Enantioselective Synthesis of (+)-Homocitric Acid Lactone, (+)-Antofine and (+)-Cryptopleurine Involving Organocatalytic Conjugate Addition Reactions

by

© Rajendar Dyapa

A thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of

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Department of Chemistry
Memorial University
St. John’s, Newfoundland

May 2014
To my family
ABSTRACT

The organocatalytic, asymmetric conjugate addition of carbon nucleophiles and heteroatom nucleophiles to electron-deficient alkenes (Michael acceptors) such as nitroalkenes, enones, and vinyl sulfones, is of interest because the products are useful synthetic intermediates. The present study examines the enantioselective, iminium ion catalyzed vinylogous Mukaiyama-Michael reaction of 5-triisopropylsilyloxy furan-2-carboxylates with acrolein. The stereoselectivity of this reaction is dependent on the nature of the furan nucleophile and the secondary amine catalyst. The Michael adduct obtained in this methodology was employed in the synthesis of (S)-homocitric acid lactone. The details of this study are described in Chapter 2.

In a separate study, the γ-nitroketone obtained from an organocatalytic Michael addition of β-nitrostyrene and 1,4-cyclohexanedione mono ethylene ketal has been utilized in alkaloid synthesis. Thus, a total synthesis of indolizidine alkaloid (+)-antofine and quinolizidine alkaloid (+)-cryptopleurine was achieved from the γ-nitroketone. Details of these investigations are described in Chapter 3 and Chapter 4.
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<table>
<thead>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>APCI</td>
<td>atmospheric pressure chemical ionization</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Boc</td>
<td><em>tert</em>-butoxycarbonyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>BuLi</td>
<td>butyl lithium</td>
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<td>cat.</td>
<td>catalytic</td>
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<tr>
<td>DCM</td>
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</tr>
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<td>de</td>
<td>diastereomeric excess</td>
</tr>
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</tr>
<tr>
<td>DIAD</td>
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</tr>
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<td>DIBAL</td>
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</tr>
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<td>DMAP</td>
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</tr>
<tr>
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<td>1,2-dimethoxyethane</td>
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<tr>
<td>DMEAD</td>
<td>di-2-methoxyethyl azodicarboxylate</td>
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DMF  \(N,N\)-dimethylformamide
DMSO  dimethyl sulfoxide
DNBA  2,4-dinitrobenzoic acid
dr    diastereomeric ratio
ds    diastereoselectivity
ee    enantiomeric excess
EI    electrospray ionization
eq.   equivalent(s)
er    enantiomeric ratio
Et    ethyl
EWG   electron withdrawing group
g    gram
h    hour
HMDS  hexamethyldisilazane
HOMO  highest occupied molecular orbital
HPLC  high performance liquid chromatography
HRMS  high resolution mass spectrum
Hz    hertz
i-Bu  isobutyl
i-Pr  isopropyl
IR    infrared
\(J\)  coupling constant
<table>
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<td>LDA</td>
<td>lithium diisopropylamide</td>
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<tr>
<td>LiHMDS</td>
<td>lithium hexamethyldisilazide</td>
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<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
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<td>M</td>
<td>molar</td>
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<td>M⁺</td>
<td>molecular ion</td>
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<td>nuclear overhauser effect</td>
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<td>Ph</td>
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<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
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<td>PMP</td>
<td>para-methoxyphenyl</td>
</tr>
<tr>
<td>PNBA</td>
<td>para-nitrobenzoic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>psi</td>
<td>pounds per square inch</td>
</tr>
<tr>
<td>PTSA</td>
<td>para-toluenesulphonic acid</td>
</tr>
<tr>
<td>pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
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<td>S_N2</td>
<td>bimolecular nucleophilic substitution</td>
</tr>
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<td>t-Bu</td>
<td>tertiary butyl</td>
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<td>triethylamine</td>
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</tr>
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<td>tetrahydrofuran</td>
</tr>
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<td>TIPS</td>
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<tr>
<td>TLC</td>
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</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
</tr>
<tr>
<td>Ts</td>
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Chapter 1

Introduction

1.1 Organocatalytic conjugate addition reactions

The conjugate addition of nucleophiles to the β-position of α,β-unsaturated carbonyl compounds (Michael reaction) is an important method to make a carbon–carbon bond.\(^1\) Due to the high demand for optically active compounds, much effort has been devoted to the development of asymmetric Michael reactions, since stereogenic centers can be constructed in the course of the Michael reaction.\(^2\) Although asymmetric conjugate additions have over the years been dominated by using chiral catalysts containing metals, small organic molecules (organocatalysts) have been developed recently as efficient catalysts for these reactions.\(^{1,2}\)

Carbon nucleophiles with active methylene groups are extensively used in direct Michael additions, whereas simple carbonyl compounds need to be activated as enol ethers or enamines prior to addition to a Michael acceptor (Figure 1.1). In this case, direct addition of unmodified carbonyl compounds to Michael acceptors would avoid unwanted chemical transformations and also reduce the overall synthetic effort.

Figure 1.1 Direct and indirect Michael addition
In this context, the concept of aminocatalysis has received considerable attention in recent years. Catalytic activation of the Michael donor may take place through enamine or enolate formation for the addition to a Michael acceptor (Figure 1.2 paths a and b). Alternatively, carbonyl containing Michael acceptors can be activated by the formation of an iminium species.

![Figure 1.2 Activation of a Michael donor and Michael acceptor](image)

1.1.1 Organocatalytic conjugate addition reactions via iminium catalysis

In 2000, MacMillan reported the activation of unsaturated aldehydes and ketones by reversible iminium ion formation with chiral amines as a highly generalized strategy for conjugate addition reactions. The formation of the iminium ion lowers the LUMO energy of the carbonyl substrate with respect to the HOMO of the nucleophile. This activation effect is similar to that associated with reactions involving metal-based Lewis acids (Scheme 1.1).
Scheme 1.1

Iminium catalysis forms the basis for several conjugate addition reactions of various Michael donors such as malonates,^6,7 nitroalkanes^8,9 and thiols^10 to enones as well as for Mukaiyama-Michael reactions of silyloxyfurans with enals.^4,5 The first iminium-catalyzed conjugate addition (malonate 2 to enone 1) was reported by Yamaguchi and co-workers^11 in 1991 using the lithium salt of S-proline 3 to obtain moderate-to-good enantioselectivities (Scheme 1.2).

Scheme 1.2

In 2003, Jørgensen developed the highly enantioselective organocatalytic Michael addition^12 of malonates such as 6 to α,β-unsaturated enones such as 5 using an imidazolidine catalyst 7, which was readily prepared from phenylalanine (Scheme 1.3).
1.1.2 Organocatalytic Mukaiyama-Michael Reaction

The Mukaiyama-Michael reaction has become a powerful method for stereoselective carbon-carbon bond formation, since it was discovered by Mukaiyama in 1974. The classical version of this reaction involves the addition of silyl enol ethers such as 9 to α,β-unsaturated carbonyl compounds 10 for the stereoselective construction of acyclic frameworks such as 11 (Scheme 1.4). The use of silyl enol ethers for additions to α,β-unsaturated carbonyls provides mild reaction conditions increasing the functional group tolerance for these Michael additions.

Scheme 1.4
In 2003, MacMillan and co-workers reported the first organocatalytic Mukaiyama-Michael-type reactions, using 5-silyloxyfurans 12 as nucleophiles to obtain products with the butenolide framework 15. The 2,4-dinitrobenzoic acid (DNBA) salt of imidazolidinone 14 catalyzed the reactions of different enals with silyloxyfurans with excellent selectivities and yields (Scheme 1.5).

Scheme 1.5

The same group also utilized silyloxyoxazoles 16 as nucleophiles. These reactions are promoted by the tryptophan derived catalyst 18 in good yields and high enantioselectivities (Scheme 1.6).

Scheme 1.6
Wang and co-workers demonstrated that aryl-substituted TMS enol ethers \( {\text{20}} \) could also be used as nucleophiles in Mukaiyama-Michael type reactions.\(^{16} \) Several alkyl and aryl TMS enol ethers \( {\text{20}} \) were added to crotonaldehyde as well as to cinnamaldehyde and its derivatives to provide the adducts \( {\text{22}} \) in moderate yields and moderate to high enantioselectivities (Scheme 1.7).

**Scheme 1.7**

Our strategy was to develop an enantioselective organocatalytic Mukaiyama-Michael addition of TIPS furan \( {\text{23}} \) to acrolein \( {\text{24}} \), to establish the \( \gamma \)-butenolide framework \( {\text{29}} \) (Scheme 8). The \( \gamma \)-butenolide skeleton is represented in numerous natural products.\(^{17} \)

The objective of these investigations was to utilize the \( \gamma \)-butenolide framework, obtained from the organocatalytic Mukaiyama-Michael reaction, in the synthesis of \( (S) \)-homocitric acid lactone (enantiomer of the natural product) and its homolog \( (R) \)-perhomocitric acid lactone.\(^{18} \) It is noteworthy that only a few examples of enantioselective organocatalytic Mukaiyama-Michael conjugate additions of furans related to \( {\text{23}} \) and \( \beta \)-substituted \( \alpha,\beta \)-unsaturated aldehydes are known, and the use of acrolein \( {\text{24}} \) as a Michael acceptor in these reactions has not been reported. Conversion of
29 to (S)-homocitric acid lactone 30 provided a new synthesis of this natural product enantiomer, and also established the stereochemistry of the Michael addition of 23 to 29.

Scheme 1.8 Enantioselective synthesis of (S)-homocitric acid lactone and (R)-perhomocitric acid lactone.

1.1.3 Organocatalytic conjugate addition reactions via enamine catalysis

Chiral amines can catalyze the asymmetric conjugate addition of aldehydes and ketones to electron-deficient alkenes (Michael acceptors) such as nitroalkenes, enones, and vinyl sulfones, by the in situ formation of enamines from the starting aldehydes and ketones. The enamine catalysis relies on reversible formation of enamines from a catalytic amount of the amine. The formation of an iminium ion is the first step of the catalytic cycle (Figure 1.3). This results in a significant increase in α-C-H acidity which facilitates enamine formation.1e
Although asymmetric conjugate additions have, over the years, been dominated by the application of chiral Lewis acids as catalysts, more recently organocatalysts have been added as efficient tools.\(^2\)

The following is a brief summary of organocatalytic conjugate addition of ketones to nitroalkenes using enamine catalysis.

In 2001, List \textit{et al.} developed the first enamine-catalyzed asymmetric Michael reaction of ketone \(\text{32}\) to nitroalkenes \(\text{33}.\)\(^{21}\) The reaction was catalyzed by (S)-proline (\(\text{34}\)) in DMSO to afford the desired \(\gamma\)-nitroketones \(\text{35}\) in high yields and good diastereoselectivities, but only low enantioselectivities (Scheme 1.9). In a related study, Enders used methanol as the solvent to obtain better enantio- and diastereoselectivities.\(^{22}\)
Since these reports, several methods have been developed for the organocatalytic Michael addition of ketones to nitroalkenes.\textsuperscript{1,2} For the vast majority of these reactions, chiral amines are used as catalysts.

### 1.2 Functionalized pyrrolidines as organocatalysts for the ketone-nitroalkene conjugate addition reaction

Several catalysts having an \(N\)-containing side chain or heterocycle were developed (Figure 1.4), and either the free amine or the corresponding salts were shown to promote the highly \textit{syn}-selective addition of cyclic and acyclic ketones \textbf{36} to nitroalkenes \textbf{33}\textsuperscript{2c,g} (Scheme 1.10). Quite often the role of the acid co-catalyst (HX, Scheme 1.10) is to promote iminium ion formation, and consequently enamine formation, which results in an overall rate acceleration and increased conversion. Numerous secondary amine based catalysts\textsuperscript{23-29} have been reported for these reactions. A selection of catalysts reported in the early days of the reaction (organocatalytic ketone-nitroalkene conjugate addition) are shown in Figure 1.4.
Scheme 1.10

Figure 1.4 Selected organocatalysts for ketone-nitroalkene conjugate addition
1.3 Chiral primary amines as organocatalysts for the ketone-nitroalkene conjugate addition reaction

Alanine 44 and alanine-containing small oligopeptides have also shown good stereoselectivities in the addition of ketones 36 to nitroalkenes 33\textsuperscript{30} (Scheme 1.11). The L-ala-L-ala dipeptide 45 was more selective than the monomer 44, while the alanine derivative 46 is a much better catalyst than 44 and 45.\textsuperscript{31}

\[
\begin{align*}
\text{R}_1 \text{K} & + \text{(cat. (30 mol\%))} \rightarrow \text{R}_1 \text{KNO}_2 \\
\text{H}_2\text{N} & \text{O} \\
\text{H}_2\text{N} & \text{O} \\
\text{H}_2\text{N} & \text{O} \\
(21\%) & syn/anti = 6/1 \\
\text{ee} & = 81\% \\
\text{H}_2\text{N} & \text{O} \\
\text{H}_2\text{N} & \text{O} \\
\text{H}_2\text{N} & \text{O} \\
(55\%) & syn/anti = 12/1 \\
\text{ee} & = 84\% \\
\text{H}_2\text{N} & \text{O} \\
\text{H}_2\text{N} & \text{O} \\
\text{H}_2\text{N} & \text{O} \\
(92\%) & syn/anti = 27/1 \\
\text{ee} & = 93\%
\end{align*}
\]

Scheme 1.11

1.4 Chiral amino-thioureas and amino-squaramides as organocatalysts for the ketone-nitroalkene conjugate addition reaction

Tsogoeva, Schmatz, and co-workers utilized primary amine derived chiral thiourea catalysts in the Michael reaction of ketones 36 nitroalkenes 33.\textsuperscript{32,33} Thiourea 47 bearing a primary amine promoted the addition of ketones to nitroalkenes (Scheme 1.12)
with moderate diastereoselectivities (up to 6:1 \(dr\)) but excellent enantioselectivities (up to 99% ee). Water plays an important role in the regeneration of the catalyst and enamine formation is accelerated by acidic additives.

Scheme 1.12

Huang and Jacobsen used a similar primary amine thiourea catalyst 49 for the conjugate addition of ketones 36 to nitroalkenes 33. While reactions performed in polar and/or protic solvents proceeded slowly, nonpolar solvents and high concentrations turned out to be beneficial. Thiourea containing catalyst 49 furnished the Michael adducts with excellent anti-selectivity (up to 20:1 \(dr\)) and enantioselectivities (up to 99%). A (Z)-enamine intermediate was proposed for the observed anti-diastereoselectivity (Scheme 1.13).
Scheme 1.13

A chiral squaramide derivative catalyst 51 was reported by Rawal and co-workers for the Michael addition of ketones 36 to nitroalkenes 33 (Scheme 1.14). The squaramide derivative afforded the desired Michael adducts with high diastereo- and enantioselectivities.35

Scheme 1.14

The objective of our study was to utilize the enantiomerically-enriched \( \gamma \)-nitroketone 55, for the stereoselective synthesis of selected alkaloids. The \( \gamma \)-nitroketone can be obtained from the organocatalytic Michael addition of an appropriate cyclic
ketone 52 and nitroalkene 53 via an enamine based Michael addition reaction (Scheme 1.15).

Scheme 1.15

The full potential of the organocatalytic ketone-nitroalkene conjugate addition reactions described above will be realized when the enantiomerically-enriched $\gamma$-nitroketone products find applications in other synthetic endeavours.\textsuperscript{36-39} We therefore chose to examine the application of $\gamma$-nitroketone 55 (1.2.4) in the synthesis of the indolizidine alkaloid (+)-antofine and the quinolizidine alkaloids (+)-julandine and (+)-cryptopleurine.\textsuperscript{40}

\textbf{Figure 1.5} Indolizidine and quinolizidine alkaloids synthesized in this study.
1.5 References


5827.


2008, 14, 9357.

Chapter 2

Enantioselective Synthesis of (S)-Homocitric Acid Lactone and (R)-Per-homocitric Acid Lactone Involving Organocatalysis

This chapter is based on the following publication:


**Contribution of authors**

S. V. Pansare: research supervisor, manuscript preparation.

S. V. Adsool: Initial synthetic experimental work.

R. Dyapa: Synthetic experimental work for a major portion of the publication.
2.1 Introduction

(R)-Homocitric acid (1, Figure 2.1) is a key intermediate in the biosynthesis of L-lysine, an essential amino acid in some yeast and fungi, and it is also a component of the Fe-Mo cofactor in nitrogenase. The unique biological profile of homocitric acid is of interest in the development of antifungal therapies and in the elucidation of the details of nitrogen fixation. Studies toward these objectives require access to enantiomerically enriched (R)-homocitric acid and its analogues, neither of which are commercially available in significant amounts. Consequently, the enantioselective synthesis of homocitric acid, invariably isolated as its γ-lactone, has been actively investigated in recent years. Syntheses of racemic homocitrate and per-homocitrate have also been reported. Close congeners of homocitrate such as the alkyl citrate, isocitrate, or α-alkyl malate motifs are key pharmacophoric units in several bioactive alkaloids, glycosides and antifungal agents. This has added to the interest in substituted α-hydroxy di- and tricarboxylic acid derivatives in recent years.

Figure 2.1 (R)-Homocitric acid (1), (S)-homocitric acid lactone (2) and (R)-per-homocitric acid lactone (3).
The following summary provides an overview of the stereoselective methods for the syntheses of (S)-homocitric acid.

### 2.2 Known synthetic routes to (S)-homocitric acid

The first enantioselective synthesis of (S)-homocitric acid lactone was reported by Thomas and co-workers in 1966 (Scheme 2.1).\(^{6g}\) The synthesis was carried out primarily to establish the absolute configuration of (R)-homocitric acid by the synthesis of its optical isomer, which could be obtained by degradation of (-)-quinic acid. In the first step of this endeavour, quinic acid was oxidized to the ketone 5 using a catalytic oxidation protocol reported by Haslam,\(^{9}\) followed by complete reduction of the ketone moiety in 5 to generate the diol 6.\(^{10}\) Periodate cleavage of the diol followed by in situ oxidation of the dialdehyde provided (S)-homocitric acid lactone.

![Scheme 2.1](image)

**Scheme 2.1**

In 1996, Biellmann and co-workers reported the enantioselective synthesis of (S)-homocitric acid lactone 2 starting from (S)-serine (Scheme 2.2).\(^{6f}\) In a sequence centered around a stereoselective Diels-Alder reaction, the authors used reported methods\(^{11}\) to make the key starting material 7 from (-)-L-serine.
Dioxolanone 7 was subjected to a Diels-Alder reaction with 1,3-butadiene to obtain the cyclohexene derivative 8. Ozonolysis of 8 followed by oxidative workup provided the diacid 9. Hydrolysis of the dioxolanone 9 provided (S)-homocitric acid lactone 2 in a low yield (16%, 96% ee). In the same report, the authors also describe the synthesis of (R)-homocitric acid lactone ent-2, which was prepared from (-)-L-lactic acid.

