Octahydro-8-(hydroxymethyl)-11,12-dimethoxyindolo[1-a]isoquinoline-6-one (270) (18 mg, 61\%) as a yellow oil. The diastereoselectivity of the reaction was determined by \textsuperscript{1}H NMR spectroscopy on the crude reaction mixture (2.5:1). Mp 192-193; \( \nu_{\max} \) (DCM)/cm\textsuperscript{-1} 3383 (OH), 2931 (ArH), 2855 (OMe), 1655 (lactam); \( \delta_\text{H} \) (400 MHz; CDCl\textsubscript{3}) 1.40-1.43 (1H, m, NCCH\textsubscript{2}CH(H)), 1.50-1.67 (5H, m, NCCH\textsubscript{2}CH\textsubscript{2}), 1.75-2.08 (10H, m, NCCH\textsubscript{2}CH(H)), 2 x CH\textsubscript{2}CH\textsubscript{2}CH, NCCCH\textsubscript{2}CH\textsubscript{2}, CHCH\textsubscript{2}CO and CH(H)CH\textsubscript{2}CH\textsubscript{2}, 2.35-2.42 (3H, m, NCCH(H)CH\textsubscript{2} and CH\textsubscript{2}CH\textsubscript{2}CO), 2.62-2.66 (2H, m, NCCCH(H)CH\textsubscript{2} and CH\textsubscript{2}CH\textsubscript{2}CO), 2.75-2.85 (2H, m, NCHCH(H)Ar and NCHCH(H)Ar), 2.91(1H, J NCHCH(H)Ar), 3.09 (1H, J NCHCH(H)Ar), 2.68-3.94 (5H, m, 2 x NCHCH\textsubscript{2}OH and NCHCH\textsubscript{2}OH), 3.86 (3H, s, CH\textsubscript{2}O), 3.88 (3H, s, CH\textsubscript{3}O), 4.00-4.04 (1H, m, NCHCH\textsubscript{2}OH'), 6.65 (1H, s, ArH), 6.72 (1H, s, ArH'), 6.88 (1H, s, ArH), 6.99 (1H, s, ArH'); \( \delta_\text{C} \) (100 MHz; CDCl\textsubscript{3}) 20.34 and 20.84 (NCCH\textsubscript{2}CH\textsubscript{2}), 20.89 and 21.06 (27.36 and 27.51 (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 29.93 and 30.14 (NCHCH\textsubscript{2}Ar), 35.70 and 36.15 (NCCH\textsubscript{2}CH\textsubscript{2}), 36.81 and 37.02 (CHCH\textsubscript{2}CO), 38.07 and 38.14 (CHCH\textsubscript{2}CO), 52.57 and 54.38 (NCHCH\textsubscript{2}OH), 55.93 and 56.02 (CH\textsubscript{3}O), 56.27 and 56.41 (CH\textsubscript{3}O), 64.73 and 65.26 (NCCH\textsubscript{2}CH\textsubscript{2}), 64.00 and 69.30 (CH\textsubscript{2}OH), 108.34 and 108.53 (ArCH), 111.73 and 112.30 (ArCH), 125.51 and 125.99 (ArC), 133.96 and 134.26 (ArC), 147.40 and 147.58 (ArC-OCH\textsubscript{3}), 148.05 and 148.15 (ArC-OCH\textsubscript{3}), 175.76 and 176.09 (CO).
\( N-(S)-1-[(1,1-\text{Dimethylethyl})-1,1-\text{diphenylsilyl}]\text{oxy})-3-(3,4-\text{dimethoxyphenyl}) \)
\( \text{propan-2-yl})-2-(4-\text{methoxy-2-oxocyclohex-3-enyl})\text{acetamide (420)} \)^\text{17} 

**Method A**

2-[4-(Methoxy)-2-oxocyclohex-3-enyl]ethanoic acid (342) (0.22 g, 1.18 mmol) was dissolved in dry DCM (30 ml), under a N\(_2\) atmosphere, and cooled to \(-15^\circ\text{C}\). HOABt (0.16 g, 1.18 mmol) and EDCI (0.23 g, 1.18 mmol) was then added and the reaction mixture was stirred at \(-15^\circ\text{C}\) for an additional 20 min. \( N\)-methylmorpholine (0.13 ml, 1.18 mmol) and (2\(S\))-1-[(1,1-\text{Dimethylethyl})-1,1-\text{diphenylsilyl}]\text{oxy})-2-amino-3-(3,4-\text{dimethoxyphenyl})propanoate (419) (0.53 g, 1.18 mmol) was then added and the reaction was stirred at \(-15^\circ\text{C}\) for an additional 3 h. After this time, the reaction was quenched with ice cold (1M) HCl and the reaction was extracted in DCM (3 x 25 ml). The organic extracts were washed with saturated NaHCO\(_3\), dried with anhydrous MgSO\(_4\) and the solvent was removed by evaporation under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:2) as the eluent affording \( N-(S)-1-[(1,1-\text{Dimethylethyl})-1,1-\text{diphenylsilyl}]\text{oxy})-3-(3,4-\text{dimethoxyphenyl})\text{propan-2-yl})-2-(4-\text{methoxy-2-oxocyclohex-3-enyl})\text{acetamide (420)} \) (0.59 g, 81%) as a yellow oil.

