TOWARDS THE TOTAL SYNTHESIS OF DAPHNIYUNNINE B

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TOWARDS THE TOTAL SYNTHESIS OF DAPHNIYUNNINE B
for the degree of ‘Doctor of Philosophy’ 2010

This thesis describes the development of a series of synthetic routes towards the first synthesis of Daphniyunnine B, a Daphniphyllum alkaloid, utilising novel reactions and cascades. Studies began with an envisaged enantioselective Michael cascade reaction, which alternatively gave rise to a novel, efficient Michael-aldol cascade reaction affording perhydroindole structures in moderate to excellent diastereoselectivity.

The enantioselective synthesis of the methyl-substituted core of Daphniyunnine B was achieved via an initial highly enantioselective organocatalytic Michael addition followed by a stereoselective organocatalytic intramolecular Michael addition.

The stereocontrolled synthesis of the AC bicyclic core of (±) Daphniyunnine B was achieved via a quaternisation cyclisation approach.

The stereocontrolled synthesis of the ACD tricyclic core of (±) Daphniyunnine B was achieved via an intramolecular Diels-Alder fragmentation reaction. Preliminary studies of an enantioselective variant are encouraging.
DECLARATION

I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning. Any work done in collaboration with a research colleague or undergraduate student is referenced in the text. All compounds in chapter seven were synthesised and characterised by myself.

John W. Ward

September 2010
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic group, (not phenyl)</td>
</tr>
<tr>
<td>BHT</td>
<td>butylated hydroxyl toluene</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>di-tert-butyl dicarbonate</td>
</tr>
<tr>
<td>bs</td>
<td>broad singlet</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1'-carbonyldiimidazole</td>
</tr>
<tr>
<td>Cl</td>
<td>chemical ionisation</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet/day(s)</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DIBALH</td>
<td>diisobutyl aluminium hydride</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalents</td>
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<tr>
<td>equiv.</td>
<td>equivalents</td>
</tr>
<tr>
<td>ES</td>
<td>electrospray</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EVK</td>
<td>ethyl vinyl ketone</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HBMC</td>
<td>heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple-quantum coherence</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IC\textsubscript{50}</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IPA</td>
<td>isopropyl alcohol</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
</tbody>
</table>
\( \rho \) para

Ph phenyl

Pr propyl

ppm parts per million

PTAP phenyltrimethylammonium tribromide

PTC phase transfer catalyst

q quartet

quat quaternary

R alkyl group

RT room temperature

s singlet

SAR structure activity relationship

SR specific rotation

t retention time (HPLC) / triplet (NMR)

TBAB tetrabutylammonium bromide

TBAF tetra-\( n \)-butylammonium fluoride

TBME \( tert \)-butyl methyl ether

TBDPS \( tert \)-butyldiphenylsilyl

\( tert \) tertiary

\( t \) tertiary

TFA trifluoroacetic acid

Tf triflate

THF tetrahydrofuran
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>TIPBA</td>
<td>2,4,6-triisopropylbenzene sulfonic acid</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonyl</td>
</tr>
<tr>
<td>TS</td>
<td>transition state</td>
</tr>
<tr>
<td>pTSA</td>
<td>toluene-4-sulfonic acid</td>
</tr>
<tr>
<td>μg</td>
<td>microgram</td>
</tr>
</tbody>
</table>
CHAPTER ONE: INTRODUCTION

1.1 THE DAPHNIPHYLLUM ALKALOIDS

*Daphniphyllum* alkaloids are a structurally diverse group of natural products found in the genus *Daphniphyllum* (Daphniphyllaceae), a genus of dioecious evergreen trees and shrubs native to central and southern Japan. There are three *Daphniphyllum* species in Japan (*D. macropodum*, *D. teijsmannii* and *D. humile*), and several other species (*D. calycinum*, *D. gracile*, *D. longeracemosum*, *D. yunnanense*, *D. longistyllum*, *D. paxianum*, *D. oldhami* and *D. glaucescens*) are distributed in New Guinea, China and Taiwan. Yamamura and co-workers initially classified these alkaloids into six structural types according to their backbone skeleton (*Daphniphylline*, *Secodaphniphylline*, *Yuzuramine*, *Daphnilactone A*, *Daphnilactone B* and *Yuzurine*), however recent isolations have necessitated the addition of several other structural motifs (*Bukittinggine*, *Daphnezomine*, *Daphnicyclidin*, *Daphmanidin*, *Daphniglaucin*, *Paxdaphnine*, *Daphlongeranine* and of particular interest *Calyciphylline*). These unusual ring systems have attracted great interest as challenging targets for total synthesis or biosynthetic studies (*Figure 1.1*)."
1.2 BIOSYNTHETIC STUDIES

A significant contribution to the understanding of the biosynthesis of *Daphniphyllum* alkaloids was made when Suzuki and Yamamura in 1973 reported feeding experiments of *Daphniphyllum* alkaloids with $^{14}$C labeled mevalonic acid. It was suggested from these results that Daphnilactone B was generated from four equivalents of mevalonic acid via a squalene intermediate. The $^{14}$C labeled atoms are indicated by asterisks *(Scheme 1.1).*

While Yamamura outlined a biosynthetic route to the *Daphniphyllum* alkaloids, a more concerted mechanism was postulated by Heathcock and co-workers, which importantly addressed the introduction of nitrogen into the complex alkaloids. Oxidation of squalene and condensation of a primary amine (perhaps an amino acid pyridoxamine) was postulated to give rise to the imine 1. Prototopic rearrangement and subsequent nucleophilic addition to the imine by another amine species could
afford 2. Intramolecular cyclisation of the enamine to the \(\alpha,\beta\)-unsaturated aldehyde and subsequent trapping of the iminium ion could give the bicycle 3. A series of rearrangements could then afford the dihydropyridine 4 which could undergo a formal hetero-Diels-Alder reaction to give 5. A final Prins-type cyclisation could then furnish proto-Daphniphylline (Scheme 1.2).\(^3,4\)

![Scheme 1.2 Postulated biosynthetic pathways of proto-Daphniphylline](image)

### 1.3 BIOMIMETIC STUDIES

With a postulated biosynthetic route outlined, Heathcock and co-workers initially focused their attention on the final stages of the polycyclization reaction leading to the Daphniphylline skeleton 11. Three simple building blocks; amide 6, \(\alpha,\beta\)-unsaturated ester 7 and iodide 8, were combined in a highly convergent conjugate addition/enolate alkylation process to obtain the ester amide 9 in high yield. Straightforward methods were then employed to convert this substance into the dialdehyde 10. Not too dissimilar to that proposed in the biosynthesis, addition of ammonia gave a
dihydropyridine motif which underwent a formal hetero-Diels-Alder reaction and Prins-type cyclisation to give 11 in 64% overall yield from 9. Alkene reduction and debenzylation followed by oxidation and esterification furnished methyl homo-Secodaphniphyllate in high yield (Scheme 1.3).

![Chemical Structures and Reactions](image)

Scheme 1.3 Reagents and conditions (a) LDA, THF, -78 °C, 6, then 7, then 8 to RT; (b) DIBAL-H, NaOH, H$_2$O, EtOH; (c) LiALH$_4$; (d) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$; (e) NH$_3$, AcOH, CH$_2$Cl$_2$; (f) 1. Pd/C, H$_2$; 2. CrO$_3$, H$_2$SO$_4$, acetone; 3. MeOH, H$_2$SO$_4$

Encouraged by their success with this cyclisation approach, they sought to intervene earlier in the biosynthetic pathway proposed in Scheme 1.2. Accordingly, dihydrosqualene dialdehyde 12 was treated with ammonia and warm acetic acid to afford the proto-Daphniphylline in 15% yield. Although only in modest yield, a great many transformations have been accomplished under simple reaction conditions. Fortuitously, replacement of ammonia which methylamine in this reaction mediated
an extraordinary pentacyclisation of dihydrosqualene dialdehyde 12 to afford dihydro-
protodaphniphylline in 65% yield (Scheme 1.4).

Scheme 1.4 Reagents and conditions (a) NH$_3$, AcOH, Heat; (b) MeNH$_2$, AcOH, Heat

The biomimetic mechanism for the synthesis of dihydro-protodaphniphylline was suggested to be similar to the biosynthesis initially proposed by Heathcock and co-workers. Condensation of the most reactive aldehyde with methylamine affords the enamine 13 which can undergo an intramolecular Michael addition to the α,β-unsaturated aldehyde. Methylamine then attacks the resultant imine 14 which undergoes enamine formation and then elimination to form the Diels-Alder precursor 15. A formal hetero-Diels-Alder reaction affords the iminium ion 16, which undergoes a Prins-like cyclisation to form the pentacyclic core 17. A 1,5 hydride shift from the methyl group of the tertiary amine to the carbocation, followed by hydrolysis on workup, completed the synthesis of dihydro-protodaphniphylline (Scheme 1.5).
1.4 INTRODUCTION TO THE DAPHNIYUNNINES

The Daphniyunnines are a family of five *Daphniphyllum* alkaloids (A-E) isolated in 2006 from the *Daphniphyllum yunnanense*, a shrub endemic to the southeast of Yunnan Province, People’s Republic of China. Daphniyunnines A-E were evaluated in bioassays for antitumor activity according to standard protocols, and pseudolaric acid B was used as a positive control. Only Daphniyunnine D was found to have moderate cytotoxic activity against two tumor cell lines, P-388 and A-549, with IC₅₀ values of 3.0 and 0.6 μM respectively. They consist of an architecturally complex and unique 6, 5, 6, 5, 7 pentacyclic core and Daphniyunnine B-E represent four rare C-22 nor-*Daphniphyllum* alkaloids that all possess an α,β-unsaturated ketone. Synthetic construction of this pentacyclic core could give access to all the family members and...
thus it was decided our synthetic efforts would be towards Daphniyunnine B (Figure 1.2).

Based on Heathcock’s biosynthetic model, it is thought that the common carbon skeleton intermediate 18, which is derived from Squalene, is the biogenetic origin of the Daphniyunnines via the Yuzurimine-type alkaloid 19 and enzyme catalytic reactions from Calyciphylline A (Scheme 1.6).9,10
1.5 STUDIES TOWARDS RELATED NATURAL PRODUCTS

To the best of our knowledge, no total syntheses of Daphniyunnine B or any of the other four family members have been reported to date. A stereoselective synthesis of the ABC tricyclic core of the closely related Calyciphylline A (Figure 1.3), however, was reported by Bonjoch and co-workers in 2005 applying a palladium catalyzed enolate alkenylation methodology.\(^\text{11}\)

![Figure 1.3 ABC tricyclic core of Daphniyunnine B and Calyciphylline A](image)

The α-allylcyclohexanedione 21 was prepared from commercially available 20. Ozonolysis and double reductive amination with benzylamine then gave the bicycle 22 in good yield. Debenzylolation and alkylation with 2,3 dibromopropene followed by hydrolysis of the acetal provided the amino tethered vinyl halide 23. The key palladium catalyzed enolate alkenylation reaction gave the tricyclic core 24 in moderate yield. Hydrogenation of the resultant alkene under standard conditions delivered hydrogen to the less hindered face of the tricycle to afford the unwanted epimeric derivative 25 of the desired product (Scheme 1.7).
Reduction of ketone 24 under Leuche conditions gave alcohol 26 which directed stereoselective hydrogenation with a cationic rhodium catalyst from the most hindered face of the tricycle affording a separable 3:1 mixture of the major and minor epimers respectively. Swern oxidation of the alcohol and acidic cleavage of the aminoborane complex completed the stereoselective synthesis of the ABC tricyclic core 27 of Calyciphylline A (Scheme 1.8).
An enantiocontrolled synthesis of the BCD tricyclic ring system of the unnatural enantiomer of (+)-Daphnicyclidin A, a related *Daphniphyllum* alkaloid, was also reported by Iwabuchi and co-workers (*Figure 1.4*). The synthesis featured a highly diastereoselective conjugate addition of nitromethane, an Ireland-Claisen rearrangement, and a tandem acyliminium/Mannich-type reaction.\(^{12}\)

The BCD tricyclic core of (-)-Daphnicyclidin was prepared from two key fragments which will be discussed separately. Initially, the primary amine fragment 32 was prepared from the commercially available cycloheptanone 28. Acylation followed by transesterification with (-)-8-phenylmenthol and dehydrogenation using Mukaiyama-Matsuo reagent gave 29 in good yield. The diastereoselective Michael addition with the lithium salt of nitromethane gave a transient enolate which was trapped by triisopropyl triflate to afford the silyl enol ether 30. According to the empirical rule developed by Oppolzer and co-workers, the configuration at the chiral center installed by this reaction was *R*, which is the unnatural enantiomer of (+)-Daphnicyclidin A. (-)-8-phenylmenthol was used rather than its enantiomeric counterpart due to its reliable utility and availability to establish an enantiocontrolled synthetic route. Reduction of the ester 30 and nitro group 31 completed the synthesis of the primary amine fragment 32 in high enantiomeric excess (*Scheme 1.9*).
The carboxylic acid fragment 37 was then prepared. The literature compound allylic alcohol 33 was prepared in four steps from D-Mannitol. This allylic alcohol was converted to the allyl ester 34 via a four step sequence in high yield. An Ireland-Claisen rearrangement of 34 followed by benzylation and silyl deprotection gave the alcohol 35 in good yield and diastereoccontrol. Acylation of the allylic alcohol and subsequent palladium catalysed formate reduction afforded the terminal alkene 36. Ozonolysis, acetal formation and debenzylation completed the synthesis of the carboxylic acid fragment 37 (Scheme 1.10).
The primary amine fragment 32 and carboxylic acid fragment 37 were smoothly converted into amide 38 in high yield. After tosylation, desilylation led to the successive elimination of the tosylate to the enone 39 which was reduced under standard hydrogenation reaction conditions to give chiral amine 40. The N-acyliminium formation of 40 under acid conditions underwent a Mannich-type reaction in moderate yield to complete the synthesis of the BCD tricycle 41 of (−)-Daphnicyclidin A (Scheme 1.11).

Scheme 1.10 Reagents and conditions (a) i) PivCl, Et₂N, ii) Dowex 50WX8, MeOH, iii) TBSCI, imidazole, iv) Propionic acid, EDCI, DMAP, CH₂Cl₂; (b) i) LHMDMS, TBSCI, HMPA, 2-Me-THF/THF, -78 °C to RT, ii) 1-Me-imidazole, TsCl, BuOH, CH₂Cl₂, iii) PPTS, MeOH, 55 °C; (c) i) CICO₂Me, pyridine, CH₂Cl₂, ii) Pd₂(dba)_3, CHCl₃, n-Bu₃P, HCO₂NH₄, DMF; (d) i) O₂, MeOH, Me₂S, p-TsOH, ii) H₂, Pd-C, AcOEt.

Scheme 1.11 Reagents and conditions (a) EDCI, DMAP, pyridine, CH₂Cl₂; (b) TsCl, Et₂N, Me₃N.HCl, CH₂Cl₂ the TBAF; (c) H₂, Pd-C, NaHCO₃, MeOH; (d) AcCl, i-PrOH, reflux.
1.6 OBJECTIVES AND AIMS

The primary objective of this work was the concise stereocontrolled total synthesis of Daphniyunnine B. There have been no reported total syntheses of the Daphniyunnines and with so few approaches towards related natural products, there is a great opportunity for novel, stereocontrolled reactions and cascades to be discovered and developed in the pursuit of the natural product.

The following chapters detail our synthetic efforts towards the total synthesis of Daphniyunnine B. Three approaches will be discussed individually and are as follows;

1. A Michael cascade approach;
2. A quaternisation cyclisation approach;
3. An intramolecular Diels-Alder fragmentation approach.
CHAPTER TWO: A MICHAEL CASCADE REACTION APPROACH TOWARDS THE TOTAL SYNTHESIS OF DAPHNIYUNNINE B

2.1 AIMS AND RETROSYNTHETIC ANALYSIS

Our aim for this approach was the concise construction of the ACD ring system 42 of Daphniyunnine B employing a key cascade reaction of three processes:

1. An enantioselective organocatalytic Michael addition;
2. Michael addition initiated intramolecular organocatalysed Michael addition;
3. Nucleophilic substitution of the pendent chloride with the resultant β-keto ester.

Further dealkyldecarboxylation, amide reduction, ene-carbocyclisation and Michael-aldol condensation and could rapidly furnish Daphniyunnine B (Scheme 2.1).

![Scheme 2.1 Retrosynthetic analysis](image)

2.2 INTRODUCTION TO MICHAEL ADDITION REACTIONS

The Michael addition reaction is an extremely useful bond forming process, first discovered over a century ago by Komnenos and Claisen and then developed by Arthur Michael whom the reaction is named after. The area is extensive and has been covered by many books and review articles as well as over ten thousand standalone communications.
Initially, Michael addition reactions were limited to the formation of racemates; however, significant developments in asymmetric catalysis have led to improved efficiency, scalability, and enantiocontrol in Michael additions.

### 2.2.1 ENANTIOSELECTIVE CATALYSIS IN MICHAEL ADDITIONS

Enantioselective catalysis in the Michael addition was initially approached with the combination of abundant metal ions with chiral ligands. A relevant example was demonstrated by Takashi Oshima in 2004 whereby a highly efficient, scalable, and enantioselective Michael addition between dimethyl malonate 43 and cyclohexenone 44 was performed under asymmetric Lewis acid catalysis using Shibasaki’s chiral aluminiumate complex 45 (Scheme 2.2).\(^{20,21}\)

![Scheme 2.2](image)

**Scheme 2.2** Reagents and conditions (a) catalyst 45 (0.1 eq.), \(^1\)BuOK (0.1 eq.), 4A Sieves, THF, 5 °C to RT

Although a powerful mode of catalysis, there are a number of drawbacks including: sensitivity toward moisture, oxygen and some functional groups are not tolerated. This form of catalysis can also be expensive and toxic.\(^{22}\) Enantioselective organocatalytic methods have been developed to overcome these drawbacks and maintain the high enantiocontrol observed with metal ion catalysis.

### 2.2.2 ENANTIOSELECTIVE ORGANOCATALYSIS IN MICHAEL ADDITIONS

Developments in enantioselective organocatalytic Michael addition reactions have been phenomenal in the past fifteen years and it remains a booming field of
research. Small organic molecules are used to facilitate and induce high efficiency and enantiocontrol in Michael additions. A few significant examples using various modes of activation will be discussed below.

Wynberg and Helder in 1975 reported the first enantioselective organocatalytic Michael addition with a measured enantiomeric excess. Michael addition between the β-keto ester 46 and methyl vinyl ketone 47 with 1 mol% of quinine 48 gave the Michael adduct 49 in good yield and modest enantiomeric excess. The absolute stereochemistry of 49 was not determined (Scheme 2.3).27

Wynberg and Helder did not investigate the origins of enantiocontrol observed with the use of catalytic quinine in the Michael addition, however it is now postulated that quinine acts in a bifunctional manner whereby both the bridge-head nitrogen and the hydroxyl group organise the nucleophile and the electrophile for reaction. Bifunctional catalysis will be discussed in more detail in Section 2.3.4.1. Enantioselective organocatalytic Michael additions have advanced considerably since these landmark studies, with covalent bond catalysis being one of the largest fields.

2.2.3 COVALENT BOND CATALYSIS
2.2.3.1 SECONDARY AMINE CATALYSIS
MacMillan and co-workers in 2002 reported highly enantioselective Michael addition by the LUMO-lowering activation of α,β-unsaturated aldehyde 51 via the reversible formation of iminium ions using an imidazolidinone catalyst 52. Attack of the
nucleophile 50 is directed by the steric bulk of the catalyst to the Si face of the electrophile in good yield and with high enantioselectivity (Scheme 2.4).²⁸

![Scheme 2.4](image)

Hayashi and co-workers in 2005 reported highly enantioselective and diastereoselective Michael additions by the HOMO-raising activation of ketones via the reversible formation of enamine ions using a prolinol derived catalyst 53. Selective formation of the anti enamine and selective shielding of the Re face of the enamine double bond by the bulky diphenylsiloxyethyl group resulted in high enantio and diastereoselective control (Scheme 2.5).²⁹
2.2.4 HYDROGEN BONDING CATALYSIS

2.2.4.1 BIFUNCTIONAL CATALYSIS

In the context of this thesis, the term bifunctional will be used to describe small molecules which have a basic site and a tuneable hydrogen bond donor site. A number of relevant examples will be discussed below.

Dixon and co-workers in 2005 reported the use of a thiourea-derivative of cinchonine 54 to catalyse highly enantioselective Michael additions of malonates to nitroolefins.\(^\text{30}\) A number of modes of action have been proposed,\(^\text{31}\) with working models within the group suggesting that the basic bridge head nitrogen of the catalyst deprotonates the malonate creating a reactive ammonium enolate. The nitroolefin is suggested to bind in a bidentate fashion to the thiourea which enhances its electrophilicity through LUMO-lowering of the acceptor and provides facial control through a conformational preference in binding (Scheme 2.6).\(^\text{32}\)
An alternative class of bifunctional catalyst was demonstrated by Deng and co-workers in 2006 using a cinchona alkaloid–derived bifunctional organocatalyst 55 in highly enantioselective Michael additions of β-keto esters with methyl vinyl ketone. Both the quinoline phenol and the quinuclidine nitrogen of the catalyst were postulated to be involved in stabilization of the transition structure via a “cage-like” structure that restricts rotation and delivers the electrophile selectively (Scheme 2.7).
Enantioselective organocatalytic Michael additions may initiate further transformations generating functionally dense multicyclic structures. The Michael Initiated Ring Closure reaction, simply referred to as the MIRC reaction, was defined in 1980 as “a general set of transformations which are initiated by a conjugate addition to an \( \alpha,\beta \)-unsaturated ester or ketone to produce an enolate which subsequently undergoes intramolecular ring closure”.

2.3 MICHAEL INITIATED RING CLOSURE REACTIONS

Many different transformations have followed the initial Michael addition, including; alkylation, aldol condensation, carbocyclisation or a subsequent Michael addition. A few relevant examples of MIRC reactions will be discussed below.

2.3.1 MICHAEL-ALDOL CASCADE

Robinson and co-workers as early as 1937 reported Michael-aldol-condensation MIRC reactions. Building on seminal work by Hajos, Parrish and Eder’s, Barbas and co-workers recently reported enantioselective Michael-aldol cascade reactions of
symmetrical cyclic ketones and $\alpha,\beta$-unsaturated ketones via secondary amine catalysis using (S)-proline 57. The mechanistic details were not reported, however the initial Michael addition could be facilitated by reversible proline-imine formation of 47, enamine formation of 56 or both. The intramolecular aldol condensation would then proceed via reversible enamine formation of the Michael adduct (Scheme 2.8).\(^{40}\)

![Scheme 2.8 Reagents and conditions (a) catalyst 57 (0.35 eq.), DMSO, 35 °C, 89h](image)

2.3.2 MICHAEL-MICHAEL CASCADE

Deng and co-workers recently reported highly enantioselective Michael-Michael cascade reactions of $\alpha,\beta$-unsaturated ketones and cyclic dicyanoalkenes using a cinchona derived primary amine organocatalyst 59. The initial highly enantioselective Michael addition is catalysed by LUMO-lowering activation of $\alpha,\beta$-unsaturated ketone 58 via reversible iminium formation with the organocatalyst 59. Facialy selective intramolecular Michael addition via reversible enamine formation of the Michael adduct gave the bicycle 60 in good yield as a single diastereoisomer in high enantiomeric excess (Scheme 2.9).\(^ {38}\)

![Scheme 2.9 Reagents and conditions (a) catalyst 59 (0.2 eq.), TFA (0.4 eq.), DIPEA (0.15 eq.), -20 °C, 96h](image)
2.3.3 MICHAEL-MICHAEL-ALDOL CASCADE

Enders and co-workers in 2006 reported an example of combining both iminium and enamine chemistry in a highly enantioselective Michael-Michael-aldol cascade reaction forming four stereocentres. Catalyst 53 activates aldehyde 61 by forming an enamine, which undergoes an enantioselective Michael addition with nitroolefin 62. α,β-unsaturated aldehyde 64 is activated by catalyst 53 as the iminium ion, which undergoes an enantioselective Michael addition with post-hydrolysis adduct 63. Intramolecular aldol condensation and hydrolysis furnishes the product 65 in high enantioselectivity and regenerates the catalyst for further cycles (Scheme 2.10).

![Scheme 2.10 Michael/Michael/aldol cascade](image-url)
2.4 A MICHAEL CASCADE REACTION APPROACH TOWARDS THE TOTAL SYNTHESIS OF DAPHNIYUNNINE B: RESULTS AND DISCUSSION

To determine whether the conceived Michael-Michael-alkylation cascade was feasible, preparation of starting materials 66 and 67 was required (Scheme 2.11).

Pyrrole-2-ones 67 are versatile synthetic intermediates owing to the presence of multiple reactive centers; the $\gamma$-methylene unit present in such a system will undergo various reactions including aldol condensations, Michael additions and Vilsmeier-Haack formylation. However, to assist in both the deprotonation and the ring closing Michael step an ester at the 3-position would be beneficial for reactivity.

2.4.1 RETROSYNTHETIC ANALYSIS OF PYRROLE-2-ONE 67

Transformation of 68 into 67 was envisaged as straightforward; acylation followed by regioselective reduction of the carbonyl proximal to the methyl group could give 69 which after elimination and tautomerism should afford 67 (Scheme 2.12).
2.4.2 PREPARATION OF PYRROLE-2-ONE 67

Ring opening of succinic anhydride 70 with allylamine and ring closure with 1,1'-carbonyldiimidazole afforded N-allyl succinimide 68 in good overall yield. Regioselective acylation of 68 using LHMDS and methyl chloroformate allowed the formation of acyl succinimide 71 also in good yield (Scheme 2.13).

\[ \text{Scheme 2.13 Reagents and conditions (a) allylamine (1.1 eq.), CDI (1.1 eq.), CH}_2\text{Cl}_2, \text{RT to reflux; (b) CICO}_2\text{Me (2.0 eq.), LHMDS (2.0 eq.), THF, -78 \degree C, 5m} \]

To continue, a regioselective reduction of this key intermediate 71 was required. Regioselective reductions of unsymmetrical succinimides are generally substrate controlled. Therefore an initial sodium borohydride reduction under standard conditions was performed to determine reactivity. Reduction of the carbonyl adjacent to the ester, leading to the undesired product, was the most rapid to afford an inseparable 3:1 mixture of regioisomers 72 (undesired) and 73 (desired) by inspection of the \(^1\text{H NMR}\) of the crude reaction mixture. Once one carbonyl is reduced, the other is rendered an amide and thus unreactive to sodium borohydride (Scheme 2.14).

\[ \text{Scheme 2.14 Reagents and conditions (a) NaBH}_4 (5.0 eq.), MeOH, 0 \degree C} \]

The bias for the reduction of the undesired carbonyl under these conditions was unacceptable for the continuation of the synthesis and accordingly alternate
methods were sought. It was conceived that a formal stoichiometric deprotonation of the 1,3 dicarbonyl system of 71 would lower the electrophilicity of these carbonyls and allow selective reduction of the desired carbonyl with a stronger reducing agent (Scheme 2.15).

![Scheme 2.15 Postulated protective deprotonation followed by reduction](image)

The regioselective reduction of this key intermediate was successfully performed on large scale utilising a novel, simple to perform, one-pot protective deprotonation of the 1,3-dicarbonyl system using sodium hydride prior to reaction with diisobutylaluminium hydride at low temperature (Scheme 2.16).

![Scheme 2.16 Reagents and conditions (a) NaH (1.0 eq.), DIBALH (2.0 eq.), THF, -78 °C, 1h](image)

With the regioselective reduction of 71 successfully solved, dehydration of hydroxy lactam 73 followed by tautomerism would furnish the desired pyrrole-2-one 67. An attractive procedure for this type of dehydration involved boiling acetic anhydride and pyridine which when carried out on 73, unexpectedly produced pyrrole acetate 74 in moderate yield. Presumably, reaction of hydroxy lactam 73 with acetic anhydride in the presence of pyridine gave 75, which under thermal elimination could form the enamide 77 via the N-acyliminium ion 76. Rather than tautomerism to the originally desired pyrrole-2-one 67, aromatisation and further reaction with acetic anhydride in the presence of pyridine gave pyrrole acetate 74 (Scheme 2.17).
Although not featuring in the retrosynthetic plan, pyrrole acetate 74 was recognised as a protected form of 67; thus standard deacetylation conditions could be employed to reveal the pyrrole-2-one 67 in situ and undergo the Michael-Michael cascade to give the bicyclic compound 78 (Scheme 2.18).
2.4.3 PROOF OF PRINCIPLE

Accordingly, a preliminary reactivity study with methyl vinyl ketone in methanol in the presence of catalytic potassium carbonate was performed. Rapid consumption of starting materials indeed lead to the construction of a perhydro indol-2-one core but, to our initial surprise, not via the originally envisaged Michael, Michael cascade. Full spectroscopic analysis revealed that diastereomeric tertiary alcohols 79a and 79b, produced in 40% yield and in 3:1 dr, were the major products of the reaction. Presumably, methoxide initiated deacetylation revealed an extended enolate I which in the presence of methyl vinyl ketone underwent rapid double Michael addition at C5. Acidic at the \( \gamma \)-position, the intermediate Michael adduct II could be deprotonated to form another extended enolate III; aldol ring closure would then give the observed diastereomeric products 79a and 79b (Scheme 2.19).

![Scheme 2.19 Reagents and conditions (a) MVK (1.0 eq.), \( \text{K}_2\text{CO}_3 \) (0.2 eq.), MeOH, RT, 30m](image)

2.4.4 DEVELOPMENT OF THE NOVEL MICHAEL-ALDOL CASCADE REACTION

Although not originally planned, the discovered cascade was still relevant as a method for accessing perhydro indol-2-one structures and thus the scope of the reaction with respect to the Michael acceptor was investigated. Pyrrole acetate 74
consumed two equivalents of electrophile, therefore performing the reaction with an excess of the electrophile was predicted to increase yields. Methyl vinyl ketone 47, ethyl vinyl ketone 80, propenyl vinyl ketone 81* and thiophene derived α,β-unsaturated ketone 82* were found to be effective substrates affording bicyclic products 79a,b and 83-85a,b in good yield with moderate diastereoselectivities [a (major) : b (minor)] (Table 2.1). The stereochemistries depicted are based on analogy with compounds 93a and 93b (Section 2.4.4.1)

![Image of reaction scheme]

**Table 2.1 Scope of reaction with respect to Michael acceptor**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Michael acceptor</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>dr (a:b)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>MeCOCH=CH₂ 47</td>
<td>79a,b</td>
<td>0.5</td>
<td>76</td>
<td>3:1</td>
</tr>
<tr>
<td>2°</td>
<td>EtCOCH=CH₂ 80</td>
<td>83a.b</td>
<td>0.5</td>
<td>75</td>
<td>3:1</td>
</tr>
<tr>
<td>3</td>
<td>COCH=CH₂ 81</td>
<td>84a,b</td>
<td>0.5</td>
<td>65</td>
<td>3:1</td>
</tr>
<tr>
<td>4°</td>
<td>COCH=CH₂ 82</td>
<td>85a,b</td>
<td>0.5</td>
<td>79</td>
<td>3:1</td>
</tr>
</tbody>
</table>

*Published results. *b* determined by inspection of the ¹H NMR of the crude mixture

Double Michael-Dieckmann condensation cascade reactions have been reported and thus we decided to include methyl acrylate 86 into our studies to perhaps introduce a carbonyl group into the bicyclic product rather than the tertiary alcohols obtained with α,β-unsaturated ketones. The carbonyl group would also be beneficial for continued studies towards the AC bicyclic core of Daphniyunnine B. When the reaction was performed with pyrrole acetate 74 under the standard reaction conditions, however, the sole product isolated was the double Michael adduct 87 in good yield rather than the desired bicyclic compound 88 (Scheme 2.20).