Huang and Li reported the synthesis of (S)-homocitric acid lactone, using Seebach’s SRS (self-regeneration of stereocenters) methodology,\textsuperscript{11a} from (S)-phenylalanine (Scheme 2.3).\textsuperscript{6a} This strategy depends on using the phenyl group as a latent carboxyl group.\textsuperscript{12}
Scheme 2.3

Thus, compound 11 was prepared from (S)-phenylalanine using a known procedure\textsuperscript{6h,11a} and then stereoselectively alkylated with allyl iodide to give dioxolanone 12. Oxidative hydroboration of compound 12 afforded corresponding alcohol 13. Compound 15 was obtained from the sequential oxidation of alcohol 13 using RuCl\textsubscript{3}/NaIO\textsubscript{4}. Compound 15 was then converted to (S)-homocitric acid lactone by using a known procedure.\textsuperscript{6b}
Tatsumi and co-workers reported a convenient route for the synthesis of (S)-homocitric acid (Scheme 2.4). The synthesis starts with readily available L-malic acid which was first reacted with pivalaldehyde to provide compound 18. Alkylation of the dianion of compound 18 with the iodide 19 afforded compound 20. The synthesis concluded with the hydrolysis of 20 to give the (S)-homocitric acid lactone 2.

![Scheme 2.4](image)

**2.3 Objective**

The objective of this study was to utilize the γ-butenolide framework, obtained from organocatalytic Mukaiyama-Michael reaction, in the synthesis (S)-homocitric acid lactone (enantiomer of natural product) and its homolog (R)-per-homocitric acid lactone.
2.4 Results and discussion

Our approach to homocitric acid lactone is based on the Mukaiyama-Michael reaction\textsuperscript{13} of silyloxy furans and $\alpha,\beta$-unsaturated aldehydes and ketones, which is a useful method for the construction of butenolides. The iminium ion catalyzed version of this reaction was pioneered by MacMillan\textsuperscript{14a,b} and other organocatalytic variants have since been developed.\textsuperscript{14c-g} We reasoned that the use of acrolein as the Michael acceptor in a conjugate addition reaction with an appropriately substituted furan would lead directly to the homocitrate lactone motif (Figure 2.2). It may be noted that only $\beta$-substituted enals had previously been examined as substrates in this reaction.\textsuperscript{14} We anticipated that acrolein would be a more challenging Michael acceptor since the stereoselectivity of the reaction appeared to depend on a $\beta$-substituent in the enal.\textsuperscript{14}

\[
\begin{align*}
\text{CHO} & \quad \text{CHO} \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{H}
\end{align*}
\]

\(n = 1, 2\)

**Figure 2.2** Retrosynthesis of (S)-homocitric acid lactone

With this objective in mind, the furans \textbf{21}\textsuperscript{15a} and \textbf{22} were readily prepared from commercially available $\gamma$-crotonolactone by adapting a literature procedure.\textsuperscript{15b} Secondary amines \textbf{23-26} were chosen as potential catalysts for the organocatalytic conjugate addition reaction of \textbf{21} and \textbf{22} with acrolein (Scheme 2.5). Orienting experiments were conducted with furan \textbf{21} and acrolein in the presence of the MacMillan first generation
catalyst 23 (Table 2.1). Although the required product was not obtained in ethereal solvents, the use of halogenated solvents was beneficial and 27 was obtained in modest yield and in 73% ee in chloroform, with water as an additive (Table 1, Entry 5). The enantioselectivity with the MacMillan catalyst 24 was low. Interestingly, a change in the ester alkyl group had a beneficial effect on enantioselection. Thus, the use of furan 22<sup>16</sup> (benzyl ester) as the nucleophile in CHCl<sub>3</sub>/H<sub>2</sub>O provided the Michael adduct 28<sup>16</sup> in 80% ee and 40% yield. Increasing the amount of acrolein (20 eq., Entry 9) was not beneficial and provided only 19% of 28 with significantly lowered enantiomeric excess (69% ee). As with 21, changing the solvent to THF was detrimental (1% ee). This observation suggests that the reaction is notably sensitive to changes in the solvent and ethereal solvents, in particular, are detrimental to enantioselection. Reactions of 22 in the presence of amines 24, 25 and 26 also provided the butenolide 28 (Table 1, entries 10-18). When 24 was used under the conditions optimized for 23 (CHCl<sub>3</sub>/H<sub>2</sub>O as the solvent) 28 was not obtained. The use of TFA as an additive (instead of water) had a pronounced effect and 28 was obtained, but with low ee (39%, entry 12). In summary, the best conditions for the synthesis of 28 employ the ester 22 with an excess (3 equivalents) of acrolein and catalyst 23 in CHCl<sub>3</sub>/H<sub>2</sub>O as the solvent.
Among the remaining catalysts, the imidazolidinone 24 was superior. Reactions with the prolinol derivative 25 were found to be very capricious in terms of enantioselectivity and the $C_2$-symmetric pyrrolidine 26 was not especially effective as a catalyst (Table 2.1). Overall, the higher efficiency of 23 over 24 is notable in this study. It may be noted that the facial selectivity for the reaction of 21 with $\beta$-substituted acroleins is known to depend on the nature of the $\beta$-substitutent and this substitutent is often necessary for good stereoselectivity.\textsuperscript{14a,d} Since these studies\textsuperscript{14a} were conducted with catalyst 24, an unambiguous stereochemical assignment for adducts 27 and 28 was not possible by analogy to the reported results. However, subsequent reactions of 28 were useful in determining the sense of asymmetric induction in the Mukaiyama-Michael reaction.
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<th>Add.</th>
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<th>28 (%)</th>
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*Chiral HPLC analysis of 28 and of the acetal with (2R,3R)-2,3-butanediol for 27. †2 equiv water. ‡0.2 equiv TFA. ‡reaction at -40 °C. †‡20 equiv acrolein. ‡reaction at 0 °C.

**Table 2.1** Catalyst survey for the Mukaiyama-Michael reaction of acrolein with furan nucleophiles

With the ester 28 (80% ee) in hand, we proceeded to convert it into the target homocitric acid lactone via a dehomologation/oxidation protocol (Scheme 2.6).
Acetalization of 28 with trimethylorthoformate followed by treatment of the crude acetal with Hunig’s base provided the enol ether 29 as a mixture of stereoisomers \((\text{trans/cis} = 2/1)\).\(^{16}\) Oxidative cleavage of the enol ether \((\text{OsO}_4/\text{NaIO}_4)\) provided the acid 30.

Scheme 2.6

Hydrogenation of 30 was anticipated to proceed with concommitant debenzylation. However, the benzyl ester in 30 was resistant to hydrogenolysis \((\text{Pd/C, 2 atm. } \text{H}_2)\) which invariably led to mixtures containing a trace of 2 and the dihydro analog of 30. Nonetheless, selective reduction of the double bond in 30 was possible \((1 \text{ atm. } \text{H}_2)\), which was followed by base hydrolysis of the ester and subsequent acidification to provide \((S)\)-homocitric acid lactone 2 \((90\% \text{ from } 30, \text{Scheme 2.6})\).

The lactone 2 obtained in this study is dextrorotatory and is therefore assigned the \((S)\) configuration \((\left[\alpha\right]_D^{23} = +39.0 \text{ (c 1, H}_2\text{O)}; \text{lit.}^{6c} \left[\alpha\right]_D^{23} = -48.9, \text{c 0.38, H}_2\text{O)}\) for the \((R)\) enantiomer). This assignment also establishes the sense of asymmetric induction in the organocatalytic Michael addition reaction leading to 28.
The proposed mechanism for the organocatalytic Mukaiyama-Michael addition to acrolein is shown in Figure 2. According to MacMillan, the imidazoline salt 23 forms an iminium ion such as 31. Two factors for stereocontrol can be identified in the reaction.\(^{14}\) 

1) Selective formation of \(E\) iminium ion 31 (Figure 2.3)

2) The benzyl group on the catalyst shields the \(si\)-face of the iminium ion.

Taking into consideration these aspects, the furan nucleophile should approach from the less hindered \(re\)-face of the iminium ion as shown in 31, which will lead to the enamine 32. Hydrolysis of enamine 32 will give aldehyde 28 and regenerate the catalyst for further catalytic cycles.

**Figure 2.3** The proposed mechanism for the organocatalytic Mukaiyama-Michael addition to acrolein
Given the recent interest in the higher homologue of \((S)\)-homocitric acid (per-homocitric acid),\(^{5d,6a}\) we converted lactone \(\text{28}\) to a homologue of \(\text{2}\). Oxidation of aldehyde \(\text{28}\) provided the corresponding acid which was hydrogenated to provide the target \((R)\)-per-homocitric acid lactone \((\text{3})\)\(^{16}\) in good yield (85%, Scheme 2.7). It may be noted that \(\text{3}\) is a desymmetrized derivative of the parent, achiral triacid.

![Scheme 2.7](image)

**Scheme 2.7**

### 2.5 Conclusion

Expedient, organocatalysis-based, enantioselective syntheses of \((S)\)-homocitric acid lactone and its homologue have been developed. Notably, the methodology also provides several butenolide intermediates that offer opportunities for chemoselective functionalization. Such reactions may find applications in the synthesis of functionalized, oxygen and nitrogen heterocycles with applications in biology and medicine.\(^{17}\)
2.6 Experimental section

Benzyl-5-triisopropylsiloxy-2-furoate (22):

\[
\text{TIPS} - \text{CO}_2\text{CH}_2\text{Ph}
\]

A solution of \text{s-BuLi} (11.6 mL, 10.5 mmol, 0.900 M solution in cyclohexanes) was added dropwise to a stirred solution of (furan-2-yloxy) triisopropylsilane (2.42 g, 10.1 mmol) in THF (12.0 mL) at -78 °C under nitrogen and the mixture was stirred at -78 °C for an hour. A solution of benzyl chloroformate (1.48 mL, 10.5 mmol) in THF (13.0 mL, cooled at -78 °C) was added, the mixture was stirred for 90 min and then warmed to room temperature. The mixture was concentrated and the residue was dissolved in ethyl acetate (20.0 mL). The solution was washed with saturated aqueous NaHCO\textsubscript{3} (2 x 10.0 mL) followed by brine (20.0 mL). The organic layer was separated, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The residue was purified by flash column chromatography on silica gel (97/3 hexanes/ether). The product obtained contained a volatile impurity which was removed at 120 °C (0.2 mmHg) to provide 1.50 g (40%) of pure \textbf{22} as an orange oil.

IR (neat): 2947, 2869, 1720, 1604, 1531, 1303, 1123 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textit{δ} 7.42-7.31 (m, 5H, Ar\textit{H}), 7.13 (d, 1H, \textit{J} = 3.5, \textit{C}H=CC=O), 5.30 (d, 1H, \textit{J} = 3.5, \textit{C}H=CO), 5.28 (s, 2H, PhCH\textsubscript{2}), 1.34-1.29 (sept, 3H, SiCH), 1.10 (d, 18H, \textit{J} = 7.5, CH\textsubscript{3}CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \textit{δ} 159.9 (COSi), 158.4 (C=O), 136.43 (CC=O), 133.9 (ArCipso), 128.7 (ArC), 128.3 (2 x ArC), 122.2 (C=CC=O), 87.7 (C=CO), 66.0
(PhC), 17.7 (CH₃CH), 12.4 (CH₃CH); HRMS (Cl+): m/z 375.1999 (375.1992 Calc. for C₂₁H₃₁O₄Si, [M+H]⁺).

(R)-Methyl 2-(formylethyl)-2,5-dihydro-5-oxofuran-2-carboxylate (27):

![Formula Image]

To a solution of the imidazolidinone 23 (9.00 mg, 0.030 mmol, 20 mol% with respect to ester 21) in chloroform (0.500 mL) was added water (6.00 μL, 0.330 mmol, 2 equiv. with respect to ester 21), acrolein (0.030 mL, 0.500 mmol) and the ester 21 (50.0 mg, 0.170 mmol) at room temperature. The mixture was stirred at room temperature for 72 h. Water (5.0 mL) was added and the mixture was extracted with dichloromethane (2 x 5.0 mL). The combined extracts were dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 6/4) to provide 8 mg (24%) of aldehyde 27 as a yellow gum.

IR (neat): 3096, 2923, 2853, 1772, 1740, 1722, 1437, 1255, 1178, 1104 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 9.75 (s, 1H, CHO), 7.43 (d, 1H, CH=CHC=O, J = 5.6), 6.19 (d, 1H, J = 5.6), 3.81 (s, 3H, CH₃), 2.61 (m, 2H, CH₂CHO), 2.55-2.50 (m, 1H, CH₂CH₂CHO), 2.31-2.25 (m, 1H, CH₂CH₂CHO); ¹³C NMR (125 MHz, CDCl₃): δ 199.4 (CHO), 171.0 (OC=O), 167.6 (CO₂CH₃), 154.3 (C=CC=O), 122.4 (C=CC=O), 88.6 (OCCO₂CH₃), 53.5 (OCH₃), 37.7 (CH₂CHO), 27.5 (CH₂CH₂); HRMS (Cl+): m/z 199.0605 (199.0606 Calc. for C₉H₁₁O₅, [M+H]⁺); ee (acetal with(2R,3R)-2,3-butanediol):
73% ($t_{\text{major}}$: 16.7 min; $t_{\text{minor}}$: 18.1 min; Chiralpak AS-H, 210 nm, hexanes/iPrOH, 92/8, 1 mL/min).

**(R)**-Benzyl-2-(formylethyl)-2,5-dihydro-5-oxofuran-2-carboxylate (28):

To a solution of the imidazolidinone salt 23 (122 mg, 0.47 mmol, 20 mol% with respect to ester 22) in chloroform (9.0 mL) and water (86.0 µL, 3.80 mmol, 2 equiv. with respect to ester 22) was added acrolein (0.460 mL, 7.20 mmol) and ester 5 (0.90 g, 2.40 mmol) at room temperature. The mixture was stirred at room temperature for 72 h. Dichloromethane (10.0 mL) was added the mixture was washed with water (1 x 10.0 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 1/1) to provide 260 mg (40%) of the aldehyde 28 as a viscous brown liquid.

IR (neat): 3092, 2929, 2735, 1768, 1102 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.70 (s, 1H, CHO), 7.41 (d, 1H, CH=CHC=O, $J$ = 5.0), 7.39-7.32 (m, 6H, ArH), 6.17 (d, 1H, $J$ = 5.0), 5.21 (s, 2H, CH$_2$Ph), 2.59-2.47 (m, 3H, CH$_2$CHO, CH$_2$CH$_2$CHO), 2.30-2.22 (m, 1H, CH$_2$CH$_2$CHO); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 199.6 (CHO), 171.1 (OC=O), 167.1 (CO$_2$Bn), 154.4 (C=CC=O), 134.7(ArCipso), 129.0 (ArC), 129.0 (ArC), 128.6 (ArC), 122.7 (C=CC=O), 88.9 (OCC=O), 68.5 (CH$_2$Ar), 37.8 (CH$_2$CHO), 27.7 (CH$_2$CH$_2$); HRMS (Cl+): $m/z$ 275.0917 (275.0919 Calc. for C$_{15}$H$_{15}$O$_5$, [M+H]$^+$); ee: 80%
\( t_{\text{minor}}: \ 50 \text{ min}; \ t_{\text{major}}: \ 67.6 \text{ min} \) (Chiralpak AS-H, 210 nm, hexanes/iPrOH, 85/15, 1 mL/min).

Other reactions of 22 with acrolein, employing different solvents and/or catalysts at selected temperatures, were carried out according to the procedure described above.

\( (R)\)-Benzy 2,5-dihydro-2-(3-methoxyallyl)-5-oxofuran-2-carboxylate (29):

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Bn} \\
\text{O} & \quad \text{O}_\text{Me}
\end{align*}
\]

Indium triflate (1.7 mg, 0.0030 mmol) was added to a solution of the aldehyde \( 28 \) (165 mg, 0.60 mmol) and trimethyl orthoformate (0.130 mL, 1.20 mmol) in dichloromethane (8.0 mL) at room temperature. The mixture was stirred for 4 min, a second portion of indium triflate (1.70 mg, 0.003 mmol) was added and the stirring was continued further for 6 min. The reaction mixture was then filtered through a plug of neutral alumina and the plug was washed with dichloromethane. The filtrate was concentrated under vacuum to provide 159 mg (83%) the dimethyl acetal of 28 as colourless oil. This was used further without purification.

IR (neat): 2932, 1773, 1456, 1128, 1057 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \)

- 7.40 (d, 3H, \( J = 3.1, \ CH=CHC=O)\), 7.40-7.30 (m, 6H, ArH), 6.16 (d, 1H, \( J = 3.1\), \( CH=CHC=O)\), 5.21 (s, 2H, \( CH_2\text{Ar)\), 4.32 (t, 1H, \( J = 5.0, \ CH(OCH_3)_2)\), 3.28 (s, 3H, \( OCH_3)\), 3.27 (s, 3H, \( OCH_3)\), 2.30-2.24 (m, 1H, \( CH_2C(OCH_3)_2)\), 2.0-1.90 (m, 1H, \( CH_2C(OCH_3)_2)\), 1.70-1.50 (m, 2H, \( CH_2CH_2)\); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \)

- 171.2 (C=C=O), 167.3 (CO\(_2\)CH\(_2\)Ph), 154.4 (CH=CHCO), 134.6 (PhCipso), 128.7 (PhC), 128.7
(PhC), 128.3 (PhC), 122.4 (CH=CHCO), 103.6 (CH(OCH3)₂), 89.5 (OCCO₂CH₂Ph), 68.1 (CH₂Ph), 53.3 (OCH₃), 52.9 (OCH₃), 30.5 (CH₂CH(OCH₃)₂), 26.6 (CH₂CH(OCH₃)₂);

HRMS (CI+): \textit{m/z} 320.1255 (320.1260 \text{ Calc. for C}_{17}H_{20}O_6, M^+) .

The above acetal (150 mg, 0.470 mmol) was dissolved in dichloromethane (0.8 mL) and \textit{N},\textit{N}-diisopropylethylamine (97.0 μL, 0.560 mmol) was added at room temperature. The mixture was cooled to -20 °C and TMSOTf (93.0 μL, 0.52 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 2.5 h after which it was concentrated and filtered through a short silica gel column (hexanes/ethyl acetate, 7/3) to provide 84 mg (62%) of \textbf{29} as a 2:1 mixture of \textit{E}:\textit{Z} isomers.