**Method B**

2-[4-(Methoxy)-2-oxocyclohex-3-enyl]ethanoic acid (342) (0.45 g, 2.22 mmol) was dissolved in dry DCM (40 ml), under a N\(_2\) atmosphere, and cooled to \(-15^\circ\text{C}\). HOABt (0.30 g, 2.22 mmol) and EDCI (0.43 g, 2.22 mmol) was then added and the reaction was stirred at \(-15^\circ\text{C}\) for an additional 20 min. \( N\)-methylmorpholine (0.24 ml, 2.22 mmol)
and (2S)-1-[(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy)-2-amino-3-(3,4-dimethoxy phenyl)propanoate (419) (1.00 g, 2.22 mmol) was then added and the reaction was stirred at \(-15^\circ\text{C}\) for a further 3 h. After this time, the reaction was quenched with ice cold (1M) HCl and the reaction was extracted in DCM (3 x 30 ml). The organic extracts were washed with saturated NaHCO₃, dried with anhydrous MgSO₄ and the solvent was removed by evaporation under reduced pressure affording N-(S)-1-[(1,1-dimethylethyl)-1,1-diphenylsilyl]oxy)-3-(3,4-dimethoxyphenyl)propan-2-yl)-2-(2-oxocyclohexyl) acetamide (420) (1.22 g, 89%) as a yellow oil.

\[\alpha\] = - 21.6 (c = 1.22, CHCl₃); \(\nu_{\text{max}}\) (DCM)/cm\(^{-1}\) 3311 (NCO), 2931 (ArH), 2855 (OMe), 1650 (CO), 1607 (NCO), 1515 (C-O); \(\delta_{\text{H}}\) (400 MHz; CDCl₃) 1.11 (9H, s, OSi(C₆H₅)₂C(CH₃)₃), 1.50-1.71 (2H, m, CH₂CH₂CHCO), 1.94-2.06 (1H, m, CH(H)CH₂CHCO), 2.19 (1H, dd, J 14.0, 6.0, NHCOCH(H)CHCO), 2.28-2.37 (1H, m, NHCOCH₂CHCO), 2.44-2.93 (4H, m, NHCOCH(H)CHCO, CH(H)CH₂CHCO and ArCH₂CHCH₂), 3.60-3.64 (2H, m, ArCH₂CHCH₂), 3.70 (3H, s, CH₃O), 3.81 (3H, s, CH₃O), 3.84 (3H, s, CH₃O), 4.20-4.27 (1H, m, ArCH₂CHCH₂), 5.33 (1H, d, J 7.6, CH=CH(CH₃O)), 6.20 (1H, d, J 9.2, NHCOCH₂CHCO), 6.70-6.75 (3H, m, ArH), 7.35-7.45 (6H, m, OSi(C₆H₅)₂C(CH₃)₃), 7.61-7.65 (4H, m, OSi(C₆H₅)₂C(CH₃)₃); \(\delta_{\text{C}}\) (100 MHz; CDCl₃) 19.38 (C(CH₃O)), 26.96 (3 x CH₃), 27.63 (CH₂), 28.89 (CH₂), 36.80 (CH₂), 37.14 (CH₂), 42.99 (CH), 51.61 (CH), 55.84 (3 x OCH₃), 64.16 (CH₂), 101.80 (CH=), 110.99 (ArCH), 112.40 (ArCH), 121.39 (ArCH), 127.80 (PhCH), 129.84 (PhCH), 130.66 (ArC), 133.27 (2 x PhC), 135.59 (PhCH), 147.45 (ArC-OCH₃), 148.74 (ArC-OCH₃), 171.31 (NCO), 178.23 (CH=CH(CH₃O)), 200.08 (CO); MS (FAB) m/z 616 [(M⁺ + 1), 7.0%]; (Found: M⁺+ 1, 616.3088. C₃₆H₄₅NO₈Si requires 616.3094).
(3S,6aS)-3-(3,4-Dimethoxyphenyl)-2,3,6,6a,7,8-hexahydro-9-methoxyoxazolo[3,2-i]indol-5-one (405)\(^{16}\)

\[
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{Me}
\end{array}
\]

\[N-(S)-1-[(1,1-Dimethylethyl)-1,1-diphenylsilyl]oxy)-3-(3,4-dimethoxyphenyl)propan-2-yl)-2-(4-methoxy-2-oxocyclohex-3-enyl)acetamide (420)\]