*α,β-unsaturated ketones 81 and 82 were prepared and kindly donated by Karen Dodd
A brief study into the Dieckmann-type condensation was undertaken and the outcomes are shown in Table 2.2.

Table 2.2 Attempted Dieckmann-type condensation reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Reaction outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(^{1})BuOK/THF, room temperature and reflux</td>
<td>Recovery of starting materials</td>
</tr>
<tr>
<td>2</td>
<td>(^{1})BuOK/DMF, room temperature and reflux</td>
<td>Recovery of starting materials</td>
</tr>
<tr>
<td>3</td>
<td>(^{1})BuOK/(^{-})BuOH, room temperature and reflux</td>
<td>Complex mixture of compounds</td>
</tr>
<tr>
<td>4</td>
<td>NaH/THF, room temperature and reflux</td>
<td>Recovery of starting materials</td>
</tr>
<tr>
<td>5</td>
<td>NaH/DMF, room temperature and reflux</td>
<td>Recovery of starting materials</td>
</tr>
<tr>
<td>6</td>
<td>LHMDS/DMF, room temperature and reflux</td>
<td>Recovery of starting materials</td>
</tr>
</tbody>
</table>
Although the Dieckmann-type condensation was unsuccessful, we were encouraged by the great success of the Michael-Michael-aldol cascade with a range of Michael acceptors, and so our attention turned toward expanding the scope by first derivatising the Michael donor. Using 71 as a common intermediate, regioselective Grignard addition with methylmagnesium bromide under the protective deprotonation reaction conditions gave 89, which after dehydration rapidly furnished the methyl-derived pyrrole acetate 90 in modest yield over two steps (Scheme 2.21).

![Scheme 2.21 Reagents and conditions](image)

Preliminary reactions of 5-methyl pyrrole acetate 90 with methyl vinyl ketone 47 using the optimal conditions for pyrrole acetate 74 gave low to moderate yields. It was found that an excess of pyrrole acetate 90 to the α,β-unsaturated ketone gave higher yields. Acrolein 91, methyl vinyl ketone 47, ethyl vinyl ketone 80, propenyl vinyl ketone 81 and thiophene derived α,β-unsaturated ketone 82 were found to be effective substrates with 90 as the Michael donor, affording bicyclic products 92a,b-96a,b in good yield with diastereoselectivities [a (major) : b (minor)] between 1:1 and 6:1 (Table 2.3).
Pyrrole acetate 90 underwent efficient Michael addition with methyl acrylate 86 to afford 97, however the Michael-Dieckmann-type reaction also, unsurprisingly, failed under the reaction conditions detailed in Table 2.2 (Scheme 2.22).

### Table 2.3 Scope of reaction with respect to Michael acceptor

<table>
<thead>
<tr>
<th>Entry</th>
<th>Michael acceptor</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Dr (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCOCH=CH₂ 91</td>
<td>92a,b</td>
<td>12</td>
<td>71</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>MeCOCH=CH₂ 47</td>
<td>93a,b</td>
<td>0.5</td>
<td>74</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>EtCOCH=CH₂ 80</td>
<td>94a,b</td>
<td>0.5</td>
<td>67</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td>COCH=CH₂ 81</td>
<td>95a,b</td>
<td>1</td>
<td>70</td>
<td>6:1</td>
</tr>
<tr>
<td>5</td>
<td>COCH=CH₂ 82</td>
<td>96a,b</td>
<td>1</td>
<td>79</td>
<td>4:1</td>
</tr>
</tbody>
</table>

*Published results.*

Pyrrole acetate 90 underwent efficient Michael addition with methyl acrylate 86 to afford 97, however the Michael-Dieckmann-type reaction also, unsurprisingly, failed under the reaction conditions detailed in Table 2.2 (Scheme 2.22).

### 2.4.4.1 DETERMINATION OF STEREOCHEMISTRY AND ORIGIN OF STEREOCONTROL

The relative stereochemistries of 93a (major) and 93b (minor) were established through nOe experiments (*Figure 2.1 and appendix*).
These experiments and analysis of the $^1$H NMR spectra for both products suggested a pseudochair conformation is adopted in which the methyl at the ring junction is placed in an axial position and the methyl of the tertiary alcohol was axial in the major and equatorial in the minor diastereoisomers. These data are consistent with stereoselectivity resulting from kinetic control in the aldol step (Scheme 2.23).

Interestingly, when cyclopentenone 98 and cyclohexenone 44 were employed in the reaction, only one diastereomeric product in each case (99 and 100 respectively) was obtained in good yield (Scheme 2.24).
The stereochemistry of 99 was established by nOe experiments. The high diastereoselectivity in the reaction is ascribed to an initial diastereoselective Michael addition followed by a facially selective aldol reaction imposed by the cyclic nature of the ketone. Although the origin of the high diastereoselectivity in the Michael addition remains to be determined, this cascade reaction provides simple access to functionally dense stereodefined structures in a one-pot process (Figure 2.2 and appendix).

When pyrrole acetate 74 was used as the Michael donor in reactions with cyclic enones, unexpected Michael-aldol-oxidation products were obtained as single diastereomeric products in moderate yield. The stereochemistry depicted in both 101 and 102 has been assigned based on analogy with the $^3$H NMR spectra of 99 (Scheme 2.25).
There is insufficient data to determine the mechanism, however the oxygen oxidation of pyrrole-2-ones is well documented in the literature and thus we can postulate a mechanistic pathway. Presumably, pyrrole acetate 74 undergoes Michael addition to cyclopentenone 98 to afford Michael adduct 103. After which, the C5 position could be sterically congested and a second Michael addition hampered. At this point, there are two possible pathways A and B. Beginning with pathway A, deprotonation of the methyl group at the 4-position allows aldol cyclisation to afford 104, which could be further deprotonated at the C5 position generating the pyrrole alkoxide 105. Autoxidation of 105 with the oxygen in the atmosphere could give the free radicals 106 and 107. It is generally accepted that the autoxidation in alkaline media initiates and propagates through a substrate radical as indicated below. The greater electronegativity of oxygen versus that of carbon makes alkoxy radicals less stable than carbon radicals and thus 106 is favoured and the peroxide 108 could be formed. Reduction of the unstable peroxide 108 furnishes the tricyclic product 101. Pathway B could proceed via autoxidation of Michael adduct 109 to give the free radicals 110 and 111 after which reaction with oxygen could generate peroxide 112. Reduction and aldol cyclisation could then furnish the tricyclic product 101 (Scheme 2.26).
INITIATION: \[ R^- + \text{Base}^\ominus \rightarrow \text{Base-H} + R^\ominus \]
\[ R^\ominus + \text{O}_2 \rightarrow R^- + \text{O}_2^\ominus \cdot \]
PROPAGATION: \[ R^- + \text{O}_2 \rightarrow R^\ominus - \text{O}_2 \cdot \]
\[ R^\ominus - \text{O}_2 \cdot + R^\ominus \rightarrow R^\ominus - \text{O}_2^\ominus + R^- \]

Autoxidation pathway

Scheme 2.26 Postulated mechanistic pathway for the formation of 101
To confirm oxidation from the air, pyrrole acetate 90, mono-substituted at the C5 position, was subjected to catalytic potassium carbonate/methanol reaction conditions under an air atmosphere to afford the aminol 113 in good yield (Scheme 2.27).

![Scheme 2.27](image)

**Scheme 2.27** Reagents and conditions (a) K₂CO₃ (0.2 eq.), MeOH, RT, air atmosphere

### 2.4.5 A POSSIBLE APPLICATION OF THE CASCADE TOWARDS THE TOTAL SYNTHESIS OF (±) DAPHNIYUNNINE B

If the cascade reactions were amenable to larger groups than methyl at the 4-position on the Michael donor, perhaps this would allow rapid synthesis of the ACD tricyclic core 42 of (±) Daphniyunnine B (Scheme 2.28).

![Scheme 2.28](image)

**Scheme 2.28** Retrosynthetic analysis

Due to the expedience and reliability of the pyrrole acetate synthesis, the ethyl derivative 117 was prepared to investigate the feasibility of this retrosynthetic plan (Scheme 2.29).
Unfortunately acrolein was not found to be an effective substrate affording a complex mixture of products. Methyl vinyl ketone underwent efficient Michael addition to afford **118** however no aldol cyclisation product **119** was observed (*Scheme 2.30*).

![Scheme 2.30](image)

It is believed that the aldol cyclisation does not occur because generation of the extended enolate **120** would incur allylic strain and therefore the equilibrium favours **118** (*Scheme 2.31*).
Pyrrole acetate 117 underwent efficient Michael addition with methyl acrylate to afford 121, however attempts to perform the Michael-Dieckmann-type reaction with the conditions detailed in Table 2.2 failed to yield the bicycle 122 (Scheme 2.32).

Although the pyrrole acetate 117 was not an effective substrate for the Michael-aldol cascade, a novel methodology for the formation of bicyclic (and tricyclic) perhydro indol-2-ones via a methoxide catalyzed deacetylation-Michael-aldol cascade of pyrrole acetates 74 and 90 with a range of α,β-unsaturated carbonyl compounds in good yields and moderate to excellent diastereoselectivities has been developed. Our attention now turned to the development of an enantioselective variant.

2.4.6 THE DEVELOPMENT OF AN ENANTIOSELECTIVE VARIANT

It was envisaged that an enantioselective variant could be achieved through replacement of potassium carbonate in methanol with a chiral organocatalyst.

2.4.6.1 PREPARATION OF THE PRO-NUCLEOPHILE 123

Pyrrole-2-one 123 (the deacetylated form of 90) was reasoned to be a more adequate nucleophile for such reactions, however as discovered previously, deacetylation under basic conditions afforded the oxidized product 113. It was found, however, that
treatment of the common intermediate 73 with 6M HCl in dichloromethane afforded the desired pro-nucleophile 123 presumably via an iminium formation and tautomerism pathway; avoiding the acetylation step of our previous synthesis in good yield (Scheme 2.33).

![Scheme 2.33](image)

**2.4.6.2 PROOF OF PRINCIPLE**

Pyrrole-2-one 123 was treated with methyl vinyl ketone and 20 mol% of 1,4-diazabicyclo[2.2.2]octane (DABCO) to afford the desired Michael adduct (±)-124 as a racemate. Presumably DABCO was not sufficiently basic for the second deprotonation and thus aldol cyclisation did not occur (Scheme 2.34).

![Scheme 2.34](image)

As discussed in section **2.2.4.1**, Deng and co-workers reported highly enantioselective Michael additions with methyl vinyl ketone using a bifunctional cinchona-derived organocatalyst 55. Accordingly, our studies began by treating pyrrole-2-one 123 with
an excess of methyl vinyl ketone in the presence of this bifunctional cinchona-derived organocatalysts 55. These reaction conditions gave the desired product (+)-124 in moderate yield and encouraging enantiocontrol (Scheme 2.35).

![Scheme 2.35 Reagents and conditions (a) catalyst 55 (0.1 eq.), MVK (4.0 eq.), CH₂Cl₂, RT, 5 h](image)

A similar cinchona-derived organocatalyst 125 has also been reported to undergo enantioselective Michael additions and was included alongside 55 into our investigations under a variety of conditions (Table 2.4).

![Catalysts 55 and 125 were prepared and kindly donated by Katherine Bogle](image)
Table 2.4 Enantioselective organocatalytic Michael addition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>125</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>5h</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>CH₂Cl₂</td>
<td>-20 °C</td>
<td>20h</td>
<td>46</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>125</td>
<td>CH₂Cl₂</td>
<td>-20 °C</td>
<td>20h</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>125</td>
<td>MeOH</td>
<td>-20 °C</td>
<td>20h</td>
<td>50</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>125</td>
<td>TBME</td>
<td>-20 °C</td>
<td>20h</td>
<td>60</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>125</td>
<td>THF</td>
<td>-20 °C</td>
<td>20h</td>
<td>53</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>125</td>
<td>PhMe</td>
<td>-20 °C</td>
<td>20h</td>
<td>53</td>
<td>86</td>
</tr>
</tbody>
</table>

* 123 (1.0 eq.), MVK (4.0 eq.), Catalyst 55 or 125 (0.1 eq.) in solvent (0.4M).

In all cases, Michael adduct (+)-124 was the product isolated; presumably, catalysts 55 and 125 were also not sufficiently basic to mediate aldol cyclisation. Both the phenanthryl and adamantoyl substituted catalysts 55 and 125 gave promising enantioselectivities at room temperature with 125 being superior (Scheme 2.35 and entry 1). Cooling of the reaction to -20°C resulted in significant improvement although prolonged reaction times were required (entries 2 and 3). A solvent screen revealed little variation in enantioselectivity for non-polar solvents with values ranging from 83-86% (entries 5-7); however with the polar, protic solvent methanol, effective loss of enantiocontrol was observed (11% ee, entry 4). In the absence of crystallinity or literature compounds to chemically correlate to, the absolute stereochemistry of Michael adduct (+)-124 was not determined.

2.4.6.3 THE POSTULATED MODE OF ACTION

Based on studies by Deng,33 simultaneous activation of the nucleophile and electrophile by the organocatalyst could afford the proposed transition structure 126 and account for high enantioselectivity. The catalyst 125 is relatively conformationally rigid with restricted rotation about the C8-C9 bond generating a “cage-like” transition structure. The basic quinuclidine nitrogen of the catalyst deprotonates 123 creating a
reactive ammonium enolate and methyl vinyl ketone \textbf{47} is selectively delivered by hydrogen bonding of the quinoline phenol (6'-OH) (\textit{Figure 2.3}).

\begin{center}
\textbf{Scheme 2.3} Proposed transition structure for the enantioselective Michael addition
\end{center}

Ethyl vinyl ketone also underwent Michael addition with \textbf{123} under the optimized enantioselective conditions described above, however with lower enantioselectivity. Once again, in the absence of crystallinity or literature compounds to chemically correlate to, the absolute stereochemistry of Michael adduct \textbf{127} was not determined (\textit{Scheme 2.36}).

\begin{center}
\textbf{Scheme 2.36} Reagents and conditions (a) catalyst \textbf{125} (0.1 eq.), EVK (4.0 eq.) PhMe, -20 °C, 20h
\end{center}

\section*{2.4.7 RING CLOSING REACTIONS}

The aldol reaction of the enantioenriched Michael adduct (+)-\textbf{124} (86% ee) was facilitated upon treatment with potassium carbonate in methanol to generate adduct (+)-\textbf{93a,b} in 92% yield and as a 2:1 mixture of diastereoisomers as observed previously in section \textbf{2.4.4}. The absolute stereochemistry was not determined (\textit{Scheme 2.37}).
In a subtle modification of reactivity, treatment of enantioenriched (+)-124 with 20 mol% of pyrrolidine in methanol afforded the 6,5-bicycle (-)-130 as a 1:1 mixture of epimers at C3. Presumably, reversible enamine formation of (+)-124 gave 128 which underwent a stereoselective intramolecular Michael addition to give 129 followed by hydrolysis to afford (-)-130 (Scheme 2.38).

That it was epimeric at C3 was proven via Krapcho dealkyldecarboxylation to give (+)-131 as a single diastereoisomer. The relative stereochemistry depicted as cis was determined by nOe studies however the absolute stereochemistry was not established (Scheme 2.39).
2.4.8 SUMMARY

In summary, a novel and efficient methodology for the formation of bicyclic (and tricyclic) perhydro indol-2-ones via a methoxide catalyzed deacetylation-Michael-aldol cascade of pyrrole acetates 74 and 90 with a range of $\alpha,\beta$-unsaturated carbonyl compounds in good yields and moderate to excellent diastereocontrol was discovered and developed (Scheme 2.40).

A novel enantioselective Michael addition of pyrrole-2-one 123 and methyl vinyl ketone utilising a cinchona-derived organocatalyst 125 was discovered and developed. A second stereoselective organocatalysed intramolecular Michael addition followed by dealkyldecarboxylation furnished the 6,5-bicycle (-)-131 as a single diastereoisomer. This structure is comparable to the AC bicyclic core of Daphniyunnine B (Scheme 2.41).
The current route features a methyl group at the C5 position of pyrrole-2-one 123 acting as a blocking group to prevent the second Michael addition. This methyl group does not feature in Daphniyunnine B and thus a removable blocking group would be required as an alternative. Stereocontrolled Michael additions have been performed with a phenylsulfanyl group at the C5 position of similar compounds. Importantly in the context of this thesis, the phenylsulfanyl group can be stereoselectively reduced afterward. Therefore preparation of pyrrole-2-one 132 and double organocatalytic Michael addition could afford bicycle 133 which after stereoselective desulfurization could furnish the desired AC bicyclic core 134 of Daphniyunnine B (Scheme 2.42).

Preliminary studies undertaken for the intramolecular Michael addition of Michael adduct 127 to give the bicycle 135 have been unsuccessful using pyrrolidine, however
the vast arena of enamine catalysis may still hold the answer to facilitate this reaction (Scheme 2.43).

If successful, combination of the phenylsulfanyl group at the C5 position of pyrrole-2-one 132 and enantioselective Michael-Michael cascade with the functionalized Michael acceptor 136 could result in bicycle 137. Subsequent alkylation and stereoselective desulfurization and dealkyldecarboxylation could rapidly construct the ACD tricyclic core 42 of Daphniyunnine B (Scheme 2.44).
CHAPTER THREE: A QUATERNISATION CYCLISATION APPROACH TOWARDS THE TOTAL SYNTHESIS OF (±) DAPHNIYUNNINE B

Alongside the Michael cascade approach to Daphniyunnine B, a parallel quaternisation cyclisation approach was investigated.

3.1 AIMS AND RETROSYNTHETIC ANALYSIS

Our aim for this approach was envisaged to employ two key transformations to rapidly construct the ABC tricyclic core 138;

1. A quaternisation cyclisation reaction;
2. An ene-carbocyclisation reaction

Further selective double alkylation and amide reduction of 138 could afford the ABCD tetracyclic core 139 which was envisaged to undergo Michael-aldol condensation to afford (±) Daphniyunnine B.

3.2 INTRODUCTION TO QUATERNISATION CYCLISATION REACTIONS

Tu and co-workers in 2006 reported extensive investigations into the construction of hydroindole structures using cyclic ketones and N-substituted iodoacetamides. Refluxing β-ketoester 140 in tetrahydrofuran in the presence of sodium hydride led to the thermodynamic sodium enolate, which was quenched with the iodoacetamide 141 to afford the desired hydroindole 142 in excellent yield (Scheme 3.1).
Although a powerful method for the construction of hydroindole structures, the products are racemic. Enantioselective quaternisation reactions have received considerable attention in recent years and have been successfully applied to many different transformations.\(^{51}\) Phase-transfer catalysis has been a very successful mode of catalysis for enantioselective alkylation reactions and a few relevant examples will be discussed below.

### 3.2.1 ENANTIOSELECTIVE ORGANOCATALYTIC ALKYLATION REACTIONS

Dolling and co-workers in 1984 pioneered the construction of compounds bearing quaternary stereocentres via alkylation reactions of keto-derived compounds 143 using cinchona-derived chiral phase-transfer organocatalysts 144. Dolling proposed that the high enantioselectivity was a result of both i) tight ion pairing established between the enolate of 143 and the hydroxyl group of the catalyst through hydrogen bonding and ii) electrostatic \(\pi-\pi\) bonding interactions (Scheme 3.3).\(^{52}\)
Recently, Dixon and co-workers reported highly enantioselective catalytic alkylation reactions of β-keto esters with aziridines using a cinchona-derived chiral phase-transfer organocatalyst 145. Based on studies within the group and previous reports, it is believed that both the anthracenylmethyl unit and adamantoyl ester in the catalyst block the Re face of the ammonium enolate, such that the electrophile can only approach from the Si face. Generally, a bulky tert-butyl ester in the pronucleophile is necessary to give high levels of enantioselectivity, presumably as this differentiates the two sides of the enolate (Scheme 3.4).
3.3 INTRODUCTION TO CARBOCYCLISATION REACTIONS

The carbocyclisation of 1,3-dicarbonyl compounds to pendent alkyne and alkene functionality, first discovered by Eglinton and Whiting\(^5\) and then developed by Conia and Perchec,\(^5\) has received much attention in recent years.\(^6\)

The reaction allows the formation of cyclic compounds bearing a methylene/methane substituent adjacent to the newly formed carbon bond and can be conducted under thermal conditions,\(^5\) strong mineral acid,\(^7\) base,\(^4\) or metal ion catalysis.\(^8\) These harsh experimental conditions limit their synthetic application. Recently, the use of transition metal catalysis has allowed a notable improvement to the reaction conditions. For example, gold(I),\(^5\) and copper(I)\(^6\) species have proved to be efficient catalysts for the cyclisation of 1,3-dicarboxyls to alkynes and alkenes.
3.3.1 ALKYNE CARBOCYCLISATIONS OF 1,3 DICARBONYL COMPOUNDS

Toste and co-workers in 2004 performed efficient gold(I)-ligand-catalysed 5-exo-dig carbocyclisation reactions of 1,3-dicarbonyl compounds with tethered alkynes (Scheme 3.5).^59

![Scheme 3.5 Reagents and conditions (a) (PPh₃)AuCl (0.01 eq.), AgOTf (0.01 eq.), CH₂Cl₂, RT](image1)

The proposed mechanism for the reaction of β-ketoester 146 is shown below. Mechanism A involves nucleophilic attack on a gold(I)-alkyne complex by the enol form of the ketoester, affording the vinyl-gold intermediate 148 which after protodemetalation affords product 147. Mechanism B proceeds via formation of the gold(I)-enolate of the ketoester followed by cis-carboauration of the alkyne to afford the vinyl gold intermediate 149 which can also undergo protodemetalation to produce the product 147 (Scheme 3.6).

![Scheme 3.6 Proposed mechanism for gold(I)-catalysed carbocyclisation reaction](image2)

Toste and co-workers in 2005 reported the first enantioselective intramolecular carbocyclisation reaction of 1,3-dicarbonyl compounds and alkynes using dual
palladium(II)/ytterbium(III) catalysis 150. The origins of enantiocontrol were not determined, however their mechanistic hypothesis involved the generation of a palladium enolate of the 1,3-dicarbonyl nucleophile 151 that could undergo Lewis acid-promoted addition to the alkyne (Scheme 3.7). 61

\[
\text{Scheme 3.7 Reagents and conditions (a) catalyst 150 (0.1 eq.), Yb(OTf)₃ (0.2 eq.), AcOH (10 equiv.), Et₂O, RT}
\]

Copper(I) catalysts have received considerable attention as alkyne activating species over the past decade. Balme and co-workers in 1999 reported efficient carbocyclisations of 1,3 dicarbonyl/sulfonyl and cyano compounds to unactivated alkynes using copper(I) catalysis (Scheme 3.8). 62

\[
\text{Scheme 3.8 Reagents and conditions (a) t-BuOK (0.15 eq.), Cul (0.1 eq.), THF, 30 °C}
\]

Dixon and co-workers in 2009 reported highly enantioselective carbocyclisations of 1,3 dicarbonyl compounds and alkynes using copper(I) triflate and bifunctional 9-amino-9-deoxyepicinchona-derived urea combination catalysis. Although once again the origins of enantiocontrol were not determined, it is postulated that the catalyst 152 has two roles; i) as a Brønsted base in the deprotonation of the β-keto ester 153, and ii) as an
effective ligand for a copper enolate which imparts high levels of enantiocontrol (Scheme 3.9).  

![Image](image_url)

Scheme 3.9 Reagents and conditions (a) catalyst 152 (0.2 eq.), CuOTf, 1/2C6H6 (0.05 eq.), CH2Cl2, RT

The use of silyl enol ethers as \(\pi\)-nucleophiles is known in similar reactions. Toste and co-workers have taken a more substituted silyl enol ether 154 and performed a gold(I)-catalysed 6-exo-dig cyclisation onto a tethered terminal alkyne (Scheme 3.10).  

![Image](image_url)

Scheme 3.10 Reagents and conditions (a) Ph3PAuCl (0.1 eq.), AgBF4 (0.1 eq.), CH2Cl2/H2O (10:1), 40 °C
3.3.2 ALKENE CARBOCYCLISATIONS OF 1,3 DICARBONYL COMPOUNDS

The literature on gold(I) species activating electron rich alkenes towards attack by carbon nucleophiles is rapidly expanding, however it remains less developed than their alkyne counterparts. Che and co-workers, have recently performed the first example of highly efficient gold(I)-catalysed intramolecular addition reactions of 1,3 dicarbonyl compounds 155 to unactivated alkenes (Scheme 3.11).^64

![Scheme 3.11 Reagents and conditions (a) Au[P(t-Bu)2(o-biphenyl)]Cl (0.05 eq.), AgOTf, (0.05 eq.), PhMe, 60 °C](image1)

A proposed mechanism for the carbocyclisation begins with the cationic gold(I) species coordinating to the alkene to give intermediate 157, which is followed by a stereoselective 6-exo-trig addition of the enol form of the β-ketoamide to generate intermediate 158. Protodemetallation then affords 156 as a single diastereoisomer (Scheme 3.12).

![Scheme 3.12 Proposed ene-carbocyclisation reaction mechanism](image2)
The use of silyl enol ethers as $\pi$-nucleophiles is known in similar reactions, however with limited success and generally require stoichiometric amounts of the transition metal salts. Saegusa and co-workers have performed palladium(II)-mediated alkenylation reactions of silyl enol ethers (Scheme 3.13).\(^{65}\)

\[
\begin{align*}
\text{OTMS} & \quad \xrightarrow{(a)} \quad 87\% \\
\text{alkene} & \quad \rightarrow \\
\text{product} & \quad \text{Scheme 3.13 Reagents and conditions (a) Pd(OAc)$_2$ (1.0 eq.), CH$_3$CN, RT}
\end{align*}
\]
3.4 A QUATERNISATION CYCLISATION APPROACH TOWARDS (±) DAPHNIYUNNINE B: RESULTS AND DISCUSSION

Assembly of the AC bicyclic core of (±) Daphniyunnine B via the quaternisation cyclisation reaction, required the preparation of starting materials 159 and 160 (Scheme 3.14).

3.4.1 THE PREPARATION OF STARTING MATERIALS 159 AND 160

The preparation of iodoacetamide 159 was performed on multi-gram scale in two steps. The amide coupling of chloroacetyl chloride 161 and allylamine gave chloroacetamide 162 in excellent yield which was smoothly converted into the iodide using standard Finkelstein reaction conditions (Scheme 3.15). ⁵⁰,⁶⁶

The preparation of 160 also went without incident on multi-gram scale, from the commercially available ketone 163, following a modified Danishefsky procedure (Scheme 3.16). ⁶⁷
3.4.2 PROOF OF PRINCIPLE

Generation of the thermodynamic enolate of 160 with sodium hydride in boiling tetrahydrofuran followed by nucleophilic substitution and cyclisation of iodoacetamide 159 afforded the desired bicycle 164 in moderate yield as a single diastereoisomer. The relative configuration of 164 was not determined as N-acyliminium ion promoted hydride reduction of the aminol is the next step (Scheme 3.17).

A variety of reaction conditions were investigated to improve the yield of this reaction and are shown in Table 3.1.
Replacing sodium hydride with lithium hexamethyldisilazane slightly increased the yield (entry 2) however lithium diisopropylamide was superior (entry 3). Inverting the equivalents of nucleophile and electrophile did not improve the yield (entries 4 and 5).

The poor yields of this reaction can be rationalised by the propensity for halo-acetamides 159 to undergo dimerisation reactions to form diketopiperazines 165 under basic environments. Presumably, within the quaternisation cyclisation reaction mixture, the thermodynamic enolate 166 could either undergo the desired nucleophilic substitution or proton transfer with the iodoacetamide 159. The latter afforded the diketopiperazine 165 which was isolated from the reaction mixture (Scheme 3.18).

Table 3.1 Screen of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (eq.)</th>
<th>Iodoacetamide 159 (eq.)</th>
<th>Isolated yield (%)</th>
<th>Yield brsm 160 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH (1.0)</td>
<td>1.1</td>
<td>31</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>LHMDS (1.0)</td>
<td>1.1</td>
<td>34</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>LDA (1.0)</td>
<td>1.1</td>
<td>39</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>LDA (1.0)</td>
<td>3.0</td>
<td>33</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>LDA (2.0)</td>
<td>1.0</td>
<td>22</td>
<td>60</td>
</tr>
</tbody>
</table>

*Ketone 160 refluxed in tetrahydrofuran for 2h and then addition of iodoacetamide 159 at -78 °C to RT*
Despite the poor yields of 164 resulting from this side reaction, scale-up of the reaction was attempted to continue with the synthesis. Unfortunately, yields plummeted over a one gram scale, however multiple one gram reactions gave adequate material to continue with the synthesis.

3.4.3 PREPARATION OF THE AC BICYCLIC CORE OF (±) DAPHNIYUNNINE B

The reduction of aminol 164 through Lewis acid mediated N-acyliminium ion formation and reduction with triethylsilane along with concurrent acetal hydrolysis gave the desired product 167 in moderate yield as a single diastereoisomer. Presumably, equatorial attack of the hydride of the silane onto the N-acyliminium ion was preferential as to avoid 1,3 diaxial interactions. A substantial amount of alcohol 168 resulting from reduction of ketone 167 formed following acetal hydrolysis and was also isolated as a 3:1 mixture of diastereoisomers. The depicted relative configuration of both 167 or 168 was not assigned, but was based on N-acyliminium ion promoted reductions of similar structures (Scheme 3.19).
An investigation into this reaction found that generation of the N-acyliminium ion with one equivalent of trifluoroacetic acid rather than boron trifluoride diethyl etherate and subsequent reduction with one equivalent of triethylsilane at low temperature were optimal conditions. Presumably, N-acyliminium ion reduction of 164 was in competition with reduction of the ketone 167 formed in the reaction mixture, therefore with the triethylsilane present in one equivalent, formation of the stable enamide 169 was observed. Addition of more triethylsilane before, during or after the reaction did not improve the yield of 167 (Scheme 3.20).