IR (neat): 2936, 1768, 1655, 1456, 1213, 1107, 1027, 922 cm⁻¹; \textbf{1}H NMR (500 MHz, CDCl₃): Major isomer:  δ 7.40 (d, 1H, \textit{J} = 5.0, CH=CHC=O), 7.36-7.32 (m, 5H, ArH), 6.33 (d, 1H, \textit{J} = 12.7, CH=CHOMe), 6.16 (d, 1H, \textit{J} = 5.6, CH=CHC=O), 5.2 (m, 2H, OCH₂Ph), 4.54-4.49 (m, 1H, CH=CHOMe), 3.43 (s, 3H, OCH₃), 2.75 (dd, 1H, \textit{J} = 14, 8, CH₂C=CHOMe), 2.56 (dd, 1H, \textit{J} = 14.0, 7.0, CH₂C=CHOMe). Visible peaks of minor isomer: δ 6.12 (d, 1H, \textit{J} = 5.6, CH=CHC=O), 5.99 (d, 1H, \textit{J} = 7.3, CH=CHOMe), 4.24-4.20 (q, 1H, \textit{J} = 7.3, CH=CHOMe), 3.55 (s, 3H, OCH₃), 2.85 (dd, 1H, \textit{J} = 14.50, 7.30 CH₂), 2.82 (dd, 1H, \textit{J} = 14.5, 7.30, CH₂C=CHOMe); \textbf{1}C NMR (125 MHz, CDCl₃): Major isomer:  δ 171.4 (C=CCO), 167.3 (CO₂CH₂Ph), 154.4 (C=CCO), 151.7 (C=COMe), 150.2 (PhCipso), 134.9 (PhC), 128.9 (PhC), 128.6 (PhC), 122.8 (C=CCO), 93.1 (C=COMe), 90.2 (OCCO₂Bn), 68.1 (CH₂Ph), 56.1 (C=COCH₃), 35.0 (CH₂C=CHOMe). Visible peaks of the minor isomer: δ 171.7 (C=CCO), 167.5 (CO₂CH₂Ph), 154.6 (C=CCO), 121.9 (PhC), 128.8 (PhC), 128.8 (PhC), 128.4 (CPh),
122.2 (C=CCO), 96.5 (C=COMe), 89.9 (OCCO₂Bn), 68.1 (CH₂Ph), 59.9 (C=COCH₃), 30.5 (CH₂C=CHOMe); HRMS (Cl+): m/z 288.1000 (288.0998 Calc. for C₁₆H₁₆O₅, M⁺).

2-((R)-2-((Benzyloxy) carbonyl)-2,5-dihydro-5-oxofuran-2-yl)acetic acid (30):

\[
\begin{align*}
\text{O} & \quad \text{\_C₂H₂O\_} & \quad \text{\_C₂H₂O\_} \\
\text{\_C₂H₂O\_} & \quad \text{\_C₂H₂O\_} & \quad \text{\_C₂H₂O\_} \\
\text{\_C₂H₂O\_} & \quad \text{\_C₂H₂O\_} & \quad \text{\_C₂H₂O\_} \\
\text{\_C₂H₂O\_} & \quad \text{\_C₂H₂O\_} & \quad \text{\_C₂H₂O\_} \\
\end{align*}
\]

A solution of osmium tetroxide (4% in water, 86.0 µL, 0.014 mmol) was added to a stirred solution of the enol ethers 29 (0.080 g, 0.28 mmol) in acetone (4.3 mL) and water (0.50 mL). The mixture was stirred for 10 min and sodium periodate (0.118 g, 0.55 mmol) was added. The mixture was stirred for 20 min and filtered through a pad of Celite. The Celite was washed with acetone and the filtrate was concentrated to provide an aqueous solution which was extracted with ethyl acetate (3 x 5.0 mL). The combined organic layers were dried (Na₂SO₄) and concentrated to provide 64 mg (95%) of (R)-benzyl-2-(formylmethyl)-2,5-dihydro-5-oxofuran-2-carboxylate as a gum. This was used further without purification.

\(^1\text{H NMR (500 MHz, CDCl}_3\): } \delta 9.71 \text{ (s, 1H, CHO), 7.56 (d, 1H, J = 5.6, CH=CHCO), 7.38-7.30 (m, 5H, ArH), 6.24 (d, 1H, J = 5.6, CH=CHO), 5.24-5.18 (AB, 2H, J = 15.0, OCH}_2\text{Ph), 3.23-3.13 (AB, 2H, J = 20.0, CH}_2\text{CHO).}

The above aldehyde (0.064 g, 0.26 mmol) was dissolved in t-butyl alcohol (5.20 mL) and 2-methyl-2-butene (0.55 mL of a 2 M solution in THF, 1.10 mmol). To this was added a solution of NaClO₂ (0.071 g, 0.79 mmol) and NaH₂PO₄ (0.033 g, 0.28 mmol) in water (1.30 mL). The mixture was stirred at room temperature for 3 h and concentrated.
The aqueous solution obtained was extracted with ether (3 x 5.0 mL). The ether layer was separated and the aqueous layer was cooled (<5 °C) and acidified (0.5 M HCl, 3.0 mL) and the acidic solution was extracted with ether (3 x 5.0 mL). The combined extracts were dried (Na₂SO₄) and concentrated to provide 64 mg (95%) of the acid 30. This was used further without purification.

$$^{1}$$H NMR (500 MHz, CDCl₃): δ 9.0-8.0 (br. 1H, CO₂H), 7.56 (d, 1H, J = 5.6, COCH=CH), 7.37-7.29 (m, 5H, PhH), 6.24 (d, 1H, J = 5.6, COCH=CH), 5.22 (s, 2H, PhCH₂O), 3.20-3.05 (AB, 2H, J = 16.9, CH₂COOH).

(S)-2-(Carboxymethyl)-tetrahydro-5-oxofuran-2-carboxylic acid ((S)-Homocitric acid) (2):

The acid 30 (47 mg, 0.17 mmol) was dissolved in ethyl acetate (3.0 mL), Pd/C (10%, 10 mg) was added and the mixture was stirred under hydrogen at atmospheric pressure for 48 h. The reaction mixture was filtered through Celite, the Celite was washed with ethyl acetate (10 mL) and the combined filtrates were concentrated to provide 40 mg (85%) of 2-((S)-2-((benzyloxy)carbonyl)-tetrahydro-5-oxofuran-2-yl)acetic acid.

$$^{1}$$H NMR (500 MHz, CDCl₃): δ 7.39-7.33 (m, 5H, ArH), 5.24 (AB, 2H, J = 12.0, OCH₂Ph), 3.19 (d, 1H, J = 17.1, CH₂COOH), 3.04 (d, 1H, J = 17.1, CH₂COOH), 2.65-2.50, (m, 3H, CH₂CH₂), 2.36-2.29 (m, 1H, COCH₂CH₂).
The above ester (38 mg, 0.14 mmol) was dissolved in THF (0.50 mL), aqueous NaOH (2 M, 0.50 mL) was added and the mixture was stirred at ambient temperature for 15 h. The THF was removed under reduced pressure and the resulting aqueous solution was extracted once with dichloromethane. The aqueous solution was cooled, acidified with HCl (0.50 M) to pH 1 and extracted with dichloromethane (3 x 5.0 mL). The combined extracts were dried (Na₂SO₄) and concentrated to provide 25 mg (97%) of (S)-homocitric acid (2) that was pure by ¹H NMR.

IR (solid): 3500-2800 (br), 1717, 1416, 1170, 1064, 942, 870 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 3.39 (d, 1H, J = 17.5, CH₂COOH), 3.05 (d, 1H, J = 17.5, CH₂COOH), 2.75-2.69 (m, 2H, CH₂C=O), 2.60-2.54 (m, 1H, CH₂CH₂), 2.47-2.40 (m, 1H, CH₂CH₂); MS (APCI negative): m/z 187 [M-H]⁻; (APCI positive): m/z 189 [M+H]⁺; [α]D²³: +39.0 (c 1, H₂O).

(R)-2-(2-Carboxyethyl)-tetrahydro-5-oxofuran-2-carboxylic acid ((R)-Per-homocitric acid) (3):

To a solution of the aldehyde (500 mg, 1.82 mmol) in t-butyl alcohol (8.0 mL) was added 2-methyl-2-butene (3.82 mL of 2 M soln. in THF, 7.65 mmol) followed by dropwise addition of a solution of NaClO₂ (494 mg, 5.46 mmol) and NaH₂PO₄ (219 mg, 1.82 mmol) in water (32.0 mL). The mixture was stirred at ambient temperature for 3 h and the t-butyl alcohol was removed under reduced pressure. The resulting mixture was extracted with ether (2 x 10.0 mL). The aqueous layer was cooled
to 0 °C and acidified with HCl (0.50 M). The acidic solution was extracted with ethyl acetate (2 x 10.0 mL) and the combined extracts were dried (Na2SO4) and concentrated to provide 500 mg (94%) of the acid as a white solid. This was pure by 1H NMR (500 MHz) and was used further without purification.

IR (neat): 3091, 1734, 1706, 1499, 1456, 1236, 1172, 1088, 1053, 905, 819, 750 cm⁻¹. 1H NMR (500 MHz, CDCl₃): δ 7.41-7.40 (d, 1H, J = 5.60, COCH=CH), 7.37-7.26 (m, 5H, PhH), 6.19-6.18 (d, 1H, J = 5.6, COCH=CH), 5.21 (s, 2H, PhCH₂O), 2.59-2.53 (m, 1H, CHCH₂COOH), 2.44-2.40 (m, CH₂COOH), 2.31-2.25 (m, CHCH₂COOH). HRMS (CI+): m/z 291.0871 (291.0869 Calc. for C₁₅H₁₄O₆, [M+H]+); [α]D²₀: + 86.0 (c 1, CH₂Cl₂).

To a solution of the above acid (100 mg, 0.34 mmol) in THF (15.0 mL) was added Pd/C (10%, 30 mg) and the mixture was shaken under hydrogen at 50 psi for 7 h. The mixture was filtered through a pad of Celite and the Celite was washed with THF (2x10.0 mL). The combined filtrates were concentrated under reduced pressure to provide 62 mg (90%) of per-homocitric acid lactone (14) that was pure by 1H NMR. If necessary, further purification can be achieved by sonication of a mixture of the diacid and chloroform (10 mg/mL) for 10-15 min. followed by decantation of the chloroform layer to remove the dissolved impurities.

IR (neat): 2938, 1733, 1709, 1243, 1169, 1074, 1044 cm⁻¹; 1H NMR (500 MHz, CDCl₃+DMSO-d₆): δ 9.25-8.25 (br, CO₂H), 2.70-2.60 (m, 1H, CH₂CO), 2.60-2.50 (m, 3H, CH₂CO), 2.48-2.38 (m, 2H, CH₂CH₂CO), 2.22-2.14 (m, 2H, CH₂CH₂CO); 13C NMR (125 MHz, CDCl₃+ DMSO-d₆): δ 175.9 (C=O), 174.8 (C=O), 173.1 (C=O), 85.6 (C-O), 85.6 (C-O),
32.4 (CH$_2$CO), 31.8 (CH$_2$CO), 29.0 (CH$_2$), 28.1 (CH$_2$); MS (APCI negative): $m/z$ 200.6 (M-2); HRMS (Cl$^+$): $m/z$ 203.0554 (203.0556 Calc. for C$_8$H$_{11}$O$_6$, [M+H]$^+$); $[\alpha]_D^{23}$: -3.8 (c 1, THF).
2.7 References


acid, see: Thomas, U.; Kalyanpur, M. G.; Stevens, C. M. Biochemistry, 1966, 5, 2513.


7) (a) Li, Z.-C.; Xu, J.-Q. Molecules 1998, 3, 31. (b) Ref. 5d.


2.8 Selected $^1$H NMR and $^{13}$C NMR spectral data
CDCl₃, 500 MHz

CDCl₃, 125 MHz
**Figure 27**

CDCl$_3$, 500 MHz

CDCl$_3$, 125 MHz
CDCl₃, 500 MHz

CDCl₃, 125 MHz
DR-3305C
DRR-02-51H

28b
CDCl₃, 500 MHz

3
CDCl₃, 500 MHz
Perhomo citric acid (13C)

3

CDCl₃, 125 MHz
Chapter 3

A Simple Enantioselective Route to Functionalized Indolizidines.

Synthesis of (+)-Antofine

This chapter is based on the following publication:


Contribution of authors

S. V. Pansare: Research supervisor, manuscript preparation

R. Lingampally: Synthetic experimental work on ipalbidine, which is the second target molecule prepared in the above publication, and manuscript preparation

R. Dyapa: Synthetic experimental work and manuscript preparation
3.1 Introduction

The indolizidine motif is a prominent structural unit in numerous alkaloids\(^1\) and also constitutes a major class of glycosidase inhibitors.\(^2\) In addition, several indolizidines have an interesting biological profile which includes antibacterial, antiviral, antitumor and antidiabetic properties.\(^3\) Aryl-substituted indolizidines are also of interest; either as bioactive natural products\(^4\) or as peptidomimetics.\(^5\) Accordingly, the synthesis of arylindolizidines continues to be intensely investigated and general synthetic strategies toward aryl-fused\(^6\text{a-c}\) or aryl-substituted indolizidines\(^6\text{d-h}\) as well as other functionalized indolizidines have been reported.\(^7\) The phenanthroindolizidine alkaloid (−)-antofine, an enantiomer of (+)-antofine, has potent anticancer activity.\(^8\) The anticancer activity may occur through the inhibition of protein and nucleic acid synthesis.\(^9\) Antofine has also shown other medicinal properties, including antibiotic, antifungal and antiviral activity.\(^10\)

![Figure 3.1 Structures of selected phenanthroindolizidine alkaloids](image)

**Figure 3.1** Structures of selected phenanthroindolizidine alkaloids
3.2 Recent syntheses of (+)-antofine

The following summary provides an overview of the recent reports since 2010 on the synthesis of enantiomerically pure antofine.

In 2010, Georg and co-workers reported an enantioselective total synthesis of (+)-antofine (Scheme 3.1).\textsuperscript{11a} Their synthesis starts with Boc-S-proline (1), which was homologated using standard Arndt-Eistert reaction conditions. The acid was first converted into diazoketone 2 which was then subjected to a Wolff rearrangement with catalytic CF\textsubscript{3}CO\textsubscript{2}Ag in the presence of freshly distilled N,O-dimethylhydroxylamine to provide the Weinreb amide 3. Ynone 4 was prepared by treatment of 3 with ethynylmagnesium bromide.
Initially, enaminone 5 was prepared from the ynone 4 by stepwise treatment with aqueous HCl in dioxane followed by addition of methanolic K₂CO₃. However, this protocol led to racemization of 4. Alternatively, a milder deprotection protocol (formic acid and NaI) was used to minimize racemization of 4. Treatment of the obtained vinyl iodide with K₂CO₃ gave enaminone 5. A Pd(II)-catalyzed C-H arylation of 5 with an appropriate organotrifluoroborate produced the aryldizolidinone 6. 1,4-Reduction of enaminone 6 using L-selectride and trapping of the resulting enolate with 2-(N,N-bis(trifluoromethanesulfonyl)amino)-5-chloropyridine (Comins reagent) provided the
triflate 7. (+)-Secoantofine (8) was prepared from 3,4-dimethoxyphenylzinc bromide and triflate 7, using the Negishi cross-coupling protocol. In the final step, the phenanthrene framework was constructed with a PhI(O_2CCF_3)_2 mediated oxidative cyclization involving the aryl groups to provide the title compound (+)-antofine.

Wang and coworkers reported a short and efficient route to enantiomerically pure antofine, involving Parham-type cycloacylation as the key step. The synthesis began with ester 10 which was prepared by a procedure described by Wang and co-workers. Reduction of ester 10 using LAH provided alcohol 11. Alcohol 11 was brominated to afford the dibromo compound 12. Amide 14 was prepared from the alkylation of (S)-N,N-diethylpyrrolidine-2-carboxamide (13) with dibromide 12, using K_2CO_3 as a base (Scheme 3.2).

![Scheme 3.2](image)

Amide 14 was treated with nBuLi to effect ring closure. Subsequent reduction of the ketone (NaBH_4) obtained in the cyclization step provided the aminol 15 stereoselectively. Dehydroxylation of 15 using triethylsilane and trifluoroacetic acid provided the title compound (+)-antofine (Scheme 3.3).
Herndon and co-workers reported an enantioselective synthesis of (+)-antofine. The key steps in their synthesis are alkyne hydration, a chromium-carbene complex mediated net [5 + 5] cycloaddition process and a Bischler-Napieralski cyclization reaction.\textsuperscript{14} The synthesis began with enantiomerically pure 2-ethynylpyrrolidine derivative 17 which was prepared in seven steps from Boc protected proline by using previously reported methods.\textsuperscript{15} Sonogashira coupling of dihaloveratrole derivative 16 with 17 provided the bromoalkyne 18 (Scheme 3.4).
Hydration of bromoalkyne 18 using mercuric trifluoroacetate, mercuric oxide and sodium hydrogen carbonate afforded the ketone 19 regioselectively. Sonagashira coupling of TMS-acetylene with bromoketone 19 afforded the ketone 20. Phenanthrene derivative 23 was obtained from a net [5 + 5] cycloaddition of ketone 20 and the carbene complex 21 involving a tandem process (isobenzofuran 20a formation followed by exo-selective intramolecular Diels-Alder reaction to form benzo-oxanorbornene 20b, opening of the benzo-oxanorbornene ring system followed by dehydration step).

Scheme 3.5
Dehydrogenation of compound 22 using palladium on carbon provided 23. Bischler-Napieralski-type cyclization of phenantherene derivative 23, using triflic anhydride, provided the corresponding cyclic amide which was reduced to the title compound (+)-antofine (Scheme 3.5).

3.3 Objective

Our interest in indolizidines stems from our studies on the organocatalytic synthesis of $\gamma$-nitroketones from cyclic ketones and 2-nitrovinylarenes via an enamine-based Michael addition reaction.\textsuperscript{16} This reaction has been extensively studied and the development of new catalysts for the process continues at a remarkable pace.\textsuperscript{17} Undoubtedly, the full potential of the organocatalytic ketone-nitroalkene Michael reaction will be realized only when the $\gamma$-nitroketone products are utilized in target oriented synthesis, but this has been relatively unexplored.\textsuperscript{18} We therefore chose to examine the application of $\gamma$-nitroketone 24 (Scheme 3.6) in the synthesis of (+)-antofine (9).