(1.95 g, 3.17 mmol) was dissolved in dry DCM (50 ml) and BF\(_3\).Et\(_2\)O (12.0 ml, 95.0 mmol) was added drop wise via syringe. The reaction mixture was heated at reflux for 96 h. After this time, the reaction was quenched with saturated NaHCO\(_3\) solution, extracted with ethyl acetate (3 x 25 ml) and dried anhydrous MgSO\(_4\). The excess solvent was removed by evaporation under reduced pressure producing a yellow oil. The residue was then purified by flash column chromatography on silica gel using 5% methanol in ethyl acetate as the eluent affording (3S,6aS)-3-(3,4-dimethoxyphenyl)-2,3,6,6a,7,8-hexahydro-9-methoxyoxazolo[3,2-i]indol-5-one (405) (0.81 g, 71%) as a yellow oil. The diastereoselectivity of the reaction was determined by \(^1\)H NMR spectroscopy on the crude reaction mixture (~1:1). 

\[\left[\alpha\right]_D = \ -27.5\ \text{c = 1.38, CHCl}_3; \nu_{\text{max}}\ \text{(DCM)/cm}^{-1} \ 2938\ (\text{ArH}), 2836\ (\text{OMe}), 1651\ \text{(lactam)}; \delta_{\text{H}}\ (400\ \text{MHz; CDCl}_3)\ 1.54-1.80\ (4\ \text{H, m, 2 x CHCH}_2\text{CH}_2), 2.20-2.27\ (1\ \text{H, m, CHCH(H)CO}), 2.29-2.40\ (2\ \text{H, m, CHCH}_2\text{CH}_2), 2.46-2.57\ (5\ \text{H, m, 2 x CHCH(H)CO, CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C} \text{H}_2\text{CO}, 2.65-2.87\ (6\ \text{H, m, 2 x NCHCH}_2\text{Ar, CHCH(H)CO and CHCH}_2\text{CO}), 3.15-3.76\ (4\ \text{H, m, 2 x NCHCH}_2\text{H}_2\text{O}), 3.70\ (3\ \text{H, s, CH}_3\text{O}), 3.84\ (3\ \text{H, s, CH}_3\text{O}), 3.86\ (3\ \text{H, s, CH}_3\text{O}), 4.11-4.23\ (2\ \text{H, m, 2 x NCHCH}_2\text{H}_2\text{Ar}), 5.31\ (1\ \text{H, s, NCHH=C(OCH}_3)), 5.35\ (1\ \text{H, s, NCCCH=C(OCH}_3)), 6.71-6.77\ (6\ \text{H, m, ArH}); \delta_{\text{C}}\ (100\ \text{MHz; CDCl}_3)\ 27.32\ \text{and 27.50\ (CHCH}_2\text{CH}_2), 28.82\ \text{and 28.91\ (CHCH}_2\text{CH}_2), 36.48\ \text{and 36.56\ (NCHCH}_2\text{Ar}), 37.17\ \text{and 37.33\ (CHCH}_2\text{CO), 43.07\ (CHCH}_2\text{CO), 52.76\ \text{and 53.05\ (NCHCH}_2\text{O}), 55.82, 55.85\ \text{and 55.97\ (3 x CH}_3\text{O}), 63.94\ \text{and 64.15\ (NCHCH}_2\text{O), 101.53\ \text{and 101.57\ (CH=C(CH}_3)), 111.09\ (2\ \text{x ArCH), 112.35\ (2\ \text{x ArCH), 121.16\ and 121.23\ (ArCH), 130.42\ (2\ \text{x ArC), 147.58\ (2\ \text{x ArC-OCH}_3), 148.84\ (2\ \text{x ArC-OCH}_3), 179.09\ (2\ \text{x CH=C(OCH}_3)), 200.88\ \text{and 201.06\ (NCO); MS (FAB) m/z 360 [(M}^+\text{ + 1), 2.9%]; (Found: M}^+\text{ + 1, 360.1819. C}_{20}\text{H}_{25}\text{NOS requires 360.1811).}
\]
(S)-3,3a,4,5-Tetrahydro-1-((S)-1-hydroxy-3-(3,4-dimethoxyphenyl)propan-2-yl)-1H-indole-2,6-dione (406)\(^{18}\)

![Chemical structure](image)