The preparation of 167, although not on multi-gram scale, allowed the production of sufficient material to permit studies into the key ene-carbocyclisation.
3.4.4 THE ENE-CARBOCYCLISATION REACTION

As discussed in section 3.3.2, ene-carbocyclisations have been successfully catalysed by various transition metal-ligand catalysts. Accordingly, we envisaged that bicycle 167 with the alkene poised for this mode of catalysis would afford the desired ABC tricyclic core 138 of (±) Daphniyunnine B (Scheme 3.21).

Numerous reaction conditions were investigated to achieve ene-carbocyclisation and are shown in Table 3.2.

![Scheme 3.21 Proposed ene-carbocyclisation of 167](image)

**Table 3.2 Screen of ene-carbocyclisation reaction conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/pre-catalyst/additive (0.2 eq.)</th>
<th>Solvent</th>
<th>Reaction outcome&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(PPh&lt;sub&gt;3&lt;/sub&gt;)AuCl/AgOTf</td>
<td>PhMe or CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Recovery of starting material</td>
</tr>
<tr>
<td>2</td>
<td>(PPh&lt;sub&gt;3&lt;/sub&gt;)AuCl/AgOTf/pyrrolidine</td>
<td>PhMe or CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Recovery of starting material</td>
</tr>
<tr>
<td>3</td>
<td>(PPh&lt;sub&gt;3&lt;/sub&gt;)AuCl/AgOTf/t-BuOK (2.0 eq.)</td>
<td>PhMe or THF or dioxane</td>
<td>Recovery of starting material</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)&lt;sub&gt;2&lt;/sub&gt;/pyrrolidine</td>
<td>PhMe or CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Recovery of starting material</td>
</tr>
<tr>
<td>5</td>
<td>CuI/t-BuOK (2.0 eq.)</td>
<td>THF</td>
<td>Recovery of starting material</td>
</tr>
<tr>
<td>6</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;/CuCl&lt;sub&gt;2&lt;/sub&gt;/TMSCl (1.0 eq.)</td>
<td>Polyethylene glycol</td>
<td>Recovery of starting material</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions began at room temperature and refluxed for 48h. <sup>b</sup> Recovery of starting material was generally incomplete averaging 60% recovery.
Toste and Che reported highly efficient alkyne and alkene carbocyclisations of 1,3-dicarbonyl compounds using gold(I)-ligand species (see sections 3.3.1 and 3.3.2). Therefore, the carbocyclisation reaction was attempted using these reaction conditions, however even after boiling in toluene and dichloromethane for 48 hours, none of the desired product was isolated (entry 1).

The concentration of enol and hence π-nucleophile is pivotal to the success of the ene-carbocyclisation. Che reported that substrates with an amide and ester functionality and thus low enol concentration did not perform the desired ene-carbocyclisation (Scheme 3.22).[^64]

![Scheme 3.22](image)

Scheme 3.22 Reagents and conditions (a) Au[P(t-Bu)₃(o-biphenyl)]Cl (0.05 eq.), AgOTf (0.05 eq.), Toluene, 50 °C

Pyrrolidine has been reported as an effective additive in carbocyclisation reactions as the reversible enamine formation generates a reactive π-nucleophile.[^71] Unfortunately, addition of pyrrolidine to the gold(I)-ligand reaction conditions described above under boiling toluene and dichloromethane afforded recovery of starting material (entry 2). Rather than catalytic amounts of pyrrolidine, stoichiometric quantities of potassium tert-butoxide were also trialled as an additive to maximise the concentration of enolate in the gold(I)-ligand reaction conditions, however also failed to yield the desired product (entry 3). Copper(I/II) and palladium (II)-ligand catalysis were also found to be ineffective catalysts (entries 4, 5 and 6).

Presumably, the desired and undesired enolates of ketone 167 are under equilibrium and hence even if the equilibrium lies heavily on the undesired enolate, the trace amount of desired enolate should perform the ene-carbocyclisation and generate the desired product 138 (Scheme 3.23).
With no product isolated under the reaction conditions detailed above, perhaps the barrier for reactivity is too high, or the enolate and alkene are unable to adopt a favourable transition structure for reactivity due to the rigidity imposed by the amide in the bicycle. It was decided that formal preparation of the silyl enol ether of bicycle 167 would determine if the ene-carbocyclisation was possible.

Toste and co-workers have performed carbocyclisations of silyl enol ethers and pendent alkynes using gold(I)-ligand catalysis (see section 3.3.1). Trimethylsilylation of ketone 167 afforded a 1:1 mixture of regioisomers 171 and 172 by inspection of the $^1$H NMR of the crude mixture. Attempts at isolation of silyl enol ethers resulted in hydrolysis to 167 on silica. The typical gold(I)-ligand reaction conditions were performed with the crude mixture of regioisomers, however failed to undergo ene-carbocyclisation with recovery of 167 (Scheme 3.24).

Scheme 3.23 Proposed equilibrium between desired and undesired enolates

Scheme 3.24 Reagents and conditions (a) Et$_3$N (3.0 eq.), TMS-OTf (3.0 eq.), CH$_2$Cl$_2$, 0 °C; (b) Ph$_3$PAuCl (0.2 eq.), AgOTf (0.2 eq.), toluene, reflux
With the transition metal-ligand catalysis failing to achieve the ene-carbocyclisation, we envisaged that \( \alpha \)-bromination of ketone 167 could give 173 which could undergo atom transfer radical cyclisation to the tricycle 174 followed by dissolving metal reduction to furnish the desired tricylic core 138 (Scheme 3.25).\(^{72}\)

The \( \alpha \)-bromination of ketone 167 with phenyltrimethylammonium tribromide\(^{73}\) was selective, however, for the undesired regioisomer 173 in good yield as a 1:1 mixture of diastereoisomers. That 173 was diastereomeric and regioselective was determined by salient singlet peaks at 4.68 and 4.49 ppm in the \( ^1H \) NMR along with the lack of double doublet peaks in the same region expected for the desired regioisomer 175. This result suggests that the thermodynamic enolate resides on the undesired side of the ketone (Scheme 3.26).

Mono-alkylation of the thermodynamic enolate of 167 with iodomethane has since been performed within the Dixon group.\(^{74}\) Therefore we could envisage synthesis of the right-hand-side of (±) Daphniyunnine B, after which, the enol of ketone 176 would be poised for ene-carbocyclisation and allow completion of the synthesis (Scheme 3.27).
The current synthesis was insufficient to obtain multi-gram quantities of perhydroindole 167 to continue with the synthesis. And in addition, there were no enantioselective steps to install the stereogenic centres required for the synthesis of Daphniyunnine B. To satisfy both of these criteria, an enantioselective and potentially scalable route was designed and pursued.

### 3.4.5 DEVELOPMENT OF AN ENANTIOSELECTIVE VARIANT

#### 3.4.5.1 RETROSYNTHETIC ANALYSIS

The enantioselective construction of 179 could arise from a highly enantioselective and efficient quaternisation cyclisation reaction of tert-butyl ester 178 and acetamide 159. Replacing 160 with the tert-butyl ester variant 178 was considered valuable for two reasons; i) bulky esters afford the greatest enantiocontrol with chiral phase-transfer catalysts in alkylation reactions\textsuperscript{75} and ii) β-keto esters undergo efficient alkylation reactions with acetamides.\textsuperscript{50} One step ester reduction to the methyl group are precedent\textsuperscript{76} however if required, step-wise ester and aminol reductions along with acetal hydrolysis could furnish enantiopure bicycle 167 (Scheme 3.28).
3.4.5.2 PREPARATION OF TERT-BUTYL ESTER 178

Surprisingly, there is a lack of general methods in the literature for the direct preparation of tert-butyl esters. Cyanoformate reagents had been used to some success, however are not commercially available, requiring three steps to prepare and in the acylation reaction cyanide is expelled.\textsuperscript{75b, 77} Indirect methods such as metal catalysed transesterification may also be used, however this requires two steps per nucleophile and is generally restricted to indanone systems.\textsuperscript{78}

3.4.5.3 DISCOVERY OF AN ALTERNATE ACYLATION METHOD

Although not too dissimilar to the acylation reagent 1-(tert-butoxycarbonyl)imidazole used by Jørgensen and co-workers in the preparation of tert-butyl esters,\textsuperscript{79} the commercially available and considerably less expensive\textsuperscript{80} tert-butyl pyrrole-1-carboxylate \textsuperscript{180}, was considered an attractive acylating agent. Treatment of the cyclic ketone \textsuperscript{163} with a base followed by addition of tert-butyl pyrrole-1-carboxylate could afford the tetrahedral intermediate \textsuperscript{181}. Heating would ensure decomposition of this intermediate to the tert-butyl ester \textsuperscript{178} and relatively low toxicity side products (pyrrole) (Scheme 3.29).

![Scheme 3.29 Proposed preparation of tert-butyl ester 178](image)

Cyclohexanone \textsuperscript{182} was chosen as a model ketone and sodium hydride as the base to determine if the reaction was viable. Generation of the sodium enolate of
cyclohexanone with sodium hydride followed by addition of tert-butyl pyrrole-1-carboxylate under boiling tetrahydrofuran reaction conditions pleasingly gave the desired tert-butyl ester 183 in good yield as a 1:1 mixture of keto/enol forms (Scheme 3.30).

![Scheme 3.30 Reagents and conditions (a) NaH (2.0 eq.), tert butyl pyrrole-1-carboxylate 180 (2.0 eq.), THF, reflux, 2h](image)

This method was successfully applied to the acylation of 1,4-cyclohexanedione monoethylene acetal 163 to afford the desired tert-butyl ester 178 on multi-gram scale in high yield and as a 3:1 mixture of keto/enol forms (Scheme 3.31).

![Scheme 3.31 Reagents and conditions (a) NaH (2.0 eq.), tert butyl pyrrole-1-carboxylate 180 (2.0 eq.), THF, reflux, 2h](image)

This efficient, scalable acylation method has since been published by colleagues in the Dixon group for the preparation of tert-butyl ester starting materials. Preparation of multi-gram quantities of 178 permitted trials of the enantioselective quaternisation cyclisation reaction.

3.4.5.4 PREPARATION OF THE RACEMATE

The treatment of β-keto ester 178 with sodium hydride in boiling tetrahydrofuran generated the thermodynamic enolate, which was quenched with iodoacetamide 159 to afford an inseparable 3:1 mixture of the desired aminol product 179 and enamide 184 in moderate yield (Scheme 3.32).
An HPLC trace of the racemate could not be obtained from this inseparable mixture of aminol 179 and enamide 184. It was anticipated that facially selective aminol/enamide reduction along with acetal hydrolysis would give 185 as a single diastereoisomer (see section 3.4.3, scheme 3.20) and thus an HPLC trace of the racemate of this compound could be obtained (Scheme 3.33).

First, however, the enantioselective quaternisation cyclisation reaction was attempted.

3.4.5.5 PROOF OF PRINCIPLE

Unfortunately, enantioselective quaternisation cyclisation reactions of 178 were extremely poor yielding and are discussed in Table 3.3.
None of the enamide 184 obtained previously was isolated from the enantioselective reactions.\textsuperscript{75c} Following a procedure by Dixon, 19% yield of the desired aminol 179 was isolated (entry 1). The yield was increased slightly with elevated temperatures (entry 2) and optimal using potassium phosphate (entry 3). Both dichloromethane and

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Entry & Base (eq.) & 178 (eq.) & 159 (eq.) & Solvent & T (°C) & Isolated yield (%) & Yield brsm 178 (%) \\
\hline
1 & 50% aq. K\textsubscript{2}HPO\textsubscript{4} (3.0) & 1.0 & 1.2 & Toluene/CHCl\textsubscript{3} (9:1) & -20 & 19 & 57 \\
2 & 50% aq. K\textsubscript{2}HPO\textsubscript{4} (3.0) & 1.0 & 1.2 & Toluene/CHCl\textsubscript{3} (9:1) & RT & 21 & 45 \\
3 & 50% aq. K\textsubscript{3}PO\textsubscript{4} (3.0) & 1.0 & 1.2 & Toluene/CHCl\textsubscript{3} (9:1) & RT & 25 & 67 \\
4 & 50% aq. K\textsubscript{3}PO\textsubscript{4} (3.0) & 1.0 & 1.2 & CH\textsubscript{2}Cl\textsubscript{2} & RT & 12 & 77 \\
5 & 50% aq. K\textsubscript{3}PO\textsubscript{4} (3.0) & 1.0 & 1.2 & THF & RT & 15 & 71 \\
6 & 50% aq. K\textsubscript{3}PO\textsubscript{4} (3.0) & 2.0 & 1.0 & Toluene/CHCl\textsubscript{3} (9:1) & RT & 17 & - \\
\hline
\end{tabular}
\caption{Screen of enantioselective reaction conditions}
\end{table}

* Catalyst 145 (0.2 eq.) used in each case and reaction times of 48h were average

* Chiral phase-transfer catalyst 145 was prepared and kindly donated by Thomas Moss
tetrahydrofuran were found to be ineffective solvents (*entries 4 and 5*). Inverting the equivalents of the optimal reaction conditions gave lower yields (*entry 6*).

The poor yields were presumably owing to the same suggested mechanisms described earlier in section **3.4.2**. These low yields combined with aminol reduction/acetal hydrolysis of the product (predicted to be poor yielding based on the studies performed on similar substrates in section **3.4.3**) to obtain an enantiomeric excess, led to no further investigations into an enantioselective synthesis of **167**.

**3.4.6 SUMMARY**

In summary, the AC bicyclic core **167** of (±) Daphniyunnine B was successfully prepared as a single diastereoisomer (*Scheme 3.34*).

An efficient, scalable acylation method for the synthesis of *tert*-butyl esters from ketones using *tert*-butyl pyrrole-1-carboxylate **180** as an acylating agent was discovered (*Scheme 3.35*).
3.4.7 FUTURE WORK

As discussed in section 3.4.4, we can regioselectively mono-alkylate ketone 167. Therefore, alkylation with a functionalised side chain (scheme 3.36, blue) followed by a second thermodynamic addition with another functionalised side chain (scheme 3.36, red) could allow the synthesis of the D and E rings at which point there would be only one site for ene-carbocyclisation and if successful could rapidly furnish (±) Daphniyunnine B (Scheme 3.36).

With respect to further studies into the ene-carbocyclisation of bicycle 167, our first act would be to reduce the amide carbonyl to the amine 186. This could create a less rigid bicyclic structure and possibly allow both the π-nucleophile of the enolate and the alkene of 186 to adopt a more favourable transition structure 187 and thus react to afford the desired ABC tricyclic core 27 of (±) Daphniyunnine B (Scheme 3.37).
CHAPTER FOUR: AN INTRAMOLECULAR DIELS-ALDER FRAGMENTATION APPROACH TOWARDS THE TOTAL SYNTHESIS OF (±) DAPHNIYUNNINE B

Thus far, we have prepared the AC bicyclic core of the natural product utilizing discovered and developed novel catalytic cascades and reactions. To advance further toward the natural product, an intramolecular Diels-Alder fragmentation approach was investigated.

4.1 AIMS AND RETROSYNTHETIC ANALYSIS

Our aim for this approach was the construction of the ACD ring system 190 employing two key transformations:

1. One-carbon homologation of α,β-unsaturated ketone 188;
2. Intramolecular Diels-Alder fragmentation of furan 189

Further enamide reduction, global acid deprotection and allylation could afford two pendent sites for carbocyclisation and complete a rapid synthesis of (±) Daphniyunnine B (Scheme 4.1).

![Scheme 4.1 Retrosynthetic analysis](image)

4.2 INTRODUCTION TO ONE-CARBON HOMOLOGATIONS OF CYCLIC KETONES

From a synthetic view-point, there are many situations whereby the lower homologue of a desired structure is more readily available. In these cases, synthetic chemists
must call upon a one-carbon homologation strategy that ideally would be synthetically simple to perform, high yielding and regioselective.

4.2.1 TRIMETHYLSILYLDIAZOMETHANE MEDIATED ONE-CARBON HOMOLOGATIONS

The use of diazomethane is one of the oldest and most direct methods for one-carbon homologation of carbonyl compounds. There are, however, many drawbacks; diazomethane solutions are not commercially available and must be prepared when required, it is hazardous and has a tendency to explode and generally low yields of the desired product are obtained due to low regioselective control and frequent side reactions such as epoxide formation and multiple carbon insertions (Scheme 4.2).

Trimethylsilyldiazomethane was introduced by Shioiri and co-workers in 1982 as a stable and safe substitute for the hazardous diazomethane, with high efficiency and regiocontrol in boron trifluoride diethyl etherate-mediated one-carbon homologations of ketones (Scheme 4.3).
The regioselectivity of the reaction can be attributed to axial attack of the trimethylsilyldiazomethane followed by a transition structure (a) whereby the bulky TMS group is on the less hindered side of the molecule and then migration of the bond antiperiplanar to the diazonium group. The initial ring homologated products (b) can undergo rearrangement to give the silyl enol ethers (c) followed by hydrolysis to the regioisomeric products 193 and 194 (Scheme 4.4).  

The use of trimethylsilyldiazomethane also limits the potential side reactions that occur with diazomethane. If the epoxide is formed, the boron trifluoride diethyl etherate can transform it into the homologated ketone and multiple carbon insertions are mainly avoided because the majority of ring homologated products will sit in their silyl enol ether form until hydrolysis on work-up.  

Scheme 4.4 Mechanism of one-carbon homologation
Cyclic \(\alpha,\beta\)-unsaturated ketones can also undergo one-carbon homologations using trimethylsilyldiazomethane. Desmaële and co-workers in 2006 reported a highly efficient and regioselective trimethylaluminium-mediated one-carbon homologation of a cyclic \(\alpha,\beta\)-unsaturated ketone 195 in their pursuit of the cyathin terpenoids (Scheme 4.5).\(^{86}\)

In combination with the theory that the trimethylsilyl group would favour occupying the sterically least hindered side in the transition structure, the high regioselectivity can be attributed to the model postulated by Gonnan and co-workers; “an sp\(^2\) hybridized carbon atom bonded to the atom serving as the origin of the migrating group generally migrate more readily than alkyl groups. This is perhaps best ascribed to the use of the p-orbital in these groups for overlap with the developing vacant orbitals present at both the origin and the terminus of the migration.”\(^{85}\)

### 4.2.2 \(\beta\)-OXIDO CARBENOID HOMOLOGATIONS

Nozaki and co-workers pioneered studies into \(\beta\)-oxido carbenoid homologations of symmetrical and unsymmetrical cyclic ketones (Scheme 4.6).\(^{87}\)

\[
\text{Scheme 4.5 Reagents and conditions (a) Me}_3\text{Al (5.0 eq.), TMSCHN}_2 (5.0 eq.), CH}_2\text{Cl}_2, \text{RT, 4h then, 3M HCl, acetone, RT, 2h}
\]

\[
\text{Scheme 4.6 Reagents and conditions (a) Br}_2\text{CH}_2 (2.0 eq.), \text{LDA (1.5 eq.), Et}_2\text{O, -95 }^\circ\text{C, then, n-BuLi (4.0 eq.)}
\]
Nucleophilic addition of a dibromomethyllithium species to the carbonyl group affords the lithium (dibromomethyl)alkoxide which after another addition of butyllithium undergoes lithium/halogen exchange and subsequent one-carbon homologation. The regioselectivity has been rationalised using the same arguments as for trimethylsilyldiazomethane, with a bromide instead of a trimethylsilyl group taking up the least sterically demanding position in the transition structure (Scheme 4.7).

\[
\begin{align*}
\text{Scheme 4.7 Rationale for regioselectivity}
\end{align*}
\]

β-oxido carbenoid homologations have also been applied to cyclic α,β-unsaturated ketones affording high yields of β,γ-unsaturated ketones with >95% regioselectivity. Unfortunately, due to the method relying heavily on strong base, yields suffer with base sensitive compounds.\textsuperscript{87a, 88}

**4.3 INTRODUCTION TO DIELS-ALDER REACTIONS OF FURANS**

The Diels-Alder reaction, since its discovery by Otto P. H. Diels and Kurt Alder\textsuperscript{89} in 1928, is one of the most studied and utilized reactions in organic synthesis. With a huge variety of dienes and dienophiles available and its simplicity to perform, the Diels-Alder reaction is an extremely powerful method for the construction of cyclohexene frameworks.\textsuperscript{90} Despite their aromaticity and hence lower reactivity, furans undergo [4+2] cycloadditions with a variety of dienophiles, such as alkenes, alkynes and allenes. Furan Diels-Alder reactions are reversible and undergo retro-Diels-Alder reactions depending on many variables including temperature, time and also substituents on both the furan and the dienophile. Exo and endo selectivities are therefore heavily dependent on these variables.\textsuperscript{91}
4.3.1 ENANTIOSELECTIVE CATALYSIS IN DIELS-ALDER REACTIONS OF FURANS

Enantioselective Diels-Alder reactions of furans relied on substrate control using chiral dienophiles until Corey in 1993 reported highly enantioselective LUMO-lowering Lewis acid catalysed Diels-Alder reactions of furans using a chiral oxazaborolidine catalyst 196 (Scheme 4.8).

![Scheme 4.8 Reagents and conditions (a) catalyst 196 (0.1 eq.), CH₂Cl₂, -78 °C, 5h]

4.3.2 INTRAMOLECULAR DIELS-ALDER REACTIONS OF FURANS (IMDAF)

IMDAF reactions consist of a furan linked by a tether to a dienophile. Substituents on the tether not only diversify the resulting adduct, but affect the stereochemistry and reaction rates. IMDAF reactions are under thermodynamic control and when bulky substituents are present on the tether, the most stable Diels-Alder adduct will be formed as to minimise non bonding interactions. Increasing the size of these substituents, increases the rate of the reaction and this effect is commonly known as the tert-butyl effect. The size of the tether is also key; short chain lengths are more amenable to efficient Diels-Alder reactions and reduced thermal lability. Intramolecular Diels-Alder reactions of furans are generally catalysed by Lewis acids.

Due to the reversibility of IMDAF reactions, in many cases the Diels-Alder adduct cannot be formed. One idea to drive such reactions was to follow the initial cycloaddition with an irreversible step. Hudlicky in 1995 reported an example of this whereby the conformationally demanding IMDAF adduct 197 could undergo cleavage.
of the hemiacetal functionality and therefore avoid the retro-Diels-Alder reaction to afford the Diels-Alder product 198. Although a low yield was obtained, it was the precedent for future investigations into intramolecular Diels-Alder fragmentation reactions of furans (Scheme 4.9).94

![Scheme 4.9 Reagents and conditions (a) toluene, sealed tube, 250 °C](image)

### 4.3.3 INTRAMOLECULAR DIELS-ALDER FRAGMENTATION REACTIONS OF FURANS (IMDAFF)
Padwa and co-workers have become dominant figures in the field of intramolecular Diels-Alder fragmentation reactions of furans and in 1998 reported a simple but very effective electron-rich/electron-rich IMDAFF reaction for the rapid construction of the hexahydroindolinone skeleton 201, which is abundant in many natural products as well as Daphniyunnine B. Investigations into the mechanism found that the initially formed oxabicyclic adduct 199 underwent a nitrogen assisted ring opening followed by subsequent hydrogen shift of the resulting zwitterion 200 to furnish the hexahydroindolinone structure 201 in good yield and as a single diastereoisomer (Scheme 4.10).95
4.3.4 APPLICATIONS IN TOTAL SYNTHESIS

Padwa and co-workers have applied this methodology to various total syntheses including their recent stereocontrolled synthesis of (±) Strychnine. The key IMDAFF reaction of furan 202 was performed using a catalytic amount of magnesium iodide in a microwave reactor to afford the desired adduct 203 in excellent yield. The total synthesis of (±) Strychnine was completed in 12 further steps and 4.4% overall yield (Scheme 4.11).  

This methodology, although powerful in the construction of natural product skeletons, has so far been demonstrated without enantiocontrol. The reaction, in general, requires harsh reaction conditions such as high temperatures and pressures. To the best of our knowledge, enantioselective inter- and intramolecular Diels-Alder reactions of furans have been exclusively catalysed by chiral Lewis acids, which generally require multi-step synthesis to prepare. An attractive and yet to be
explored mode of catalysis in the Diels-Alder reactions of furans is enantioselective organocatalysis. Conventional enantioselective organocatalytic Diels-Alder reactions have developed considerably in recent years and have quickly become a vast field of Diels-Alder chemistry.

4.3.5 ENANTIOSELECTIVE ORGANOCATALYSIS IN DIELS-ALDER REACTIONS

4.3.5.1 SECONDARY AMINE CATALYSIS

MacMillan and co-workers in 2000 reported the first highly enantioselective Diels-Alder reaction by the LUMO-lowering activation of $\alpha,\beta$-unsaturated aldehydes via the reversible formation of iminium ions using an imidazolidinone catalyst 204. Selective formation of the $E$-iminium isomer avoiding nonbonding interactions between the substrate alkene and the geminal methyl substituents along with effective shielding of the $Re$ face of the dienophile, leaves the $Si$ face exposed to cycloaddition (Scheme 4.12).  

![Scheme 4.12](image)

Scheme 4.12 Reagents and conditions (a) catalyst 204 (0.05 eq.), MeOH-H$_2$O, 23 °C, 21h
MacMillan then utilized this strategy in the total synthesis of solanapyrone D. The key organocatalytic intramolecular Diels-Alder reaction of 205 gave the bicycle 206 as essentially one diastereoisomer in high enantiomeric excess. The synthesis was completed in a further 5 steps and 18% overall yield (Scheme 4.13).\textsuperscript{99}

\begin{center}
\begin{center}
\textbf{Scheme 4.13} Reagents and conditions (a) catalyst 204 (0.2 eq.), MeCN, 5 °C
\end{center}
\end{center}

\textbf{4.3.5.2 CINCHONA ALKALOID-DERIVED CATALYSIS IN DIELS-ALDER REACTIONS}

Cinchona alkaloids are abundant in nature and exist as pseudoenantiomeric pairs, exemplified by quinine and quinidine. As a result, their use in enantioselective organocatalysis enables access to both enantiomers of the resultant product material as required.

\textbf{4.3.5.2.1 BRØNSTED BASE CATALYSIS}

Riant and Kagan in 1989 reported the first base-catalysed enantioselective Diels-Alder reaction using 1 mol% of quinidine 207 to generate the Diels-Alder product 210 in moderate enantioselectivity. The authors proposed that quinidine 207 was acting in a bifunctional manner, whereby the hydroxyl group was activating the maleimide 209 through hydrogen bonding and the quinuclidine nitrogen by forming an ionic pair with anthrone 208. This organisation of both the nucleophile and electrophile by quinidine ensured stereocontrol (Scheme 4.14).\textsuperscript{100}
Deng and co-workers in 2007 reported highly enantioselective organocatalytic Diels-Alder reactions using a quinidine-derived organocatalyst 211. Deng postulated that the bifunctional organocatalyst 211 in the enantioselective Diels-Alder reaction simultaneously raised the energy of the HOMO of the diene 212 and lowered the energy of the LUMO of the electron-deficient dienophile 213 while orienting the two reactants to exert stereocontrol (Scheme 4.15).\textsuperscript{101}
4.3.5.2.2 PRIMARY AMINE CATALYSIS

Deng and co-workers also reported highly enantioselective Diels-Alder reactions by the LUMO-lowering activation of $\alpha,\beta$-unsaturated ketones via the reversible formation of iminium ions using a primary amine derived cinchona alkaloid organocatalyst 214. Deng reasoned that organocatalyst 214 would function similarly to that of MacMillan’s secondary amine catalyst 204 as described earlier (see section 4.3.5.1), however unlike MacMillan’s imidazolidinone catalyst, the primary amine catalyst is readily available from an abundant natural source after a high yielding transformation (Scheme 4.16).102
4.4 AN INTRAMOLECULAR DIELS-ALDER FRAGMENTATION APPROACH TOWARDS THE TOTAL SYNTHESIS OF (±) DAPHNIYUNNINE B: RESULTS AND DISCUSSION

To establish whether the key one-carbon homologation and intramolecular Diels-Alder fragmentation reactions were feasible, we envisaged the rapid construction of a simplified model system 217, which could be derived from commercially available Hagemann’s ester 215 and the readily available amidofuran 216 (Scheme 4.17).

![Scheme 4.17 Retrosynthetic analysis](image)

4.4.1 PREPARATION OF AMIDOFURAN 216

Curtius rearrangement of 2-furoyl chloride 218 and sodium azide in tert-butanol gave the amidofuran 216 in good yield and multi-gram scale (Scheme 4.18).^{103}

![Scheme 4.18 Reagents and conditions (a) sodium azide (1.1 eq.), tert-butanol, reflux, 12h](image)

4.4.2 PREPARATION OF α,β-UNSATURATED CYCLIC KETONE 217

Direct amide coupling of Hagemann’s ester 215 with amidofuran 216 was not an option as the hydrolysis product 220 undergoes decarboxylation to 219. Therefore an alternate approach was sought (Scheme 4.19).^{104}
McAndrew reported preparation of the allylic alcohol 221 from Hagemann’s ester 215 which was considered an attractive intermediate for nucleophilic substitution with amidofuran 216 to afford 222.\textsuperscript{105, 106} Acetal hydrolysis could form the $\beta,\gamma$-unsaturated ketone 223, which was predicted to undergo tautomerism to the desired stable conjugated $\alpha,\beta$-unsaturated cyclic ketone 217 (\textit{Scheme 4.20}).

Acetal formation with ethylene glycol under catalytic acid conditions followed by lithium aluminium hydride reduction gave the allylic alcohol 221 in good yield over two steps (\textit{Scheme 4.21}).
The preparation of allylic alcohol 221 permitted investigations into the nucleophilic substitution with amidofuran 216. Preliminary studies found that tosylation of allylic alcohol 221 under standard conditions resulted in the exothermic production of diene 224 upon isolation in good yield. Mesylation and halogenation of the allylic alcohol 221 also gave products unstable upon isolation generating the diene 225 (Scheme 4.22).106

A one-pot method was therefore designed to avoid isolation of the activated intermediate. Tosylation of allylic alcohol 221 under standard conditions followed by addition of the lithium salt of amidofuran 216 gave the desired adduct 222 in modest yield (Scheme 4.23).

Although in modest yield, adequate material was in-hand to attempt the hydrolysis of the acetal. Treatment of 222 with 1.0 M hydrochloric acid in tetrahydrofuran directly afforded the desired α,β-unsaturated cyclic ketone 217 in poor yield. Presumably, the
acidic conditions promoted the alkene isomerism into conjugation and could also be responsible for furan decomposition and the low yields (Scheme 4.24).  

To avoid prolonged exposures to acid, and thus minimize side reactions and increase yields, a more reactive dimethyl acetal variant was sought. Acetal formation, not too dissimilar to that described earlier (see scheme 4.21) was performed with methanol under acidic conditions and followed by reduction with lithium aluminium hydride to afford the desired allylic alcohol 225 in good yield over two steps (Scheme 4.25).

The one-pot reaction conditions established earlier for the nucleophilic substitution of allylic alcohol 225 with the lithium salt of amidofuran 216 gave the desired product 226 in a similar modest yield (Scheme 4.26).
A range of reaction conditions were investigated to increase yields and are shown in Table 4.1.