Scheme 3.6
3.4 Results and discussion

Our studies began with the synthesis of the appropriate γ-nitroketone starting material for (±)-antofine (9). The organocatalytic Michael addition of cyclohexane-1,4-dione monoethylene ketal and 4-methoxy-β-nitrostyrene, employing the triamine salt catalyzed protocol developed in the Pansare group, provided the nitroketone 24 in good yield and stereoselectivity (er = 96/4, dr > 19/1). Baeyer-Villiger oxidation of 24 provided the lactone 28 in excellent yield (98%). Methanolysis of 28 and subsequent hydrolysis of the ketal generated the highly functionalized octanoate 29 (Scheme 3.7, 88% over two steps) that has all the required carbon atoms for the indolizidine framework.

Scheme 3.7
Reduction of the nitroketone 29 with zinc in aq. ammonium chloride provided the nitrone 30 which was anticipated to undergo a stereoselective reduction due to the 1,3 disposition with the secondary alcohol stereocenter. Treatment of 30 with L-Selectride® or LAH at -78 °C resulted in reduction of the ester. Reduction with NaBH₄ was stereorandom and also led to reduction of the ester, indicating the need for a milder reducing agent. Accordingly, Me₄NBH(OAc)₃ was examined which gratifyingly provided the hydroxylamine 31 (83%) as a single diastereomer, presumably via a hydroxyl-directed reduction (Scheme 3.8). At this stage, 31 was assigned the shown stereochemistry which was assumed to derive from an intramolecular, hydroxyl directed reduction of 30.¹⁹ Reduction of the N-O bond in 31 was achieved with indium metal to provide a mixture of the amino ester 32 and the corresponding indolizidinone 33 resulting from cyclization of the amino ester. This product mixture was treated with DIPEA in refluxing isopropyl alcohol to complete the lactamization (Scheme 3.8).
Scheme 3.8

The synthesis of (+)-antofine (9) was achieved from the lactam 33. Oxidation of 33 (pyridine.SO₃) provided the ketolactam 34. Conversion of 34 to the enol triflate 35 followed by a Suzuki-Miyaura coupling²⁰ of 35 with 3,4-dimethoxyphenylboronic acid furnished the lactam 36. Reduction of the amide in 36 provided secoantofine 8. Finally, oxidative biaryl coupling in 8 employing VOF₃ provided (+)-antofine (Scheme 3.9) (9, 77%)
In conclusion, an organocatalytic Michael addition based enantioselective synthesis of the indolizidine framework was developed. This approach has potential applications in the synthesis of congeners and analogs of the target alkaloids by a) variation in the ketone, nitrostyrene and the aryl cross-coupling partner, and b) embellishment of the propanoate side chain in 31. The utility of our strategy is augmented by the large number of methods available for the stereoselective synthesis of a variety of \( \gamma \)-nitroketones.\(^{21} \)
3.6 Experimental section

(7S)-7-[(1R)-1-(4-Methoxyphenyl)-2-nitroethyl]-1,4-dioxaspiro[4.5]decan-8-one (24):

To a solution of 1,4-cyclohexanedicarboxylate monoethylene ketal (13.0 g, 83.7 mmol), \(N^1,N^1\)-dimethyl-\(N^2\)-(((S)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine \(16\) (572 mg, 3.34 mmol) and \(p\)-toluenesulfonic acid monohydrate (634 mg, 3.34 mol) was added a solution of 4-methoxy-\(\beta\)-nitrostyrene (3.00 g, 16.7 mmol) in DMF (30 mL) and the resulting solution was stirred at ambient temperature for 48 h. Ethyl acetate (100 mL) was added and the solution washed with water, aq. HCl (3 N), dried (Na\(_2\)SO\(_4\)) and concentrated. The residue obtained was purified by flash chromatography on silica gel to provide 4.60 g of a solid. This was dissolved in ethyl acetate (23 mL) and precipitated by addition of hexanes (70 mL). The procedure was repeated once to provide 3.50 g (62%) of 24 with 96% ee. In repeated runs, 24 was obtained in 90-96% ee.

IR (neat): 2897, 2360, 1712, 1548, 1512, 1247, 1132, 1026, 950, 832 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.09 (d, 2H, \(J = 8.7\), ArH), 6.85 (d, 2H, \(J = 8.7\), ArH), 4.91 (dd, 1H, \(J = 12.3, 4.8\), CH\(_2\)NO\(_2\)), 4.56 (dd, 1H, \(J = 12.3, 9.9\), CH\(_2\)NO\(_2\)), 4.00-3.83 (m, 4H, OCH\(_2\)CH\(_2\)O), 3.78 (s, 3H, OCH\(_3\)), 3.04-2.98 (m, 1H, ArCH), 2.72-2.66 (dt, 1H, \(J = 13.8, 6.4\), COCH), 2.48-2.43 (m, 1H, COCH\(_2\)), 2.07-2.01 (m, 1H, COCH\(_2\)), 1.98-1.92 (dt, 1H, \(J = 13.3, 5.2\), CHCH\(_2\)), 1.72-1.68 (m, 1H, CHCH\(_2\)), 1.57-1.51 (apparent t, 2H, \(J = 13.4, 6.4\), COCH), 1.51-1.43 (m, 1H, COCH\(_2\)), 1.49-1.44 (m, 1H, COCH\(_2\)), 1.36-1.30 (m, 1H, COCH), 1.18-1.14 (m, 1H, COCH), 0.83 (t, 3H, CH\(_3\)).
CH$_2$CH$_2$), $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 210.4 (CO), 159 (ArC), 129.2 (2xArC), 129.0 (ArC), 114.4 (2xArC), 107.1 (OCO), 79.1 (CH$_2$NO$_2$), 64.8 (OCH$_2$CH$_2$O), 64.6 (OCH$_2$CH$_2$O), 55.2 (OCH$_3$), 48.3 (COCH), 42.7 (CHCH$_2$NO$_2$), 39.3 (COCH$_2$), 38.6 (CH$_2$), 35.1 (CH$_2$); MS (APCI, pos.): $m/z$ 336 (M+1); HRMS (EI): $m/z$ 335.1367 (335.1369 calc. for C$_{17}$H$_{21}$NO$_6$ (M$^+$)); HPLC (Chiralpak AS-H, hexane/2-propanol: 60/40, flow rate 1.0 mL/min, 254 nm): $t_{\text{minor}} = 9.45$ min, $t_{\text{major}} = 12.97$ min, ee = 93%, dr = 20:1 (average values from multiple reactions).

(S)-7-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro[4.6]undecan-9-one (28):

To a solution of the nitroketone 24 (3.10 g, 9.24 mol) in anhydrous dichloromethane (60 mL) at ambient temperature, was added solid sodium phosphate (3.21 g, 12.0 mol) followed by $m$-chloroperbenzoic acid (~77%, 4.94 g, 28.7 mmol). The resulting white slurry was stirred vigorously for 16 h. Dichloromethane (100 mL) was added and the solution was washed with 5% aq. NaOH (2 x 60 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated to provide 3.20 g (98%) of 28 as a white, solid foam. This material was pure by $^1$H NMR (500 MHz) and was directly used further.
IR (neat): 2962, 1736, 1550, 1514, 1249, 1154, 1117, 1099, 1029, 834 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.15 (d, 2H, \(J = 11.6\), Ar\(H\)), 6.89 (d, 2H, \(J = 11.6\), Ar\(H\)), 4.94 (dd, 1H, \(J = 12.6, 4.7\), CH\(_2\)NO\(_2\)), 4.76-4.69 (m, 2H, CH\(_2\)NO\(_2\),(CO)OCH\(_2\)O), 3.89-3.85 (m, 2H, OCH\(_2\)CH\(_2\)O), 3.80 (4H, OCH\(_3\), OCH\(_2\)CH\(_2\)O), 3.62-3.58 (dt, 1H, \(J = 9.3, 4.7\), Ar-CH\(_3\)), 3.54-3.51 (m, 1H, OCH\(_2\)CH\(_2\)O), 2.88-2.81 (m, 1H, CH\(_2\)CO), 2.65-2.60 (m, 1H, CH\(_2\)CO), 1.93-1.89 (m, 2H, CH\(_2\)(C)CH\(_2\)), 1.86-1.79 (m, 2H, CH\(_2\)(C)CH\(_2\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 173.5 (CO), 159.5 (Ar\(C\)), 129.3 (2xAr\(C\)), 127.8 (Ar\(C\)), 114.6 (2xAr\(C\)), 107.2 (OC\(_O\)), 77.7 (CH\(_2\)NO\(_2\)), 75.8 (COC\(_O\)), 65.0 (OCH\(_2\)CH\(_2\)O), 64.3 (OCH\(_2\)CH\(_2\)O), 55.3 (OCH\(_3\)), 48.1 (OCHCH\(_2\)), 41.5 (CHCH\(_2\)NO\(_2\)), 33.1 (CH\(_2\)(C)CH\(_2\)), 29.3 (CH\(_2\)(C)CH\(_2\)); HRMS (Cl): \(m/z\) 351.1308 (351.1318 calc. for C\(_{17}\)H\(_{21}\)NO\(_7\) [M+H]\(^+\)).

**Methyl 3-(2-((2S, 3R)-2-hydroxy-3-(4-methoxyphenyl)-4-nitrobutyl)-1, 3-dioxolan-2-yl) propanoate (28a):**

![Image of the compound](image)

A solution of the lactone 28 (3.4 g, 9.7 mmol) in methanol (70 mL) was cooled to 0 °C and potassium carbonate (2.67 g, 19.4 mmol) was added. The mixture was stirred at room temperature for 30 min. The mixture was cooled to 0 °C, neutralized with aq. HCl (0.5 M) and the solution was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated to provide 3.5 g (95%) of the
nitroketal 28a as a light brown gum. This material was pure by $^1$H NMR (500 MHz) and was directly used further.

IR (neat): 3501, 2956, 1732, 1548, 1514, 1249, 1179, 1134, 1030, 831 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.10 (d, 2H, $J = 8.6$, ArH), 6.85 (d, 2H, $J = 8.6$, ArH), 5.04 (dd, 1H, $J = 12.7$, 5.2, CH$_2$NO$_2$), 4.58 (dd, 1H, $J = 9.7$, 12.7, CH$_2$NO$_2$), 4.05-4.02 (m, 1H, ArCH) 4.01-3.91 (m, 4H, OCH$_2$CH$_2$O), 3.86 (s, 1H, CHO$_2$H), 3.78 (s, 3H, ArOCH$_3$) 3.64 (s, 3H, OCH$_3$), 3.42-3.37 (dt, 1H, $J = 5.3$, 9.5, CHOH), 2.25-2.16 (m, 2H, CO$_2$CH$_2$), 2.02-1.97 (m, 1H, CH$_2$(CH)$_2$), 1.79-1.85 (m, 1H, CH$_2$(CH)$_2$), 1.64-1.62 (m, 2H, CH$_2$(CH)$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 173.5 (CO$_2$CH$_3$), 159.2 (ArC), 129.2 (ArC), 129.1 (ArC), 114.5 (ArC), 110.9 (OCO), 78.5 (CH$_2$NO$_2$), 70.0 (CHOH), 65.1 (OCH$_2$CH$_2$O), 64.7 (OCH$_2$CH$_2$O), 55.2 (ArOCH$_3$), 51.7 (CO$_2$CH$_3$), 50.3 (HO-CCH$_2$), 40.5 (Ar-CH), 31.7 (CH$_2$CH$_2$CO$_2$CH$_3$), 28.5 (CH$_2$CO$_2$CH$_3$); MS (APCI, pos.): $m/z$ 366 (M-OH); HRMS (Cl): $m/z$ 384.1647 (384.1658 calc. for C$_{18}$H$_{26}$NO$_8$[M+H]$^+$.)

(6$S$,7$R$)-Methyl 6-hydroxy-7-(4-methoxyphenyl)-8-nitro-4-oxooctanoate (29):

To a solution of the nitroketal 28a (3.50 g, 10.3 mmol) in methanol (70 mL) at 0 °C, was added aq. HCl (6 N, 40 mL), and the mixture was stirred at room temperature overnight. The methanol was removed under reduced pressure and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried
(Na₂SO₄) and concentrated to provide 2.90 g (95%) of the nitroketone 29 as a light brown solid. This material was pure by ¹H NMR (500 MHz) and was directly used further.

IR (neat): 3436, 2953, 1723, 1710, 1553, 1514, 1380, 1251, 1204, 1179, 1157, 1102, 1032, 819 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.10 (d, 2H, J = 6.6, ArH), 6.87 (d, 2H, J = 6.6, ArH), 5.07 (dd, 1H, J = 5.1, 12.8, CH₂NO₂), 4.60 (dd, 1H, J = 9.9, 12.8, CH₂NO₂), 4.24-4.19 (m, 1H, Ar-CH), 3.79 (s, 3H, ArOCH₃) 3.65 (s, 3H, OCH₃), 3.55 (d, 1H, J = 4, CHOH) 3.51-3.46 (dt, 1H, J = 5.2, 9.8, CHOH), 2.57-2.64 (m, 4H, CH₂COCH₂), 2.41-2.52 (m, 2H, CH₂CO₂CH₃ ); ¹³C NMR (125 MHz, CDCl₃): δ 209.7 (CO), 173.1 (CO₂CH₃), 159.3 (ArC) 129.0 (2xArC), 128.6 (ArC), 114.6 (OCO), 78.4 (CH₂NO₂), 69.8 (CHOH), 55.2 (ArCOCH₃), 51.9 (CO₂CH₃), 49.2 (HO-CCH₂CO), 47 (Ar-CH), 37.7 (COCH₂), 27.4 (CH₂CO₂CH₃); MS (APCI, pos.): m/z 322 (M-OH); HRMS (CI): m/z 322.1284 (322.1291 calc. for C₁₆H₂₀NO₆ (M-OH)).

(3R,4S)-4-Hydroxy-6-(3-methoxy-3-oxopropyl)-3-(4-methoxyphenyl)-2,3,4,5-tetrahydropyridine-1-oxide (30):

A solution of NH₄Cl (0.37g, 6.0 mmol) in water (5 mL) was added to a solution of the nitroketone 29 (2.3 g, 6.0 mmol) in THF (20 mL). Activated Zn powder (4.4 g, 0.060 mmol) was added and the mixture was stirred vigorously at room temperature under nitrogen for 3 h. The mixture was filtered (Celite), the residue was washed with
THF, and the combined filtrates were concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL) and the mixture was washed with water (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to provide 2.0 g, (95%) of **30** as brown foam. This material was pure by $^1$H NMR (500 MHz) and was directly used further. An analytical sample was obtained by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH, 95/5).

IR (neat): 2953, 1738, 1512, 1434, 1249, 1175, 1134, 1070, 1033 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.22 (d, 2H, $J = 8.6$, ArH), 6.88 (d, 2H, $J = 8.6$, ArH), 4.34-4.29 (br t, 1H, $J = 13.3$, ArCH), 4.18 (br s, 1H, CHOCH), 3.89 (dd, 1H, $J = 14.9, 5.5$, CH$_2$N), 3.79 (s, 3H, ArOCH$_3$), 3.68 (s, 3H, CO$_2$CH$_3$), 3.20 (dd, 1H, $J = 11.9, 4.8$, CH$_2$N), 2.94-2.68 (m, 6H, CH$_2$C=NN, COCH$_2$CH$_2$, COCH$_2$)$_{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.7 (CO), 159.1 (ArC), 144.7 (C=NO), 129.7 (ArC), 128.8 (2xArC), 114.3 (2 x ArC), 65.2 (CH$_2$NO), 57.8 (Ar-CH), 55.3 (OCH$_3$), 51.8 (CO$_2$CH$_3$), 43.7 (CHOH), 38.7 (CH$_3$CO$_2$CH$_3$), 28.3 (N=CCH$_2$), 27.5 (N=CCH$_2$); MS (APCI, pos.): m/z 308 (M+1); HRMS (CI): m/z 308.1499 (308.1498 calc. for C$_{16}$H$_{22}$NO$_5$ [M+H]$^+$).
Methyl 3-(2R,4S,5S)-4-hydroxy-5-(4-methoxyphenyl)-N-hydroxypiperidin-2-yl)propanoate (31):

To a solution of tetramethylammonium triacetoxyborohydride (3.2 g, 0.012 mol) in acetonitrile (10 mL) was added acetic acid (10 mL). The mixture was stirred at 0 °C for 5 min and a solution of the nitrone 30 (1.9 g, 0.006 mol) in acetonitrile (5 mL) was added. The mixture was stirred at 0 °C for 1 h and the pH of the solution was adjusted (pH 7 to 8) with aqueous NaOH (5% solution). The mixture was extracted with dichloromethane (2 x 50 mL) and the combined extracts were dried (Na₂SO₄) and concentrated to give 1.59 g (83%) of 31 as a white solid. This material was pure by ¹H NMR (500 MHz) and was directly used further.