(3S,6aS)-3-(3,4-Dimethoxybenzyl)-2,3,6,6a,7,8-hexahydro-9-methoxyoxazolo[3,2-i]indol-5-one (405) (0.68 g, 1.89 mmol) was dissolved in a mixture of THF (20 ml) and H\(_2\)O (20 ml). To the resulting solution was added (2M) HCl (20 ml) via syringe. The reaction mixture was then stirred at 55°C (oil bath temperature) overnight. After this time, the excess THF was removed by evaporation under reduced pressure. The resulting solution was then quenched with saturated NaHCO\(_3\) solution, extracted with ethyl acetate (3 x 30 ml), washed with H\(_2\)O (15 ml) and dried with anhydrous MgSO\(_4\). The excess ethyl acetate was then removed by evaporation under reduced pressure producing a yellow oil. The residue was then purified by flash column chromatography on silica gel using 100% ethyl acetate as the eluent affording (S)-3,3a,4,5-tetrahydro-1-((S)-1-hydroxy-3-(3,4-dimethoxyphenyl)propan-2-yl)-1H-indole-2,6-dione (406) (0.41 g, 62%) as a colourless solid. Mp 101-103°C; \([\alpha]_D = -59.8\) (c = 1.27, CHCl\(_3\)); \(\nu_{\text{max}}\) (DCM)/cm\(^{-1}\) 3417 (OH), 2936 (ArH), 2836 (OMe), 1731 (CO), 1737 (lactam), 1598 (C=C); \(\delta_H\) (400 MHz; CDCl\(_3\)) 1.54-1.88 (2H, m, 2 x CHCH(H)CH\(_2\)), 2.12-2.35 (6H, m, 2 x CHCH(H)CH\(_2\), 2 x CHCH\(_2\)CH(H) and 2 x CHCH(H)CO), 2.50-2.54 (2H, m, 2 x CHCH\(_2\)CH(H)), 2.60-2.73 (2H, m, 2 x CHCH(H)CO), 2.79-2.95 (2H, m, 2 x CHCH\(_2\)CO), 2.98-3.12 (4H, m, NCHCH\(_2\)Ar), 3.84 (3H, s, CH\(_3\)O), 3.86 (3H, s, CH\(_3\)O), 3.87-3.90 (2H, m, 2 x NCHCH(H)O), 4.01-4.15 (2H, m, 2 x NCHCH(H)O), 4.16-4.32 (2H, m, 2 x NCHCH\(_2\)Ar), 5.52 (1H, s, NC=CHCO), 5.60 (1H, s, NC=CHCO), 6.69-6.78 (6H, m, ArH); \(\delta_C\) (100 MHz; CDCl\(_3\)) 27.79 and 27.84 (CHCH\(_2\)CH\(_2\)), 32.70 (CHCH\(_2\)CH\(_2\)), 33.78 (NCHCH\(_2\)Ar), 35.01 and 35.06 (CHCH\(_2\)CO), 35.29 and 35.48 (CHCH\(_2\)CO), 37.15 (NCHCH\(_2\)O), 55.89 and 55.97 (2 x CH\(_3\)O), 61.24 and 62.07 (NCHCH\(_2\)O), 103.14 (CHCO), 111.16 (2 x ArCH), 112.06 (2 x ArCH), 121.09 and 121.13 (ArCH), 129.17 and 129.27 (2 x ArC), 147.94 (2 x ArC-OCH\(_3\)), 148.79 (2 x ArCOCH\(_3\)), 159.98 (C=O), 161.16 (2 x ArC=O), 163.54 (C=O), 172.30 (C=O), 173.04 (C=O).
ArC-\text{OCH}_3), 176.68 and 176.87 (NCO), 197.31 and 197.46 (2 x CO); MS (FAB) m/z 346 [M\textsuperscript{+}, 32.4%]; (Found: M\textsuperscript{+}, 346.1653. C_{19}H_{23}NO_5 requires 346.1655).
3.8 Towards the lactol precursor of (-)-xylopinine

2-(3,4-Dimethoxyphenyl)ethanol (Homoveratryl alcohol) (455)\textsuperscript{2,19}

![Chemical structure](attachment://structure.png)

Chlorotrimethylsilane (3.96 ml, 40.8 mmol) was added under nitrogen atmosphere to a stirring solution of lithium borohydride (10.2 ml of a 2M solution in THF, 20.4 mmol) in THF (20 ml) over a period of 2 min. Homoveratric acid (454) (2.00 g, 10.2 mmol) was then added portionwise over a period of 5 min and the reaction mixture was allowed to stir at room temperature for a further 24 h. After this time, methanol (30 ml) was added slowly to the reaction mixture and the excess solvent was removed by evaporation under reduced pressure. The residue was then dissolved in 10% potassium hydroxide solution (40 ml); extracted with DCM (3 x 30 ml) and dried with anhydrous MgSO\textsubscript{4}. The solvent was then removed by evaporation under reduced pressure affording 2-(3,4-dimethoxyphenyl)ethanol (Homoveratryl alcohol) (455) (1.80 g, 97%) as a colourless solid. Mp 48-49°C; Lit: Mp 47-79°C;\textsuperscript{2,19} (Found: C, 65.85; H, 7.71. C\textsubscript{10}H\textsubscript{14}O\textsubscript{3} requires C, 65.92; H, 7.74 %); \(\nu_{\text{max}}\) (DCM)/cm\(^{-1}\) 3394 (OH), 2936 (Sp\(^{3}\) CH), 2834 (OCH\textsubscript{3}), 1516 (C-O); \(\delta_{\text{H}}\) (400 MHz; CDCl\textsubscript{3}) 1.51 (1H, br s, OH), 2.81 (2H, t, \(J = 6.4\), CH\textsubscript{2}CH\textsubscript{2}OH), 2.83 (2H, t, \(J = 6.4\), CH\textsubscript{2}CH\textsubscript{2}OH), 3.87 (3H, s, OCH\textsubscript{3}), 3.88 (3H, s, OCH\textsubscript{3}), 6.76-6.84 (3H, m, ArH); \(\delta_{\text{C}}\) (100 MHz; CDCl\textsubscript{3}) 38.73 (CH\textsubscript{2}), 55.82 (OCH\textsubscript{3}), 55.91 (OCH\textsubscript{3}), 63.75 (CH\textsubscript{2}), 111.29 (ArCH), 112.11 (ArCH), 120.91 (ArCH), 130.91 (ArC), 147.66 (ArC-OCH\textsubscript{3}), 148.96 (ArC-OCH\textsubscript{3}); MS (EI) m/z 182 [M\textsuperscript{+}, 26.5%]; (Found: M\textsuperscript{+}, 182.0944. C\textsubscript{10}H\textsubscript{14}O\textsubscript{3} requires 182.0943).
3,4-Dihydro-6,7-dimethoxy-1H-isochromene (456)