Table 4.1 Optimisation of nucleophilic substitution

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Activation of alcohol</th>
<th>Amidofuran 216&lt;sup&gt;b&lt;/sup&gt;</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base (1.1 eq.)</td>
<td>Activating reagent (1.1 eq.)</td>
<td>Base (1.5 eq.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N</td>
<td>Tosyl chloride</td>
<td>KHMDS</td>
<td>0 °C-RT</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>LHMDS</td>
<td>Tosyl chloride</td>
<td>LHMDS</td>
<td>-78 °C-reflux</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>LHMDS</td>
<td>Tosyl chloride</td>
<td>KHMDS</td>
<td>-78 °C-RT</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>n-BuLi</td>
<td>Tosyl chloride</td>
<td>KHMDS</td>
<td>-78 °C-RT</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Tetrahydrofuran was used as the solvent in each case; <sup>b</sup> amidofuran 216 (1.5 eq.)

The use of the potassium salt of amidofuran 216 gave the desired product in higher yield than the lithium salt (entry 1). Deprotonation of the allylic alcohol 225 at low temperature with LHMDS followed by addition of the potassium salt of amidofuran 216 further increased the yield (entry 3) and finally, deprotonation with n-BuLi gave...
the desired product in optimal yield (entry 4). Using these optimal reaction conditions, however with slightly modified equivalents, the desired product 226 was obtained on multi-gram scale in good yield (Scheme 4.27).

![Scheme 4.27](image)

**Scheme 4.27** Reagent and conditions (a) n-BuLi (1.0 eq.), tosyl chloride (1.05 eq.), then; amidofuran 216 (1.07 eq.), KHMDPS (1.07 eq.), THF, -78 °C to RT

The adduct 226 was then converted into the β,γ-unsaturated ketone 223 under mild acidic conditions and without further purification was smoothly converted into the desired α,β-unsaturated cyclic ketone 217 under catalytic base conditions in high yield on multi-gram scale (Scheme 4.28).

![Scheme 4.28](image)

**Scheme 4.28** Reagent and conditions (a) 0.1M HCl:THF (1:1), RT, 10m; (b) K₂CO₃ (0.2 eq.), MeOH, RT, 10m

With the preparation of the α,β-unsaturated cyclic ketone 217 now efficient and reliable, we decided that this would be a good model system to determine if the key intramolecular Diels-Alder fragmentation reaction was viable.
4.4.3 PROOF OF PRINCIPLE
Following the procedure by Padwa, the α,β-unsaturated cyclic ketone (±)-217 with a sub-stoichiometric amount of butylated hydroxytoluene (antioxidant) under boiling toluene reaction conditions gave the desired 5,6,6 tricycle (±)-227 in good yield as a single diastereoisomer and a mixture of enol:keto forms (>20:1) (Scheme 4.29).

![Scheme 4.29 Reagent and conditions (a) BHT (0.2 eq.), PhMe, reflux, 2d](image)

4.4.4 DETERMINATION OF STEREOCHEMISTRY AND ORIGIN OF STEREOCONTROL
The relative stereochemistry of (±)-227 was established through nOe experiments (Figure 4.1 and appendix).

![Figure 4.1 nOe experiments of (±)-227](image)

With respect to the proposed mechanism displayed below, the cis stereochemistry of (±)-227 is controlled by restricted addition of the tethered furan from the lower face of the dienophile. Nitrogen assisted ring opening of the oxabicyclic adduct 228 followed by subsequent hydrogen shift of the resulting zwitterion 229 could give the 1,3 diketone (±)-230. The methine proton between the 1,3 dicarbonyl exists almost exclusively as the enol product (±)-227 and with the relative stereochemistry set, the Diels-Alder adduct (±)-227 is obtained as a single diastereoisomer (Scheme 4.30).
The Boc-group on the nitrogen has restricted rotation at room temperature and therefore protons and carbons in close proximity become very broad and sometimes indistinguishable by NMR. Therefore high temperature NMR experiments were performed to enable full characterization. Upon heating, along with sharpening of peaks, came an increase in concentration of the keto form (enol:keto, from >20:1 to ~4:1) as seen when the room temperature and 90 °C ¹H NMR are compared. The alkene proton is a broad singlet at 5.6 ppm at room temperature and becomes a doublet (major: enol-form) and triplet (minor: keto-form) at 90 °C. This data suggests that the more rigid enol-form restricts the alkene proton to only couple to one proton alpha to the enol, whereas in the keto-form the alkene proton can couple to both protons alpha to the carbonyl (Figure 4.2 and 4.3).
Figure 4.2 $^1$H NMR in deuterated DMSO at room temperature of (±)-227 and (±)-230

Figure 4.3 $^1$H NMR in deuterated DMSO at 90°C of (±)-227 and (±)-230
The $^{13}$C NMR at 90°C gives a very clear picture of the mixture of enol:keto forms. A section of the spectra highlighting the key carbons has been selected. When the $^{13}$C NMR is performed at room temperature, the quaternary alkene carbon (146.7 ppm) and quaternary Boc-group carbon (80.2 ppm) are very weak and broad (Figure 4.4).

Finally, MM2 calculations can illustrate the differing conformations of both the enol and keto forms. The minimized energy of the enol form is calculated to be 0.958 kJ/mol greater than that of the keto form (Figure 4.5).
Having proven the intramolecular Diels-Alder fragmentation reaction was viable for furan (±)-217, to access the desired $\beta,\gamma$-unsaturated ketone (±)-231, a regioselective one-carbon homologation was required. If successful, intramolecular Diels-Alder fragmentation reaction of (±)-231 would give the ACD tricyclic core (±)-232 of (±) Daphniyunnine B (Scheme 4.31).

![Scheme 4.31 Envisaged preparation of (±)-232](image)

### 4.4.5 PREPARATION OF $\beta,\gamma$-UNSATURATED CYCLIC KETONE (±)-231

Gratifyingly, our initial reactions using trimethylaluminium as the Lewis acid and trimethylsilyldiazomethane at low temperature gave the desired 7-ring homologue (±)-231 along with regioisomer (±)-233 in moderate yield as a separable 3:1 mixture of regioisomers (Scheme 4.32).85

![Scheme 4.32 Reagent and conditions (a) Me₃Al (2.0 eq.), TMSCN₂ (2.0 eq.), CH₂Cl₂, -78 °C to RT, 1h; (b) 1M HCl:THF (1:1), RT, 30m](image)

A screen of reaction conditions were performed in an attempt to increase the yield of the two step process and are shown in Table 4.2.
Preliminary studies found that two equivalents of both trimethyldiazomethane and trimethylaluminium were optimal for the homologation step in dichloromethane. Desilylation with hydrochloric acid in tetrahydrofuran rather than acetone was found to be superior to both tetrabutylammonium fluoride and methanolic hydrochloric acid (entries 1, 2 and 3). A solvent screen revealed that ethereal solvents were not as efficient or regioselective as dichloromethane in the one-carbon homologation step (entries 4 and 5). Toluene gave higher yields than ethereal solvents however dichloromethane was superior (entry 6). Replacing the Lewis acid of trimethylaluminium with borontrifluoride diethyl etherate gave the desired product (±)-231 in poor yield along with a complex mixture of side-products (Scheme 4.33).

### Table 4.2 Solvent screen and desilylation reaction conditions screen

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solvent</th>
<th>Desilylation conditions</th>
<th>Yield 231 + 233 (%)</th>
<th>Ratio&lt;sup&gt;b&lt;/sup&gt; (231:233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>TBAF, THF, -78 °C</td>
<td>36</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>HCl, MeOH, 0 °C</td>
<td>23</td>
<td>3:1</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>HCl, THF, RT</td>
<td>45</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>As above</td>
<td>32</td>
<td>2:1</td>
</tr>
<tr>
<td>5</td>
<td>Et₂O</td>
<td>As above</td>
<td>29</td>
<td>2:1</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>As above</td>
<td>40</td>
<td>3:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Two equivalents of trimethyldiazomethane and trimethylaluminium were used in each case; <sup>b</sup> Based on isolation
Although the optimal reaction conditions for one-carbon homologation were only moderate in yield, sufficient material was obtained to permit trials of the key intramolecular Diels-Alder fragmentation reaction.

Following the procedure by Padwa, the $\beta,\gamma$-unsaturated cyclic ketone $\mathbf{(\pm)-231}$ and a sub-stoichiometric amount of butylated hydroxyl toluene under boiling toluene reaction conditions gave the desired 5,6,7 tricycle $\mathbf{(\pm)-232}$ in 77% yield as a 2:1 mixture of diastereoisomers. The relative stereochemistry depicted was not determined, however has been assigned based on the nOe studies performed on the 5,6,6 tricycle $\mathbf{(\pm)-227}$ discussed previously in section 4.4.4 (Scheme 4.34).}

Not too dissimilar to the mechanism proposed in section 4.4.4, the stereochemistry of $\mathbf{(\pm)-232}$ is controlled by restricted addition of the tethered furan from the lower face of the dienophile. Nitrogen assisted ring opening of the oxabicyclic adduct $\mathbf{234}$ followed by subsequent hydrogen shift of the resulting zwitterion $\mathbf{235}$ could give the 1,4 diketone $\mathbf{236}$. The methine proton alpha to the ketone can undergo enol/keto
tautomerism under the reaction conditions and thus the stereochemistry here is scrambled and explains the mixture of diastereoisomers of (±)-232 (Scheme 4.35).

![Scheme 4.35 Proposed origins of stereocontrol](image)

The major diastereoisomer of (±)-232 was isolated from the mixture to assist with the characterisation. The $^1$H NMR is comparable to the model 5,6,6 tricycle (±)-227 with the characteristic broad alkene proton around 6.0 ppm. Salient features to note in the $^{13}$C NMR are the two ketone peaks around 204 and 208 ppm, Boc-group carbonyl at 152.2 ppm, quaternary alkene carbon at 144.8 ppm and the second alkene carbon at 97.4 ppm (Figure 4.6 and 4.7).

![Figure 4.6 $^1$H NMR of (±)-232 at 70°C in C$_6$D$_6$](image)
The intramolecular Diels–Alder fragmentation reaction of furan (±)-231 gives the ACD tricyclic core (±)-232 of (±) Daphniyunnine B and family members (see section 1.4), which has all the correct functionality in place (Figure 4.8).

Along with the β,γ-unsaturated cyclic ketone (±)-231, the 7-ring α,β-unsaturated cyclic ketone regioisomer (±)-233 was also isolated from the one-carbon homologation reaction. Not too dissimilar to the one-carbon lower homologue (±)-217, the dienophile is in conjugation with the ketone and therefore will benefit from LUMO-lowering. The 7-ring α,β-unsaturated cyclic ketone (±)-233 underwent intramolecular Diels–Alder fragmentation using a sub-stoichiometric amount of butylated hydroxyl toluene under boiling toluene reaction conditions to give the 5,6,7 tricycle (±)-236 as a
single diastereoisomer in good yield as mixture of enol:keto forms (~5:1) (Scheme 4.36).

**Scheme 4.36** Reagent and conditions (a) BHT (0.2 eq.), PhMe, reflux, 3d

4.4.6 RETROSYNTHETIC ANALYSIS FOR THE COMPLETION OF (±) DAPHNIYUNNINE B

With a route to the ACD tricyclic core of (±) Daphniyunnine B established, it was envisaged that much of the same chemical synthesis could be used in the rapid construction of the appropriately functionalized α,β-unsaturated cyclic ketone 188. A regioselective one-carbon homologation of 188 could afford the β,γ-unsaturated cyclic ketone 189 which was envisaged to undergo diastereoselective intramolecular Diels-Alder fragmentation to give the 5,6,7 tricycle 190 after enamide reduction, global deprotection and allylation. Carbocyclisation of the pendent alkene and alkyne could then furnish (±) Daphniyunnine B (Scheme 4.37).

**Scheme 4.37** Retrosynthetic analysis
4.4.6.1 PREPARATION OF α,β-UNSATURATED KETONE 188

The preparation of alcohol 238 was performed in two high yielding steps from the commercially available propargylic alcohol 237 using Shindo’s procedure. The alcohol 238 was then converted into the bromide 239 under typical Appel reaction conditions in excellent yield on multi-gram scale (Scheme 4.38).

Hagemann’s ester 215 in the presence of potassium tert-butoxide was coupled with bromide 239 to afford 240 in good yield and on multi-gram scale following a procedure by Banerjee (Scheme 4.39).

Acetal formation and reduction of 240 was attempted using the reaction conditions previously described (see scheme 4.25) however desilylation was a major side product. This problem was quickly solved with lower equivalents of acid and a solvent combination of tetrahydrofuran and methanol. Lithium aluminium hydride reduction then gave the allylic alcohol 241 in moderate yield (Scheme 4.40).
Nucleophilic substitution of alcohol 241 with amidofuran 216 was attempted with previously optimised reaction conditions (see scheme 4.27) however none of the desired product 243 was isolated. Presumably, the activated species of allylic alcohol 241 was even more susceptible to the elimination process described earlier (see scheme 4.22) affording the highly substituted stable diene 242 and not the desired product 243. The diene 242 was not isolated however inspection of the $^1$H NMR of the crude mixture revealed a salient singlet peak at 5.35 ppm which is characteristic of the previously isolated diene 224 (Scheme 4.41).

After attempting a range of different bases and equivalent combinations with no success, it was clear that neutral reaction conditions were required. Typical Mitsunobu reaction conditions pleasingly gave the desired product 243 albeit in low yield. Three equivalents of amidofuran 216, DIAD and triphenylphosphine were found to be optimal conditions allowing formation of the desired adduct 243 in consistently modest yields on multi-gram scale (Scheme 4.42).
Acetal hydrolysis of 243 required a higher concentration of acid than expected from previous studies (see scheme 4.28) however gratifyingly gave the desired ketone 244 in near quantitative yield (Scheme 4.43).

The alkene isomerism to afford the α,β-unsaturated ketone was previously achieved with catalytic amounts of potassium carbonate in methanol (Scheme 4.28). With the previous nucleophilic substitution step suffering under basic conditions (Scheme 4.41), it was not surprising when these conditions gave an extremely poor yield of α,β-unsaturated cyclic ketone 188 along with a complex mixture of side-products (Scheme 4.44).
A range of reaction conditions were attempted to obtain the desired $\alpha,\beta$-unsaturated cyclic ketone 188 in greater yield and are shown in Table 4.3.

Table 4.3 Optimisation of alkene isomerism

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pyrrolidine (0.4 eq.), MeOH, RT, 12h</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>Triethylamine (0.4 eq.), THF, RT, 12h</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>N, N-Diisopropylethylamine (0.4 eq.), THF, RT, 12h</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>1,8-Diazabicycloundec-7-ene (0.4 eq.), THF, RT, 12h</td>
<td>80</td>
</tr>
</tbody>
</table>

Pyrrolidine in methanol gave similarly low yields (entry 1), however tertiary amines were much more efficient (entry 2-4) with DBU providing the greatest yield (entry 4, scheme 4.45).
The preparation of α,β-unsaturated cyclic ketone 188 permitted trials of the key one-carbon homologation reaction. A range of different reaction conditions were attempted and are shown in Table 4.4.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₃Al (2.0 eq.), TMSCHN₂ (2.0 eq.), CH₂Cl₂, -78 °C to RT</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>2</td>
<td>BF₃. Et₂O (2.0 eq.), TMSCHN₂ (2.0 eq.), CH₂Cl₂, -78 °C to RT</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Br₂ (2.0 eq.), LDA (2.0 eq.), THF, then BuLi (2.0 eq.), -78 °C to RT</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Br₂ (2.0 eq.), LDA (2.0 eq.), THF, -78 °C to RT</td>
<td>Complex mixture of products</td>
</tr>
</tbody>
</table>

Unfortunately, preliminary studies using the successful method employed previously using trimethylaluminium and trimethylsilyldiazomethane in dichloromethane gave a complex mixture of products (see scheme 4.32 and entry 1). Replacing trimethylaluminium with boron trifluoride diethyl etherate was also unsuccessful (entry 2). β-oxido carbenoid homologations were also trialled, however also without success (entry 3). This method involves significant amounts of base, which as
discovered earlier, could contribute to side reactions. Isolation of the intermediate diastereomeric alcohols was also attempted but also gave a complex mixture of compounds (entry 4).

My own studies into the one-carbon homologation of $\alpha,\beta$-unsaturated cyclic ketone 188 ceased at this point however studies are ongoing by colleagues within the Dixon group.

The intramolecular Diels-Alder fragmentation approach towards (±) Daphniyunnine B has been met with a great deal of success so far, however the products are racemic. Therefore an enantioselective variant was investigated.

4.4.7 DEVELOPMENT OF AN ENANTIOSELECTIVE VARIANT

As discussed earlier (see section 4.3.4), to the best of our knowledge, no enantioselective variations of the intramolecular Diels-Alder fragmentation reaction of furans (IMDAFF) have been reported in the literature. Conventional enantioselective Diels-Alder reactions, however, have been heavily studied with great success. Therefore it was envisaged that LUMO-lowering activation of the conjugated dienophile 233 via the reversible formation of iminium ions using a chiral primary/secondary amine organocatalyst could give the desired ACD tricyclic core 236 of Daphniyunnine B with high enantiocontrol. Condensation of the chiral amine onto the carbonyl group, could generate the diastereomeric compound 245 which under equilibrium was hoped to undergo dynamic kinetic resolution to afford the ACD tricycle 236 as a single enantiomer in good yield (Scheme 4.46).
The 7-ring $\alpha,\beta$-unsaturated ketone 233 is the minor product, obtained in only 11% yield, from the one-carbon homologation of the 6-ring $\alpha,\beta$-unsaturated ketone $(\pm)$-217. Therefore preliminary studies were performed with this easily accessible one-carbon lower homologue $(\pm)$-217 to ascertain if the reaction was viable. Secondary amine catalysis was considered a reasonable place to begin the investigation as MacMillan used his imidazolidinone catalyst 204 to perform the first highly enantioselective Diels-Alder reaction.97 A series of secondary amine catalysts were available in the Dixon laboratory including MacMillan’s imidazolidinone catalyst 204 (see section 4.3.5.1), Jørgensen’s proline-derived catalyst 53 (see section 2.2.3.1) and $(S)$-proline 57 were probed for reactivity however the IMDAFF reaction did not take place and starting material was recovered in each case. Presumably, the secondary amine would favourably form the stable enamine 247 rather than the iminium ion 246, therefore the dienophile was unavailable for reaction (Scheme 4.47).
Primary amine organocatalysis was considered to be a more suitable mode of catalysis as, presumably, there would be less bias for the enamine. Deng and co-workers reported highly enantioselective Diels-Alder reactions with the TFA-salt of primary amine organocatalyst 214 in dichloromethane at low temperature (see section 4.3.5.2.2). Therefore preliminary studies employed a catalytic amount of 214 (20 mol%) under a range of solvents at room temperature for 72 hours and are shown in Table 4.5.

![Quinidine derived catalyst](image)

**Table 4.5** Solvent screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion by $^1$H NMR (%)&lt;sup&gt;*&lt;/sup&gt;</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>~20</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>1,4-dioxane</td>
<td>~30</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>~30</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>~10</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>*</sup> Based on consumption of starting material (±)-217

The low conversion and enantiomeric excess at room temperature determined dichloromethane was not a suitable solvent for the reaction (entry 1). 1,4-dioxane gave slightly higher conversion and enantiomeric excess to dichloromethane, however
tetrahydrofuran was superior with 81% enantiomeric excess (entries 2 and 3). Low conversion and no enantiomeric excess was observed when polar protic solvents were employed (entry 4). In the absence of crystallinity or literature compounds to chemically correlate to, the absolute stereochemistry of the Diels-Alder adduct (+)-227 was not determined.

The high enantiomeric excess generated in tetrahydrofuran was not surprising as Chen and co-workers reported highly enantioselective 1,3 dipolar cycloadditions in this solvent using primary amine organocatalyst 248 at elevated temperatures (Scheme 4.48).  

![Scheme 4.48](image)

**Scheme 4.48** Reagents and conditions (a) catalyst 248 (0.1 eq.), TIPBA (0.2 eq.), THF, 40 °C, 36h

With a suitable solvent and catalyst chosen, optimal reaction conditions were sought to achieve full conversion and maintain high enantiocntrol (Table 4.6).
Table 4.6 Attempt to achieve full conversion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol%)</th>
<th>Temperature (°C)</th>
<th>Conversion by ¹H NMR (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>23</td>
<td>~45</td>
<td>-</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>50</td>
<td>~60</td>
<td>-</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>50</td>
<td>~80&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>50</td>
<td>100&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25</td>
<td>81</td>
</tr>
</tbody>
</table>

<sup>a</sup> i) Based on consumption of starting material (±)-217; ii) After 72h; <sup>b</sup> 96h; <sup>c</sup> 120h

High catalyst loading and elevated temperature gave complete conversion after 120 hours and a 25% yield with maintained high enantiomeric excess (entry 4).

4.4.7.1 POSTULATED MODE OF ACTION

Condensation of the chiral primary amine organocatalyst onto the carbonyl group, generates two diastereomeric compounds 249 and 250 which under equilibrium are believed to adopt the least hindered transition structure 249 via the enamine intermediate 251. Intramolecular Diels-Alder fragmentation reaction and hydrolysis of the iminium ion affords the enantioenriched single diastereoisomer (+)-227. These preliminary results point to perhaps a dynamic kinetic resolution taking place as complete conversion and high enantiomeric excess are observed. Chiral primary and secondary amine organocatalysts are used to catalyse may different transformations and generally use an acid counter ion to facilitate the reaction. With acid sensitive functional groups in both the starting material (±)-217 and product (+)-227, the low yields are presumably due to acid mediated decomposition pathways (Scheme 4.49).
4.4.8 SUMMARY

In summary, the synthesis of the 5,6,6-tricycle (±)-227 was achieved in 6 steps and 35% overall yield from Hagemann’s ester 215 (Scheme 4.50).

Scheme 4.49 Proposed mode of action for enantioselective intramolecular Diels-Alder fragmentation

Scheme 4.50 Synthesis of 5,6,6 tricycle (±)-227
The synthesis of the ACD tricyclic core (±)-232 of (±) Daphniyunnine B from the commercially available Hagemann’s ester 215 was achieved in 7 steps and 10% overall yield. The 5,6,7 tricycle regioisomer (±)-236 was also prepared as a single diastereoisomer (Scheme 4.51).

![Scheme 4.51 Synthesis of ACD tricyclic core (±)-232 and (±)-236 of (±) Daphniyunnine B](image)

The synthesis of the highly functionalized α,β-unsaturated cyclic ketone 188 was achieved in 5 steps and 10% overall yield, however the attempts at one-carbon homologation to afford the one-carbon higher homologue 189 were unsuccessful (Scheme 4.52).

![Scheme 4.52 Synthesis of the α,β-unsaturated ketone 188](image)

A novel, enantioselective intramolecular Diels-Alder fragmentation reaction of furan (±)-217 using a primary amine organocatalyst 214 was discovered (Scheme 4.53).
4.4.9 FUTURE WORK

One-carbon homologation of 188 could allow the preparation of the $\beta,\gamma$-unsaturated cyclic ketone 189 which after a further 4 steps could rapidly complete the synthesis of $(\pm)$ Daphniyunnine B (Scheme 4.54).

The encouraging preliminary results obtained with the enantioselective intramolecular Diels-Alder fragmentation reaction of $\alpha,\beta$-unsaturated cyclic ketone $(\pm)$-217 could be further investigated and developed with a series of primary amine organocatalysts and counter acids. This would then lead to application of the reaction to the 7-ring unsaturated cyclic ketone $(\pm)$-233 to potentially give enantioenriched 236 (Scheme 4.55).
Scheme 4.55 Postulated enantioselective synthesis of ent-236
CHAPTER FIVE: CONCLUSION

In conclusion, this thesis describes three approaches towards the total synthesis of Daphniyunnine B. The first approach was initially designed to construct the ACD tricyclic core via an enantioselective double Michael cascade process, however alternatively gave rise to a Michael-aldol cascade reaction. This cascade was further developed with a range of $\alpha,\beta$-unsaturated ketones affording highly functionalized perhydroindole bicyclic and tricyclic compounds in good yields and moderate to excellent diastereosecontrol (70% average yield with diastereoselectivities between 1:1 and >95:5 over 13 examples). The initially planned enantioselective double Michael cascade was realized, albeit in a step-wise process. A novel highly enantioselective Michael addition utilising bifunctional organocatalysis (53% yield and 86% ee) was followed by a further stereocontrolled organocatalytic intramolecular Michael addition to obtain the methyl-derived AC bicyclic core of Daphniyunnine B.

The second approach was designed to prepare the ABC tricyclic core via a quaternisation cyclisation reaction followed by an ene-carbocyclisation. The AC bicyclic core was successfully prepared utilising the quaternisation cyclisation reaction, however the key ene-carbocyclisation reaction failed to yield the ABC tricyclic core. The reasons for the lack of reactivity remain inconclusive however one explanation is that the enolate and the alkene cannot adopt a favourable transition structure due to the rigidity of the bicycle imposed by the amide motif. An enantioselective variant and potentially scalable route was also pursued with the discovery of an alternate method for the preparation of tert-butyl esters from ketones using tert-butyl pyrrole-1-carboxylate as the acylating agent. Unfortunately, when the enantioselective quaternisation cyclisation reaction was performed, the bicyclic product was obtained in poor yield and thus this approach was discontinued.

Finally, the third approach successfully employed an intramolecular Diels-Alder fragmentation reaction to construct the ACD tricyclic core of (±) Daphniyunnine B in 7 steps and 10% overall yield. Following the success of this approach, our aim was to use the same methods to construct a highly functionalized ACD tricyclic core to allow the rapid completion of the natural product. The synthesis was relatively
straightforward until a brief study into the key one-carbon homologation reaction failed to yield the desired Diels-Alder precursor. Preliminary studies into an enantioselective variant have revealed very encouraging results with a model 6,6,5 tricyclic system being obtained in 81% ee.
CHAPTER SIX: EXPERIMENTAL

6.1 GENERAL EXPERIMENTAL
For all reactions conducted under anhydrous conditions glassware was dried in an oven at 100 °C and carried out under a nitrogen atmosphere, unless otherwise stated.

SOLVENTS AND REAGENTS
Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Reagents used were obtained from commercial suppliers or purified according to standard procedures. Petrol refers to distilled light petroleum of fraction (40 – 65 °C). Anhydrous tetrahydrofuran and diethyl ether were freshly distilled from sodium-benzophenone.

CHROMATOGRAPHY
Flash column chromatography was performed with commercial solvents using Merck Kieselgel 60 silica gel (200-400 mesh). Thin layer chromatography (TLC) was performed on aluminium or glass plates pre-coated with Merck Kieselgel 60 F254 and visualised by ultra-violet radiation or by staining with either aqueous basic potassium permanganate or vanillin. Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on a Hewlett-Packard Series 1050 series system (column conditions are given with the compound).

MELTING POINTS
Melting points were recorded on a Gallenkamp melting point apparatus with the sample contained in a thin glass tube at ambient pressure and are uncorrected.

POLARIMETRY
Optical rotations were recorded using an Optical Activity AA-1000 polarimeter; specific rotations (\([\alpha]_D\)) are reported in \(10^{-1}\) deg cm\(^{-2}\) g\(^{-1}\); concentrations (c) are quoted in g (100 mL\(^{-1}\)); D refers to the D-line of sodium (589 nm); temperatures (t) are given in degrees Celsius (°C).
INFRARED SPECTROSCOPY

Infrared spectra were recorded on a Perkin Elmer Spectrum RX1 FTIR spectrometer (thin film deposited onto a sodium chloride plate). Only selected absorbences ($\nu_{\text{max}}$) are reported.

NMR SPECTROSCOPY

$^1$H, $^{13}$C, DEPT, COSY and HMQC NMR spectra were recorded on Bruker 500, 400 MHz and Varian 300 MHz spectrometers. Chemical shifts ($\delta_{\text{H}}$) are quoted in parts per million (ppm $\pm$ 0.01 ppm) downfield of tetramethylsilane, relative to the residual protiosolvent ($\delta_{\text{H}}$ (CHCl$_3$) = 7.26 ppm) against an internal deuterium lock. Coupling constants ($J$) are given in Hertz (Hz $\pm$ 0.5 Hz). The $^1$H NMR spectra are reported as follows: $\delta$ / ppm (multiplicity, number of protons, coupling constants $J$ / Hz, assignment). DEPT and two-dimensional NMR spectroscopy (COSY and HMQC) were used where appropriate to assist the assignment of the signals in the $^1$H NMR and $^{13}$C NMR spectra.

MASS SPECTROMETRY

Low resolution mass spectrometry (electron impact / chemical ionisation) was recorded on a Micromass Trio 2000 quadropole mass spectrometer and (electrospray) on a Micromass Platform II spectrometer. High resolution mass spectra (accurate mass) were recorded on a Thermo Finnigan Mat95XP mass spectrometer.

6.2 EXPERIMENTAL FOR CHAPTER TWO

$^{(+)}$-1- Allyl-3-methylpyrrolidine-2,5-dione; 68$^{43}$

A solution of methyl succinic anhydride (1.61 mL, 17.0 mmol) and allylamine (1.42 mL, 17.0 mmol) in dichloromethane (160 mL) was stirred for 12 hours before 1, 1'-
carbonyldiimidazole (3.13 g, 19.0 mmol) was added in one portion. The reaction mixture was stirred for a further 2 hours at room temperature and refluxed for 0.5 hours. The mixture was cooled to room temperature, washed with 0.1 M hydrochloric acid (2 x 50 mL) then brine (40 mL), dried (MgSO₄), filtered and concentrated \textit{in vacuo} to afford essentially pure 68 (2.24 g, 87%) as a light yellow oil.