IR (neat): 3518, 3203, 2920, 1715, 1511, 1437, 1245, 1205, 1175, 1105, 1025, 981, 819 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.15 (d, 2H, J = 8.7, ArH), 6.88 (d, 2H, J = 8.7, ArH), 3.93 (d, 1H, J = 12.3 ArCH), 3.79 (s, 3H, OCH₃), 3.69 (s, 3H, COCH₃), 3.52-3.44 (t, 1H, J = 10.1, OCH), 3.31-3.13 (m, 1H, ArCHCH₂), 3.07-2.9 (m, 1H, ArCHCH₂), 2.53-2.32 (m, 2H, COCH₂), 2.22-2.14 (m, 1H, NCH), 2.04-1.98 (dt, 1H, J = 13.3, 5.2, OCHCH₂), 1.92-1.84 (m, 1H, OCHCH₂), 1.74-1.66 (m, 1H, NCHCH₂), 1.54-1.50 (m, 1H, NCHCH₂); MS (APCI, pos.): m/z 272 (M-OCH₃+1), 310 (M+1); HRMS (CI): m/z 310.1636 (310.1654 calc. for C₁₆H₂₄NO₅ [M+H]).
(6R,7S,8aS)-Hexahydro-7-hydroxy-6-(4-methoxyphenyl)indolizin-3(5H)-one (33):

The hydroxylamine 31 (1.65 g, 5.34 mmol) was dissolved in a mixture of EtOH (20 mL) and saturated aqueous NH₄Cl (10 mL). Indium powder (1.2 g, 0.01 mol) was added and the mixture was heated to reflux for 4 h. The mixture was cooled, filtered through a pad of Celite, and the filtrate was concentrated. The residue was diluted with dichloromethane (40 mL) and the aqueous layer was separated. The organic layer was washed with saturated aqueous NaHCO₃ solution (3 x 10 mL) dried (Na₂SO₄) and concentrated to give 1.04 g of a yellow gum. This material is a mixture of the amino ester and the cyclization product (lactam 33, ~30%). The mixture was therefore directly converted to the lactam as follows:

To a solution of the crude amino ester 32 and lactam 33 mixture (1.00 g) in THF (15 mL) was added diisopropylethyl amine (1.5 mL, 0.0080 mol) and the solution was heated to reflux for 5 h. The THF was removed under reduced pressure, the residue was dissolved in dichloromethane (30 mL) and the resulting solution was washed with aqueous HCl (0.5 M, 2 x 10 mL). The organic layer was dried (Na₂SO₄) and concentrated to provide 0.82 g (60% from 31) of the lactam (33) as a pale yellow foam. This material was pure by ¹H NMR (500 MHz) and was directly used further.
IR (neat): 3356, 2923, 1651, 1542, 1242, 1175, 1027, 828 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.17 (d, 2H, J = 8.7, ArH), 6.89 (d, 2H, J = 8.7, ArH), 4.13 (br s, 1H, CHO\(_2\)), 4.12 (dd, 1H, J = 4.7, 12.6, NCH\(_2\)), 3.97-3.91 (m, 1H, ArCH\(_3\)), 3.8 (s, 3H, OCH\(_3\)), 3.37-3.32 (t, 1H, J = 12.6, NCH\(_3\)), 2.81-2.77 (dt, 1H, J = 4.6, 1.8, NCH), 2.44-2.41 (br t, 2H, J = 7.1, COCH\(_2\)), 2.29-2.22 (m, 1H, CH\(_2\)CHO\(_2\)), 2.21-2.16 (m, 1H, NCH\(_2\)CH\(_2\)), 1.65-1.61 (m, 2H, CH\(_2\)CH\(_2\)), 1.6-1.52 (dt, 1H, J = 2.4, 9.6, NCH\(_2\)CH\(_2\)), \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 173.6 (C\(_O\)), 158.8 (ArC\(_{ipso}\)), 131.5 (ArC\(_{ipso}\)), 128.6 (ArC), 114.2 (ArC), 69.1 (CHO\(_2\)), 55.3 (OCH\(_3\)), 50.8 (NCH), 44.8 (NCH\(_2\)), 39.6 (ArCH), 38.1 (HOCH\(_2\)CH\(_2\)), 30.6 (NCOCH\(_2\)), 24.7 (NCH\(_2\)CH\(_2\)); MS (APCI, pos.): m/z 262 (M+1); HRMS (El): m/z 261.1364 (261.1365 calc. for C\(_{15}\)H\(_{19}\)NO\(_3\) (M+)).

\((6R,8aS)-\text{Hexahydro-6-(4-methoxyphenyl)indolizine-3,7-dione (34)}:\)

To a stirred solution of the alcohol 31 (0.20 g, 0.77 mmol) in dichloromethane (7 mL) was added DMSO (3.5 mL) followed by DIPEA (1 mL) at 0 °C. Solid SO\(_3\) pyridine (365 mg, 2.30 mmol) was added portion wise and the mixture was stirred at 0 °C for 1 h. Water (3 mL) was added and the mixture was diluted with dichloromethane (10 mL). The mixture was washed with water (2 x 15 mL) and the organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated to provide a brown solid which was purified by flash chromatography on silica gel (EtOAc) to provide 0.14 g (70%) of 34 as a white solid.
IR (neat): 2955, 1714, 1673, 1515, 1455, 1239, 1186, 1036, 833 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.06 (d, 2H, J = 8.7, ArH), 6.90 (d, 2H, J = 8.7, ArH), 4.59 (dd, 1H, J = 13.1, 6.9, ArCCH), 4.01-3.96 (m, 1H, NCH) 3.80 (s, 3H, OCH₃), 3.63 (dd, 1H, J = 12.0, 6.9, NCH₂), 3.11-3.06 (t, 1H, J = 12.5, NCH₂), 2.74 (dd, 1H, J = 3.8, 13.6, COCH₂), 2.56-2.46 (m, 2H, COCH₂, NCOCH₂) 2.44-2.40 (m, 2H, NCOCH₂CH₂, COCH₂CH₂), 1.83-1.79 (m, 1H, COCH₂CH₂); ¹³C NMR (75 MHz, CDCl₃): δ 205.5 (CO), 173.5 (NCO), 159.1 (ArCOCCH₃), 130.0 (ArCH), 126.4 (ArC), 114.1 (ArCH), 57.2 (NCH), 55.3 (OCH₃), 54.9 (ArCCH), 48.6 (NCH₂), 45.1 (COCH₂), 29.7 (NCOCH₂), 24.7 (COCH₂CH₂); MS (APCI pos.): m/z 260.1 (M+1); HRMS (CI+): m/z 259.1214 (259.1208 calc. for C₁₅H₁₇NO₃ M⁺).

(S)-1,2,3,5,8,8a-Hexahydro-6-(4-methoxyphenyl)-3-oxoindolin-7-yl trifluoromethanesulfonate (35):

![Diagram]

To a suspension of KH (54 mg, 0.39 mmol) in THF (2 mL) was added ketone 34 (0.10 g, 0.39 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h and N-phenyl bis-trifluoromethanesulfonimide (152 mg, 0.42 mmol) was added in one portion and the mixture was stirred for 1h at room temperature. Water (5 mL) was added and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated to give a brown gum, which was purified by flash
chromatography on silica gel (EtOAc) to provide 105 mg (70%) of 35 as a pale brown liquid.

IR (neat): 2962, 2840, 1693, 1609, 1243, 1201, 1000, 832 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.24 (d, 2H, J = 8.8, ArH), 6.92 (d, 2H, J = 8.8, ArH), 4.75 (dd, 1H, J = 2.3, 18.0, NCH₂) 3.95-3.92 (m, 1H, NCH), 3.82 (s, 3H, OCH₃), 3.73-3.69 (br d, 1H, J = 18.0, NCH₂), 2.70 (dd, 1H, J = 4.3, 16.3, COCH₂), 2.61-2.55 (m, 1H, COCH₂), 2.53-2.49 (m, 2H, C=CH₂) 2.45-2.38 (m, 1H, COCH₂CH₂), 1.88-1.81(m, 1H, COCH₂CH₂); ¹³C NMR (75 MHz, CDCl₃): δ 173.7 (C=O), 160.0 (TfOC=O), 139.5 (ArCOCH₃), 129.6 (ArC), 127.9 (ArCH), 124.8 (TfOC=C), 115.2 (q, J = 109.4, CF₃), 114.1 (ArCH), 55.3 (OCH₃), 53.3 (NCH), 43.0 (NCH₂), 35.5 (C=CC₂CH₂), 29.6 (COCH₂CH₂), 24.3 (COCH₂); MS (APCI pos.): m/z 392.1 (M+1); HRMS (CI+): m/z 391.0704 (391.0701 calc. for C₁₆H₁₆NO₅SF₃, M⁺).

(S)-1,2,8,8a-Tetrahydro-7-(3,4-dimethoxyphenyl)-6-(4-methoxyphenyl)indolizin-3(5H)-one (36):

To a stirred solution of the enol triflate 35 (85 mg, 0.22 mmol) and 3,4-dimethoxyphenyl boronic acid (44 mg, 0.24 mmol) in dioxane (4 mL) was added aq. Na₂CO₃ (69 mg, 0.65 mmol; degassed with N₂ for 20 min) and the mixture was degassed
with nitrogen for 15 min. Pd(PPh$_3$)$_4$ (13 mg, 0.011 mmol) was added and the mixture was heated with stirring at 85 °C for 90 min. The mixture was cooled to ambient temperature, diluted with EtOAc (15mL) and the mixture was washed with water (2 x 5ml). The organic layer was dried (Na$_2$SO$_4$) and concentrated to give a brown gum, which was purified by flash chromatography on silica gel (EtOAc) to provide 67 mg (80%) of 36 as a pale yellow gum.

IR (neat): 2965, 2834, 1729, 1674, 1510, 1454, 1243, 1027, 834 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.97 (d, 2H, $J$ = 8.7, ArH), 6.70 (d, 3H, $J$ = 8.7, ArH), 6.62 (dd, 1H, $J$ = 1.9, 8.3, ArH), 6.42 (d, 1H, 1.9, ArH), 4.71 (dd, 1H, $J$ = 2.2, 18.4, NCH$_2$), 3.93-3.88 (m, 1H, NCH$_2$), 3.82 (s, 3H, OCH$_3$), 3.78 (br s, 1H, NCH$_2$), 3.74 (s, 3H, OCH$_3$), 3.56 (s, 3H, OCH$_3$), 2.74 (dd, 1H, $J$ = 3.1, 16.7, COCH$_2$), 2.52-2.49 (t, 2H, $J$ = 7.9, COCH$_2$, C=CCH$_2$), 2.45-2.37 (m, 2H, C=CCH$_2$,COCH$_2$CH$_2$), 1.88-1.77 (m, 1H, COCH$_2$CH$_2$);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 173.9 (C=O), 158.4 (ArCOCH$_3$), 148.1 (ArCOCH$_3$), 147.5 (ArCOCH$_3$), 134.3 (ArCC=C), 131.8 (C=CCH$_2$CH), 131.5 (C=CCH$_2$N), 130.6 (ArC), 130.2 (ArCH), 120.8 (ArCH), 113.6 (ArCH), 112.9 (ArCH), 110.6 (ArCH), 55.7 (NCH), 55.6 (OCH$_3$), 55.2 (OCH$_3$), 53.4 (OCH$_3$), 44.4 (NCH$_2$), 38.7 (C=CCH$_2$CH), 30.1 (COCH$_2$CH$_2$), 24.9 (COCH$_2$); MS (APCI positive): $m/z$ 380.2 (M+1); HRMS (CI+): $m/z$ 379.1791 (379.1784 calc. for C$_{23}$H$_{25}$NO$_4$, M$^+$).
(S)-1,2,3,5,8,8a-Hexahydro-7-(3,4-dimethoxyphenyl)-6-(4-methoxyphenyl)indolizine
(secoantofine, 8):

To a suspension of LiAlH₄ (16 mg, 0.42 mmol) in dry THF (1.5 mL) at 0 °C was slowly added a solution of the lactam 36 (0.04 g, 0.1 mmol) in THF (1 mL). After stirring for an hour at 0 °C, the mixture was stirred at ambient temperature for 24 h. It was then cooled to 0 °C and water (8 µL, 0.42 mmol), 1 N NaOH (8 µL) and water (24 µL), were added sequentially with vigorous stirring. The precipitated inorganic salts were filtered and washed with dichloromethane. The combined filtrates were dried (Na₂SO₄) and concentrated to provide 31 mg (80%) of 8 as a pale yellow gum. This material was pure by ¹H NMR (500 MHz) and was directly used further.

IR (neat): 2962, 1606, 1509, 1458, 1243, 1168, 1139, 1022, 832, 810 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.97 (d, 2H, J = 8.7), 6.69-6.66 (m, 4H), 6.47 (br d, 1H, J = 1.1), 3.86 (d, 1H, J = 15.8), 3.81 (s, 3H), 3.73 (s, 3H), 3.54 (s, 3H), 3.30 (dt, 1H, J = 7.0, 1.6), 3.07 (dt, 1H, J = 16.0, 3.2), 2.77-2.68 (m, 1H), 2.45-2.35 (m, 2H), 2.24 (apparent q, 1H, J = 9.0), 2.14-2.06 (m, 1H), 1.97-1.90 (m, 1H), 1.87-1.80 (m, 1H), 1.60-1.51 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 158.0, 147.9, 147.1, 135.1, 133.6, 132.7, 132.6, 130.2, 120.7, 113.4, 113.1, 110.4, 60.4, 57.9, 55.7, 55.5, 55.1, 54.3, 38.6, 30.9, 21.5; MS (APCI
positive): \( m/z \) 366.4 (M+1); HRMS (Cl+): \( m/z \) 365.1986 (365.1999 calcd. For C\(_{23}\)H\(_{27}\)NO\(_3\) (M\(^+\))); \( [\alpha]^{23}_D = +148 \) (c = 0.4, CHCl\(_3\); Lit.\(^{22}\) \( [\alpha]^{25}_D = +169 \) (c 1, CHCl\(_3\), for the \( S \) enantiomer)).

\((S)-2,3,6\)-Trimethoxy-9,11,12,13,13a,14-hexahydrodibenzo[f,h]pyrrolo[1,2-b]isoquinoline ((+)-antofine) (9):

\[
\begin{array}{c}
\text{H}_3\text{CO} \\
\text{H}_3\text{CO} \\
\text{OCH}_3 \\
\end{array}
\]

To a solution of 8 (25 mg, 0.068 mmol) in dichloromethane (1.5 mL) at 0 \(^\circ\)C was added VOF\(_3\) (40 mg, 0.32 mmol) and the mixture was stirred for 15 min. Trifluoroacetic acid (70 \( \mu \)L, 0.90 mmol) was added and stirring was continued for 75 min at 0 \(^\circ\)C. Aqueous NaOH (10%, 2 mL) was added and the mixture was warmed to room temperature. The biphasic was separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated to give the crude product. Purification by flash chromatography on silica gel (CH\(_2\)Cl\(_2\)/methanol, 97.5/2.5) provided 19 mg (77%) of 9 as a pale cream colored solid.

IR (neat): 2961, 1616, 1510, 1469, 1418, 1257, 1233, 1203, 1169, 1127, 1032, 913, 843, 813 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.92 (s, 1H, Ar\( H \)), 7.91 (d, 1H, \( J = 2.4 \), Ar\( H \)), 7.82 (d, 1H, \( J = 9.0 \), Ar\( H \)), 7.32 (s, 1H, Ar\( H \)), 7.20 (dd, 1H, \( J = 9.0, 2.4 \), Ar\( H \)), 4.7 (d, 1H, \( J = 14.6 \)), 4.11 (s, 3H, OCH\(_3\)), 4.06 (s, 3H, OCH\(_3\)), 4.00 (s, 3H, OCH\(_3\)), 3.70 (brd,
1H, J = 14.6), 3.47 (dt, 1H, J = 8.5, 1.6), 3.35 (brd, 1H), 2.90 (m, 1H), 2.51-2.44 (m, 2H), 2.26-2.24 (m, 1H), 2.04-2.02 (m, 1H), 1.95-1.85 (m, 1H), 1.82-1.72 (m, 1H); 13C NMR (75 MHz, CDCl₃): δ 157.5, 149.4, 148.4, 130.2, 127.1, 126.6, 125.5, 124.3, 124.1, 123.5, 114.9, 104.7, 104.0, 103.9, 60.3, 56.0, 55.9, 55.5, 55.1, 53.8, 33.7, 31.3, 21.6; MS (APCI, pos.): m/z 364.4 (M+1); HRMS (CI+): m/z 364.1922 (364.1913 calc. for C₂₃H₂₆NO₃ [M+H]+); [α]₂₃⁰D = +118 (c = 0.4, CHCl₃; Lit.²² [α]₂₅⁰D = +111 (c 1, CHCl₃, for the S enantiomer)).
3.7 References


3.8 Selected $^1$H NMR and $^{13}$C NMR spectral data
24
CDCl₃, 500 MHz

24
CDCl₃, 125 MHz
28a
CDCl₃, 500 MHz

28a
CDCl₃, 125 MHz
$\text{CDCl}_3$, 500 MHz

$\text{CDCl}_3$, 125 MHz
**33**

CDCl₃, 125 MHz

**34**

CDCl₃, 300 MHz
34
CDCl₃, 125 MHz

35
CDCl₃, 500 MHz
Parameter | Value
--- | ---
1. Data File Name: ZJ/NMR300/00/04/0001/D1002-35/1
2. Title: **CDCl₃, 125 MHz**

35

Parameter | Value
--- | ---
1. Data File Name: ZJ/NMR300/00/04/0001/D1002-35/1
2. Title: **DR-3572/1**

36

Parameter | Value
--- | ---
1. Data File Name: ZJ/NMR300/00/04/0001/D1002-35/1
2. Title: **CDCl₃, 500 MHz**
8
CDCl₃, 125 MHz

2
CDCl₃, 500 MHz
CDCl$_3$, 125 MHz
3.9 HPLC chromatogram for nitroketone 24
Chapter 4

Enantioselective approach to functionalized quinolizidines: synthesis of

(+)-julandine and (+)-cryptopleurine

This chapter is based on the following publication:


**Contribution of authors**

S. V. Pansare: Research supervisor, manuscript preparation.

R. Dyapa: Synthetic experimental work and manuscript preparation.
4.1 Introduction

The quinolizidine motif is a prominent structural unit in numerous alkaloids. The structurally related phenanthroquinolizidine alkaloids are also well known and these have attracted considerable interest due to their anticancer, antiviral, amoebicidal and anti-inflammatory activities. For example, the secophenanthroquinolizidine alkaloid (+)-julandine (1) has antimicrobial activity and the corresponding phenanthroquinolizidine (-)-cryptopleurine (2), an enantiomer of (+)-cryptopleurine, has also shown excellent biological activities such as antiviral, amoebicidal and anticancer activity. The synthesis of quinolizidines, aryl-fused quinolizidines and phenanthroquinolizidines has therefore continued to engage synthetic chemists over the years.

Figure 4.1 (+)-Julandine (1) and (+)-Cryptopleurine (2)
4.2 Reported syntheses of (+)-cryptopleurine

The following summary provides an overview of the syntheses of cryptopleurine in enantiomerically enriched form.