To a stirring solution of 2-(3,4-Dimethoxyphenyl)ethanol (Homoveratryl alcohol) (455) (2.00 g, 11.0 mmol) in trifluoroacetic acid (10 ml) was added para-formaldehyde (0.40 g) at room temperature. This suspension was allowed to stir at this temperature for 1 h. The mixture was then diluted with the addition of ethyl acetate (30 ml) and washed with saturated sodium carbonate solution and brine (30 ml). The organic layer was separated, dried with anhydrous MgSO₄ and the excess solvent was removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:4) as the eluent affording 3,4-dihydro-6,7-dimethoxy-1H-isochromene (456) (1.77 g, 83%) as an colourless solid. Mp 80-83°C; Lit: Mp 82-83°C;²⁰ (Found: C, 68.07; H, 7.23. C₁₁H₁₄O₃ requires C, 68.02; H, 7.27 %); v max (DCM)/cm⁻¹ 2934 (sp³ CH), 2834 (ArOCH₃), 1783 (C-O), 1124, 1097 (CH₂OCH₂); δₜ (400 MHz; CDCl₃) 2.76 (2H, t, J 5.6, CH₂CH₂OH), 3.84 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.94 (2H, t, J 5.6, CH₂CH₂OH), 4.70 (2H, s, ArCH₂O), 6.48 (1H, s, ArH), 6.62 (1H, s, ArH); δC (100 MHz; CDCl₃) 27.84 (CH₂), 55.931 (2 x OCH₃), 65.44 (CH₂), 67.65 (CH₂), 107.31 (ArCH), 111.67 (ArCH), 125.03 (ArC), 126.67 (ArC), 147.52 (ArC-OCH₃), 147.64 (ArC-OCH₃); MS (EI) m/z 194 [M⁺, 100%]; (Found: M⁺, 194.0942. C₁₁H₁₄O₃ requires 194.0943).
3,4-Dihydro-6,7-dimethoxy-1H-isochromen-1-one (457)\textsuperscript{21,22}

![Chemical Structure Image]

To a stirring solution of 3,4-Dihydro-6,7-dimethoxy-1H-isochromene (456) (1.00 g, 5.15 mmol) and triethylbenzylammonium chloride (TEBAC) (3.52 g, 15.5 mmol) in dry DCM (100 ml) was added finely ground potassium permanganate (2.44 g, 15.5 mmol). This mixture was then heated at reflux for 20 h. Upon cooling in an ice/salt bath, sodium bisulphite (10 g) in water (25 ml) was added with vigorous stirring until the purple colour had completely discharged. The aqueous layer was then separated and extracted with chloroform (3 x 20 ml). The combined organic layers were then washed with water (2 x 50 ml), dried with anhydrous MgSO\(_4\) and the excess solvent was removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:4) as the eluent affording 3,4-dihydro-6,7-dimethoxy-1H-isochromen-1-one (457) (0.95 g, 89\%) as an colourless solid. Mp 139-141°C; Lit: Mp 140-141°C\textsuperscript{21,22} (Found: C, 62.95; H, 5.74. C\(_{11}\)H\(_{12}\)O\(_4\) requires C, 63.45; H, 5.81 %); \(\nu\text{ max} \) (DCM)/cm\(^{-1}\) 2945 (sp\(^3\) CH), 2834 (OCH\(_3\)), 1716 (CO); \(\delta\text{H} \) (400 MHz; CDCl\(_3\)) 2.98 (2H, t, \(J\) 6.0, CH\(_2\)CH\(_2\)OCO), 3.93 (3H, s, OCH\(_3\)), 3.95 (3H, s, OCH\(_3\)), 4.51 (2H, t, \(J\) 6.0, CH\(_2\)CH\(_2\)OCO), 6.69 (1H, s, ArH), 7.56 (1H, s, ArH); \(\delta\text{C} \) (100 MHz; CDCl\(_3\)) 27.50 (CH\(_2\)), 56.18 (OCH\(_3\)), 56.19 (OCH\(_3\)), 67.38 (CH\(_2\)), 109.09 (ArCH), 111.81 (ArCH), 117.42 (ArC), 133.96 (ArC), 148.48 (ArC-OCH\(_3\)), 153.61 (ArC-OCH\(_3\)), 165.23 (CO); MS (EI) m/z 208 [M\(^+\), 100\%]; (Found: M\(^+\), 208.0734. C\(_{11}\)H\(_{12}\)O\(_4\) requires 208.0736).
3,4-Dihydro-3-hydroxy-6,7-dimethoxy-1H-isochromen-1-one (453)\textsuperscript{23}