\textsuperscript{1}H NMR (500 MHz, CDCl₃) \(\delta_H 5.78 \text{ (ddt, 1H, } J = 17.1\text{Hz, } 10.2\text{Hz and } 5.8\text{Hz, NCH₂CH)}\), 5.20-5.18 (m, 2H, NCH₂CH₂CH₃), 4.09 (td, 2H, \(J = 5.9\text{Hz and } 1.4\text{Hz, NCH₂})\), 2.93 (dd, 1H, \(J = 17.7\text{Hz and } 9.1\text{Hz, 1 of COCH₂CH})\), 2.86 (m, 1H, COCH₂CH₃), 2.33 (dd, 1H, \(J = 17.7\text{Hz and } 4.2\text{Hz, 1 of COCH₂CH})\), 1.35 (d, 3H, \(J = 7.2\text{Hz, CHCH₃})\); \textsuperscript{13}C NMR (125 MHz, CDCl₃) \(\delta_C 180.1 \text{ (N=O), 176.0 \text{ (N=O), 130.7 \text{ (allyl-C), 118.1 \text{ (allyl-C), 40.8 \text{ (NCH₂), 36.4 \text{ (COCHCH₃), 34.6 \text{ (COCH₂CH), 16.8 \text{ (CH₃).}}} }}\)

\(\textsuperscript{1}H NMR \text{ and } \textsuperscript{13}C NMR \text{ in agreement with the literature}

(\pm)-Methyl 1-allyl-4-methyl-2,5-dioxopyrrolidine-3-carboxylate; 71

To a stirred solution of 68 (1.03 g, 6.73 mmol) and methyl chloroformate (1.27 mL, 13.5 mmol) in dry tetrahydrofuran (10 mL) at -78 °C was added a 1M solution of lithium hexamethyldisilazane in tetrahydrofuran (12.7 mL, 13.5 mmol) drop-wise. The reaction mixture was stirred at -78 °C for 5 minutes and until TLC confirmed complete consumption of starting material before addition of saturated ammonium chloride solution (5 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between dichloromethane (50 mL) and distilled water (50 mL) and further extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated \textit{in vacuo}. Purification by column chromatography (diethyl ether : light petroleum ether 1 : 1 to 3 : 1) afforded 71 (1.2 g, 86%) as a 5:1 mixture of diastereoisomers and a colourless oil.
IR \( \nu_{\text{max}} \) (oil): 2959 (CH), 1785 (C=O), 1735 (C=O) and 1702 (C=O); **Major:** \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.79-5.66 (m, 1H, NCH\(_2\)CH), 5.19-5.06 (m, 2H, NCH\(_2\)CH\(_2\)), 4.06 (m, 2H, NCH\(_2\)), 3.78 (s, 3H, CO\(_2\)CH\(_3\)), 3.37 (d, 1H, \( J = 5.4 \) Hz, CHCO\(_2\)Me), 3.22-3.14 (m, 1H, CHCH\(_3\)), 1.35 (d, 3H, \( J = 7.5 \) Hz, CHCH\(_3\)); **\( ^{13} \)C NMR** (125 MHz, CDCl\(_3\)) \( \delta \) C 177.9 (C=O), 170.9 (C=O), 168.0 (C=O), 130.0 (allyl-C), 118.4 (allyl-C), 54.1 (CO\(_2\)CH\(_3\)), 53.2 (CHCO\(_2\)Me), 41.3 (allyl-C), 39.1 (CHCH\(_3\)), 15.4 (CHCH\(_3\)); **Minor observed:** \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 3.76 (s, 3H, CO\(_2\)CH\(_3\)), 3.14-3.08 (m, 1H, CHCH\(_3\)), 1.24 (d, 3H, \( J = 7.5 \) Hz, CHCH\(_3\)); **MS** m/z (ES\(^+\)): 234 ([M+Na]\(^+\)); **HRMS** Found [M+Na]\(^+\) 234.0735 (C\(_{10}\)H\(_{13}\)NNaO\(_4\)) requires (M) 234.0737.

(\( \pm \))-Methyl 1-allyl-5-hydroxy-4-methyl-2-oxopyrrolidine-3-carboxylate; 73

\[ \text{NaH (1.0 eq.)} \quad \text{DIBAI-H (2.0 eq.)} \quad \text{THF, -78 °C, 1h} \]

A solution of 71 (2.0 g, 9.48 mmol) in dry tetrahydrofuran (80 mL) was added drop-wise via cannula to a stirred suspension of 60% sodium hydride in oil (0.23 g, 9.48 mmol) in dry tetrahydrofuran (80 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 minutes and then cooled to -78 °C before a 1.0 M solution of diisobutylaluminium hydride in hexanes (19.9 mL, 19.9 mmol) was added drop-wise. The solution was stirred for 1 h at -78 °C and until TLC confirmed complete consumption of starting material, followed by quench with addition of a saturated solution of sodium potassium tartrate (20 mL). The reaction mixture was stirred at room temperature until the two layers were clearly visible. The layers were separated and the aqueous layer extracted with dichloromethane (2 \times 100 mL). The organic layers were combined, dried (MgSO\(_4\)) and concentrated in vacuo. Purification by column chromatography (diethyl ether : light petroleum ether 1 : 1 to 3 : 1) afforded 73 (1.43 g, 71%) as a single diastereoisomer and a colourless oil.
IR $\nu_{\text{max}}$(oil): 3369 (OH), 2958 (CH), 1741 (C=O), 1681 (C=O); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 5.74 (ddt, 1H, $J = 17.1$ Hz, 10.1 Hz, and 5.3 Hz, NCH$_2$CH$_2$), 5.11 (t, 1H, $J = 5.8$ Hz, CH$_2$OH), 4.17 (dt, 2H, $J = 5.3$ Hz and 1.6 Hz, NCH$_2$), 3.8 (s, 3H, OCH$_3$), 3.27 (d, 1H, $J = 10.2$ Hz, CH$_2$OH), 2.8 (dqd, 1H, $J = 10.2$ Hz, 7.0 Hz, and 5.8 Hz, CH$_2$CH$_3$), 2.38 (d, 1H, $J = 5.9$ Hz, OCH$_3$), 1.18 (d, 3H, $J = 7.0$ Hz), CH$_3$-CO$_2$; $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 168.0 (C=O), 169.9 (C=O), 132.6 (allyl-C), 118.6 (allyl-C), 82.9 (CHOH), 53.5 (CH$_2$CO$_2$Me), 52.7 (CO$_2$CH$_3$), 43.3 (CH)$_3$, 37.3 (allyl-C), 12.7 (CH$_3$)H; MS $m/z$ (ES$^+$): 236 ([M+Na]$^+$). HRMS Found [M+Na]$^+$ 236.1003 (C$_{10}$H$_{15}$NNaO$_4$) requires (M) 236.1001.

Methyl 2-acetoxy-1-allyl-4-methyl-1H-pyrrole-3-carboxylate; 74

To a stirred solution of 73 (0.24 g, 0.94 mmol) in dry tetrahydrofuran (15 mL) was added dry pyridine (2.23 mL, 28.2 mmol) and acetic anhydride (1.41 mL, 14.1 mmol) consecutively at room temperature. The reaction mixture was refluxed for 2 days and until TLC confirmed complete consumption of starting material. The reaction mixture was partitioned between ethyl acetate (100 mL) and water (100 mL) and the organic layer further washed with saturated ammonium chloride solution (3 x 75 mL) then water (75 mL) then brine (50 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether : light petroleum ether 1 : 1) afforded 74 (0.15 g, 68%) as an off-white solid.

MP 59-61 °C; IR $\nu_{\text{max}}$(solid) 2950 (CH), 1787 (C=O), 1702 (C=O); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 6.15 (s, 1H, pyrrole-$H$), 5.82 (ddt, 1H, $J = 16.5$ Hz, 10.2 Hz and 5.6 Hz, NCH$_2$CH$_2$), 5.19 (d, 1H, $J = 10.2$ Hz, 1 of NCH$_2$CH$_2$H), 5.11 (d, 1H, $J = 16.5$ Hz, 1 of NCH$_2$CH$_2$H), 4.23 (d, 2H, $J = 5.6$ Hz, NCH$_2$), 3.74 (s, 3H, CO$_2$CH$_3$), 2.32 (s, 3H, acetate-CH$_3$) and 2.19 (s, 3H, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 168.4 (C=O), 164.4 (C=O), 139.4 (pyrrole-C), 132.5
(allyl-C), 119.1 (pyrrole-C), 118.0 (allyl-C), 113.9 (pyrrole-C), 101.1 (pyrrole-C), 50.6 (CO₂CH₃), 47.4 (allyl-C), 20.4 (acetate-CH₃), 12.6 (CH₃); **MS m/z** (Cl⁺): 260 ([M+Na]⁺); **HRMS** Found [M+H]⁺ 238.1067 (C₁₂H₁₆NO₄) requires (M) 238.1074. Analysis calculated for C₁₂H₁₆NO₄: C, 60.75; H, 6.37; N, 5.90; O, 26.98. Found: C, 60.23; H, 6.22; N, 5.75.

**General procedure A for the Michael−Michael−aldol reaction**

To a stirred solution of pyrrole acetate 74 (0.42 mmol) in MeOH (0.2 M) was added α,β-unsaturated ketone 47,80-82 (1.86 mmol) and K₂CO₃ (0.08 mmol) at room temperature. The reaction was stirred at this temperature until TLC confirmed complete consumption of starting material. The reaction was quenched by addition of acetic acid (0.16 mmol) and concentrated *in vacuo*. Purification by column chromatography gave the Michael−Michael−aldol product.

(±)-Methyl 1-allyl-2'-hydroxy-2'-methyl-2-oxo-5-(3''-oxobutyl)-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 79a,b

Following the general procedure A described above with α,β-unsaturated ketone 47, the Michael-Michael-aldol product 79a,b was obtained following purification by column chromatography (diethyl ether : light petroleum ether, 4:1) as a 3:1 mixture of diastereoisomers and a yellow oil (112 mg, 76%).

**IR** ν<sub>max</sub> (oil) 3550-3200 (OH), 2953 (CH), 1760 (C=O), 1715 (C=O) 1686 (C=O); **Major 79a**: ¹H NMR (500 MHz; CDCl₃) δH 5.87-5.77 (m, 1H, NCH₂CH₂), 5.22 (d, 1H, J = 17.1Hz, 1 of NCH₂CHCH₃), 5.11 (d, 1H, J = 10.0Hz, 1 of NCH₂CHCH₃), 4.06 (dd, 1H, J = 15.3Hz and 5.4Hz, NCH₂H₆), 3.86 (s, 3H, CO₂CH₃), 3.74 (dd, 1H, J = 15.3Hz and 6.7Hz, NCH₂H₆), 3.59 (d, 1H, J = 12.6Hz, 1'-CH₃H₆), 2.34 (dd, 1H, J = 13.8Hz and 8.4Hz, 1''-CH₃H₆), 2.31 (d, 1H,
\[ J = 12.6 \text{Hz}, \ 1'\text{-CH}_{2}\text{H}_3, \ 2.20-2.18 \text{ (m, 2H, 4'-CH}_3\text{H}_2), \ 2.10-1.96 \text{ (m, 2H, 2''-CH}_3\text{H}_2 \text{ and 1''-CH}_3\text{H}_3), \ 2.05 \text{ (s, 3H, 4''-CH}_3\text{H}_3), \ 1.89 \text{ (dd, 1H, J = 15.0Hz and 10.3Hz, 2''-CH}_3\text{H}_3), \ 1.77-1.67 \text{ (m, 1H, 3'-CH}_3\text{H}_3), \ 1.40 \text{ (s, 3H, 2''-CH}_3\text{H}_3 \text{ and 1''-CH}_3\text{H}_3), \ 1.31 \text{ (dt, 1H, J = 14.0Hz and 4.4Hz, 3'-CH}_3\text{H}_3); \]

\[ ^{13}C \text{ NMR (125 MHz; CDCl}_3 \text{)} \delta \text{C} \ 206.9 \text{ (3''-C}=\text{O), 170.3 (4-\text{C)}, 166.2 (2-\text{C}=\text{O), 162.8 (CO}_2\text{CH}_3), 133.5 (\text{allyl-C}, 123.7 (3-C), 118.2 (\text{allyl-C), 74.9 (2'-C), 66.0 (5-C), 52.0 (CO}_2\text{CH}_3), 42.3 (\text{allyl-C), 39.7 (1'-CH}_2\text{), 36.5 (4''-CH}_3\text{H}_3), 35.6 (2''-CH}_2\text{H}_2, 30.2 (4'-CH}_2\text{), 25.9 (2''-CH}_3\text{), 25.7 (1''-CH}_2); \text{ Minor 79b observed:} ^1H \text{ NMR (500 MHz; CDCl}_3 \text{)} \delta \text{H} \ 3.50 \text{ (d, 1H, J = 13.8Hz, 1'}\text{-C}_\text{H}\text{A}_\text{H}\text{B}, \ 2.23 \text{ (d, 1H, J = 13.8Hz, 1'}\text{-CH}_\text{A}_\text{H}\text{B}, \ 2.03 \text{ (s, 3H, 4''-C}_\text{H}_3\text{H}_3) \text{ and 1.13 (s, 3H, 2''-CH}_3\text{H}_3); } ^{13}C \text{ NMR (125 MHz; CDCl}_3 \text{)} \delta \text{C} \ 133.7 \text{ (allyl-C), 118.0 (allyl-C), 74.0 (2'-C); MS m/z (ES+): 358 ([M+Na]+); HRMS Found [M+Na]+ 358.1617 (C}_{18}H_{25}NaO_5 \text{ requires (M) 358.1625.}}

(±)-Methyl 1-allyl-2'-ethyl-2'-hydroxy-2-oxo-5-(3''-oxopentyl)-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 83a,b

Following the general procedure A described above with α,β-unsaturated ketone 80, the Michael-Michael-aldol product 83a,b was obtained following purification by column chromatography (diethyl ether : light petroleum ether, 4:1) as a 3:1 mixture of diastereoisomers and a light yellow oil (115 mg, 75%).

IR \( \nu_{\text{max}} \) (oil) 3700-3300 (OH), 2940 (CH), 1760 (C=O), 1710 (C=O) 1690 (C=O); Major 83a:

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \text{)} \delta \text{H} \ 5.92-5.71 \text{ (m, 1H, NCH}_2\text{CH}_2), \ 5.20 \text{ (d, 1H, J = 17.1Hz, 1 of NCH}_2\text{CHCH}_2, \ 5.09 \text{ (d, 1H, J = 10.1Hz, 1 of NCH}_2\text{CHCH}_2), \ 4.04 \text{ (dd, 1H, J = 15.4Hz and 6.4Hz, NCH}_3\text{H}_3), \ 3.84 \text{ (s, 3H, CO}_2\text{CH}_3), \ 3.75 \text{ (dd, 1H, J = 14.4Hz and 6.4Hz, NCH}_3\text{H}_3), \ 3.63 \text{ (d, 1H, J = 13.5Hz, 1''-CH}_3\text{H}_3, \ 2.31-2.27 \text{ (m, 4H, 2''-CH}_2\text{ and 4''-CH}_2), \ 2.26-2.23 \text{ (m, 1H,}}

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Following the general procedure A described above with $\alpha_\beta$-unsaturated ketone 81, the Michael-Michael-aldol product 84a,b was obtained following purification by column chromatography (neat diethyl ether) as a 3:1 mixture of diastereoisomers and a light yellow oil (117 mg, 65%).

**IR** $\nu_{\text{max}}$(oil) 3423 (OH), 2931 (CH), 1741 (C=O), 1713 (C=O), 1686 (C=O); **Major 84a:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 6.82-6.71 (m, 1H, 5″-CH$_2$), 6.05-5.96 (m, 1H, 4″-CH$_2$), 5.91-5.73 (m, 1H, NCH$_2$CHCH$_2$), 5.78 (m, 1H, 1″′-CH$_2$), 5.64 (m, 1H, 2″′-CH$_2$), 5.23 (d, 1H, J = 17.1 Hz, 1 of NCH$_2$CHCH$_2$), 5.11 (d, 1H, J = 10.1 Hz, 1 of NCH$_2$CHCH$_2$), 4.08 (m, 1H, NCH$_2$H$_2$), 3.87
(±)-Methyl-1-allyl-2'-hydroxy-2-oxo-5-{3''-oxo-6''-(thiophen-2-yl)hexyl}-2'-(3''- (thiophen-2-yl)propyl)-hexahydro-1H-indole-3-carboxylate; 85a,b

Following the general procedure A described above with α,β-unsaturated ketone 82, the Michael-Michael-aldol product 85a,b was obtained following purification by column chromatography (neat diethyl ether) as a 3:1 mixture of diastereoisomers and a light yellow oil (176 mg, 79%). The diastereoisomers were partially separated and characterized individually.

85a: IR v max (oil) 3600-3100 (OH), 2948 (CH), 1736, 1714 (C=O), 1677 (C=O); 1H NMR (500 MHz, CDCl3) δ H 7.11 (dd, 1H, J = 5.1Hz and 1.0Hz, thiophene-H), 6.90 (ddd, 1H, J = 5.1Hz and 3.4Hz, thiophene-H), 6.89 (dd, 1H, J = 5.1Hz and 3.4Hz, thiophene-H), 6.75 (d, 2H, J = 3.4Hz, thiophene-H), 5.81 (ddt, 1H, J = 17.0Hz, 10.1Hz and 6.5Hz, NCH2CH), 5.22 (dd, 1H, J = 17.0Hz and 1.1Hz, 1 of NCH2CHCH2), 5.11 (d, 1H, J = 10.1Hz, 1 of NCH2CHCH2), 4.05 (dd, 1H, J = 15.4Hz and 6.2Hz, NCH3), 3.85 (s, 3H, CO2CH3),
3.72 (dd, 1H, J = 15.4Hz and 6.8Hz, NCH₃H₃), 3.66 (d, 1H, J = 12.8Hz, 1'-CH₃H₃), 2.78 (dd, 4H, J = 14.8Hz and 7.5Hz, 3''-CH₂ and 6''-CH₂), 2.34 (t, 4H, J = 7.4Hz, 2''-CH₂ and 4''-CH₂), 2.25 (d, 1H, J = 12.8Hz, 1'-CH₃H₃), 2.16-2.08 (m, 1H, 3'-CH₃H₃), 2.04-1.95 (m, 1H, 4'-CH₃H₃), 1.87 (m, 4H, 1''-CH₂ and 4''-CH₂), 1.85-1.73 (m, 1H, 4'-CH₃H₃), 1.71-1.58 (m, 4H, 2''-CH₂ and 5''-CH₂), 1.40 (m, 2H, 1'''-CH₂) and 1.24 (ddd, 1H, J = 13.2Hz, 7.6Hz and 4.7Hz, 3'-CH₃H₃). ¹³C NMR (125 MHz, CDCl₃) δc 208.5 (3''-C=O), 169.7 (4-C), 166.0 (2-C=O), 162.7 (CO₂CH₃), 144.7 (thiophene-C), 144.0 (thiophene-C), 133.5 (allyl-C), 126.8 (thiophene-C), 126.7 (thiophene-C), 124.5 (thiophene-C), 124.2 (3-C), 124.1 (thiophene-C), 123.3 (thiophene-C), 123.1 (thiophene-C), 118.1 (allyl-C), 76.3 (2'-C), 65.9 (5-C), 52.0 (CO₂CH₃), 42.3 (allyl-C), 41.8 (4''-CH₂), 38.1 (1''-CH₂), 36.3 (2''-CH₂), 35.3 (3''-CH₂), 35.0 (5''-CH₂), 33.5 (3'-CH₂), 29.9 (4'-CH₂), 28.9 (CH₂), 26.0 (CH₂), 25.3 (CH₂) and 25.0 (1''-CH₂); MS m/z (ES+): 578 ([M+Na]⁺); HRMS Found [M+Na]⁺ 578.2016 (C₂₅H₃₇N⁺NaO₅S₂) requires (M) 578.2005.

85b: IR νmax(oil) 3600-3100 (OH), 2952 (CH), 1735, (C=O), 1721 (C=O), 1673 (C=O); ¹H NMR (500 MHz, CDCl₃) δh 7.12 (dd, 1H, J = 5.3Hz and 0.8Hz, thiophene-H), 6.92 (dd, 1H, J = 5.3Hz and 3.6Hz, thiophene-H), 6.90 (dd, 1H, J = 5.3Hz and 3.6Hz, thiophene-H), 6.79 (d, 1H, J = 3.6Hz, thiophene-H), 5.83 (ddt, 1H, J = 17.0Hz, 10.0Hz and 6.5Hz, NCH₂CH₃), 5.22 (d, 1H, J = 17.0Hz, 1 of NCH₂CHCH₂), 5.10 (d, 1H, J = 10.0Hz, 1 of NCH₂CHCH₂), 4.04 (dd, 1H, J = 15.4Hz and 6.5Hz, NCH₃H₃), 3.86 (s, 3H, CO₂CH₃), 3.76 (dd, 1H, J = 15.4Hz and 6.5Hz, NCH₃H₃), 3.48 (d, 1H, J = 13.6Hz, 1'-CH₃H₃), 2.87 (t, 2H, J = 7.3Hz, 6''-CH₂), 2.79 (t, 2H, J = 7.3Hz, 3''-CH₂), 2.33 (t, 2H, J = 7.3Hz, 2''-CH₂), 2.26-2.18 (m, 1H, 3'-CH₃H₃), 2.17 (d, 1H, J = 13.6Hz, 3'-CH₃H₃), 2.11-2.06 (m, 2H, 4''-CH₂), 1.98-1.89 (m, 2H, 4'-CH₂), 1.88 (t, 2H, J = 7.3Hz, 2''-CH₂), 1.85-1.74 (m, 3H, 5''-CH₂) and 1.73-1.62 (m, 5H, 1'''-CH₂, 3'-CH₃H₃ and 1''-CH₂); ¹³C NMR (125 MHz, CDCl₃) δc 208.6 (3''-C=O), 170.8 (4-C), 166.0 (2-C=O), 163.5 (CO₂CH₃), 144.6 (thiophene-C), 144.0 (thiophene-C), 133.7 (allyl-C), 126.8 (thiophene-C), 125.2 (3-C), 124.5 (thiophene-C), 124.4 (thiophene-C), 123.3 (thiophene-C), 123.1 (thiophene-C), 117.9 (allyl-C), 76.1 (2'-C), 66.4 (5-C), 52.1 (CO₂CH₃), 42.8 (allyl-C), 42.2, 41.8 (4''-CH₂), 36.9 (2''-CH₂), 35.7 (3''-CH₂ and 6''-CH₂), 32.4 (3'-CH₂), 30.0 (4'-CH₂), 28.9 (CH₂), 25.6 (CH₂), 25.3 (CH₂) and 25.0 (1''-CH₂); MS m/z (ES+): 578 ([M+Na]⁺); HRMS Found [M+Na]⁺ 578.2012 (C₂₅H₃₇N⁺NaO₅S₂) requires (M) 578.2005.
To a stirred solution of 74 (100 mg, 0.42 mmol) in MeOH (2 mL) was added methyl acrylate (0.16 mL, 1.85 mmol) and K₂CO₃ (12 mg, 0.08 mmol) at room temperature. The reaction was stirred until TLC confirmed complete consumption of starting material before addition of acetic acid (10 μL, 0.17 mmol) and concentrated in vacuo. Purification by column chromatography (neat diethyl ether) gave 87 (113 mg, 77%) as a yellow oil.

IR νₑₑₑ /cm⁻¹ (oil) 1738 (C=O), 1695 (C=O) and 1437 (C=C); ¹H NMR (500 MHz, CDCl₃) δH 5.92-5.79 (m, 1H, NCH₂CH), 5.25 (d, 1H, J = 17.0Hz, 1 of NCH₂CHCH₂), 5.10 (d, 1H, J = 10.0Hz, 1 of NCH₂CHCH₂), 4.02 (m, 2H, NCH₂), 3.82 (s, 3H, CO₂CH₃), 3.58 (s, 6H, 2 × OCH₃), 2.15 (td, 2H, J = 11.6Hz and 4.8Hz, COCH₂CH₂), 2.14 (s, 3H, CH₃), 2.03-1.95 (m, 2H, COCH₂CH₂), 1.89 (ddd, 2H, J = 16.1Hz, 10.9Hz and 5.0Hz, COCH₂CH₂), 1.74 (ddd, 2H, J = 16.1Hz, 10.9Hz and 5.0Hz, COCH₂CH₂); ¹³C NMR (125 MHz, CDCl₃) 172.4 (2 × CO₂), 168.1 (N=O), 166.4 (CO₂), 162.5 (quat. C=O), 132.5 (allyl-Ω), 126.2 (quat. C=Ω), 118.7 (allyl-Ω), 69.5 (N=O), 51.8 (3 × OCH₃), 42.3 (NCH₂), 29.4 (2 × COCH₂), 27.2 (2 × COCH₂CH₂), 12.2 (CH₃) MS m/z (ES+): 390 ([M+Na]+); Found [M+H]+ 368.1708 (C₁₈H₂₆NO₇) requires (M) 368.1704.
A solution of 71 (2.94 g, 14.0 mmol) in dry tetrahydrofuran (115 mL) was added dropwise via cannula to a stirred suspension of 60% sodium hydride in oil (0.56 g, 14.0 mmol) in dry tetrahydrofuran (115 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 minutes and then cooled to −78 °C before a 3.0 M solution of methylmagnesium bromide in diethyl ether (21.0 mL, 63.0 mmol) was added drop-wise. The solution was warmed to room temperature and stirred for 2 hours and until TLC confirmed complete consumption of starting material. The reaction was quenched by addition of a saturated solution of ammonium chloride (50 mL). The layers were separated and the aqueous layer extracted with dichloromethane (2 × 100 mL). The organic layers were combined, dried (MgSO₄), filtered and concentrated in vacuo to give the crude product which was purified by column chromatography (ethyl acetate : light petroleum ether, 1 : 1 - 3 : 1) to afford 89 (1.9 g, 60%) as single diastereoisomer and a colourless oil.

**IR** ν<sub>max</sub> (oil); 3600-3200 (OH), 1742 (C=O), 1690 (C=O); **¹H NMR** (500 MHz, CDCl₃) δ<sub>H</sub> 5.84 (ddt, 1H, J = 17.1Hz, 10.6Hz and 5.9Hz, NCH₂CH), 5.22 (d, 1H, J = 17.1Hz, 1 of NCH₂CHCH₂), 5.15 (d, 1H, J = 10.6Hz, 1 of NCH₂CHCH₂), 5.02-3.97 (m, 2H, NCH₂CHCH₂), 5.02-3.97 (m, 2H, NCH₂CHCH₂), 3.97 (ddt, 1H, J = 17.1Hz, 10.6Hz, 5.9Hz, NCH₂CH), 2.98-2.68 (bs, 1H, OH), 2.57 (dq, 1H, J = 10.7Hz and 6.9Hz, CH₂CH), 1.51 (s, 3H, CH₃), 1.44 (d, 3H, J = 6.9Hz, CH₂CH₃); **¹³C NMR** (125 MHz, CDCl₃) δ<sub>C</sub> 170.1 (C=O), 170.0 (C=O), 134.0 (allyl-Ç), 117.3 (allyl-Ç), 89.8 (quat. Ç), 53.6 (CH₂CO₂Me), 52.7 (CO₂CH₃), 42.8 (CH₂CH₃), 42.1 (allyl-Ç), 24.7 (CH₃) and 11.9 (CH₂CH₃); **MS m/z** (ES+): 250.3 ([M+Na]<sup>+</sup>); **HRMS** Found [M+Na]<sup>+</sup> 250.1054 (C₁₁H₁₇NNaO₄) requires (M) 250.1050.
Methyl 2-acetoxy-1-allyl-4,5-dimethyl-1H-pyrrole-3-carboxylate; 90

Pyridine (13.0 mL, 0.16 mol) and acetic anhydride (7.60 mL, 0.81 mol) were added to a stirred solution of 89 (1.22 g, 5.37 mmol) in dry tetrahydrofuran (88 mL). The reaction mixture was refluxed for 3 days and until TLC confirmed complete consumption of starting material, then allowed to cool to room temperature. The reaction mixture was quenched by addition of a saturated aqueous copper sulfate solution (50 mL). The organic layer was washed further with another portion of saturated aqueous copper sulfate solution (50 mL), followed by saturated sodium hydrogen carbonate solution (50 mL). The layers were separated and the organic layers combined, dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether : light petroleum ether, 4 : 6) gave a yellow oil, which was triturated with light petroleum ether to afford 90 (569 mg, 45%) as an off-white solid.

**MP** 51-54 °C; **IR** νmax (solid) 2985 (CH), 2950 (C=CH), 2988 (C=O), 1690 (C=O); **¹H NMR** (500 MHz, CDCl₃) δH 5.78 (ddt, 1H, J = 17.0Hz, 10.1Hz and 4.8Hz, NCH₂CH₂), 5.14 (d, 1H, J = 10.1Hz, 1 of NCH₂CH₂H₂), 4.92 (d, 1H, J = 17.0Hz, 1 of NCH₂CH₂H₂), 4.28-4.25 (m, 2H, NCH₂CH₂H₂), 3.73 (s, 3H, CO₂CH₃), 2.32 (s, 3H, acetate-CH₃), 2.16 (s, 3H, NCCCH₃) and 2.04 (s, 3H, CH₃); **¹³C NMR** (125 MHz, CDCl₃) δC 168.8 (C=O), 164.6 (C=O), 138.7 (pyrrole-Ç), 132.5 (allyl-Ç), 120.3 (pyrrole-Ç), 116.8 (allyl-Ç), 114.3 (pyrrole-Ç), 100.1 (pyrrole-Ç), 50.6 (CO₂CH₃), 44.5 (allyl-Ç), 20.5 (acetate-CH₃), 10.8 (CH₃) and 8.9 (CH₃); **MS m/z** (Cl⁺): 252 ([M+H⁺]); **HRMS** Found [M+H⁺] 252.1223 (C₁₃H₁₈NO₄) requires (M) 252.1230. Analysis calculated for C₁₃H₁₈NO₄: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.97; H, 7.55; N, 5.60.
General procedure B for the Michael–aldol reaction

To a stirred solution of pyrrole acetate 90 (0.40 mmol) in MeOH (0.2 M) was added α,β-unsaturated ketone 91,47,80-82 (0.27 mmol) and K₂CO₃ (0.08 mmol) at room temperature. The reaction was stirred at this temperature until TLC confirmed complete consumption of starting material. The reaction was quenched by addition of acetic acid (0.16 mmol) and concentrated in vacuo. Purification by column chromatography gave the Michael–aldol product.

(±)-Methyl 1-allyl-2'-hydroxy-5-methyl-2-oxo-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 92a,b

Following the general procedure B described above with α,β-unsaturated ketone 91, the Michael-aldol product 92a,b was obtained following purification by column chromatography (diethyl ether : light petroleum ether, 5:1) as a 1:1 mixture of diastereoisomers and a light yellow oil (50 mg, 71%).