Rapoport and co-workers reported an enantioselective synthesis of (+)-cryptopleurine (Scheme 1).\textsuperscript{12d} The key step in their synthesis is an intramolecular Friedel-Crafts acylation reaction. The synthesis began with phenanthrene carboxylic acid 5, which was prepared from 3 and 4 according to the reported procedure.\textsuperscript{15} Reduction of 5 to the alcohol and subsequent bromination provided the bromide 6. Optically pure diisopropyl α-amino adipate was coupled with the bromide 6 to provide the alkylated diester 7 which was treated with 6 N KOH to provide the amido acid 8 (Scheme 4.1).
Amido ketone 9 was obtained by the cyclization of the amido acid 8 using oxalyl chloride in DMF followed by SnCl₄ treatment. Hydrogenation of 9 (Pd(OH)₂/C) provided a mixture of amido alcohols 10a,b which was converted to the phenanthraquinolizidinone 11 by a two step dehydroxylation involving conversion to the corresponding iodide and subsequent dehalogenation. Finally the amide in 11 was reduced with LAH to provide the title compound (+)-cryptopleurine.
Wang and co-workers reported a short and efficient route (Scheme 4.2) to enantiomerically pure (+)-cryptopleurine, involving Parham-type cycloacylation as the key step. The synthesis begins with reduction of ester 12 with LAH to provide the alcohol 13. Alcohol 13 was brominated to afford the dibromo compound 14. Amide 16 was prepared from the alkylation of (S)-N,N-diethylpiperidinedine-2-carboxamide (15) with dibromide 14, using K$_2$CO$_3$ as base. Amide 16 was treated with $n$BuLi to effect cyclization to provide the intermediate ketone which was subsequently reduced to 17. Dehydroxylation of aminol 17 using triethylsilane and trifluoroacetic acid provided the title compound (+)-cryptopleurine.

Scheme 4.2
4.3 Objective

The interest in quinolizidines is an outcome of our ongoing studies on the development and application of the organocatalytic ketone-nitroalkene Michael addition reaction.\textsuperscript{16} This reaction has been extensively studied and although the development of new catalysts for the process continues at a significant pace, further application of the nitroketone Michael adducts has progressed relatively slowly.\textsuperscript{16} It was therefore decided to examine the utility of a suitable $\gamma$-nitroketone in a general approach to the quinolizidine motif. The initial target of the investigation was the naturally occurring (+)-julandine, since only one enantioselective synthesis of the unnatural (-)-julandine has been reported.\textsuperscript{10a} In addition, cryptopleurine can be obtained in one step by the oxidative cyclization of julandine\textsuperscript{10e} and hence a route to julandine would also establish an access to cryptopleurine (2).

\begin{center}
\begin{tikzpicture}
% Diagram code goes here
\end{tikzpicture}
\end{center}

4.4 Retrosynthetic analysis for the diaryl quinolizidine motif

Retrosynthetically, the 2,3-diaryl quinolizidine motif of julandine may be accessible by aryl cross coupling from a 7-aryl quinolizidinone such as A (Figure 4.2) which derives from the functionalized piperidine B. This piperidine intermediate can be
made from the reductive cyclization of the nitroketone C which can be obtained by the reductive opening of the lactone D. Ultimately, lactone D derives from a Baeyer-Villiger oxidation of the corresponding γ-nitroketone which leads us to the organocatalytic, ketone-nitroalkene Michael addition of an appropriate cyclic ketone and nitroalkene.

![Diagram](image)

**Figure 4.2**

### 4.5 Results and Discussion

The organocatalytic Michael addition of cyclohexane-1,4-dione monoethylene ketal and 4-methoxy-β-nitrostyrene employing a chiral pyrrolidine-based triamine catalyst\(^{14a,17j}\) provided the requisite γ-nitroketone 18 in good yield and stereoselectivity (er = 96/4, dr >19/1, Scheme 4.4). Baeyer-Villiger oxidation of 18 provided the corresponding lactone 22 which was reduced with sodium borohydride to the nitrodiol 23 (92%, 2 steps). The primary alcohol in 23 was then selectively acetylated to provide the acetate 24 (94%) which was converted to the nitroketone 25 (Scheme 4.4) by deketalization with iodine in acetone (95%).\(^{18}\)
With the nitroketone 25 in hand, the construction of the quinolizidine framework was initiated. This process involved the preparation of a suitably substituted piperidine from 25 and then constructing the quinolizidine by cyclization. Reduction of the nitroketone 25 with zinc in aq. ammonium chloride provided the nitrone 26, presumably from the hydroxylamine derived from 26. Reduction of the nitrone 26 with tetramethylammonium triacetoxyborohydride provided the N-hydroxy piperidine 27 as a single diastereomer (Scheme 4.5). The stereoselectivity of this reduction is presumably due to an intramolecular, hydroxyl-directed reduction of 26. Reduction of the N-O bond in 27 (TiCl₃ followed by aqueous NaOH¹⁹) provided the corresponding amino alcohol 28 which was protected to provide 29. Conversion of 29 into the quinolizidine motif
required a one carbon homologation. This was achieved by conversion of the primary alcohol of 29 to the mesylate and subsequent cyanation to provide 30.

![Chemical structure](image)

Scheme 4.5

Conversion of 30 to the corresponding quinolizidinone 33 could be accomplished by hydrolysis of the nitrile 30 to the acid 31, followed by esterification with concommitant removal of the Boc group and subsequent cyclization of the resulting aminoester 32 (63% overall). The overall conversion of 30 to 33 could also be achieved in one step (30%) by treatment of 30 with HCl in methanol followed by basification of the crude product. However, the multi-step procedure proceeds with higher overall yield (63%) and is therefore the method of choice. Oxidation of 33 provided the ketolactam 34.
which was then converted to the enol triflate 35 (Scheme 4.6). This is the key intermediate for the target alkaloids.

Scheme 4.6

The conversion of 35 to (+)-julandine (1) was achieved by a Suzuki cross-coupling reaction with 3,4-dimethoxyphenyl boronic acid to generate the lactam 36 followed by reduction with LAH to give 1 (73%, 2 steps). As expected, oxidative cyclization of 1 with thallium trifluoroacetate\textsuperscript{10e} provided (+)-cryptopleurine (2, 62%, Scheme 4.7).
Scheme 4.7

4.6 Conclusion

In conclusion, an efficient synthesis of functionalized quinolizidines was developed from a simple $\gamma$-nitroketone starting material which is readily available from the organocatalytic ketone-nitroalkene Michael addition reaction. The methodology was applied in the first total synthesis of the natural enantiomer of the diarylquinolizidine alkaloid (+)-julandine and the structurally related phenanthroquinolizidine alkaloid (+)-cryptopleurine. The synthetic strategy should be particularly amenable to the preparation of focused libraries of analogs of these alkaloids by judicious selection of the nitroalkene and the aryl component in the cross-coupling step. This possibility as well as other synthetic applications of nitroketones and nitrones related to 18 and 26 are the focus of ongoing investigations in the Pansare group.
4.7 Experimental section

(7S)-7-[(1R)-1-(4-Methoxyphenyl)-2-nitroethyl]-1,4-dioxaspiro[4.5]decan-8-one (18):

![Chemical structure of 18]

To a solution of 1,4-cyclohexanedione monoethylene ketal (13.0 g, 83.7 mmol), $N^1,N^1$-dimethyl-$N^2$-((($S$)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine$^{16a}$ (572 mg, 3.34 mmol) and $p$-toluene sulfonic acid monohydrate (634 mg, 3.34 mol) was added a solution of 4-methoxy-$\beta$-nitrostyrene (3.00 g, 16.7 mmol) in DMF (30 mL) and the resulting solution was stirred at ambient temperature for 48 h. Ethyl acetate (100 mL) was added and the solution washed with water, aq. HCl (3 N), dried (Na$_2$SO$_4$) and concentrated. The residue obtained was purified by flash chromatography on silica gel to provide 4.60 g of a solid. This was dissolved in ethyl acetate (23 mL) and precipitated by addition of hexanes (70 mL). The procedure was repeated once to provide 3.50 g (62%) of 18 with 96% ee. In repeated runs, 18 was obtained in 90-96% ee. Spectroscopic data for 18 is in agreement with that reported in the literature.$^{17j}$
(S)-7-((R)-1-(4-methoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro[4.6]undecan-9-one (22):

To a solution of the nitroketone 18 (3.10 g, 9.25 mmol) in anhydrous dichloromethane (60 mL) at ambient temperature, was added solid sodium phosphate (3.21 g, 12.0 mol) followed by m-chloro perbenzoic acid (~77%, 4.94 g, 28.7 mmol). The resulting white slurry was stirred vigorously for 16 h. Dichloromethane (100 mL) was added and the solution was washed with 5% aq. NaOH (2 x 60 mL). The organic layer was dried (Na₂SO₄) and concentrated to provide 3.20 g, (98%) of 22 as a white, solid foam. This material was pure by ¹H NMR (500 MHz) and was used in the next step without purification. Spectroscopic data for 22 is in agreement with that reported in the literature.¹⁷¹ [α]²³_D = + 58.3 (c 1, CHCl₃).
(2S,3R)-1-(2-(3-Hydroxypropyl)-1,3-dioxolan-2-yl)-3-(4-methoxyphenyl)-4-nitrobutan-2-ol (23):

To a solution of the lactone 22 (2.85 g, 8.11 mmol) in ethanol (30 mL), was added sodium borohydride (0.46 g, 12.1 mmol). The mixture was stirred at room temperature for 3 h, then cooled to 0 °C and the solution was acidified (pH~5) with aq. HCl (0.5 M). The acidic solution was extracted with EtOAc (2 x 50 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated to provide 2.70 g (94%) of the diol 23 as a pale yellow gum. This material was pure by ¹H NMR and was used in the next step without purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc).

IR (neat): 3493, 2960, 2837, 1550, 1511, 1378, 1248, 1059 1028, 829 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.10 (d, 2H, J = 8.6, ArH), 6.85 (d, 2H, J = 8.6, ArH), 5.04 (dd, 1H, J = 5.2, 12.7, CH₂NO₂), 4.59 (dd, 1H, J = 9.7, 12.7, CH₂NO₂), 4.05-3.99 (m, 1H, Ar-CH), 3.99-3.93 (m, 5H, CH₂OH, OCH₂CH₂O), 3.78 (s, 3H, OCH₃), 3.55 (t, 2H, J = 6.2, CH₂OH), 3.42-3.38 (td, 1H, J = 5.2, 9.5, CHOH), 1.70-1.57 (m, 4H, CH₂CHOH, CH₂C₆H₄OH), 1.50-1.39 (m, 2H, CH₂CH₂OH); ¹³C NMR (75 MHz, CDCl₃): δ 159.2 (ArC-OCH₃), 129.3 (ArCᵢₚₖₛ), 129.1 (2 x ArC), 114.5 (2 x ArC), 111.8 (OCO), 78.5 (CH₂NO₂), 70.1 (CHOH), 64.9 (OCH₂CH₂O), 64.6 (OCH₂CH₂O), 62.6 (CH₂OH), 55.3 (ArOCH₃),
50.3 (HO-CHCH₂), 40.3 (Ar-CHCH₂), 33.3 (CH₂CCH₂), 26.7 (CH₂CH₂OH); MS (API-ES): m/z 378 (M+Na); MALDI-TOF MS: 378.1611 (378.1529 calc. for C₁₇H₂₅NO₇Na (M+Na)); [α]²³D = + 40.5 (c 1, CHCl₃).

3-(2-((2S,3R)-2-Hydroxy-3-(4-methoxyphenyl)-4-nitrobutyl)-1,3-dioxolan-2-yl)propyl acetate (24):

A solution of the diol 23 (2.10 g, 5.91 mmol) in dry dichloromethane (35 mL) was cooled to -78 °C and acetyl chloride (0.50 mL, 7.09 mmol) and collidine (1.43 mL, 11.8 mmol) were added. The solution was stirred at -78 °C for 4 h and then diluted with dichloromethane (50 mL). The resulting solution was warmed to ambient temperature and washed with aq. HCl (0.5 M, 2 x 25 mL). The organic layer was dried (Na₂SO₄) and concentrated to provide 2.20 g (94%) of the acetate 24 as a pale yellow gum. This material was pure by ¹H NMR and was used in the next step without purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc/hexanes, 6:4).

IR (neat): 3496, 2961, 1731, 1550, 1513, 1375, 1242, 1141, 1032, 829 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.10 (d, 2H, J = 8.7, ArH), 6.85 (d, 2H, J = 8.7, ArH), 5.04 (dd, 1H, J = 5.3, 12.7, CH₂NO₂), 4.59 (dd, 1H, J = 9.6, 12.7, CH₂NO₂), 3.99-3.92 (m, 8H, Ar-
CH, CHO, OCH₂CH₂O, CH₂OAc) 3.78 (s, 3H, ArOCH₃), 3.42-3.38 (td, 1H, J = 5.3, 9.5, CHOH), 2.03 (s, 3H, COCH₃) 1.67-1.64 (m, 3H, CHCH₂Cₖₖₖ, CₖₖₖCH₂), 1.50-1.46 (m, 3H, CHCH₂Cₖₖₖ, CH₂CH₂OAc); ¹³C NMR (75 MHz, CDCl₃): δ 171.6 (C(O)CH₃), 159.7 (ArC-CH₂O), 129.8 (ArCₚₚₚ), 129.6 (2 x ArC), 115.0 (2 x ArC), 112.0 (OCO), 79.0 (CH₂NO₂), 70.6 (CH₂OAc), 65.5 (CHOH) 65.2 (OCH₂CH₂O), 64.7 (OCH₂CH₂O), 55.8 (OCH₃), 50.8 (CHCH₂Cₖₖₖ) 40.9 (Ar-CH), 33.8 (CₖₖₖCH₂CH₂), 23.5 (OC(O)CH₃) 21.5 (CH₂CH₂O); MS (API-ES, pos.): m/z 420.4 (M+Na); MALDI-TOF MS: 420.1704 (420.1634 calc. for C₁₉H₂₇NO₈Na (M+Na)); [α]²³D = +23.6 (c 0.5, CHCl₃).

(6S,7R)-6-Hydroxy-7-(4-methoxyphenyl)-8-nitro-4-oxooctyl acetate (25):

A solution of the ketal 2₄ (2.20 g, 5.50 mmol) and iodine (0.070 g, 0.55 mmol) in acetone (20 mL) was stirred at ambient temperature for 1 h. The acetone was removed under reduced pressure and the residue was diluted with dichloromethane. The resulting solution was washed successively with aqueous Na₂S₂O₃ (5% w/v, 2 x 25 mL) and brine (1 x 25 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to provide 1.85 g (95%) of the nitroketone 2₅ as a yellow solid. This material was pure by ¹H NMR and was used in the next step without purification. Mp: 77-80 °C;
IR (neat): 3402, 2955, 1735, 1708, 1548, 1380, 1253, 1227, 1111, 1036, 820 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.09 (d, 2H, J = 8.7, ArH), 6.87 (d, 2H, J = 8.7, ArH), 5.07 (dd, 1H, J = 5.1, 12.8, CH₂NO₂), 4.60 (dd, 1H, J = 9.8, 12.8, CH₂NO₂), 4.21-4.18 (m, 1H, ArCH₂), 4.03-4.01 (br t, 2H, J = 6.3, CH₂OAc), 3.79 (s, 3H, OCH₃), 3.49-3.44 (m, 2H, CHOH, CHO), 2.43-2.37 (m, 4H, CH₂COCH₂) 2.01 (s, 3H, COCH₃), 1.86-1.82 (m, 2H, CH₂CH₂O); ¹³C NMR (75 MHz, CDCl₃): δ 210.6 (CO) 171.0 (OC(O)CH₃), 159.4 (ArC-OCH₃), 129.0 (2 x ArC), 128.6 (ArC₂ipso), 114.7 (2 x ArC), 78.4 (CH₂NO₂), 69.6 (CHOH), 63.3 (CH₂OAc), 55.3 (OCH₃), 49.1 (CH₂C(O)), 46.8 (ArCH), 39.7 (C(O)CH₂), 22.4 (CH₂CH₂CO), 20.9 (OC(O)CH₃); MS (API-ES, pos.): m/z 376 (M+Na); MALDI-TOF MS: 376.1443 (376.1372 calc. for C₁₇H₂₃NO₇Na, (M+Na).

(3R,4S)-4-Hydroxy-6-(3-acetoxypropyl)-3-(4-methoxyphenyl)-2,3,4,5-tetrahydropyridine-1-oxide (26):

A solution of NH₄Cl (0.297 g, 5.55 mmol) in water (5 mL) was added to a solution of the nitroketone 25 (1.96 g, 5.55 mmol) in THF (24 mL). Activated Zn powder (3.51 g, 55.5 mmol) was added and the mixture was stirred vigorously at room temperature under nitrogen for 3 h. The mixture was filtered through Celite, the residue was washed with THF, and the combined filtrates were concentrated under reduced pressure. The residue was diluted with dichloromethane (50 mL) and the solution was
washed with water (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to provide 1.60 g (90%) of 26 as a pale yellow foam. This material was pure by $^1$H NMR and was used in the next step without purification.

IR (neat): 2948, 1735, 1509, 1459, 1230, 1140, 1031, 826 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.21 (d, 2H, $J = 8.7$, ArH), 6.90 (d, 2H, $J = 8.7$, ArH), 4.37-4.32 (apparent br t, 1H, $J = 13.4$, ArCH), 4.20-4.19 (br s, 1H, CHO), 4.14-4.11 (t, 2H, $J = 6.5$, CH$_2$OAc), 3.92 (dd, 1H, $J = 5.5$, 14.9, CH$_2$N), 3.80 (s, 3H, OCH$_3$), 3.25-3.21 (m, 1H, CH$_2$N), 2.89-2.53 (m, 4H, CH$_2$C=N, C=NCH$_2$CH$_2$) 2.01 (s, 3H, COCH$_3$), 1.99-1.92 (m, 2H, CH$_2$CH$_2$OAc); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.1 (COCH$_3$), 159.0 (Ar-C=OCH$_3$), 145.0 (C=NO) 129.4 (ArC$_{ipso}$), 128.7 (2 x ArC), 114.3 (2 x ArC), 65.1 (CHO), 63.8 (OCH$_2$), 57.5 (OCH$_3$), 55.2 (CH$_2$NO), 43.5 (Ar-CH), 37.6 (CH$_2$C=N), 28.1 (CH$_2$CH$_2$O), 23.5 (COCH$_3$) 20.9 (N=CCH$_2$); MS (APCI, pos.): m/z 322.4 (M+1); MALDI-TOF MS: 344.1557 (344.1474 calcd for C$_{17}$H$_{23}$NO$_5$Na (M+Na)).

3-((2$R$,4$S$,5$S$)-4-Hydroxy-5-(4-methoxyphenyl)-N-hydroxypiperidin-2-yl)propylacetate (27):

To a solution of tetramethylammonium borohydride (2.62 g, 9.96 mmol) in acetonitrile (14 mL) was added acetic acid (14 mL). The mixture was stirred at 0 °C for 5 min and a solution of the nitrone 26 (1.6 g, 4.98 mmol) in acetonitrile (6 mL) was added.
The mixture was stirred at 0 °C for 1 h and then basified (pH ~ 8) with aqueous NaOH (5% solution). The mixture was extracted with dichloromethane (2 x 60 mL) and the combined extracts were dried (Na₂SO₄) and concentrated to give 1.48 g (92%) of 27 as a brown viscous material. This material was pure by ¹H NMR and was used in the next step without purification. An analytical sample was obtained by flash chromatography on silica gel (CH₂Cl₂/MeOH, 98:2).