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

To a stirring mixture of water (50 ml) and 3,4-Dihydro-6,7-dimethoxy-1H-isochromen-1-one (457) (1.00 g, 4.81 mmol) was added potassium hydroxide (0.40 g, 7.21 mmol). This mixture was allowed to stir at room temperature for 24 h. The resulting yellow solution was then acidified (pH 1-2) with 2M sulphuric acid, extracted with diethyl ether (3 x 30 ml) and dried with anhydrous MgSO\textsubscript{4}. The excess diethyl ether was then removed by evaporation under reduced pressure at 0°C affording 2-(2-hydroxyethyl)-4,5-dimethoxybenzoic acid (458) (1.08 g, 100%), as an colourless solid. Oxidation of this hydroxy intermediate then proceeded without purification due to relactonisation.

**Oxidation with Dess-Martin Periodinane (DMP)**

2-(2-Hydroxyethyl)-4,5-dimethoxybenzoic acid (458) (1.08 g, 4.77 mmol) was dissolved in dry DCM (10 ml) under a nitrogen atmosphere and was added \textit{via} cannula to a solution of Dess-Martin periodinane (2.02 g, 4.77 mmol) in dry DCM (25 ml) also under a nitrogen atmosphere. The mixture was left to stir at room temperature for a further 20 h. After this time, the excess DCM was removed by evaporation under reduced pressure. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:1) as the eluent affording 3,4-dihydro-3-hydroxy-6,7-dimethoxy-1H-isochromen-1-one (453) (0.59 g, 55%) as a colourless solid.
Oxidation with Stabilised IBX (SIBX)

2-(2-Hydroxyethyl)-4,5-dimethoxybenzoic acid (458) (1.08 g, 4.77 mmol) was dissolved in dry DCM (15 ml) and SIBX (0.54 g, 0.96 mmol) was added. The suspension was then stirred at room temperature for 20 h. After this time, the excess DCM was removed by evaporation under reduced pressure. The residue was dissolved in ethyl acetate and filtered through celite. The filtrate was then washed with ethyl acetate (40 ml), extracted with water (3 x 40 ml) and dried with anhydrous MgSO₄. The excess solvent was removed by evaporation under reduced pressure affording a yellow solid. Purification by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:1) as the eluent afforded 3,4-dihydro-3-hydroxy-6,7-dimethoxy-1H-isochromen-1-one (453) (0.32 g, 30%) as a colourless solid.

Mp 168-170°C; Lit: Mp 168°C;\(^{23}\) \(\nu_{\text{max}}\) (DCM)/cm\(^{-1}\) 3358 (OH), 2938 (ArOCH₃), 1700 (CO), 1605 (C-O); \(\delta_H\) (400 MHz; CDC\(_3\)) 3.06-3.31 (2H, m, CH\(_2\)CH(O)OH), 3.92 (3H, s, OCH\(_3\)), 3.96 (3H, s, OCH\(_3\)), 5.95 (1H, br s, CH\(_2\)CH(O)OH), 6.73 (1H, s, ArH), 7.55 (1H, s, ArH); \(\delta_C\) (100 MHz; CDCl\(_3\)) 33.58 (CH\(_2\)), 56.17 (OCH\(_3\)), 56.23 (OCH\(_3\)), 95.80 (CH\(_3\)), 110.17 (ArCH\(_3\)), 111.47 (ArCH\(_2\)), 116.65 (ArC), 130.82 (ArC), 148.50 (ArC-OCH\(_3\)), 154.16 (ArC-OCH\(_3\)), 164.98 (CO); MS (EI) m/z 224 [M\(^+\), 65.6%]; (Found: M\(^+\), 224.0687. C\(_{11}\)H\(_{12}\)O\(_5\) requires 224.0685).
3.9 Towards the asymmetric synthesis of (-)-xylopine

(3S,10aR)-3-(3,4-Dimethoxyphenyl)-2,3,10,10a-tetrahydro-7,8-dimethoxyoxazolo[3,2-b]isoquinolin-5-one (467)