IR ν_max(oil) 3387 (OH), 2920 (CH), 1741, (C=O), 1680 (C=O); Major 92a: ¹H NMR (500 MHz, CDCl₃) δ_H 5.82 (m, 1H, NCH₂C₃H₇), 5.21 (d, 1H, J = 17.2Hz, 1 of NCH₂CHCH₂), 5.12 (d, 1H, J = 10.0Hz, 1 of NCH₂CHCH₂), 4.40 (bs, 1H, OH), 4.11 (d,1H, J = 15.8Hz and 5.8Hz, NCH₃H₃), 3.92 (dd, 1H, J = 15.9Hz and 6.4Hz, NCH₃H₃), 3.85 (s, 3H, CO₂C₃H₇), 3.70 (dt, 1H, J = 14.2Hz and 3.2Hz, 1'-CH₃H₃), 2.48 (dd, 1H, J = 14.2Hz and 3.2Hz, 1'-CH₃H₃), 1.90-1.66 (m, 3H, 1 of 3'-CH₂ and 4'-CH₂) and 1.37 (s, 3H, 5'-CH₃); ¹³C NMR (125 MHz, CDCl₃) δ_C 171.5 (2-C=O), 165.5 (C=O), 163.8 (4-C), 163.3 (4-C), 134.6 (allyl-C), 124.0 (3-C), 117.3 (allyl-C), 71.7 (2'-C), 64.0 (5-C), 52.0 (OC₃H₃), 42.1 (NCH₃H₃), 35.0 (1'-C), 33.0 (4'-C), 29.7 (3'-C), 21.1 (CH₃);

Minor 92b observed: ¹H NMR (500 MHz, CDCl₃) δ_H 3.75-3.72 (m, 1H, 1'-CH₃H₃), 2.30 (dd, 1H, J = 10.9Hz and 12.6Hz, 1'-CH₃H₃), 2.20-2.15 (m, 1H, 1 of 3'-CH₂), 2.03-1.97 (m, 3H, 1 of 3'-CH₂), 1.73-1.50 (m, 3H, 1 of 3'-CH₂) and 1.35 (s, 3H, 5'-CH₃).
1H, 1 of 3'-CH$_3$, 1.90-1.66 (m, 2H, 1 of 3'-CH$_2$ and 1 of 4'-CH$_3$), 1.64-1.54 (m, 1H, 1 of 4'-CH$_3$) and 1.33 (s, 3H, 5-CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ$_C$ 171.1 (2-Ç=O), 165.5 (Ç=O), 134.4 (allyl-Ç), 121.9 (3-Ç), 117.1 (allyl-Ç), 68.7 (2'-Ç), 68.3 (5-Ç), 52.0 (OCH$_3$), 42.0 (NCH$_2$), 34.7 (1'-Ç), 30.4 (4'-Ç), 28.4 (3'-Ç), 20.4 (CH$_3$); MS m/z (ES+): 266 ([M+H]$^+$); HRMS Found [M+H]$^+$ 266.1385 (C$_{14}$H$_{20}$NO$_4$) requires (M) 266.1387.

(±)-Methyl-1-allyl-2'-hydroxy-2',5-dimethyl-2-oxo-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 93a,b

Following the general procedure B described above with α,β-unsaturated ketone 47, the Michael-aldol product 93a,b was obtained following purification by column chromatography (diethyl ether : light petroleum ether, 4:1) as a 2:1 mixture of diastereoisomers and a yellow oil (55 mg, 74%).

IR $\nu_{max}$ (oil) 3550-3200 (OH), 2950 (CH), 1759 (C=O), 1690 (C=O); Major 93a: $^1$H NMR (500 MHz, CDCl$_3$) δ$_H$ 5.86-5.77 (m, 1H, NCH$_2$CH$_2$), 5.20 (d, 1H, J = 17.1Hz, 1 of NCH$_2$CH$_2$CH$_2$), 5.11 (d, 1H, J = 10.1Hz, 1 of NCH$_2$CH$_2$CH$_2$), 4.10 (dd, 1H, J = 15.6Hz and 6.6Hz, NCH$_2$CH$_2$), 3.89 (dd, 1H, J = 15.6Hz and 6.6Hz, NCH$_2$CH$_2$), 3.84 (s, 3H, CO$_2$CH$_3$), 3.61 (d, 1H, J = 12.8Hz, 1'-CH$_3$H$_8$), 2.47 (d, 1H, J = 12.8Hz, 1'-CH$_3$H$_8$), 2.12 (dt, 1H, J = 13.3Hz and 2.9Hz, 3'-CH$_3$H$_{8m}$), 1.82 (dt, 1H, J = 14.1Hz and 4.1Hz, 4'-CH$_3$H$_8$), 1.76-1.66 (m, 1H, 4'-CH$_3$H$_8$), 1.37 (s, 3H, 5-CH$_3$), 1.28-1.22 (m, 1H, 3'-CH$_3$H$_8$), 1.12 (s, 3H, 2'-CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ$_C$ 172.6 (3-Ç), 172.0 (4-Ç), 165.6 (Ç=O), 163.1 (CO$_2$CH$_3$), 134.3 (allylÇ), 117.2 (allylÇ), 74.7 (2'-Ç), 63.8 (5-Ç), 51.9 (CO$_2$CH$_3$), 42.2 (allylÇ), 39.5 (1'-Ç), 35.6 (3'-Ç), 35.5 (4'-Ç), 25.8 (5-CH$_3$), 21.1(2'-CH$_3$); Minor 93a observed: $^1$H NMR (500 MHz, CDCl$_3$) δ$_H$ 3.54 (d, 1H, J = 13.9Hz, 1'-CH$_3$H$_8$), 2.34 (d, 1H, J = 13.9Hz, 1'-CH$_3$H$_8$), 2.04-2.00 (m, 1H, 3'-CH$_3$H$_8$), 1.40 (s, 3H, 2'-CH$_3$), 1.31 (s, 3H, 5-CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ$_C$ 165.5 (Ç=O), 163.8 (CO$_2$CH$_3$), 134.4 (allylÇ), 117.1 (allylÇ), 73.8 (2'-Ç),
52.0 (CO₂CH₃), 42.1 (allyl-©), 38.4 (1'-©), 35.3 (3'-©), 34.4 (4'-©), 30.7 (5-CCH₃), 20.5 (2'-CCH₃); **MS m/z (ES+):** 302 ([M+Na]⁺); **HRMS** Found [M+H]⁺ 280.1549 (C₁₅H₂₂NO₃) requires (M) 280.1543.

(±)-Methyl-1-allyl-2'-ethyl-2'-hydroxy-5-methyl-2-oxo-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 94a,b

Following the general procedure B described above with α,β-unsaturated ketone 80, the Michael-aldol product 94a,b was obtained following purification by column chromatography (diethyl ether : light petroleum ether, 4:1) as a 4:1 mixture of diastereoisomers and a light yellow oil (52 mg, 67%).

**IR** νₓₘₐₓ(oil) 3550-3200 (OH), 2900, 2800 (CH), 1720 (C=O), 1685 (C=O); **Major 94a:** ¹H NMR (500 MHz, CDCl₃) δₓ 5.86-5.76 (m, 1H, NCH₂CH₃), 5.19 (d, 1H, J = 17.1Hz, 1 of NCH₂CHCH₂), 5.10 (d, 1H, J = 10.1Hz, 1 of NCH₂CHCH₂), 4.09 (dd, 1H, J = 15.8Hz and 5.9Hz, NCH₃H₃), 3.87 (dd, 1H, J = 15.8Hz and 6.7Hz, NCH₃H₃), 3.83 (s, 3H, OCH₃), 3.67 (d, 1H, J = 13.0Hz, 1'-CH₃H₃), 2.41 (d, 1H, J = 13.0Hz, 1'-CH₃H₃), 2.08 (dt, 1H, J = 13.3Hz and 4.0Hz, 3'-CH₃H₃), 1.83-1.76 (m, 1H, 4'-CH₃H₃), 1.73 (dt, 1H, J = 14.0Hz and 4.0Hz, 4'-CH₃H₃), 1.43-1.37 (m, 2H, CH₂CH₃), 1.37 (s, 3H, 5-CH₃), 1.34 (q, 1H, J = 7.4Hz, 1 of CH₂CH₃), 1.19 (m, 1H, 3'-CH₃H₃), 0.85 (t, 3H, J = 7.4Hz, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) δₓ 173.0 (3-©), 172.0 (4-©), 165.6 (©=O), 163.1 (CO₂CH₃), 134.3 (allyl-©), 117.2 (allyl-©), 76.4 (2'-©), 64.1 (5-©), 51.8 (CO₂CH₃), 42.1 (allyl-©), 37.6 (1'-©), 34.8 (3'-©), 32.8 (4'-©), 29.4 (CH₂CH₃), 21.4 (5-CH₃), 6.7 (CH₂CH₃); **Minor 94b observed:** ¹H NMR (500 MHz, CDCl₃) δₓ 3.84 (s, 3H, OCH₃), 3.51 (d, 1H, J = 13.8Hz, 1'-CH₃H₃), 2.28 (d, 1H, J = 13.9Hz, 1'-CH₃H₃), 1.64 (q, 1H, J = 7.6Hz, 1 of CH₂CH₃), 1.53 (m, 1H, 4'-CH₃H₃), 1.30 (s, 3H, 5-CH₃), 0.97 (t, 3H, J = 7.5Hz, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) δₓ 163.9
Following the general procedure B described above with α,β-unsaturated ketone 81, the Michael-aldol product 95a,b was obtained following purification by column chromatography (diethyl ether : light petroleum ether, 4:1) as a 6:1 mixture of diastereoisomers and a yellow oil (56 mg, 70%).

**IR v<sub>max</sub>** (oil) 3600-3300 (OH), 2948 (CH), 1741 (C=O), 1714 (C=O), 1679 (C=O); **Major 95a**: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 5.92-5.75 (m, 2H, NCH<sub>2</sub>C<sub>H</sub> and 1''-CH<sub>H</sub><sub>2</sub>), 5.65 (dd, 1H, J = 15.5Hz and 1.5Hz, 2''-CH<sub>H</sub><sub>2</sub>), 5.26-5.19 (m, 1H, 1 of NCH<sub>2</sub>CH<sub>C</sub>H<sub>2</sub>), 5.12 (dd, 1H, J = 10.1Hz and 1.3Hz, 1 of NCH<sub>2</sub>CH<sub>C</sub>H<sub>2</sub>), 4.11 (ddt, 1H, J = 15.7Hz, 5.8Hz and 1.5Hz, NH<sub>A</sub>H<sub>B</sub>), 3.98-3.89 (m, 1H, NCH<sub>A</sub>H<sub>B</sub>), 3.87 (s, 3H, CO<sub>2</sub>C<sub>H</sub>), 3.55 (dd, 1H, J = 13.9Hz and 2.1Hz, 1''-CH<sub>A</sub>H<sub>B</sub>), 2.44 (d, 1H, J = 13.9Hz, 1''-CH<sub>A</sub>H<sub>B</sub>), 2.20-2.03 (m, 1H, 3''-CH<sub>A</sub>H<sub>B</sub>), 1.73 (dd, 3H, J = 6.4Hz and 1.5Hz, 3'''-CH<sub>H</sub><sub>3</sub>), 1.71-1.58 (m, 3H, 3''-CH<sub>H</sub><sub>2</sub>, 4''-CH<sub>H</sub><sub>2</sub>), 1.39 (s, 3H, 5-CH<sub>H</sub><sub>3</sub>), and 1.34 (s, 3H, 5-CH<sub>H</sub><sub>3</sub>); **<sup>13</sup>C NMR** (125 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 172.7 (3-<sub>C</sub>), 172.0 (4-<sub>C</sub>), 165.5 (2-<sub>C</sub>=O), 163.9 (CO<sub>2</sub>C<sub>H</sub>), 137.1 (1''-<sub>C</sub>), 134.6 (allyl-<sub>C</sub>), 127.6 (2''-<sub>C</sub>), 117.1 (allyl-<sub>C</sub>), 75.4 (2'-<sub>C</sub>), 63.7 (5-<sub>C</sub>), 52.1 (CO<sub>2</sub>C<sub>H</sub>), 42.1 (allyl-<sub>C</sub>), 37.3 (1''-<sub>C</sub>H<sub>2</sub>), 35.3 (3''-<sub>C</sub>), 33.5 (4''-<sub>C</sub>), 20.4 (5-CH<sub>H</sub><sub>2</sub>) and 17.6 (3''-CH<sub>H</sub><sub>3</sub>); **Minor 95b observed**: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 2.53 (d, 1H, J = 13.1Hz, 1''-CH<sub>A</sub>H<sub>B</sub>); **MS m/z** (ES+): 328 ([M+Na]<sup>+</sup>); **HRMS Found [M+Na]<sup>+</sup> 328.1527 (C<sub>17</sub>H<sub>23</sub>NNaO<sub>4</sub>) requires (M) 328.1519
Following the general procedure B described above with α,β-unsaturated ketone 82, the Michael-aldol product 96a,b was obtained following purification by column chromatography (diethyl ether : light petroleum ether, 4:1) as a 4:1 mixture of diastereoisomers and a yellow oil (72 mg, 69%).

**IR** ν_{max} (oil) 3700-3200 (OH), 2948, (CH), 1736 (C=O), 1690 (C=O); **Major 96a**: ¹H NMR (500 MHz, CDCl₃) δ_H 7.10 (d, 1H, J = 5.1Hz, 7''-CH₂), 6.75 (d, 1H, J = 2.8Hz, 5''-CH), 5.83 (ddt, 1H, J = 16.9Hz, 10.2Hz and 6.0Hz, NCH₂CH₂), 5.21 (d, 1H, J = 16.9Hz, 1 of NCH₂CH₂CH₂), 5.13 (d, 1H, J = 10.2Hz, 1 of NCH₂CH₂CH₂), 4.11 (dd, 1H, J = 16.1Hz and 6.0Hz, NCH₃H), 3.90 (dd, 1H, J = 16.1Hz and 6.0Hz, NCH₃H), 3.85 (s, 3H, CO₂CH₃), 3.71 (d, 1H, J = 13.0Hz, 1''-CH₃H), 2.84-2.71 (m, 2H, 3''-CH₂), 2.40 (d, 1H, J = 13.0Hz, 1''-CH₃H), 2.09 (dt, 1H, J = 13.3Hz and 3.5Hz, 3''-CH₃H), 1.88-1.77 (m, 3H, 4''-CH₂ and 2''-CH₂), 1.73 (dt, 1H, J = 14.1Hz and 4.0Hz, 2''-CH₃H), 1.48-1.36 (m, 2H, 1''-CH₂), 1.39 (s, 3H, 5''-CH₃) and 1.20 (dt, 1H, J = 12.6Hz and 5.1Hz, 3''-CH₃H); **¹³C NMR** (125 MHz, CDCl₃) δ_C 172.1 (3-ęż), 171.5 (4-ęż), 165.6 (2-ęż=O), 163.1 (CO₂CH₃), 144.7 (4''-ęż), 134.4 (allyl-ęż), 126.7 (6''-CH), 124.2 (5''-CH), 123.1 (7''-CH), 117.3 (allyl-ęż), 76.4 (2''-ęż), 63.7 (5-ęż), 52.0 (CO₂CH₃), 42.2 (allyl-ęż), 37.9 (1''-CH₂), 36.3 (5-CH₃), 35.0 (C₃-CH₂), 33.6 (4''-CH₂), 29.9 (3''-CH₂), 25.0 (2''-CH₂), 21.4 (1''-CH₂); **Major 96b observed**: ¹H NMR (500 MHz, CDCl₃) δ_H 7.12 (d, 1H, J = 5.1Hz, 7''-CH₂), 6.92 (dd, 1H, J = 5.1Hz and 3.5Hz, 6''-CH), 6.89 (dd, 1H, J = 5.1Hz and 3.4Hz, 6''-CH), 6.80 (d, 1H, J = 2.8Hz, 5''-CH), 4.09 (dd, 1H, J = 16.1Hz and 6.0Hz, NCH₃H), 3.93 (dd, 1H, J = 16.1Hz and 6.0Hz, NCH₃H), 3.86 (s, 3H, CO₂CH₃), 3.54 (d, 1H, J = 13.8Hz, 1''-CH₃H), 2.87 (t, 2H, J = 7.3Hz, 3''-CH₂), 2.30 (d, 1H, J = 13.8Hz, 1''-CH₃H), 1.31 (s, 3H, 5''-CH₃); 126.8 (6''-CH), 124.3 (5''-CH), 123.2 (7''-CH),...
42.1 (allyl-\(\cdot\)), 36.8 (1'-\(\cdot\)CH\(_2\)), 35.5 (3'-\(\cdot\)CH\(_2\)); **MS** \(m/z\) (ES\(^+\)): 412 ([M+Na\(^+\)]; **HRMS** Found [M+Na\(^+\)]\(^{1+}\) 412.1540 (C\(_{21}\)H\(_{27}\)NNaO\(_4\)S) requires (M) 412.1553.

(\(\pm\))-Methyl-1-allyl-5-(3-methoxy-3-oxopropyl)-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate; 97

![Reaction Scheme](image)

To a stirred solution of 90 (100 mg, 0.42 mmol) in MeOH (2 mL) was added methyl acrylate (0.08 mL, 0.93 mmol) and K\(_2\)CO\(_3\) (12 mg, 0.08 mmol) at room temperature. The reaction was stirred until TLC confirmed complete consumption of starting material before quenched by addition of acetic acid (10 \(\mu\)L, 0.17 mmol) and concentrated in vacuo. Purification by column chromatography (neat diethyl ether) gave 97 (101 mg, 82\%) as a yellow oil.

**IR** \(\nu_{\text{max}}\) /cm\(^{-1}\) (oil) 2954 (CH), 1750 (C=O), 1700 (C=O), 1436 (C=C); **\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta_H\) 5.87-5.75 (m, 1H, NCH\(_2\)CH\(_2\)CH\(_3\)), 5.20 (d, 1H, \(J = 17.1\) Hz, 1 of NCH\(_2\)CH\(_2\)CH\(_2\)), 5.09 (d, 1H, \(J = 10.1\) Hz, 1 of NCH\(_2\)CH\(_2\)CH\(_2\)), 3.98 (d, 1H, \(J = 15.6\) Hz, 1 of NCH\(_2\)CH\(_2\)), 3.82 (s, 3H, CO\(_2\)CH\(_3\)I), 3.79 (m, 1H, 1 of NCH\(_2\)), 3.59 (s, 3H, OCH\(_3\)), 3.21 (m, 1H, 1 of COCH\(_2\)), 1.97 (m, 1H, 1 of COCH\(_2\)), 1.89 (dd, 1H, \(J = 15.9\) Hz, 10.5Hz and 5.1Hz, 1 of COCH\(_2\)), 1.73 (dd, 1H, \(J = 15.9\) Hz, 10.5Hz and 5.1Hz, 1 of COCH\(_2\)), 1.29 (s, 3H, CH\(_3\)I); **\(^{13}\)C NMR** (125 MHz, CDCl\(_3\)) \(\delta_C\) 172.6 (N\(\equiv\)C=O), 170.3 (CO\(_2\)), 165.9 (CO\(_2\)), 163.1 (quat. C=\(\equiv\)), 133.5 (allyl-\(\cdot\)), 124.6 (quat. C=C), 117.6 (allyl-\(\cdot\)), 67.0 (N\(\equiv\)), 51.8 (2 \times OCH\(_3\)), 42.1 (NCH\(_2\)), 29.5 (COCH\(_2\)CH\(_3\)), 27.6 (COCH\(_2\)CH\(_3\)), 23.2 (CH\(_3\)), 12.2 (CH\(_3\)); **MS** \(m/z\) (ES\(^+\)): 318 ([M+Na\(^+\)]; **HRMS** Found [M+H\(^+\)]\(^{1+}\) 296.1503 (C\(_{15}\)H\(_{22}\)NO\(_3\)) requires (M) 296.1492.
Following the general procedure B described above with α,β-unsaturated ketone 98, the Michael-aldol product 99 was obtained following purification by column chromatography (neat diethyl ether) as a single diastereoisomer and a colourless oil (56 mg, 72%).

\[
\text{IR } \nu_{\text{max}} \text{(oil) } 3325 \text{ (OH), 2928 (CH), 1741, (C=O), 1730 (C=O), 1684 (C=O);} \\
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3) \delta \text{H} 5.79 (dddd, 1H, } J = 17.2Hz, 10.0Hz, 7.2Hz \text{ and } 5.8Hz, \text{NCH}_2\text{CH}_2), 5.23 (dd, 1H, } J = 17.1Hz \text{ and } 1.4Hz, \text{1 of } \text{NCH}_2\text{CH}(CH)_2), 5.12 (dd, 1H, } J = 10.1Hz \text{ and } 1.2Hz, \text{1 of } \text{NCH}_2\text{CH}(CH)_2), 4.16 (ddt, 1H, } J = 15.5Hz, 5.8Hz \text{ and } 1.5Hz, \text{NCH}_2\text{H}_6), 3.87 (s, 3H, OC\text{H}_3), 3.75 (dd, 1H, } J = 15.5Hz \text{ and } 7.2Hz, \text{NCH}_2\text{H}_6), 3.57 (dd, 1H, } J = 13.3Hz \text{ and } 3.0Hz, \text{1 of } \text{1''-CH}_2\text{H}_6), 2.69 (d, 1H, } J = 13.3Hz, \text{1 of } \text{1''-CH}_2\text{H}_6) 2.44 (t, 1H, } J = 5.0Hz, \text{4'-CH}), 2.02-1.86 (m, 2H, 3'-CH), 1.66-1.62 (m, 1H, 1 of 2''-CH), 1.55-1.49 (m, 2H, 1''-CH), 1.42 (s, 3H, 5'-CH), 1.16-1.08 (m, 1H, 1 of 2''-CH); \text{\textsuperscript{13}C NMR (125 MHz; CDCl}_3) \delta \text{C} 171.2 (2-C=O), 166.5 (C-O), 163.4 (4-C), 134.0 (allyl-C), 123.8 (3-C), 117.9 (allyl-C), 80.5 (2'-C), 67.3 (5-C), 52.1 (OCH), 42.6 (3'-C), 42.5 (NCH), 41.1 (1''-C), 40.9 (1'-C), 35.7 (4'-C), 23.1 (CH), 22.0 (3'-C); MS m/z (ES+): 314 ([M+Na]^+); \text{HRMS} \text{ Found [M+H]^+ 292.1541 (C}_{16}\text{H}_{22}\text{NO}_4) requires M 292.1543.
(±)-Methyl 8-hydroxy-2-methyl-4-oxo-3-(prop-2-en-1-yl)-3-
azatricyclo[6.3.1.0
2,6]dodec-5-ene-5-carboxylate; 100

Following the general procedure B described above with α,β-unsaturated ketone 44,
the Michael-aldol product 100 was obtained following purification by column
chromatography (neat diethyl ether) as a single diastereoisomer and a colourless oil
(55 mg, 68%).

IR ν\text{max}(\text{oil}) 3390 (OH), 2919 (CH), 1736, (C=O), 1713 (C=O), 1674 (C=O);
\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ\textsubscript{H} 5.94 (ddt, 1H, \(J = 16.6\text{Hz}, 10.1\text{Hz} \) and 6.5Hz, NCH\textsubscript{2}CH\textsubscript{2}), 5.24 (dd, 1H, \(J = 17.1\text{Hz} \) and 1.4Hz, 1 of NCH\textsubscript{2}CH\textsubscript{2}), 5.14 (dd, 1H, \(J = 10.1\text{Hz} \) and 1.2Hz, 1 of NCH\textsubscript{2}CH\textsubscript{2}), 4.02 (ddt, 1H, \(J = 15.3\text{Hz} \), 6.3Hz and 1.3Hz, NCH\textsubscript{2}CH\textsubscript{2}), 3.91 (dd, 1H, \(J = 15.4\text{Hz} \) and 6.5Hz, NCH\textsubscript{2}CH\textsubscript{2}), 3.86 (s, 3H, OCH\textsubscript{3}), 3.70 (dd, 1H, \(J = 14.8\text{Hz} \) and 2.7Hz, 1'-CH\textsubscript{2}H\textsubscript{6}), 2.65 (dd, 1H, \(J = 14.8\text{Hz} \) and 1.8Hz, 1 of 1'-CH\textsubscript{2}H\textsubscript{6}), 2.41 (m, 1H, 4'-CH\textsubscript{2}), 2.13 (ddd, 1H, \(J = 13.1\text{Hz} \), 5.2Hz and 2.8Hz, 1 of 3'-CH\textsubscript{2}), 1.85 (dd, 1H, \(J = 11.9\text{Hz} \) and 2.8Hz, 1 of 3'-CH\textsubscript{2}), 1.68 (td, 1H, \(J = 13.1\text{Hz} \) and 3.0Hz, 1 of 3''-CH\textsubscript{2}), 1.63-1.48 (m, 2H, 1 of 1''-CH\textsubscript{2} and 1 of 3''-CH\textsubscript{2}), 1.46 (s, 3H, 5'-CH\textsubscript{3}), 1.35 (m, 3H, 1 of 1''-CH and 2''-CH\textsubscript{2}); \textsuperscript{13}C NMR (125 MHz; CDCl\textsubscript{3}) δ\textsubscript{C} 174.5 (2-C=O), 166.8 (C=O), 163.3 (4'-C), 133.9 (allyl-C), 121.5 (3-C), 117.7 (allyl-C), 72.7 (2'-C), 67.2 (5-C), 51.9 (OCH\textsubscript{3}), 42.8 (NCH\textsubscript{2}), 40.9 (1''-C), 40.5 (1'-C), 39.0 (3'-C), 38.8 (4'-C), 25.8 (3''-C), 25.2 (2'-C), 20.8 (CH\textsubscript{3}); MS m/z (ES\textsuperscript{+}): 328 ([M+Na\textsuperscript{+}]); HRMS Found [M+Na\textsuperscript{+}] 328.1520 (C\textsubscript{17}H\textsubscript{23}NNaO\textsubscript{4}) requires (M) 328.1519
(±)-Methyl 2,8-dihydroxy-4-oxo-3-(prop-2-en-1-yl)-3-azatricyclo[6.2.1.0²,6]undec-5-ene-5-carboxylate; 101

Following the general procedure B described above with α,β-unsaturated ketone 98, the Michael-aldol product 101 was obtained following purification by column chromatography (neat diethyl ether) as a single diastereoisomer and a colourless oil (47 mg, 60%).

IR ν_max(oil) 3317 (OH), 2956 (CH), 1733, 1690 (C=O); ¹H NMR (500 MHz, MeOD) δ_H 5.70 (ddddd, 1H, J = 17.3Hz, 10.2Hz 7.4Hz and 5.3Hz, NCH₂CH₂), 5.15 (dd, 1H, J = 17.1Hz and 1.3Hz, 1 of NCH₂CHCH₂), 5.01 (dd, 1H, J = 10.1Hz and 0.9Hz, 1 of NCH₂CHCH₂), 3.95 (ddt, 1H, J = 15.7Hz, 5.6Hz and 1.6Hz, NCH₃H₆), 3.74 (s, 3H, OCH₃), 3.70 (dd, 1H, J = 14.7Hz and 7.7Hz, NCH₃H₆), 3.26 (dd, 1H, J = 13.1Hz and 3.0Hz, 1'-CH₃H₆), 2.63 (dd, 1H, J = 13.1Hz and 1.8Hz, 1'-CH₃H₆), 2.48 (dd, 1H, J = 6.6Hz and 5.2Hz, 4'-CH₂), 2.13 (d, 1H, J = 11.4Hz, 3'-CH₃H₆), 1.69 (ddd, 1H, J = 11.4Hz, 5.0Hz and 3.1Hz, 3'-CH₃H₆), 1.67-1.58 (m, 1H, 1 of 2''-CH₂), 1.46 (ddt, 1H, J = 12.8Hz, 5.1Hz and 1.9Hz 1 of 1''-CH₂), 1.40-1.33 (m, 1H, 1 of 1''-CH₂), 0.84 (m, 1H, 1 of 2''-CH₂); ¹³C NMR (125 MHz, MeOD) δ_C 171.2 (2-C=O), 170.7 (C=O), 166.5 (quat. C=C), 137.6 (H₃C=CH₂), 126.3 (quat. C=C), 120.4 (HC=CH₂), 93.9 (5-C), 83.0 (2'-OH), 54.9 (OCH₃), 45.1, 44.7, 44.4, 43.4, 38.1, 26.7; MS m/z (ES+): 316 ([M+Na]+); HRMS Found [M+Na]+ 316.1166 (C₁₅H₁₉NNaO₅) requires (M) 316.1155
(±)-Methyl 2,8-dihydroxy-4-oxo-3-(prop-2-en-1-yl)-3-azatricyclo[6.3.1.0^2,6]dodec-5-ene-5-carboxylate 102:

Following the general procedure B described above with α,β-unsaturated ketone 44, the Michael-aldol product 102 was obtained following purification by column chromatography (neat diethyl ether) as a single diastereoisomer and a colourless oil (45 mg, 54%).

**IR** ν_{max}(oil) 3302 (OH), 2919 (CH), 1718, (C=O), 1687 (C=O); **^1H NMR** (400 MHz, MeOD) δ_{H} 5.83 (ddddd, 1H, J = 17.4Hz, 10.1Hz, 7.4Hz and 5.6Hz, NCH_{2}CH), 5.18 (dd, 1H, J = 17.1Hz and 1.4Hz, 1 of NCH_{2}CHCH$_2$), 5.03 (dd, 1H, J = 10.1Hz and 1.3Hz, 1 of NCH$_2$CHCH$_2$), 3.84 (m, 2H, NCH$_3$), 3.74 (s, 3H, OCH$_3$), 3.38 (dd, 1H, J = 14.5Hz and 2.7Hz, 1'-CH$_3$H$_{3b}$), 2.61 (dd, 1H, J = 14.5Hz and 1.6Hz, 1'-CH$_3$H$_{3a}$), 2.46-2.41 (m, 1H, 2'-OCH), 2.30 (ddd, 1H, J = 12.4Hz, 4.9Hz and 3.0Hz, 1 of 3'-CH$_{2}$), 1.72-1.65 (m, 1H, 1 of 1''-CH$_2$), 1.53-1.22 (m, 7H, 3'-CH$_3$, 4'-CH$_3$, 1''-CH$_2$, 2” and 3”-CH$_2$); **^13C NMR** (125 MHz, MeOD) δ_{C} 172.1 (2-C=O), 168.6 (C=O), 164.2 (quat. C=C), 135.3 (HC=CH$_2$), 121.8 (quat. C=C), 118.1 (HC=CH$_2$), 90.7 (5-C), 73.0 (2'-OH), 52.3 (OCH$_3$), 42.5, 41.0, 40.8, 40.4, 39.0, 25.2, 21.8; **MS** m/z (ES+): 330 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 330.1312 (C$_{16}$H$_{21}$NNaO$_5$) requires (M) 330.1312

(±)-Methyl 1-allyl-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate; 113
To a stirred solution of 90 (100 mg, 0.42 mmol) in MeOH (2 mL) was added K$_2$CO$_3$ (11 mg, 0.08 mmol) at room temperature under an air atmosphere. The reaction was stirred until TLC analysis confirmed complete consumption of starting material. The reaction was quenched by addition of acetic acid (10 μL, 0.16 mmol) and concentrated in vacuo. Purification by column chromatography (neat diethyl ether) afforded 113 (77 mg, 85%) as a light yellow oil.

**IR** $\nu_{\text{max}}$ (oil); 3322 (OH), 2925 (CH), 1741 (C=O), 1715 (C=O), 1690 (C=O);

**$^1$H NMR** (500 MHz, CDCl$_3$) $\delta$H: 5.84 (m, 1H, NCH$_2$CH), 5.21 (dd, 1H, $J = 17.2$Hz and 1.3Hz, 1 of NCH$_2$CHCH$_2$), 5.13 (dd, 1H, $J = 10.2$Hz and 1.2Hz, 1 of NCH$_2$CHCH$_2$), 4.02 (ddt, 1H, $J = 15.8$Hz, 5.2Hz, and 1.4Hz, 1 of NCH$_2$CHCH$_2$), 3.94 (dd, 1H, $J = 16.0$Hz and 6.6Hz, 1 of NCH$_2$CHCH$_2$), 3.84 (s, 3H, OCH$_3$), 3.30 (s, 1H, OH), 2.30 (s, 3H, (OH)CH$_3$), 1.45 (s, 3H, CCH$_3$);

**$^{13}$C NMR** (125 MHz, CDCl$_3$) $\delta$C: 170.1 (C=O), 165.0 (C=O), 163.1 (quat. C=C), 133.9 (allyl-C), 122.1 (quat. C=C), 117.2 (allyl-C), 89.2 (COH), 51.9, 41.1, 22.0, 11.9;

**MS** $m/z$ (ES+): 248 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 248.0881 (C$_{11}$H$_{15}$NNaO$_4$) requires (M) 248.0893.