IR (neat): 3415, 2923, 1731, 1512, 1238, 1032, 819 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.14 (d, 2H, J = 8.7, ArH), 6.88 (d, 2H, J = 8.5, ArH), 4.10-4.07 (t, 2H, J = 6.7, OCH₂), 3.91 (br s, 1H, CHOH), 3.79 (s, 3H, OCH₃), 3.58-3.48 (m, 1H, NCH), 3.31-3.20 (m, 2H, NCH₂, CHOH), 3.03 (br d, J = 12.4, 1H, CH₂N), 2.86-2.82 (m, 1H, ArCH), 2.11-2.00 (m, 5H, COCH₃, CHCH₂CH), 1.74-1.55 (m, 2H, CH₂CH₂OAc), 1.50-1.42 (m, 2H, NCHCH₂); MS (APCI, pos.): m/z 324.2 (M+1); HRMS (CI): m/z 324.1812 (324.1811 calc. for C₁₇H₂₆NO₅ [M+H]+); [α]23²₅ = + 39.1 (c 0.7, CHCl₃).

(2S,4S,5R)-2-(3-Hydroxypropyl)-5-(4-methoxyphenyl)piperidin-4-ol (28):

To a stirred solution of the hydroxylamine 27 (0.90 g, 2.8 mmol) in methanol (20 mL) was added aq. TiCl₃ (3.77 mL, 4.17 mmol) at 0 °C and the mixture was stirred at 0 °C for 4 h. Aqueous NaOH (20% w/v, 27 mL) was added and the mixture was filtered to remove inorganic salts. The residue washed with methanol and the combined filtrates
were concentrated under reduced pressure. The resulting aqueous solution was extracted with dichloromethane (3 x 40 mL) and the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated to provide 0.65 g (88%) of the amino alcohol 28 as a yellow solid. This material was pure by $^1$H NMR and was used in the next step without purification.

Mp:138-140 ºC; IR (neat): 3554, 2910, 2843, 1511, 1461, 1240, 1182, 1056, 1026, 817 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.13 (d, 2H, $J = 8.7$, ArH), 6.89 (d, 2H, $J = 8.7$, ArH), 4.10 (d, 1H, $J = 2.32$, CHOH), 3.79 (s, 3H, OCH$_3$), 3.64-3.54 (m, 2H, CH$_2$OH), 3.38-3.35 (t, 1H, $J = 12.5$, NCH$_2$), 3.08-3.03 (m, 1H, NCH) 3.00 (dd, 1H, $J = 4$, 12.5, NCH$_2$), 2.79-2.74 (m, 1H, ArCH), 1.96-1.92 (dt, 1H, $J = 13.8$, 3.0, CHCH$_2$CH), 1.79-1.75 (m, 1H, CHCH$_2$CH), 1.65-1.57 (m, 3H, NCHCH$_2$, CH$_2$CH$_2$OH), 1.42-1.39 (m, 1H, NCHCH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 158.6 (ArC-CH$_3$), 132.8 (ArC$_{ipso}$), 128.77 (2 x ArC), 114.2 (2 x ArC), 69.3 (CHOH), 62.8 (CH$_2$OH), 55.3 (OCH$_3$), 49.8 (CHNH), 46.7 (CH$_2$NH), 44.1 (Ar-CH), 39.4 (CHCH$_2$CH), 35.6 (NHCHCH$_2$) 30.4 (CH$_2$CH$_2$OH); MS (APCI, pos.): m/z 266.2 (M+1); MALDI-TOF MS: 266.1796 (266.1756 calc. for C$_{15}$H$_{24}$NO$_3$ [M+H]$^+$).

(2S,4S,5R)-tert-Butyl 4-hydroxy-2-(3-hydroxypropyl)-5-(4-methoxyphenyl) piperidine-1-carboxylate (29):
To a solution of the aminol 28 (0.850 g, 3.21 mmol) and triethylamine (0.54 mL, 3.84 mmol) in dry dichloromethane (10 mL) at 0 °C was slowly added a solution of the (Boc)2O (0.706 g, 3.24 mmol) in dichloromethane (5 mL). The mixture was stirred at ambient temperature for 16 h, saturated NaHCO₃ was added and the aqueous phase was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were washed with aqueous HCl (0.5 M, 2 x 25 mL). The organic layer was dried (Na₂SO₄) and concentrated to provide 1.1 g (94%) of 29 as a pale yellow gum. This material was pure by ¹H NMR and was used in the next step without purification. An analytical sample was obtained by purification by flash chromatography on silica gel (EtOAc).

IR (neat): 3403, 2936, 1658, 1511, 1420, 1246, 1164, 1067, 823 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.25 (d, 2H, J = 8.7, ArH), 6.85 (d, 2H, J = 8.7, ArH), 4.48-4.46 (br m, 1H, NCH₂), 4.32 (br dd, 1H, J = 3.4, 14.1 NCH₂), 4.21-4.14 (m, 1H, CHOH), 3.80 (s, 3H, OCH₃), 3.72-3.70 (m, 2H, CH₂OH), 3.35 (dd, 1H, J = 4.2, 14.1, NCH₂), 3.06 (br m, 1H, ArCH), 1.89-1.53 (m, 6H, CH₂CH₂CH, NCH₂, CH₂CH₂OH), 1.46 (s, 9H, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃): δ 158.8 (ArC-OCH₃), 155.3 (CO₂Bu), 130.8 (2 x ArC), 130.2 (ArCipso), 113.8 (2 x ArC) 80.1 (C(CH₃)₃), 66.4 (CHOH), 62.6 (CH₂OH), 55.3 (OCH₃), 50.8 (NCH), 44.4 (CH₂N), 42.8 (ArCH), 33.0 (CH₂CH₂CH), 29.3 (NCH₂), 28.5 (C(CH₃)₃), 27.6 (CH₂CH₂OH); MS (APCI, pos.): m/z 266.2 (M-Boc+2); HRMS (Cl): m/z 266.1751 (266.1756 calc. for C₁₃H₂₄NO₃ (M-Boc +2H); [α]²³_D = + 68.2 (c 1, CHCl₃).
3-((2S,4S,5R)-1-(tert-Butoxycarbonyl)-4-hydroxy-5-(4-methoxyphenyl)piperidin-2-yl)propyl methanesulfonate (29a):

To a stirred solution of 29 (1.10 g, 3.01 mmol) in dichloromethane (15 mL) was added DIPEA (0.53 mL) followed by methanesulfonyl chloride in dichloromethane (10 mL) over 15 min. at 0 °C. The mixture was stirred at 0 °C for 3 h. Cold water (10 mL) was added and the organic layer was separated, washed with water (3 x 25 mL), brine (1 x 25 mL) dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 2:8) to provide 0.85 g (64%) of 29a as a white solid.

Mp: 140-144 °C; IR (neat): 3441, 2937, 1676, 1511, 1418, 1353, 1247, 1167, 915, 830 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.23 (d, 2H, J = 8.7, ArH), 6.85 (d, 2H, J = 8.7, ArH), 4.46 (br m, 1H, NCH₂), 4.29-4.18 (m, 3H, NCH₂, OCH₂), 4.16-4.14 (m, 1H, CHOH), 3.79 (s, 3H, OCH₃), 3.33 (dd, 1H, J = 4.1, 14.2, NCH₂), 3.07-3.05 (m, 1H, ArCH) 3.02 (s, 3H, SO₂CH₃), 1.92-1.61 (m, 6H, CHCH₂CH, NCHCH₂, CH₂CH₂O), 1.45 (s, 9H, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃): δ 158.8 (ArC-OCH₃), 155.0 (CO₂tBu), 130.8 (2 x ArC), 130.1 (ArCipso), 113.9 (2 x ArC), 80.2 (C(CH₃)₃), 69.7 (CH₂O), 66.4 (CHOH), 55.3 (OCH₃), 50.4 (NCH), 44.4 (CH₂N), 42.8 (ArCH), 37.4 (SO₂CH₃), 33.0 (CHCH₂CH), 28.5 (C(CH₃)₃), 27.2 (NCHCH₂), 26.3 (CH₂CH₂OMs); MS (APCI, pos.):
m/z 344.1 (M-Boc+2); HRMS (Cl): m/z 344.1538 (344.1532 calc. for C$_{16}$H$_{26}$NO$_5$S (M-Boc+2H)).

(2S,4S,5R)-tert-Butyl-2-(3-cyanopropyl)-4-hydroxy-5-(4-methoxyphenyl)piperidine-1-carboxylate (30):

To a solution of the mesylate 29a (0.820 g, 1.85 mmol) in anhydrous DMSO (15 mL), at ambient temperature, was added NaCN (18.0 g, 3.69 mmol). The mixture was stirred at 70 ºC for 2 h and cooled to ambient temperature. Ethyl acetate (40 mL) was added and the mixture was washed with water (3 x 30 mL) and brine (30 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated to provide 0.65 g (95%) of 30 as a yellow solid. This material was pure by $^1$H NMR and was used in the next step without purification.

IR (neat): 3447, 2934, 2248, 1678, 1511, 1416, 1246, 1162, 1113, 831 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.22 (d, 2H, $J = 8.7$, ArH), 6.85 (d, 2H, $J = 8.7$, ArH), 4.46 (br s, 1H, NCH$_2$), 4.32 (br dd, 1H, $J = 2.2$, 14.2, NCH$_2$), 4.19-4.13 (m, 1H, CHOH), 3.79 (s, 3H, OCH$_3$), 3.33 (dd, 1H, $J = 4.0$, 14.2, NCH$_2$), 3.07-3.05 (m, 1H, ArCH), 2.44 (t, 2H, $J = 6.8$, CH$_2$CN), 2.04-1.96 (m, 1H, CHCH$_2$CH), 1.80-1.77 (m, 1H, CHCH$_2$CH), 1.70-1.62 (m, 4H, NCHCH$_2$, CH$_2$CH$_2$CN) 1.46 (s, 9H, C(CH$_3$)$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 158.8 (ArC-OCH$_3$), 155.0 (CO$_2$Bu), 130.7 (2 x ArC), 130.0 (ArC$_{ipso}$), 119.5 (CN), 113.8
(2 x ArC), 80.2 (C(CH3)3), 66.3 (CHOH), 55.3 (OCH3), 50.0 (NCH), 44.4 (CH2N), 42.8 (Ar-CH), 33.1 (CHCH2CH), 30.2 (NCHCH2), 28.4 (C(CH3)3), 22.5 (CH2CH2CN), 17.0 (CH2CN); MS (APCI, pos.): m/z 275.3 (M-Boc+2); HRMS (Cl): m/z 375.2292 (375.2284 calc. for C21H31N2O4 [M+H]+); [α]23 D = +27.0 (c 0.6, CHCl3).

4-((2S,4S,5R)-1-(tert-butoxycarbonyl)-4-hydroxy-5-(4-methoxyphenyl)piperidin-2-yl)-butanoic acid (31):

A solution of the nitrile 30 (0.610 g, 1.63 mmol) in aqueous NaOH (2 M, 6 mL) and ethanol (6 mL) was heated at 85 ºC for 16 h. The ethanol was removed under reduced pressure and resulting solution was acidified (pH ~ 4) with aqueous HCl (0.5 M). The acidic solution was extracted with dichloromethane (2 x 50 mL) and the combined extracts were dried (Na2SO4) and concentrated to provide 0.61 g (95%) of 31 as a brown solid. This material was pure by 1H NMR and was used in the next step without purification.

Mp: 88-90 ºC; IR (neat): 3423, 2933, 1666, 1511, 1418, 1245, 1160, 1033, 829, 730 cm⁻¹; 1H NMR (500 MHz, CDCl3): δ 7.22 (d, 2H, J = 7.9, ArH), 6.84 (d, 2H, J = 7.9, ArH), 4.42 (br s, 1H, NCH), 4.31 (br d, 1H, J = 13.9, NCH2), 4.14-4.12 (br m, 1H, CHOH), 3.79 (s, 3H, OCH3), 3.32 (br dd, 1H, J = 2.7, 13.9, NCH2), 3.03 (br s, 1H, ArCH), 3.0-2.5 (br, CO2H), 2.39 (br s, 2H, CH2COOH), 1.79-1.61 (m, 6H, CHCH2CH, NCHCH2,
CH₂CH₂COOH), 1.45 (s, 9H, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃): δ 178.4 (CO₂H), 158.7 (Ar-C-OCH₃ or CO₂Bu), 155.1 (Ar-C-OCH₃ or CO₂Bu), 130.8 (2 x ArC), 130.3 (ArCipso), 113.7 (2 x ArC), 80.1 (C(CH₃)₃), 66.3 (CHOH), 55.2 (ArOCH₃), 50.7 (NCH), 44.2 (CH₂N), 42.8 (Ar-CH), 34.1 (CH₂CO₂H), 32.3 (CHCH₂CH), 30.2 (NCHCH₂), 28.4 (C(CH₃)₃), 21.8 (CH₂CH₂CO₂H); MS (APCI, pos.): m/z 294.2 (M-Boc+2); HRMS (CI pos.): m/z 294.1711 (294.1705 calc. for C₁₆H₂₄NO₄ (M-Boc+2H).

Methyl 4-((2S,4S,5R)-4-hydroxy-5-(4-methoxyphenyl)piperidin-2-yl)butanoate (32):

To a solution of the acid 31 (0.600 g, 1.53 mmol) in methanol (12 mL) at 0 ºC was added SOCl₂ (0.510 mL, 7.02 mmol) and the mixture was stirred at ambient temperature for 16 h. The methanol was removed under reduced pressure, the residue was diluted with dichloromethane (25 mL) and the resulting solution was washed with water (10 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to provide 0.43 g, (91%) of 32 as an off white solid. This material was pure by H NMR and was used in the next step without purification.

IR (neat): 3123, 2940, 1727, 1610, 1510, 1433, 1240, 1168, 1030, 828 cm⁻¹;¹H NMR (500 MHz, CDCl₃): δ 7.14 (d, 2H, J = 8.6, ArH), 6.87 (d, 2H, J = 8.6, ArH), 4.08-4.07 (br m, 1H, CHO), 3.79 (s, 3H, ArOCH₃), 3.67 (s, 3H, CO₂CH₃), 3.39-3.31 (t, 1H, J = 12.0, NCH₂), 3.00-2.91 (m, 2H, NCH, ArCH), 2.84-2.79 (m, 1H, NCH₂), 2.37-2.32 (t, 2H, J =
7.4, \(CH_2CO_2CH_3\), 1.99-1.92 (dt, 1H, \(J = 2.9, 13.6, CHCH_2CH\)), 1.73-1.63 (m, 4H, CHCH_2CH, \(CH_2CH_2CO\), CHNH), 1.49-1.35 (m, 2H, NCHCH_2); \(^{13}\)C NMR (75 MHz, CDCl_3): \(\delta\) 174.0 (CO_2CH_3), 158.5 (ArC-OCH_3), 133.3 (ArCipso), 128.8 (2 x ArC), 114.1 (2 x ArC), 69.3 (CHOH), 55.3 (ArOCH_3), 51.6 (CO_2CH_3), 49.4 (NHCH), 47.0 (CH_2N), 44.8 (ArCH), 39.5 (CHCH_2CH), 36.4 (NHCHCH_2), 34.1 (CH_2CO_2CH_3), 21.4 (CH_2CH_2CO_2CH_3); MS (APCI, pos.): \(m/z\) 308.3 (M+1); HRMS (CI): \(m/z\) 308.1861 (308.1862 calc. for C_{17}H_{26}NO_4 [M+H]^+) 

\((7R,8S,9aS)\)-hexahydro-8-hydroxy-7-(4-methoxyphenyl)-1H-quinolizin-4(6H)-one (33):

To a solution of the amino ester 32 (0.380 g, 1.23 mmol) in THF (6 mL) was added diisopropylethyl amine (752 \(\mu\)L, 4.31 mmol) and the solution was heated to reflux for 16 h. Additional diisopropylethylamine (0.250 mL, 1.43 mmol) was added and the mixture was refluxed for 2 h. The THF was removed under reduced pressure, the residue was dissolved in dichloromethane (30 mL) and the resulting solution was washed with aqueous HCl (0.5 M, 2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 246 mg (73%) of the lactam 33 as a pale yellow foam. This material was pure by \(^1\)H NMR and was used in the next step without purification.
IR (neat): 3349, 2945, 1606, 1478, 1442, 1245, 1171, 1035, 831 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.14 (d, 2H, \(J = 8.7\), ArH), 6.89 (d, 2H, \(J = 8.7\), ArH), 4.76 (dd, 1H, \(J = 4.2\), 12.8, NCH\(_2\)), 4.1 (br m, 1H, CHO\(_{\text{OH}}\)), 3.8 (s, 3H, OCH\(_3\)), 3.78-3.74 (m, 1H, NCH), 3.20-3.15 (t, 1H, \(J = 12.8\), NCH\(_2\)), 2.85-2.81 (br m, 1H, ArCH), 2.48-2.40 (m, 1H, NCOCH\(_2\)), 2.38-2.31 (m, 1H, NCOCH\(_2\)), 2.02-1.97 (m, 2H, CHCH\(_2\)CH, CHO\(_{\text{H}}\)), 1.86-1.82 (m, 1H, NCHCH\(_2\)CH\(_2\)), 1.74-1.68 (m, 3H, CHCH\(_2\)CH, COCH\(_2\)CH\(_2\)) 1.55-1.48 (m, 1H, CHCH\(_2\)CH\(_2\)); \(^1\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 169.6 (NCO), 158.7 (ArC-\text{OCH}_3), 131.9 (ArC\(_{\text{ipso}}\)), 128.6 (2 x ArC), 114.2 (2 x ArC), 68.7 (CHO\(_{\text{OH}}\)), 55.3 (OCH\(_3\)), 50.0 (NCH), 45.3 (CH\(_2\)N), 40.3 (Ar-CH), 39.6 (CHCH\(_2\)CH), 33.0 (COCH\(_2\)), 29.7 (NCHCH\(_2\)), 19.1 (CH\(_2\)CH\(_2\)CO); MS (APCI, pos.): \(m/z\) 276.5 (M+1); HRMS (CI): \(m/z\) 275.1526 (275.1521 calc. for C\(_{16}\)H\(_{21}\)NO\(_3\) (M+)).