(2S)-2-Amino-3-[3,4-dimethoxyphenyl]propan-1-ol (264) (264 mg, 1.25 mmol) and 3,4-dihydro-3-hydroxy-6,7-dimethoxy-1H-isochromen-1-one (453) (280 mg, 1.25 mmol) was refluxed in toluene under Dean-Stark conditions for 48 h. After this time, the resulting yellow solution was allowed to cool down and then the excess toluene was removed by evaporation under reduced pressure to yield a yellow/brown oil. The residue was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (bp 40-60°C) (1:1) as the eluent affording (3S,10aS)-3-(3,4-dimethoxyphenyl)-2,3,10a-tetrahydro-7,8-dimethoxyoxazolo[3,2-b]isoquinoline-5-one (467) (280 mg, 57%) as a yellow oil. δH (400 MHz; CDCl3) 2.75-2.82 (2H, m, ArCH(H)CHO & NCHCH(H)Ar), 3.05 (1H, dd, J 14.6, 4.1, ArCH(H)CHO), 3.36 (1H, dd, J 13.5, 2.8, NCHCH(H)Ar), 3.77 (3H, s, OCH3), 3.87 (3H, s, OCH3), 3.94 (3H, s, OCH3), 3.95 (3H, s, OCH3), 3.97-4.01 (1H, m, NCHCH(H)O), 4.11 (1H, dd, J 9.2, 1.0, NCHCH(H)O), 4.37-4.44 (1H, m, NCHCH2O), 5.03 (1H, dd, J 11.7, 4.0, NCHO), 6.69 (1H, s, ArH), 6.77 (1H, s, ArH), 6.82 (1H, s, ArH), 7.60 (1H, s, ArH); δC (100 MHz; CDCl3) 34.49 (CH2), 37.64 (CH2), 55.74 (OCH3), 55.87 (OCH3), 56.11 (NCHCH2O), 56.12 (OCH3), 56.33 (OCH3), 70.07 (CH2), 87.18 (NCHO), 109.77 (ArCH), 110.60 (ArCH), 111.12 (ArCH), 112.59 (ArCH), 121.48 (ArCH), 122.24 (ArC), 127.99 (ArC), 130.31 (ArC), 147.73 (ArC-OCH3), 148.41 (ArC-OCH3), 148.87 (ArC-OCH3), 152.18 (ArC-OCH3), 161.64 (NCO).
Attempted preparation: (S)-5,6,13,13a-Tetrahydro-6-(hydroxymethyl)-2,3,10,11-tetramethoxy-8H-dibenzo[a,q]quinoliz-8-one (468)

(3S,10αR)-3-(3,4-Dimethoxyphenyl)-2,3,10α-tetrahydro-7,8-dimethoxyoxazolo[3,2-b]isoquinolin-5-one (467) (0.28 g, 0.15 mmol) was dissolved in dry DCM (20 ml) under a nitrogen atmosphere. The mixture was cooled to -78°C and 3 equivalents of TiCl₄ (0.25 ml, 2.25 mmol) was added dropwise by syringe. After stirring at this temperature for 15 min, the brown suspension was allowed to warm to room temperature where it was then stirred for a further 20 h. The mixture was then quenched with saturated ammonium chloride solution (20 ml), extracted with DCM (3 x 30 ml) and dried over anhydrous MgSO₄. The solvent was removed by evaporation under reduced pressure producing a yellow/orange oil. The residue was purified by flash column chromatography on silica gel using ethyl acetate/light petroleum (bp 40-60°C) (1:1) as the eluent affording the product as a yellow oil. δH (400 MHz; CDCl₃): The ¹H NMR spectrum of the crude product showed no trace of starting material or the enamide, the β-elimination by-product. However, we are unable to say for certain that this is the desired product. Crude δC (100 MHz; CDCl₃) 29.70 (CH₂), 34.29 (CH₂), 55.08 (OCH₃), 55.71 (OCH₃), 55.76 (CH), 56.53 (2 x OCH₃), 63.17 (CH₂), 105.25 (ArCH), 111.05 (ArCH), 111.92 (ArCH), 121.13 (ArCH), 124.97 (ArC), 129.94 (ArC), 147.55 (ArC-OCH₃), 148.67 (ArC-OCH₃), 153.91 (2 x ArC-OCH₃), 169.16 (NCO).
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Chapter 4 Appendix
A formal asymmetric synthesis of both enantiomers of the *Erythrina* alkaloid 3-demethoxyerythratidinone

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Abstract—A formal asymmetric synthesis of both enantiomers of the *Erythrina* alkaloid 3-demethoxyerythratidinone is reported through the application of a highly functionalised lactam template as an N-acyliminium precursor.

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There has been much interest in the synthesis of these alkaloids and derivatives (including pyrroloisoquinoline precursors) over recent years. 2

3-Demethoxyerythratidinone, 1, was isolated from *Erythrina lysistemon* in 1973 by Barton and co-workers. 3 Despite being structurally one of the simplest of the *Erythrina* class of alkaloid, it was not until 1984 that Tsuda reported the first total synthesis, in racemic form, of this natural product. 4 Almost a decade later this same group reported an asymmetric route to the enantiomeric form of the natural product, the so-called 'enantio-(-)-3-demethoxyerythratidinone'. 4

We have recently concerned ourselves with the development of novel, efficient and stereoselective routes to complex heterocyclic targets by employing N-acyliminium intermediates in cyclisation reactions. 5 In a recent publication we detailed a novel approach to an erythrinane-like ring system through the application of a Meyers chiral lactam template. We now wish to report the successful application of our methodology to construct a functionalised erythrinane ring system in a highly stereoselective manner, thus representing a formal asymmetric synthesis of both enantiomers of the natural product, 3-demethoxyerythratidinone.