(±)-1-Allyl-3-ethylpyrrrolidine-2,5-dione; 114

A solution of ethyl succinic anhydride (1.10 g, 8.73 mmol) and allylamine (0.72 mL, 9.60 mmol) in dichloromethane (40 mL) was stirred for 12 hours at room temperature before 1,1’-carbonyldiimidazole (1.56 g, 9.60 mmol) was added in one portion. The reaction mixture was stirred for a further 2 hours at room temperature and then refluxed for 0.5 hours. The mixture was cooled to room temperature and washed with 1.0 M hydrochloric acid (20 mL). The layers were separated and the aqueous layer was further extracted with dichloromethane (2 × 20 mL). The organic layers were combined, dried (MgSO$_4$), filtered and concentrated in vacuo to afford 114 (1.16 g,
80%) as a light yellow oil. The compound was used in the next step without further purification.

**IR** $\nu_{\text{max}} / \text{cm}^{-1}$ (oil) 1700 (C=O), 1428 (C=O) and 1395 (C=C); $^1\text{H NMR}$ (500 MHz, CDCl$_3$) $\delta_H$

- 5.78 (ddt, 1H, $J = 16.1\text{Hz}$, 10.3Hz and 5.8Hz, NCH$_2$CH$H_2$),
- 5.21 (d, 1H, $J = 16.1\text{Hz}$, 1 of NCH$_2$CH$H_2$),
- 5.17 (d, 1H, $J = 10.3\text{Hz}$, 1 of NCH$_2$CH$H_2$),
- 4.10 (d, 2H, $J = 5.8\text{Hz}$, NCH$_2$),
- 2.84 (dd, 1H, $J = 17.7\text{Hz}$ and 9.0Hz, 1 of COCH$H_2$CH$_3$),
- 2.78 (dt, 1H, $J = 9.0\text{Hz}$ and 4.1Hz, COCH$H_2$CH$_3$),
- 2.40 (dd, 1H, $J = 17.7\text{Hz}$ and 4.1Hz, 1 of COCH$_2$CH$_3$),
- 1.93 (dqd, 1H, $J = 14.9\text{Hz}$, 7.4Hz and 4.1Hz, 1 of CH$_2$CH$_3$),
- 1.67-1.57 (m, 1H, 1 of CH$_2$CH$_3$),
- 0.98 (t, 3H, $J = 7.4\text{Hz}$, CH$_3$); $^{13}\text{C NMR}$ (125 MHz, CDCl$_3$) $\delta_c$

- 179.4 (N=O),
- 176.2 (N=O),
- 130.8 (allyl-\C),
- 118.2 (allyl-\C),
- 41.1 (NCH$_2$),
- 40.8 (COCHCH$H_2$CH$_3$),
- 33.8 (COCH$_2$CH$_3$),
- 24.4 (COCH$H_2$CH$_3$),
- 10.8 (CH$_3$); **MS** $m/z$ (ES$^+$): 190 ([M+Na$^+$]);

(±)-Methyl 1-allyl-4-ethyl-2,5-dioxopyrrolidine-3-carboxylate; 115

![Diagram of reaction](image)

To a stirred solution of 114 (1.50 g, 9.04 mmol) and methyl chloroformate (1.40 mL, 18.1 mmol) in dry tetrahydrofuran (9.6 mL) at -78 °C was added a 1.0 M solution of lithium hexamethyldisilazane in tetrahydrofuran (14.0 mL, 18.1 mmol) drop-wise. The reaction mixture was stirred at -78 °C for 5 minutes and until TLC confirmed complete consumption of starting material before addition of saturated ammonium chloride solution (5 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between dichloromethane (50 mL) and distilled water (50 mL) and further extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with brine, dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (diethyl ether : light petroleum ether 1 : 1 to 3 : 1) afforded 115 (1.6 g, 79%) as a single diastereoisomer and a colourless oil.
IR νmax /cm⁻¹ (oil) 2967 (CH), 1700 (C=O), 1428 (C=O) and 1395 (C=C); ¹H NMR (300 MHz, CDCl₃) δH 5.77 (ddt, 1H, J = 17.0Hz, 10.2Hz and 5.7Hz, NCH₂CH), 4.11 (d, 2H, J = 5.7Hz, NCH₂), 3.82 (s, 3H, CO₂CH₃), 3.47 (d, 1H, J = 5.0Hz, CH₂CO₂CH₃), 3.14 (dt, 1H, J = 9.8Hz and 5.0Hz, CH₂CH₂CH₃), 1.98 (qd, 1H, J = 14.1Hz and 7.5Hz, 1 of CH₂CH₃), 1.67 (qd, 1H, J = 14.1Hz and 7.4Hz, 1 of CH₂CH₃), 0.99 (t, 3H, J = 7.5Hz, CH₃); ¹³C NMR (125 MHz, CDCl₃) δC 177.1 (C=O), 171.2 (C=O), 168.3 (CO₂), 130.1 (allyl-C), 118.3 (allyl-C), 53.3 (CHCO₂CH₃), 51.8 (CO₂CH₃), 45.6 (NCH₂), 41.2 (CHCH₂CH₃), 23.5 (CH₂CH₃), 10.7 (CH₂CH₃); MS m/z (ES⁺): 248 ([M+Na]⁺); HRMS Found [M+Na]⁺ 248.0895 (C₁₁H₁₅NNaO₄) requires (M) 248.0893.

(±)-Methyl 1-allyl-4-ethyl-5-hydroxy-5-methyl-2-oxopyrrolidine-3-carboxylate; 116

A solution of 115 (1.20 g, 5.33 mmol) in dry tetrahydrofuran (36 mL) was added drop-wise via cannula to a stirred solution of 60% sodium hydride in oil (213 mg, 5.33 mmol) in dry tetrahydrofuran (36 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 minutes and then cooled to −78 °C before a 3.0 M solution of methylmagnesium bromide in diethyl ether (8.0 mL, 24.0 mmol) was added drop-wise. The solution was stirred for 1 hour at −78 °C, warmed to room temperature and stirred for 2 hours and until TLC confirmed consumption of starting material before addition of a saturated solution of ammonium chloride (40 mL). The layers were separated and the aqueous layer extracted with dichloromethane (2 × 40 mL). The organic layers were combined, dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate : light petroleum ether 1 : 1 to 3 : 1) afforded 116 (752 mg, 59%) as a 8:1 mixture of diastereoisomers and a colourless oil.
IR ν<sub>max</sub> /cm<sup>-1</sup> (oil) 3700-3200 (OH), 1744 (C=O), 1680 (C=O); Major: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 5.88-5.76 (m, 1H, NCH<sub>2</sub>), 5.19 (d, 1H, J = 15.4Hz, 1 of NCH<sub>2</sub>CH<sub>2</sub>), 5.13 (d, 1H, J = 10.2Hz, 1 of NCH<sub>2</sub>CH<sub>3</sub>), 3.92-3.87 (m, 2H, NCH<sub>2</sub>), 3.77 (s, 3H, CO<sub>2</sub>CH), 3.33 (dd, 1H, J = 10.1Hz and 2.6 Hz, COCH<sub>2</sub>CH<sub>3</sub>), 2.47 (ddt, 1H, J = 10.1Hz, 4.8Hz and 1.8Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.57-1.46 (m, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 170.9 (C=O), 170.3 (CO<sub>2</sub>), 133.8 (allyl-C), 117.3 (allyl-C), 90.0 (NCOH), 53.0 (CO<sub>2</sub>CH), 49.6 (NCH<sub>2</sub>), 41.9 (COCH<sub>2</sub>COCH<sub>3</sub>), 25.6 (CH<sub>2</sub>CH<sub>3</sub>), 23.9 (C<sub>2</sub>H), 21.5 (CH<sub>2</sub>CH<sub>3</sub>), 10.3 (CH<sub>2</sub>CH<sub>3</sub>); Minor observed: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 3.27 (d, 1H, J = 5.6Hz, COCH<sub>2</sub>COCH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 130.5 (allyl-C), 117.0 (allyl-C), 86.1 (NCOH), 52.6 (CO<sub>2</sub>CH), 42.0 (COCH<sub>2</sub>COCH<sub>3</sub>), 26.8 (CH<sub>2</sub>CH<sub>3</sub>), 12.2 (CH<sub>2</sub>CH<sub>3</sub>); MS m/z (ES+): 264 ([M+Na]<sup>+</sup>); HRMS Found [M+Na]<sup>+</sup> 264.1207 (C<sub>12</sub>H<sub>19</sub>NNaO<sub>4</sub>) requires (M) 264.1206.

**Methyl 2-acetoxy-1-allyl-4,5-dimethyl-1H-pyrrole-3-carboxylate 117**

Pyridine (2.45 mL, 30.3 mol) and acetic anhydride (1.40 mL, 15.2 mol) were added to a stirred solution of 116 (244 mg, 1.00 mmol) in dry tetrahydofuran (13 mL) and refluxed for 2 days and until TLC confirmed complete consumption of starting material. The reaction mixture was cooled to room temperature and quenched by addition of a saturated aqueous copper sulfate solution (20 mL). The organic layer was washed further with another portion of saturated aqueous copper sulfate solution (20 mL), followed by saturated sodium hydrogen carbonate solution (20 mL). The layers were separated and the organic layers combined, dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether : light petroleum ether 1 : 2 ) afforded 117 (126 mg, 50%) as a yellow oil.
IR ν<sub>max</sub> /cm<sup>-1</sup> (oil) 1789 (C=O), 1703 (C=O) and 1540 (C=C); <sup>1</sup>H NMR (500 MHz) δ<sub>H</sub> 5.85 (ddd, 1H, J = 17.0 Hz, 10.4 Hz and 5.6 Hz, NCH<sub>2</sub>CH<sub>2</sub>), 5.20 (d, 1H, J = 10.4 Hz, 1 of NCH<sub>2</sub>CHCH<sub>2</sub>), 5.12 (d, 1H, J = 17.0 Hz, 1 of NCH<sub>2</sub>CHCH<sub>2</sub>), 4.27 (2H, J = 5.6 Hz, NCH<sub>2</sub>), 3.75 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 2.68 (q, 2H, J = 7.4 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.33 (s, 3H, CH<sub>3</sub>), 2.09 (s, 3H, NCC<sub>2</sub>H<sub>4</sub>), 1.16 (t, 3H, J = 7.4 Hz, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 168.5 (C=O), 164.3 (C=O<sub>2</sub>), 139.6 (pyrrole-C), 132.6 (allyl-C), 126.0 (pyrrole-C), 114.1 (allyl-C), 112.6 (pyrrole-C), 100.5 (pyrrole-C), 50.6 (CO<sub>2</sub>CH<sub>3</sub>), 47.6 (NCH<sub>2</sub>), 20.5 (acetate-CH<sub>3</sub>), 20.2 (CH<sub>2</sub>CH<sub>3</sub>), 13.7 (CH<sub>2</sub>CH<sub>3</sub>), 11.1 (CH<sub>3</sub>); MS m/z (ES+): 288 (M+Na)<sup>+</sup>; HRMS Found [M+Na]<sup>+</sup> 288.1209 (C<sub>14</sub>H<sub>19</sub>NNaO<sub>4</sub>) requires (M) 288.1207.

(±)-Methyl 1-allyl-4-ethyl-5-methyl-2-oxo-5-(3'-oxobutyl)-2,5-dihydro-1H-pyrrole-3-carboxylate; 118

![Reaction Scheme](attachment:image)

To a stirred solution of 117 (100 mg, 0.37 mmol) in MeOH (2 mL) was added methyl vinyl ketone (58 µL, 0.83 mmol) and K<sub>2</sub>CO<sub>3</sub> (12 mg, 0.08 mmol) at room temperature and stirred until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with addition of acetic acid (10 µL, 0.17 mmol) and concentrated in vacuo. Purification by column chromatography (neat diethyl ether) gave 118 (81 mg, 75%) as a yellow oil.

IR ν<sub>max</sub> /cm<sup>-1</sup> (oil) 1742 (C=O), 1715 (C=O), 1684 (C=C); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 5.85 (ddt, 1H, J = 17.1 Hz, 10.1 Hz and 6.3 Hz, NCH<sub>2</sub>CH<sub>2</sub>), 5.22 (dd, 1H, J = 17.1 Hz and 1.3 Hz, 1 of NCH<sub>2</sub>CHCH<sub>2</sub>), 5.12 (dd, 1H, J = 10.1 Hz and 1.3 Hz, 1 of NCH<sub>2</sub>CHCH<sub>2</sub>), 4.00 (dd, 1H, J = 15.6 Hz and 6.3 Hz, 1 of NCH<sub>2</sub>), 3.88 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.76 (dd, 1H, J = 15.6 Hz and 6.3 Hz, 1 of NCH<sub>2</sub>), 2.71 (dq, 1H, J = 13.3 Hz and 7.6 Hz, 1 of CH<sub>2</sub>CH<sub>3</sub>), 2.39 (dq, 1H, J = 13.3 Hz and 7.6 Hz, 1 of CH<sub>2</sub>CH<sub>3</sub>), 2.17-1.86 (m, 4H, COH<sub>2</sub>CH<sub>2</sub>), 2.05 (s, 3H, CH<sub>3</sub>), 1.35 (m,
3H, CH₃), 1.18 (t, 3H, J = 7.5, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) δC 206.7 (C=O), 175.4 (N=C=O), 166.3 (CO₂), 163.2 (quat. C=C), 133.5 (allyl-C), 117.7 (allyl-C), 117.6 (quat. C=C), 67.4 (N), 52.0 (CO₂CH₃), 42.1 (NCH₃), 37.0 (CO₃CH₂), 30.2 (CO₂CH₂CH₃), 23.0 (NCCH₃), 20.0 (CH₂CH₃), 13.1 (CH₂CH₃); MS m/z (ES⁺): 316 ([M+Na]⁺); HRMS Found [M+Na]⁺ 316.1514 (C₁₆H₂₃NNaO₄) requires (M) 316.1519

(±)-Methyl 1-allyl-4-ethyl-5-(3-methoxy-3-oxopropyl)-5-methyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate; 121

To a stirred solution of 117 (100 mg, 0.37 mmol) in MeOH (2 mL) was added methyl acrylate (74 µL, 0.83 mmol) and K₂CO₃ (12 mg, 0.08 mmol) at room temperature and stirred until TLC confirmed complete consumption of starting material. The reaction was quenched by addition of acetic acid (10 µL, 0.17 mmol) and concentrated in vacuo. Purification by column chromatography (neat diethyl ether) gave 121 (90 mg, 79%) as a yellow oil.

IR νₘₐₓ /cm⁻¹ (oil) 2952 (CH), 1740 (C=O), 1714 (C=O), 1694 (C=O); ¹H NMR (500 MHz, CDCl₃) δH 5.86 (ddt, 1H, J = 16.8Hz, 10.1Hz and 6.4Hz, NCH₂CH₃), 5.24 (d, 1H, J = 16.8Hz, 1 of NCH₂CHCH₂), 5.13 (d, 1H, J = 10.1Hz, 1 of NCH₂CHCH₂), 4.04 (dd, 1H, J = 15.6Hz and 6.4Hz, 1 of NCH₂), 3.87 (s, 3H, CO₂CH₃), 3.80 (dd, 1H, J = 15.6Hz and 6.4Hz, 1 of NCH₂), 3.63 (s, 3H, CO₂CH₃), 2.73 (dq, 1H, J = 15.1Hz and 7.6Hz, 1 of CH₂CH₃), 2.41 (dq, 1H, J = 15.1Hz and 7.5Hz, CH₂CH₃), 2.17 (ddd, 1H, J = 15.9Hz, 11.0Hz and 5.3Hz, 1 of CO₂CH₂), 2.08 (ddd, 1H, J = 15.9Hz, 10.5Hz and 5.4Hz, 1 of CO₂CH₂), 1.94 (ddd, 1H, J = 15.9Hz, 10.5Hz and 5.3Hz, 1 of CO₂CH₂), 1.80 (ddd, 1H, J = 16.5Hz, 11.0Hz and 5.4Hz, 1 of CO₂CH₂), 1.36 (s, 3H, CH₃), 1.20 (t, 3H, J = 7.6Hz, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) δC 175.1 (N=C=O), 172.8 (CO₂), 166.2 (CO₂), 163.1 (quat. C=C), 133.5 (allyl-C), 124.6
(quat. C=\(\equiv\)), 117.7 (allyl-\(\equiv\)), 67.5 (N\(\equiv\)), 52.0 (2 \times \text{CO}_2\text{CH}_3), 42.1 (N\text{CH}_2), 29.8 (\text{COCH}_2), 27.9 (\text{COCH}_2\text{CH}_3), 23.0 (\text{CH}_3), 20.0 (\text{CH}_2\text{CH}_3), 13.1 (\text{CH}_2\text{CH}_3); \text{MS } m/z \text{ (ES+): 332 ([M+Na]^+)}; \text{HRMS Found [M+Na]^+ 332.1473} (\text{C}_{16}\text{H}_{23}\text{NNaO}_5) \text{ requires (M) 332.1468} (±)

\((\pm)\)-Methyl 1-allyl-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate; 123

6.0 M HCl (50 mL) was added to a solution of 73 (300 mg, 1.31 mmol) in dichloromethane (50 mL) at room temperature. The reaction was stirred for 2 hours before the layers were separated and the aqueous layer extracted with dichloromethane (2 \times 10 mL). The organic layers were combined, dried (MgSO_4) and concentrated \textit{in vacuo} to afford the crude residue which was filtered through silica (ethyl acetate) affording essentially pure 123 (181 mg, 66\%) as a yellow oil. Due to the reactivity of 123 with oxygen it was used in the next step within 1 hour. The compound was assigned based on \(^1\text{H NMR and mass spectrometry data.}\)

\(^1\text{H NMR (500 MHz, CDCl}_3\)) \(\delta\) 5.72 (m, 1H, N\text{CH}_2\text{CH}_3), 5.15 (m, 2H, N\text{CH}_2\text{CHCH}_2), 4.44 (dd, 1H, \(J = 4.7\text{Hz and 15.6Hz}, \text{NCH}_2\text{H}_8\)), 3.95 (q, 1H, \(J = 7.0\text{Hz}, \text{NCH}_2\text{CH}_3\)), 3.81 (s, 3H, \text{CO}_2\text{CH}_3), 3.61 (dd, 1H, \(J = 7.5\text{Hz and 15.7Hz}, \text{NCH}_2\text{H}_8\)), 2.28 (s, 3H, \text{CH}_3), 1.28 (d, 3H, \(J = 7.0\text{Hz}, \text{NCH}_2\text{CH}_3\)); \text{MS } m/z \text{ (ES+): 232 ([M+Na]^+}).
(+)-Methyl 1-allyl-4,5-dimethyl-2-oxo-5-(3-oxobutyl)-2,5-dihydro-1H-pyrrole-3-carboxylate; 124

PREPARATION OF RACEMATE COMPOUND (±)-124
To a solution of 123 (50 mg, 0.19 mmol) in dichloromethane (1.3 mL) was added methyl vinyl ketone (67 µL, 0.76 mmol) and 4-diazabicyclo[2.2.2]octane (2 mg, 0.02 mmol) at room temperature. The reaction was stirred at this temperature until TLC confirmed complete consumption of starting material and then concentrated in vacuo. Purification by column chromatography (Ethyl acetate : light petroleum ether, 4 : 1) gave (±)-124 (53 mg, 72%) as a yellow oil.

PREPARATION OF ENANTIOENRICHED COMPOUND (+)-124
To a solution of 123 (50 mg, 0.19 mmol) in toluene (1.3 mL) was added methyl vinyl ketone (80 µL, 0.91 mmol) and organocatalyst 125 (9 mg, 0.02 mmol) at −20 °C. The reaction was stirred for 18 h at this temperature and then concentrated in vacuo. Purification by column chromatography (Ethyl acetate : light petroleum ether, 4 : 1) gave (+)-124 (28 mg, 53% yield, 86% ee) as a yellow oil. [Chiralpak OJ, Hexanes / IPA 90:10, 1.0 mL / min, λ 230 nm, t (minor) = 39.775 min, t (major) = 46.875 min]

IR ν_{max}(oil) 2949 (CH), 1742 (C=O), 1715 (C=O), 1690 (C=O); [α]_D^{26} +10 (c 1.25, CHCl₃);

^{1}H NMR (500 MHz; CDCl₃) δₜ 5.88-5.78 (m, 1H, NCH₂CH), 5.21 (d, 1H, J = 17.2Hz, 1 of
NCH₂CH₂H₂), 5.10 (d, 1H, J = 10.1 Hz, 1 of NCH₂CH₂H₂), 3.97 (dd, 1H, J = 15.7 Hz and 6.3 Hz, NCH₂H₂), 3.86 (s, 3H, OCH₃), 3.80 (dd, 1H, J = 15.7 Hz and 6.3 Hz, NCH₂H₂), 2.18 (s, 3H, COCH₃), 2.13-1.98 (m, 2H, CH₂CH₂CO), 2.04 (s, 3H, COCH₃), 1.96-1.81 (m, 2H, CH₂CH₂CO), 1.31 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃, δC 206.7 (C=O), 170.8 (quat. C=C), 166.1 (N=C=O), 163.2 (CO₂CH₃), 133.5 (allyl-C), 124.4 (quat. C=C), 117.7 (allyl-C), 67.0 (NCH₂), 51.9 (OCH₃), 42.1 (allyl-C), 36.7 (CH₂C=O), 30.1 (COCH₃), 28.0 (CH₂CH₂C=O), 23.2 (CH₃), 12.3 (CH₃); MS m/z (ES⁺) 302 (M+Na⁺); HRMS Found [M+Na⁺]⁺ 302.1364 (C₁₃H₂₁NNaO₄) requires (M) 302.1363.

(+) -Methyl 1-allyl-4,5-dimethyl-2-oxo-5-(3′-oxopentyl)-2,5-dihydro-1H-pyrrolo-3-carboxylate; 127

![Diagram]

To a solution of 123 (50 mg, 0.19 mmol) in toluene (1.3 mL) was added ethyl vinyl ketone (95 μL, 0.91 mmol) and organocatalyst 125 (9 mg, 0.02 mmol) at −20 °C. The reaction was stirred for 18 h and then concentrated in vacuo. Purification by column chromatography (Ethyl acetate : light petroleum ether, 4 : 1) gave 127 (36 mg, 65% yield, 36% ee) as a yellow oil. [Chiralpak OJ, Hexanes / IPA 98:2, 1.0 mL / min, λ 230 nm, t (minor) = 52.631 min, t (major) = 53.223 min]

IR νmax/cm⁻¹ (oil) 2978 (CH), 1744 (C=O), 1711 (C=O), 1638 (C=O); ¹H NMR (500 MHz) δH 5.84 (ddt, 1H, J = 16.8 Hz, 10.1 Hz and 6.3 Hz, NCH₂CH₂H₂), 5.22 (dd, 1H, J = 17.1 Hz and 1.3 Hz, 1 of NCH₂CH₂H₂), 5.11 (dd, 1H, J = 10.1 Hz and 1.3 Hz, 1 of NCH₂CH₂H₂), 3.99 (dd, 1H, J = 15.6 Hz and 6.3 Hz, 1 of NCH₂), 3.87 (s, 3H, CO₂CH₃), 3.81 (dd, 1H, J = 15.6 Hz and 6.3 Hz, 1 of NCH₂), 2.30 (q, 2H, J = 7.3, COCH₂CH₃), 2.20 (s, 3H, CH₃), 2.15-2.07 (m, 1H, 1 of COCH₂CH₃), 2.06-1.92 (m, 2H, 1 of COCH₂CH₂ and 1 of COCH₂CH₃), 1.84 (ddd, 1H, J = 13.2 Hz, 10.5 Hz and 3.6 Hz, 1 of COCH₂CH₃), 1.32 (s, 3H, CH₃), 0.99 (t, 3H, J = 7.3 Hz, COCH₂CH₃); ¹³C NMR (125 MHz, CDCl₃, δC 209.5 (C=O), 171.0 (N=C=O), 166.1 (CO₂), 163.3 (quat. C=C), 133.6 (allyl-C), 124.5 (quat. C=C), 117.7 (allyl-C), 67.1 (N=C), 52.0

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(CO₂CH₃), 42.1 (NCH₂), 36.2 (COCH₂CH₃), 35.4 (COCH₂CH₂), 28.1 (COCH₂CH₂), 23.2 (CH₃), 12.3 (CH₃), 7.7 (COCH₂CH₃); **MS m/z** (ES+) 318 ([M+Na]⁺); **HRMS** Found [M+Na]⁺ 318.1676 (C₁₆H₂₅N₂NaO₄) requires (M) 318.1676.

(+)-**Methyl-1-allyl-2'-hydroxy-2',5-dimethyl-2-oxo-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 93a,b**

To a stirred solution of enantioenriched **124** (50 mg, 0.18 mmol) in MeOH (2 mL) was added K₂CO₃ (5 mg, 0.04 mmol) at room temperature. The reaction mixture was stirred at this temperature until TLC confirmed complete consumption of starting material. The reaction mixture was quenched by addition of acetic acid (4.8 µL, 0.08 mmol) and concentrated *in vacuo*. Purification by column chromatography (neat diethyl ether) gave **93a,b** (46 mg, 92%) as a 2:1 mixture of diastereoisomers and a yellow oil.

The ¹H NMR was identical to **93a,b** which was previous prepared with pyrrole acetate **90** and methyl vinyl ketone under catalytic potassium carbonate in methanol reaction conditions. [α]D²⁵: +85 (c 1.25, CHCl₃).

(-)-**Methyl 1-allyl-4,5-dimethyl-2,2'-dioxooctahydro-1H-indole-3-carboxylate; 130**
To a solution of 124 (63 mg, 0.22 mmol) in dry MeOH (1 mL) was added pyrrolidine (1.8 μL, 0.02 mmol) drop-wise at room temperature. The reaction mixture was stirred for 18 hours and then concentrated in vacuo. Purification by column chromatography (neat ethyl acetate) gave 130 (39 mg, 66%) as a 1:1 mixture of diastereoisomers and a yellow oil.

IR ν_{max}(oil) 2954 (CH), 1722 (C=O), 1716 (C=O), 1682 (C=O); [α]_D^{25} : -30 (c 0.48, CHCl₃);

130a: ¹H NMR (500 MHz, CDCl₃) δ_H 5.90 (ddt, 1H, J = 16.2Hz, 10.3Hz and 6.0Hz, NCH₂CH₂), 5.27 (ddd, 1H, J = 17.2Hz, 3.8Hz and 1.4Hz, 1 of NCH₂CH₂H₂), 5.17 (ddd, 1H, J = 10.2Hz, 5.0Hz and 1.2Hz, 1 of NCH₂CH₂H₂), 3.98 (ddd, 1H, J = 15.7Hz, 5.9Hz and 1.3Hz, NCH₂H₃), 3.88-3.77 (m, 1H, NCH₂H₃), 3.75 (s, 3H, CO₂CH₃), 3.36 (s, 1H, 3-C₃H), 2.78 (d, 1H, J = 14.4Hz, 1'-CH₃H₃), 2.56 (d, 1H, J = 14.8Hz, 1'-CH₃H₃), 2.31-2.14 (m, 2H, 4'-CH₂ and 3'-CH₂), 1.39 (s, 3H, 5-CH₃), 1.21 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ_C 208.8 (C=O), 169.2 (N=C=O), 168.5 (CO₂Me), 134.1 (allyl-C), 117.8 (allyl-C), 64.5 (5-C), 58.8 (3-C₃H), 52.4 (OCH₃), 51.6 (1'-CH₂), 47.2 (NCH₂), 44.4 (4'-CH₂), 36.3 (3'-CH₂), 33.0 (4-C), 22.1 (CH₃), 21.9 (CH₃); 130b observed: ¹H NMR (500 MHz, CDCl₃) δ_H 3.74 (s, 3H, CO₂CH₃), 3.23 (s, 1H, 3-C₃H), 2.12-1.88 (m, 4H, 4'-CH₂ and 3'-CH₂), 1.24 (s, 3H, 5-CH₃), 1.12 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ_C 208.6 (C=O), 169.1 (N=C=O), 168.2 (CO₂Me), 133.7 (allyl-C), 117.4 (allyl-C), 63.6 (5-C), 57.8 (3-C₃H), 46.9 (NCH₂), 42.9 (4'-CH₂), 35.5 (3'-CH₂), 32.1 (4-C), 21.8 (CH₃), 20.9 (CH₃); MS m/z (ES+) 302 ([M+Na]⁺);

HRMS Found [M+Na]⁺ 302.1364 (C₁₅H₂₁NNaO₄) requires (M) 302.1368.

(+) -1-Allyl-4,5-dimethyltetrahydro-1H-indole-2,2′(3H,6H)-dione; 131

![Diagram of chemical structures](image)

To a solution of 130 (30 mg, 0.11 mmol) in dimethylsulfoxide (1 mL) was added water (1 drop) and sodium chloride (10 mg, 0.17 mmol). The reaction was heated at 175 °C...
for 2 hours and cooled to room temperature before addition of water (5ml). The aqueous layer was extracted with ethyl acetate (3 x 10 mL) dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. Purification by column chromatography (neat ethyl acetate) gave 131 (21 mg, 85%) as a single diastereoisomer and a yellow oil.

IR $\nu_{max}$(oil) 2971 (CH), 1715 (C=O), 1681 (C=O); $[\alpha]_D^{25}$: +31 (c 1.3, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 5.82 (ddt, 1H, $J = 17.1$Hz, 10.2Hz and 6.1Hz, NCH$_2$CH), 5.16 (qd, 1H, $J = 17.2$Hz and 1.4Hz, 1 of NCH$_2$CHCH$_3$), 5.09 (qd, 1H, $J = 10.1$Hz and 1.3Hz, 1 of NCH$_2$CHCH$_3$), 3.81 (d, 2H, $J = 5.9$Hz, NCH$_2$), 2.40 (d, 1H, $J = 14.4$, 1'-CH$_2$H), 2.22 (m, 5H, 1'-CH$_2$H, 3'-CH$_2$ and 3'-CH$_2$), 2.05 (tt, 1H, $J = 15.0$Hz and 5.5Hz, 4'-CH$_2$H), 1.89 (s, 3H, 5-C), 1.08 (s, 3H, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 209.6 (C=O), 173.2 (NC=O), 134.5 (allyl-C), 117.2 (allyl-C), 64.4 (5-C), 50.2 (1'-CH$_2$), 44.7 (NCH$_2$), 42.7 (3'-CH$_2$), 42.6 (4'-CH$_2$), 36.2 (3'-CH$_2$), 32.6 (3'-CH$_2$), 23.4 (CH$_3$), 21.7 (CH$_3$); MS m/z (ES+) 244 ([M+Na]$^+$); HRMS Found [M+H]$^+$ 222.1500 (C$_{13}$H$_{20}$O$_2$N) requires (M) 222.1489.