\textit{(3R,9aS)-Hexahydro-3-(4-methoxyphenyl)-1H-quinolizine-2,6-dione (34):}

![Chemical Structure](image)

To a stirred solution of the alcohol 33 (0.45 g, 1.63 mmol) in dichloromethane (15 mL) was added DMSO (8 mL) followed by DIPEA (2.4 mL) at 0 °C. Solid SO\(_3\)-pyridine (781 mg, 4.90 mmol) was added in small portions and the mixture was stirred at 0 °C for 1 h. Water (10 mL) was added and the mixture was diluted with dichloromethane (20 mL). The mixture was washed with water (2 x 30 mL) and the organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated to provide 420 mg (94%) of 34 as a brown solid.
Mp: 88-90 °C; IR (neat): 2921, 1719, 1547, 1447, 1338, 1242, 1171, 1022, 826 cm⁻¹; ¹H NMR (500 MHz,CDCl₃): δ 7.06 (d, 2H, J = 8.7, ArH), 6.89 (d, 2H, J = 8.7, ArH), 5.12 (dd, 1H, J = 12.7, 6.2, NCH₂), 3.85-3.82 (m, 1H, NCH) 3.79 (s, 3H, OCH₃), 3.64 (dd, 1H, J = 12.7, 6.2, NCH₂), 3.00-2.91 (t, 1H, J = 12.4, ArCH), 2.58-2.55 (m, 2H, COCH₂), 2.50-2.46 (m, 2H, NCOCH₂), 2.18-2.09 (m, 1H, NCH), 1.72-1.63 (m, 1H, NCHCH₂) ; ¹³C NMR (75 MHz, CDCl₃): δ 206.2 (CO), 169.4 (NCO), 159.0 (ArCOCH₃),129.9 (2 x ArC), 126.8 (ArC), 114.1 (2 x ArC), 56.0 (NCH), 55.4 (OCH₃), 55.3 (ArCCH), 48.3 (NCH₂), 47.7 (COCH₂), 32.8 (NCOCH₂), 29.6 (COCH₂CH₂), 18.9 (NCHCH₂); MS (APCI pos.): m/z 274.1 (M+1); HRMS (Cl+): m/z 273.1371 (273.1365 calc. for C₁₆H₁₉NO₃, M⁺).

(S)-4,6,7,8,9,9a-Hexahydro-3-(4-methoxyphenyl)-6-oxo-1H-quinolizin-2-yl trifluoromethanesulfonate (35):

To a suspension of KH (66 mg, 0.50 mmol) in THF (2 mL) was added the ketone 34 (136 mg, 0.50 mmol) at 0 ºC. The mixture was stirred at room temperature for 2 h and a solution of N-phenylbistrifluoromethanesulfonimide (195 mg, 0.55 mmol) in THF (2 mL) was added dropwise at 0 ºC. The mixture was then stirred for 0.5 h at room temperature. Water (7 mL) was added and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated to give a brown
viscous material which was purified by flash chromatography on silica gel (EtOAc) to provide 150 mg (74%) of 35 as a yellow gum.

IR (neat): 2942, 1642, 1512, 1412, 1206, 1138, 1036, 833 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.26 (d, 2H, J = 8.8, ArH), 6.91 (d, 2H, J = 8.8, ArH), 5.28 (d, 1H, J = 18.4, NCH₂), 3.82 (s, 3H, OCH₃), 3.82-3.77 (m, 1H, NCH), 3.64 (d, 1H, J = 18.4, NCH₂), 2.79-2.72 (m, 1H, COCH₂), 2.52-2.49 (m, 1H, COCH₂), 2.49-2.43 (m, 2H, C=CCH₂) 2.20-2.11 (m, 1H, COCH₂CH₂), 1.99-1.89 (m, 1H, COCH₂CH₂), 1.81-1.61 (m, 2H, NCHCH₂); ¹³C NMR (75 MHz, CDCl₃): δ 169.6 (C=O), 160.0 (TfOC=C), 139.3 (ArCOCH₃), 129.7 (2 x ArC), 128.0 (ArC), 124.8 (TfOC=C), 122.5 (q, J = 346.4, CF₃), 114.0 (2 x ArC), 55.3 (OCH₃), 52.7 (NCH), 45.5 (NCH₂), 35.6 (C=CCH₂CH), 32.8 (COCH₂), 28.3 (NCHCH₂), 18.2 (COCH₂CH₂); MS (APCI pos.): m/z 406.1 (M+1); HRMS (Cl⁺): m/z 405.0865 (405.0858 calc. for C₁₇H₁₈NO₅SF₃, M⁺).

(S)-2,3,9,9a-Tetrahydro-8-(3,4-dimethoxyphenyl)-7-(4-methoxyphenyl)-1H-quinolizin-4(6H)-one (36):

To a stirred solution of the enol triflate 35 (150 mg, 0.370 mmol) and 3,4-dimethoxyphenyl boronic acid (74 mg, 0.41 mmol) in dioxane (6 mL) was added a degassed, aqueous solution of Na₂CO₃ (118 mg, 1.11 mmol, in 0.50 mL water) and the
mixture was degassed with a stream of nitrogen for 15 min. Pd(PPh_3)_4 (21 mg, 0.019 mmol) was added and the mixture was heated with stirring at 85 °C for 90 min. The mixture was then cooled to ambient temperature, diluted with EtOAc (15mL) and the resulting mixture was washed with water (2 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give a brown gum. This was purified by flash chromatography on silica gel (CH_2Cl_2/methanol, 98.5:1.5) to provide 120 mg (82%) of 36 as a white solid.

Mp: 94-101 °C; IR (neat): 2944, 1635, 1510, 1454, 1245, 1173, 1028, 824 cm^-1; ^1^HNMR (500 MHz, CDCl_3): δ 7.0 (d, 2H, J = 8.7, ArH), 6.71-6.68 (m, 3H, ArH), 6.62 (dd, 1H, J = 8.3, 2, ArH), 6.43 (s, 1H, ArH), 5.20 (d, 1H, J = 18.7 NCH_2), 3.81 (s, 3H, OCH_3), 3.81-3.79 (m, 1H, NCH), 3.73 (s, 3H, OCH_3), 3.72-3.68 (d, 1H, J = 18.7, NCH_2), 3.55 (s, 3H, OCH_3), 2.60-2.57 (m, 2H, C=CHCH_2), 2.48-2.46 (t, 2H, J = 12.7, COCH_2), 2.16-2.11 (m, 1H, NCHCH_2) 1.91-1.88 (m, 1H, COCH_2CH_2), 1.81-1.72 (m, 2H, COCH_2CH_2, NCHCH_2) ; ^1^C NMR (75 MHz, CDCl_3): δ 169.4 (C=O), 158.4 (ArC-OCH_3), 148.1 (ArC-OCH_3), 147.5 (ArC-OCH_3), 133.9 (ArCC=C), 131.9 (C=CCH_2CH), 131.2 (C=CCH_2N), 131.1 (ArC), 130.4 (2 x ArC) 120.6 (ArCH), 113.5 (2 x ArC), 113.0 (ArC), 110.6 (ArC), 55.7 (NCH), 55.6 (OCH_3), 55.2 (OCH_3), 52.8 (OCH_3), 46.8 (NCH_2), 38.9 (C=CCH_2CH), 33.0 (COCH_2), 28.7 (NCHCH_2), 18.5 (COCH_2CH_2); MS (APCI pos.): m/z 394.2 (M+1); HRMS (Cl+): m/z 394.2016 (394.2018 calc. for C_{24}H_{28}NO_4, [M+H]^+).
(S)-4,6,7,8,9,9a-Hexahydro-2-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)-1H-quinolizine ((+)-Julandine, 1):

To a suspension of LiAlH₄ (38 mg, 0.096 mmol) in dry THF (1.5 mL) at 0 °C was slowly added a solution of the lactam 36 (0.10 g, 0.25 mmol) in THF (2 mL). The mixture was stirred for an hour at 0 °C and then at ambient temperature for 24 h. It was then cooled to 0 °C and water (18 μL, 1 mmol), 1 N NaOH (1 mL) and water (48 μL), were added sequentially with vigorous stirring. The precipitated inorganic salts were filtered and washed with dichloromethane. The combined filtrates were dried (Na₂SO₄) and concentrated to give a yellow gum. This was purified by flash chromatography on silica gel (CHCl₃/MeOH, 99:1) to provide 63 mg (89%) of 1 as a pale yellow gum.

IR (neat): 2928, 1604, 1509, 1458, 1242, 1172, 1029, 830 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.98 (d, 2H, J = 8.6, ArH), 6.69-6.67 (m, 4H, ArH), 6.46 (br s, 1H, ArH), 3.81 (s, 3H, OCH₃), 3.73 (s, 3H, OCH₃), 3.62-3.59 (br d, 1H, J = 16.5), 3.53 (s, 3H, OCH₃) 3.10-3.03 (m, 2H), 2.55-2.51 (br d, 1H, J = 18.1), 2.41-2.30 (m, 2H), 2.11-2.10 (m, 1H), 1.86-1.80 (m, 2H), 1.75-1.70 (br m, 2H), 1.36-1.35 (br m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 158.0, 147.9, 147.2, 134.5, 133.2, 131.5, 131.3, 130.2, 120.5, 113.4, 113.0, 110.5, 62.8, 60.4, 57.9, 55.7, 55.6, 55.5, 55.2, 39.6, 33.3, 30.0, 25.9, 24.4; MS (APCI pos.): m/z 380.5 (M+1); HRMS (CI+): m/z 379.2151 (379.2147 calc. for C₂₄H₂₉NO₃, M⁺).
[α]$_{23}^D$ = +88.8° (c 0.5, CHCl$_3$, Lit.$^7$a [α]$_{26}^D$ = -71.6° (c 0.33, CHCl$_3$ for the R-enantiomer).

(S)-2,3,6-Trimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinoline ((+)-Cryptopleurine) (2):

A modification of the literature procedure was employed.$^7$c To a stirred solution of 1 (65 mg, 0.17 mmol) in dichloromethane (10 mL) at ambient temperature was added thallium (III) trifluoroacetate (94 mg, 0.17 mmol) and the mixture was stirred for 30 min. The volatiles were removed under reduced pressure, water (5 mL) was added to the residue and the mixture was basified with saturated aqueous sodium carbonate. The mixture was then extracted with chloroform (2 x 15 mL). The combined extracts were dried and concentrated. The residue obtained was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH, 98:2) to give a yellow solid which was recrystallized from chloroform/acetone to give 40 mg (62%) of 2 as a white crystalline solid.

Mp: 190-194 °C (Lit.$^{20}$ mp. 197-198 °C (benzene); IR (neat): 2926, 1610, 1509, 1467, 1253, 1141, 1040, 846, 748, 632 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.91 (s, 1H), 7.9 (d, 1H $J$ = 2.6), 7.26 (s, 1H), 7.20 (dd, 1H, $J$ = 2.6, 9), 4.44 (d, 1H, $J$ = 15.5), 4.10 (s, 3H), 4.06 (s, 3H), 4.01 (s, 3H), 3.64 (d, 1H, $J$ = 15.3), 3.28 (d, 1H, $J$ = 10.8), 3.11 (dd, 1H, $J$ = 15.3), 3.11 (dd, 1H, $J$ = 10.8), 3.11 (dd, 1H, $J$ = 10.8), 3.11 (dd, 1H, $J$ = 10.8).
4, 16.3), 2.92-2.86 (m, 1H), 2.43-2.39 (t, 1H, \( J = 10.3 \)), 2.34-2.28 (td, 1H, \( J = 3.8, 11.5 \)),
2.04 (d, 1H, \( J = 13.9 \)), 1.89 (d, 1H, \( J = 12.3 \)), 1.81-1.77 (m, 2H), 1.56-1.44 (m, 2H); ¹³C
NMR (75 MHz, CDCl₃): \( \delta \) 157.4, 149.4, 148.3, 130.1, 126.5, 125.7, 124.5, 124.1, 123.7,
123.4, 114.8, 104.7, 103.9, 103.9, 57.6, 56.3, 56.2, 56.0, 55.9, 55.5, 34.8, 33.9, 26, 24.4;
MS (APCI pos.): \( m/z \) 378.1 (M+1); HRMS (Cl+): \( m/z \) 377.1990 (377.1991 calc. for
\( C_{24}H_{29}NO_3, M^+ \); \( [\alpha]^{23}_D = +104.6^\circ \) (c 0.55, CHCl₃); Lit. ⁹d \( [\alpha]^{23}_D = +106^\circ \) (c 1, CHCl₃)).
4.8 References:


4.9 Selected $^1$H NMR and $^{13}$C NMR spectral data
**Parameter**  
1. Data File Name: Z/ NMR300 (data) rdxpap/ nmr/ DR-379BA/ 1/ rid 
2. Title: DR-379BA/ 3

**Value**

![NMR Spectrum of CDCl₃, 500 MHz](image)

**Parameter**  
1. Data File Name: Z/ NMR300 (data) rdxpap/ nmr/ BR-05-1462/ 1/ rid 
2. Title: dxt

**Value**

![NMR Spectrum of CDCl₃, 75 MHz](image)
Parameter | Value
---|---
1. Data File Name | CDCl3, 75 MHz
2. Title | CDCl3, 75 MHz

Parameter | Value
---|---
1. Data File Name | CDCl3, 500 MHz
2. Title | CDCl3, 500 MHz
32
CDCl₃, 75 MHz

33
CDCl₃, 500 MHz
CDCl₃, 75 MHz

34

CDCl₃, 500 MHz

35
Parameter | Value
--- | ---
1. Comment | DRR-05-96A-C
2. Title | Cross-coupling

1. CDCl₃, 500 MHz
2. CDCl₃, 500 MHz
Chapter 5
Conclusions

5.1 Summary of the thesis

The organocatalytic, enantioselective Mukaiyama-Michael reaction of silyloxy furans (1 & 2) and acrolein was developed. The methodology was used in an enantioselective syntheses of (S)-homocitric acid lactone and its homologue. Secondary amines 3-6 were chosen as potential catalysts for the organocatalytic conjugate addition reaction of 1 and 2 with acrolein (Scheme 5.1). After an extensive optimization study using various solvents and additives, the use of furan 2 (benzyl ester) as the nucleophile in CHCl₃/H₂O provided the Michael adduct 8 in 80% ee and 40% yield using 3 as the catalyst.

Scheme 5.1
Using the Michael adduct 8 (80% ee) as the starting material, the synthesis of the target homocitric acid lactone was completed via a dehomologation/oxidation protocol (Scheme 5.2).

**Scheme 5.2**

Michael adduct 8 was also used in the synthesis of (R)-per-homocitric acid lactone (Scheme 5.3), which is a desymmetrized version of parental achiral triacid.

**Scheme 5.3**

In summary, an expedient, organocatalysis-based, enantioselective syntheses of (S)-homocitric acid lactone and its homologue have been developed. Notably, the methodology also provides several butenolide intermediates that offer opportunities for chemoselective functionalization. Such reactions may find applications in the synthesis of functionalized, oxygen and nitrogen heterocycles with applications in biology and medicine.

In the second project, an enantioselective synthesis of the indolizidine alkaloid (+)-antofine was developed from an enantiomerically enriched γ-nitroketone.
Enantiomerically pure γ-nitroketones and their derivatives are an important class of organic compounds due to their utility as building blocks for the asymmetric synthesis of natural products and biologically active molecules. The organocatalytic Michael addition of a monoprotected cyclohexane 1,3-dione and selected 4-methoxy-β-nitro styrenes in the presence of a proline-derived triamine catalyst provided the enantioenriched γ-nitroketone 13 (ee = 90%, dr ≥19/1). Oxidative ring expansion of the nitroketone and subsequent methanolysis provided a 8-nitro-4-oxooctanoate 15. This is stereoselectively transformed to the key, functionalized piperidine intermediate 16 which is readily converted to (+)-antofine (Scheme 5.4).

Scheme 5.4
In the third project, we have used the enantioenriched $\gamma$-nitroketone 13 in the syntheses of quinolizidine alkaloids (+)-julandine and (+)-cryptopleurine. Oxidative ring expansion of the nitroketone 13, followed by reductive ring-opening, leads to a suitably functionalized nitrodiol 18 which was stereoselectively converted to the functionalized piperidine 19. (+)-Julandine was obtained by employing a homologation/cross coupling reaction sequence on piperidine derivative 19. Oxidative cyclization of (+)-julandine using thallium trifluoroacetate provided the title compound (+)-cryptopleurine (Scheme 5.5).

Scheme 5.5
In summary, an efficient synthesis of functionalized indolizidines and quinolizidines was developed from a simple \( \gamma \)-nitroketone starting material which is readily available from the organocatalytic ketone–nitroalkene Michael addition reaction. The methodology was applied in the total synthesis of indolizidine alkaloid (+)-antofine and the first total synthesis of the natural enantiomer of the diaryl quinolizidine alkaloid (+)-julandine. The structurally related phenanthroquinolizidine alkaloid (+)-cryptopleurine was prepared from (+)-julandine. The synthetic strategy should be particularly amenable to the preparation of focused libraries of analogs of these alkaloids by judicious selection of the nitroalkene and the aryl component in the cross-coupling step.

5.2 Future work

Organocatalytic Michael addition of cyclic ketones 21 and \( \alpha \)-nitrostyrenes 22 (prepared by \textit{in situ} elimination of the corresponding nitroacetates\(^1\)) would be an interesting methodology to synthesize enantiomerically pure \( \gamma \)-nitroketones 23 (Scheme 5.6). These \( \gamma \)-nitroketones and their derivatives may be useful as building blocks for the asymmetric synthesis of natural products and biologically active compounds as detailed below.

\[ \text{Scheme 5.6} \]
The Michael adducts 23 can be potentially converted to the corresponding nitrones 24. These nitrones would be useful in the stereoselective synthesis of 2-aryl octahydroindoles 25 (Scheme 5.7). These octahydroindoles may have applications in diversity oriented synthesis\(^2\) and medicinal chemistry\(^3\)\(^-\)\(^5\).

![Scheme 5.7](image)

**Scheme 5.7**

In addition, the octahydroindoles 25 may also have applications in target oriented synthesis. Oxidative ring expansion of the γ-nitroketone 23 followed by reductive ring opening would lead to the 8-nitro-4oxooctonate 27. This is a potential precursor of functionalized quinolizidines such as 28. These quinolizidines could be transformed into natural products such as subcosine I (29), lasubine I (30) and lasubine II (31) (Scheme 5.8).
Scheme 5.8
5.3 References