Although the chiral lactams pioneered by Meyers have been widely utilised in asymmetric synthesis, 6 to the best of our knowledge, the present application, as a
precursor in an N-acyliminium mediated cyclisation reaction leading to erythrinane targets, represents a novel use of this popular chiral template. In order to access the more highly functionalised alkaloid skeleton we were required to prepare the protected keto-acid substrate 3. This compound was readily accessed by enolate alkylation and subsequent ester group hydrolysis of the commercially available mono-protected diketone 2, as shown in Scheme 1.

Our synthesis of the required lactam substrate 5 then followed similar methodology to that previously described by us, with the required β-aminoalkanol 4 prepared in 97% yield by reduction of the commercially available amino acid, 3-(3,4-dimethoxyphenyl)-L-alanine, with LiBH4 in the presence of Me3SiCl in THF for 24 h at room temperature. Condensation of substrates 3 and 4 under Dean-Stark conditions in toluene for 48 h gave a 65% yield of the desired lactam 5 as a single diastereoisomer (Scheme 2). The formation of a single product diastereoisomer of lactam 5 from the racemic keto-acid 3 requires the epimerisation of the stereogenic centre adjacent to the ketone during the reaction, and this fact has been noted previously for similar substrates in the preparation of polycyclic lactams for use as N-acyliminium precursors.

With 5 in hand, we turned our attention to the proposed asymmetric cyclisation. On treating lactam 5 with 3 equiv of TiCl4 as Lewis acid activator at low temperature in dichloromethane for 20 h we were pleased to isolate the tetracyclic product 6 in an excellent 92% yield. Perhaps not unexpectedly, the cyclisation under strong Lewis acid conditions had been accompanied by concomitant deprotection of the ketal protecting group. Reducing the number of equivalents of the Lewis acid did not result in selective formation of the corresponding cyclisation product with the ketal group intact, and instead an inseparable product mixture was obtained. Indeed, since the removal of the protecting group did not hinder the immediate progress of our work, we favoured the use of excess Lewis acid to achieve clean and complete deprotection at this stage. 1H NMR analysis of the crude product mixture revealed the formation of a 10:1 mixture of product diastereoisomers.

The major diastereoisomer 6 was isolated by column chromatography. In our previous work on the synthesis of the related compound 7, prepared by analogous chemistry, we were able to determine the relative stereochemistry by X-ray crystallography. In this present case we were unable to obtain suitable crystals for X-ray, however the absence of an NOE between the protons at positions 4 and 13a supports the proposed structure; one would not expect a change in product stereochemistry to be favoured on simply introducing the remote protecting group in this current series. The stereochemical outcome of this cyclisation reaction can be rationalised using the same conformational model as previously proposed by our group for related cyclisations. The presence of an asymmetric centre next to the iminium carbon may also act to influence the formation of the new chiral centre on cyclisation. If this were to be a contributing factor, one can appreciate that the aromatic ring approaches the planar acyliminium intermediate from the direction of least steric hindrance.

Removal of the pendant hydroxymethyl substituent (auxiliary) from the tetracyclic product 6 was achieved by application of a three-step procedure (Scheme 3). Dess-Martin periodinane oxidation of the primary alcohol proceeded in 93% yield to provide aldehyde 8. We then employed our favoured Rh-catalysed decarboxylation protocol to access enamide 9 in 55% yield; a small amount of target compound 10 (6%) was also produced directly in this reaction. The auxiliary removal

**Scheme 1.**

**Scheme 2.**
sequence was completed by catalytic hydrogenation of the crude mixture from the previous step to furnish the amidoketone 10 in 79% yield.

The formal asymmetric synthesis of (+)-demethoxyerythroididine, the natural enantiomer, simply required re-protection of the ketone functional group using ethylene glycol as shown in Scheme 3. Compound 11 has been converted by others to the natural product atenol in racemic form by a four-step sequence.4

The formal asymmetric synthesis of the unnatural enantiomer followed an identical synthetic route, beginning however with the enantiomeric form of the original amino acid substrate to access the required lactam substrate 12, which had the opposite optical rotation value to that obtained for lactam 5. Intermediate 13 gave an optical rotation of +39.6, compared to -36.9 for compound 10. The enantio-target 14, gave an optical rotation of +21.7, compared to -26.1 for compound 11.

To summarise, we report the first synthetic application of our recently developed asymmetric N-acyliminium cyclisation methodology. Our approach allows a facile and highly stereoselective formal asymmetric synthesis of both enantiomers of the alkaloid 3-demethoxyerythroididine.

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References and notes


Appendix

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