6.3 EXPERIMENTAL FOR CHAPTER THREE

$\textbf{N-Allyl-2-chloroacetamide; 162}^{56}$

![Chemical Reaction Diagram]

To a stirred solution of allylamine (3.13 mL, 41.8 mmol) and triethylamine (6.17 mL, 43.9 mmol) in dry tetrahydrofuran (126 mL) at 0 °C was added chloroacetyl chloride 161 (5.00 g, 44.3 mmol) in dry tetrahydrofuran (84 mL) drop-wise via cannula over a 1 hour period. The reaction mixture was warmed to room temperature and stirred for 12 hours. The reaction mixture was concentrated in vacuo, diluted with distilled water (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers
were washed with brine (2 x 100 mL), dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo} to afford essentially pure 159 (5.87 g, 99%) as an orange oil.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 6.71 (bs, 1H, NH), 5.84 (dq, 1H, \(J = 10.7\)Hz and 5.6Hz, NCH\textsubscript{2}CH\textsubscript{2}), 5.19 (dd, 2H, \(J = 20.8\)Hz and 13.7Hz, NCH\textsubscript{2}CHCH\textsubscript{2}), 4.07 (s, 2H, COCH\textsubscript{2}Cl), 3.93 (t, 2H, \(J = 5.7\)Hz, NCH\textsubscript{2}) \(\textsuperscript{1}H NMR in agreement with literature; MS }\textit{m/z} (EI/CI): 134 ([M +H]\textsuperscript{+}).

\centering
\textbf{N-Allyl-2-iodoacetamide; 159}\textsuperscript{112}

To a stirred solution of 162 (5.87 g, 44.1 mmol) in acetone (113 mL) was added sodium iodide (7.25 g, 48.6 mmol) and refluxed for 2 hours. The resulting reaction mixture was cooled to room temperature, diluted with dichloromethane (200 mL) and washed with saturated aqueous sodium thiosulfate (3 x 100 mL). The combined organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and concentrated \textit{in vacuo} to afford 159 (8.3 g, 84%) as a white solid.

\textbf{M.P.} 57-60 °C; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 6.13 (s, 1H, NH), 5.85 (ddd, 1H, \(J = 22.6\)Hz, 10.7Hz and 5.6Hz, NCH\textsubscript{2}CH\textsubscript{2}), 5.21 (dd, 2H, \(J = 27.6\)Hz and 14.2Hz, NCH\textsubscript{2}CHCH\textsubscript{2}), 3.91 (dt, 2H, \(J = 5.7\)Hz and 1.2Hz, NCH\textsubscript{2}), 3.73 (s, 2H, COCH\textsubscript{2}Cl) \(\textsuperscript{1}H NMR in agreement with literature; MS }\textit{m/z} (EI/CI): 225 ([M +H]\textsuperscript{+})
To a stirred solution of diisopropylamine (9.47 mL, 67.2 mmol) in dry tetrahydrofuran (200 mL) at -78 °C was added a 1.6 M solution of n-butyl lithium in hexanes (40 mL, 64.0 mmol) via syringe. The resultant colourless solution was stirred at -78 °C for 5 minutes, warmed to 0 °C for 10 minutes and subsequently re-cooled to -78 °C. A solution of 1,4-cyclohexanedione monoethylene acetal 163 (10.0 g, 64.02 mmol) in dry tetrahydrofuran (40 mL) was then added drop-wise via cannula and stirred at -78 °C for 0.5 hours before iodomethane (4.78 mL, 76.8 mmol) was added drop-wise. The reaction mixture was stirred at -78 °C for 0.5 hours, warmed to room temperature and stirred for a further 12 hours and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was washed with water (2 x 100 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate : light petroleum ether 1 : 1 to 3 : 1) afforded 160 (6.75g, 62%) as a off-white crystalline solid.

**M.P.** 46-49 °C; **¹H NMR** (500 MHz, CDCl₃) δH 3.88 (m, 4H, OCH₂CH₂O), 2.59 (m, 1H, COCH), 2.49 (dddt, 1H, J = 14.0Hz, 6.2Hz and 0.9Hz, CHCH₃H₈), 2.22 (dddt, 1H, J = 14.3Hz, 5.1Hz and 2.9Hz, CHCH₃H₈), 1.90 (dddt, 2H, J = 14.7Hz, 6.1Hz and 3.6Hz, COCH₂), 1.82 (dd, 1H, J = 13.6Hz and 5.0Hz, 1 of COCH₂CH₂), 1.58 (t, 1H, J = 13.2Hz, 1 of COCH₂CH₂), 0.87 (d, 3H, J = 6.6Hz, CHCH₃) **¹H NMR in agreement with literature; MS m/z (ES+): 193 ([M +Na]+)**
(±)-1'-Allyl-5-hydroxy-4-methylhexahydrospiro[[1,3]dioxolane-2,2'-indol]-2'(1'H)-one; 164

To a stirred solution of diisopropylamine (0.87 mL, 6.17 mmol) in dry tetrahydrofuran (15 mL) at -78 °C was added a 1.6 M solution of n-butyl lithium in hexanes (3.67 mL, 5.88 mmol) via syringe. The resultant colourless solution was stirred at -78 °C for 5 minutes, warmed to 0 °C and then to room temperature. A solution of 160 (1.0 g, 5.88 mmol) in dry tetrahydrofuran (15 mL) was then added drop-wise via cannula and the resultant reaction mixture was refluxed for 2 hours. The reaction mixture was cooled to room temperature and then to -78 °C before a solution of N-allyl-2-iodoacetamide 159 (1.45 g, 6.47 mmol) in dry tetrahydrofuran (30 mL) was added drop-wise via cannula. The reaction mixture was stirred at -78 °C for 10 minutes and then warmed to room temperature and stirred at this temperature until TLC confirmed complete consumption of starting material. The reaction mixture was quenched at -78 °C by addition of saturated aqueous ammonium chloride solution (5 mL) and partitioned between dichloromethane (100 mL) and water (200 mL). The aqueous phase was further extracted with dichloromethane (3 x 100 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate : light petroleum ether 5:1 to neat ethyl acetate) afforded 164 (612 mg, 39%) as a single diastereoisomer and a viscous yellow oil.

IR ν<sub>max</sub>(oil) 3358 (OH), 2937 (CH), 1671 (C=O); <sup>1</sup>HNMR (500 MHz, CDCl₃) δ<sub>H</sub> 5.90 (ddt, 1H, J = 16.6Hz, 10.1Hz and 6.4Hz, NCH₂CH), 5.25 (dd, 1H, J = 17.2Hz and 1.4Hz, 1 of NCH₂CHCH₂), 5.15 (dd, 1H, J = 10.1Hz and 1.2Hz, 1 of NCH₂CHCH₂), 4.07 (dd, 1H, J = 15.9Hz and 6.6Hz, NCH₂H₃), 3.92 (m, 4H, OCH₂CH₂O), 3.74 (dd, 1H, J = 15.5Hz and 6.5Hz, NCH₂H₃), 2.28 (q, 2H, J = 16.3Hz, 3-CH₂), 1.45-2.04 (m, 6H, 1’, 3’ and 4’-CH₂),
1.23 (s, 3H, CH₃); $^{13}$C NMR (125 MHz, CDCl₃) δ: 175.0 (N=O), 134.8 (allyl-C), 117.4 (allyl-C), 108.6 (2'-C), 94.6 (5-C), 64.4 (2 x OCH₂CH₂O), 46.8 (NCH₂), 43.5 (1'-C), 42.0 (3-C), 37.2 (3'-C), 31.1 (4-C), 25.5 (4'-C), 20.8 (CH₃); **MS m/z** (ES+): 268 ([M+H]+); **HRMS**: Found [M+H]+ 268.1550 (C₁₄H₂₂NO₄) requires (M) 268.1543

Along with the desired product 164, diketopiperazine 165 was isolated from the reaction mixture.

**1,4-Diallylpiperazine-2,5-dione; 165**

![Structure of 1,4-Diallylpiperazine-2,5-dione](image)

Compound 165 was assigned based on $^1$H NMR and mass spectrometry data. No further data was collected. **$^1$H NMR** (300 MHz, CDCl₃) δ: 5.87-5.83 (m, 2H, NCH₂CH), 5.27-5.11 (m, 4H, NCH₂CH₂CH), 4.09 (s, 4H, NCH₂CO), 3.98 (m, 4H, NCH₂CH); **MS m/z** (ES+): 217 ([M+Na]+); **HRMS**: Found [M+Na]+ 217.1555 (C₁₂H₂₀NO₃) requires (M) 217.1552

**(+)-1-Allyl-4-methyltetrahydro-1H-indole-2,2'(3H,6H)-dione; 167**

![Reaction Scheme](image)

To a stirred solution of 164 (182 mg, 0.68 mmol) and triethylsilane (108 μl, 0.68 mmol) in dry dichloromethane (10 mL) at -20 °C was added trifluoroacetic acid (680 μl, 0.68 mmol) drop-wise. The reaction mixture was warmed to 0 °C and stirred at this temperature until TLC confirmed complete consumption of starting material. The
The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate solution (2 mL) and partitioned between dichloromethane (25 mL) and water (50 mL). The aqueous phase was further extracted with dichloromethane (3 x 25 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (light petroleum ether : ethyl acetate 1 : 5 to neat ethyl acetate) afforded 167 (61 mg, 43%) as a single diastereoisomer and a light yellow oil.

IR ν_max (oil) 2953 (CH), 1713 (C=O), 1687 (C=O); 

1H NMR (500 MHz, CDCl₃) δ H 5.75 (tdd, 1H, J = 17.4Hz, 10.3Hz and 5.1Hz, NCH₂CH), 5.24 (dd, 2H, J = 12.3Hz and 5.7Hz, NCH₂CHCH₂), 4.37 (dd, 1H, J = 15.4Hz and 5.0Hz, NCH₂H₆), 3.53 (dd, 1H, J = 15.4Hz and 7.4Hz, NCH₆H₆), 2.46 (d, 1H, J = 15.1Hz, 1 of 3-CH₆H₆), 3.47 (t, 1H, J = 4.7Hz, 5-CH), 2.31 (s, 2H, 1'-CH₂), 2.35 (d, 1H, J = 15.1Hz, 1 of 3-CH₆H₆), 2.27-2.24 (m, 2H, 3'-CH₂), 2.05 (2H, m, 3'-CH₂), 1.23 (s, 3H, CH₃); 

13C NMR (125 MHz, CDCl₃) δ C 210.0 (C=O), 172.9 (N=O), 132.3 (allyl-C), 118.5 (allyl-C), 62.2 (5-C), 49.8 (1'-C), 45.3 (3-C), 43.3 (NCH₂), 36.6 (3'-C), 34.3 (4-C), 28.6 (4'-C), 23.9 (CH₃); MS m/z (ES±): 230 ([M+Na]+); HRMS: Found [M+Na]⁺ 230.1157 (C₁₆H₁₇NNaO₂) requires (M) 230.1152

Two side products of this reaction were isolated and characterized;

(±)-1-Allyl-4-methyl-4,1’-dihydro-1H-indole-2,2’(3H,6H)-dione; 169

169 (15 mg, 11%) was isolated as a yellow oil. IR ν_max (oil) 2996 (CH), 1713 (C=O), 1689 (C=O); 

1H NMR (500 MHz, CDCl₃) δ H 5.67 (tdd, 1H, J = 21.9Hz, 10.7Hz and 5.5Hz, NCH₂CH), 5.12 (m, 2H, NCH₂CHCH₂), 4.83 (t, 1H, J = 3.8Hz, 4'-CH), 4.16 (dd, 1H, J = 16.0Hz and 5.3Hz, NCH₆H₆), 3.97 (dd, 1H, J = 16.0Hz and 5.7Hz, NCH₆H₆), 2.59 (d, 1H, J =
$= 14.8$Hz, $1' \text{-CH}_2\text{H}_3$), 2.95-2.92 (m, 2H, 3'-CH$_2$), 2.51 (d, 1H, $J = 14.8$Hz, 1'-CH$_3$H$_3$), 2.47 (d, 1H, $J = 16.7$Hz, 1 of 3-CH$_3$), 2.35 (d, 1H, $J = 16.7$Hz, 1 of 1 of 3-CH$_3$), 1.12 (s, 3H, CH$_3$);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ c 207.5 (C=O), 173.0 (N=C=O), 146.5 (5-C), 131.2 (allyl-C), 121.3 (4'-C), 117.5 (allyl-C), 51.2 (1'-C), 44.5 (NCH$_2$), 42.3 (3'-C), 37.6 (3-C), 37.5 (4-C), 25.9 (CH$_3$); MS $m/z$ (ES+): 228 ([M+Na]$^+$); HRMS: Found [M+H]$^+$ 206.1177 (C$_{12}$H$_{16}$NO$_2$) requires (M) 206.1175

$(\pm)$-1-Allyl-2'-hydroxy-4-methylhexahydro-1H-indol-2(3H)-one; 168

**168** (7 mg, 5%) was isolated as an inseperable 3:1 mixture of diastereoisomers and a colourless oil. IR $\nu_{\text{max}}$(oil) 3399 (OH), 2928 (CH), 1670 (C=O); **Major: $^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ h 5.65 (tdd, 1H, $J = 15.3$Hz, 10.1Hz, 7.7Hz and 5.1Hz, NCH$_2$CH$_2$), 5.14 (m, 2H, NCH$_2$CHCH$_2$), 4.27 (m, 1H, NCH$_3$H$_3$), 4.19 (s, 1H, OH), 3.78 (dt, 1H, $J = 8.1$Hz and 3.9Hz, 2'-CH$_2$OH), 3.37 (dd, 1H, $J = 15.2$Hz and 7.6Hz, NCH$_3$H$_3$), 3.05 (m, 1H, 5-CH$_2$), 2.32 (d, 1H, $J = 16.3$Hz, 3-CH$_3$H$_3$), 2.05-2.20 (m, 2H, 3'-CH$_2$), 1.93 (d, 1H, $J = 16.3$Hz, 3-CH$_3$H$_3$), 1.86 (dd, 1H, $J = 13.8$Hz and 2.9Hz, 1'-CH$_3$H$_3$), 1.79-1.47 (m, 2H, 4'-CH$_2$) 1.32 (dd, 1H, $J = 13.8$Hz and 9.2Hz, 1'-CH$_3$H$_3$), 1.12 (s, 3H, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ c 174.2 (N=C=O), 132.7 (allyl-C), 118.3 (allyl-C), 66.7 (2'-C), 60.6 (5-C), 47.1 (1'-C), 43.2 (3-C), 42.6 (NCH$_2$), 37.7 (3'-C), 29.6 (4'-C), 28.7 (CH$_3$), 23.7 (4-C); **Minor observed: $^1$H NMR** (500 MHz, CDCl$_3$) $\delta$ h 3.67 (m, 1H, 2'-CH$_2$OH), 3.17 (t, 1H, $J = 3.3$Hz, 5-CH$_2$), 1.12 (s, 3H, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ c 173.6 (N=C=O), 132.8 (allyl-C), 117.9 (allyl-C), 66.6 (2'-C), 61.8 (5-C), 43.4 (1'-C), 42.9 (3-C), 42.4 (NCH$_2$), 36.9 (3'-C), 30.2 (4'-C), 24.4 (CH$_3$), 21.6 (4-C); MS $m/z$ (ES+): 232 ([M+Na]$^+$), HRMS: Found [M+Na]$^+$ 232.1311 (C$_{12}$H$_{19}$NNaO$_2$) requires (M) 232.1309
To a stirred solution of 167 (50 mg, 0.24 mmol) in dry tetrahydrofuran (2 mL) was added phenyltrimethylammonium tribromide (PTAP) (108 mg, 0.28 mmol) in one portion at room temperature and stirred until TLC confirmed complete consumption of starting material. The reaction mixture was quenched by addition of saturated aqueous sodium hydrogen sulfate solution (1 mL) and partitioned between diethyl ether (20 mL) and distilled water (20 mL). The aqueous phase was further extracted with diethyl ether (3 x 10 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (light petroleum ether : ethyl acetate 1 : 5 to neat ethyl acetate) afforded 173 (55 mg, 80%) as a 1:1 mixture of diastereoisomers and a yellow oil.

Compound 173 was assigned based on ¹H NMR and mass spectrometry data. No further data was collected. 173a: ¹H NMR (500 MHz, CDCl₃) δH 5.73 (m, 1H, NCH₂C), 5.25 (m, 2H, NCH₂CHCH₂), 4.68 (s, 1H, 1'-CH), 4.35 (ddd, 1H, J = 15.5Hz, 13.5Hz and 5.0Hz, 1 of NCH₂), 3.71 (t, 1H, J = 4.2Hz, 5-CH), 3.58-3.45 (m, 1H, 1 of NCH₂), 2.60-2.33 (m, 4H, 3'-CH₂, 1 of 3-CH₂, 1 of 4'-CH₂), 2.23 (d, 1H, J = 18.0Hz, 1 of 3-CH₂), 2.14 (m, 1H, 1 of 4'-CH₂), 1.49 (s, 3H, CH₃); 173b observed: ¹H NMR (500 MHz, CDCl₃) δH 4.49 (s, 1H, 1'-CH), 3.58-3.45 (m, 1H, 5-CH), 2.60-2.33 (m, 2H, 3-CH₂), 2.14 (m, 1H, 1 of 4'-CH₂), 2.07 (m, 1H, 1 of 4'-CH₂), 1.34 (s, 3H, CH₃); MS m/z (ES+): 308 ([M +Na]+).
To a stirred solution of cyclohexanone 182 (1.0 g, 10.19 mmol) in dry tetrahydrofuran (50 mL) at room temperature was added 60% sodium hydride in oil (0.86 g, 21.39 mmol) in one portion and the resultant reaction mixture was stirred at room temperature for 10 minutes before a solution of tert-butyl pyrrole-1-carboxylate (3.40 mL, 21.39 mmol) in dry tetrahydrofuran (20 mL) was added drop-wise and refluxed for 2 hours and until TLC confirmed complete consumption of starting material. The reaction mixture was cooled to room temperature, acidified with 1.0 M hydrochloric acid (200 mL) and partitioned between ethyl acetate (100 mL). The aqueous phase was further extracted with ethyl acetate (2 x 100 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (light petroleum ether : diethyl ether 3 : 1 to 1 : 1) afforded 183 (1.05 g, 66%) as a 1:1 mixture of keto:enol forms and a light brown oil.

183a: ¹H NMR (500 MHz, CDCl₃) δH 12.40 (bs, 1H, OH), 2.35-2.33 (m, 2H, 2-C₆H₂), 2.23 (t, 2H, J = 6.4Hz, 5-C₆H₂), 1.91 (m, 2H, 4-C₆H₂), 1.66 (m, 2H, 3-C₆H₂), 1.47 (s, 9H, OC(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δC 172.7 (6-C), 169.3 (CO₂C), 98.9 (1-C), 80.7 (OC(CH₃)₃), 29.9 (5-C), 29.2 (2-C), 28.0 (3 x OC(CH₃)₃), 27.2, 22.5; 183b: ¹H NMR (500 MHz, CDCl₃) δH 3.26 (ddd, 1H, J = 1.0Hz, 8.8Hz and 5.6Hz, 1’-CH), 2.49 (m, 2H, 5’-CH₂), 2.14 (m, 2H, 2’-CH₂), 2.03 (m, 2H, 4’-CH₂), 1.82 (m, 2H, 3’-CH₂), 1.49 (s, 9H, OC(CH₃)₃); 206.9 (6’-C), 171.3 (CO₂C), 81.9 (OC(CH₃)₃), 57.9 (1’-C), 41.5 (5’-C), 28.3 (3 x OC(CH₃)₃), 23.1, 22.8, 22.0. ¹H and ¹³C NMR in agreement with the literature
To a stirred solution of 1,4-cyclohexanedione monoethylene acetal 163 (5.00 g, 32.0 mmol) in dry tetrahydrofuran (250 mL) at room temperature was added 60% sodium hydride in oil (2.69 g, 67.2 mmol) in one portion and the resultant reaction mixture was stirred at room temperature for 10 minutes before a solution of tert-butyl pyrrole-1-carboxylate (11.24 mL, 67.23 mmol) in dry tetrahydrofuran (50 mL) was added dropwise and refluxed for 2 hours and until TLC confirmed complete consumption of starting material. The reaction mixture was cooled to room temperature, acidified with 1.0 M hydrochloric acid (300 mL) and partitioned between ethyl acetate (2 x 150 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (light petroleum ether : diethyl ether 3 : 1 to 1 : 1) afforded 178 (6.3 g, 77%) as a 3:1 mixture of enol:keto forms and a light brown oil.

**IR** ν\textsubscript{max}(oil) 2976 (CH), 1737 (C=O), 1651 (C=O); **Major 178a**: \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ\textsubscript{H} 12.40 (bs, 1H, OH), 4.00 (m, 8H, OCH\textsubscript{2}CH\textsubscript{2}O), 2.47 (t, 2H, J = 6.8Hz, 5-CH\textsubscript{2}), 2.42 (s, 2H, 2-CH\textsubscript{2}), 1.82 (t, 2H, J = 6.8Hz, 4-CH\textsubscript{2}), 1.48 (s, 9H, OC(CH\textsubscript{3})\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ\textsubscript{C} 171.9 (6-\textsuperscript{C}), 168.6 (CO\textsubscript{2}C), 107.4 (3-\textsuperscript{C}), 96.4 (1-\textsuperscript{C}), 81.2 (OC(CH\textsubscript{3})\textsubscript{3}), 64.7 (OC\textsubscript{2}CH\textsubscript{2}O), 64.6 (OC\textsubscript{2}CH\textsubscript{2}O), 34.5 (2\textsuperscript{-C}), 33.2 (4-\textsuperscript{C}), 30.2, 27.9 (3 x OC(CH\textsubscript{3})\textsubscript{3}); **Minor 178b observed**: \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ\textsubscript{H} 3.50 (dd, 1H, J = 6.0Hz and 10.1Hz, 1'-CH\textsubscript{3}), 2.61 (m, 2H, 5'-CH\textsubscript{2}), 2.38 (m, 1H, 1 of 2'-CH\textsubscript{2}), 2.10 (dd, 1H, J = 6.0Hz and 13.6Hz, 1 of 2'-CH\textsubscript{2}), 2.03 (m, 2H, 4'-CH\textsubscript{2}), 1.47 (s, 9H, OC(CH\textsubscript{3})\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ\textsubscript{C} 205.4 (6'-\textsuperscript{C}), 170.2 (CO\textsubscript{2}C), 106.8 (3'-\textsuperscript{C}), 81.8 (OC(CH\textsubscript{3})\textsubscript{3}), 54.7 (1'-\textsuperscript{C}), 38.1 (2'-\textsuperscript{C}), 36.4 (4'-\textsuperscript{C}), 28.3 (3 x OC(CH\textsubscript{3})\textsubscript{3}), 27.8; **MS m/z** (ES+): 274 ([M +NH\textsubscript{4}]\textsuperscript{+}); **HRMS**: Found [M+Na]\textsuperscript{+} 279.1203 (C\textsubscript{13}H\textsubscript{20}NaO\textsubscript{5}) requires (M) 279.1203
(±)-tert-Butyl 1-allyl-5-hydroxy-2'-oxooctahydrospiro[[1,3]dioxolane-2,2'-indole]-4-carboxylate; 179 and (±)-tert-Butyl 1-allyl-2-oxo-3,4,1',3',4'-hexahydrospiro[[1,3]dioxolane-2,2'-indole]-4-carboxylate; 184

To a stirred solution of 178 (100 mg, 0.39 mmol) in dry tetrahydrofuran (4 mL) was added 60% sodium hydride in oil (190 mg, 0.47 mmol) portion-wise and stirred at room temperature for 0.5 hours. A solution of N-allyl-2-iodoacetamide 159 (83 mg, 0.37 mmol) in dry tetrahydrofuran (3 mL) was added drop-wise via cannula and stirred at room temperature until TLC confirmed complete consumption of starting material. The reaction mixture was quenched by addition of saturated aqueous ammonium chloride solution (5 mL) and partitioned between dichloromethane (10 mL) and water (20 mL). The aqueous phase was further extracted with dichloromethane (3 x 10 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate : light petroleum ether 5 : 1 to neat ethyl acetate) afforded 179 and 184 (77 mg, ~56%) as an inseparable 3:1 mixture of compounds and a viscous yellow oil.

The inseparable mixture of compounds 179 and 184 was assigned based on ¹H NMR, ¹³C NMR and mass spectrometry data of the mixture. Compound 179 was isolated as a single compound in the enantioselective reaction and characterised fully at this stage (see overpage). 179: ¹H NMR (500 MHz, CDCl₃) δH 5.85 (ddt, 1H, J = 16.5Hz, 10.2Hz and 6.2Hz NCH₂CH), 5.22 (d, 1H, J = 17.1Hz, 1 of NCH₂CHCH₂), 5.12 (d, 1H, J = 10.2Hz, 1 of NCH₂CHCH₂), 5.00 (bs, 1H, OCH₃), 3.92 (m, 6H, OCH₂CH₂O and NCH₂), 2.74 (d, 1H, J = 16.2Hz, 3-CH₃), 2.36 (d, 1H, J = 16.2Hz, 3-CH₃), 2.63 (dd, 1H, J = 2.3Hz and 14.1Hz, 1'-CH₃), 2.21 (d, 1H, J = 4.6Hz, 1 of 3'-CH₃), 2.11 (td, 1H, J = 14.7Hz and 4.6Hz, 1 of 3'-CH₃), 1.73 (d, 1H, J = 14.1Hz, 1 of 1'-CH₃), 1.56-1.63 (m, 2H, 4'-CH₂), 1.48 (s, 9H,
To a stirred solution of 178 (50 mg, 0.20 mmol) in toluene/chloroform (9:1) (1 mL) was added a solution of N-allyl-2-iodoacetamide 159 (39 mg, 0.17 mmol) and catalyst 145 (24 mg, 0.02 mmol) in toluene/chloroform (9:1) (1.5 mL) drop-wise. A solution of potassium phosphate (127 mg) in water (254 μL) was added drop-wise and the reaction mixture was warmed to 40 °C and stirred until TLC confirmed consumption of starting material 178. The reaction mixture was partitioned between dichloromethane (10 mL) and distilled water (10 mL). The aqueous phase was further extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over sodium
sulfate, filtered and concentrated in vacuo. Purification by column chromatography (light petroleum ether : ethyl acetate 1 : 5 to neat ethyl acetate) afforded 179 (15 mg, 25%; 67% brsm 178) as a single diastereoisomer and a light yellow viscous oil.

IR \( \nu_{\text{max}} \) (oil) 3417 (OH), 2975 (CH), 1713 (C=O), 1702 (C=O); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \)

5.85 (ddt, 1H, \( J = 16.5 \text{Hz}, 10.2 \text{Hz} \) and \( 6.2 \text{Hz} \)) NCH\(_2\)CH\(_3\)), 5.12 (d, 1H, \( J = 10.2 \text{Hz} \)) NCH\(_2\)CH\(_3\)), 5.00 (bs, 1H, OH), 3.92 (m, 6H, OCH\(_2\)CH\(_2\)O and NC\(_H_2\)), 2.74 (d, 1H, \( J = 16.2 \text{Hz} \)) 3-CH\(_A\)H\(_B\)), 2.36 (d, 1H, \( J = 16.2 \text{Hz} \)) 3-CH\(_A\)H\(_B\)), 2.26 (dd, 1H, \( J = 2.3 \text{Hz} \) and 14.1Hz, 1' C\(_H_2\)), 2.21 (d, 1H, \( J = 4.6 \text{Hz} \)) 3'-CH\(_A\)H\(_B\))

To a stirred solution of 2-furoyl chloride 218 (10.0 g, 76.61 mmol) in tert-butanol (80 ml) was added sodium azide (5.10 g, 84.3 mmol) portion-wise at room temperature. The reaction mixture was stirred at room temperature for 20 hours and then refluxed for a further 12 hours. The resultant mixture was concentrated in vacuo and purified by flash column chromatography (light petroleum ether : ethyl acetate, 4 : 1) to afford 216 (12.3 g, 88%) as a off-white solid.
MP 98-100 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta_H\) 7.06 (dd, 1H, \(J = 2.0\)Hz and \(1.0\)Hz, NCCCHCH\(H\)), 6.58 (bs, 1H, NCCCH\(CH\)), 6.34 (dd, 1H, \(J = 3.0\)Hz and \(2.2\)Hz, NCC\(H\)CH), 6.04 (bs, 1H, NH), 1.50 (s, 9H, C(CH\(_3\))\(_3\)), \(^1\)H NMR \(\text{in agreement with the literature; MS} \ m/z \ (\text{ES}+) \ 206 ([\text{M}+\text{Na}]^+)\).

\[(6\text{-Methyl-1,4-dioxaspiro[4.5]dec-6-en-1-yl})\text{methanol}; 221^{105}\]

To a stirred solution of Hagemann’s ester 215 (3.00 g, 1.65 mmol) in ethylene glycol (50 mL) was added trimethylorthoformate (5.43 mL, 4.94 mmol) followed by para-toluene sulfonic acid (0.03 g, 0.02 mmol) in one portion and stirred for 12 hours at room temperature and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated aqueous potassium carbonate (100 mL) and the organic layer extracted with ethyl acetate (20 mL). The aqueous layer was further extracted with ethyl acetate (3 x 10 mL), dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo} to afford the crude acetal (3.71 g).

To a stirred solution of lithium aluminium hydride (1.88 g, 4.94 mmol) in dry tetrahydrofuran (60 mL) was added crude acetal (3.71 g, 1.65 mmol) in dry tetrahydrofuran (40 mL) drop-wise via cannula at 0 °C. The reaction mixture was stirred for 10 minutes and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with methanol, followed by addition of sodium sulphate decahydrate until the mixture became sluggish. The mixture was diluted with diethyl ether until stirring freely, then dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo}. The crude residue was purified by flash column chromatography (neat diethyl ether) to afford 221 (2.15 g, 71%) as a light yellow oil.
IR $\nu_{\text{max}}$(oil) 3408 (OH), 2945 (CH); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 4.05 (s, 2H, CH$_2$OH), 3.15 (s, 4H, OCH$_2$CH$_2$O), 2.22 (s, 2H, 5-CH$_3$), 2.20 (m, 2H, 2-CH$_2$), 1.82 (m, 2H, 3-CH$_2$), 1.70 (s, 3H, CH$_3$), $^1$H NMR in agreement with the literature; MS m/z (ES+) 207 ([M+Na]$^+$).

3-Methyl-4-methylene cyclohex-2-enone; 224$^{105}$

To a stirred solution of alcohol 221 (100 mg, 0.54 mmol) in dry tetrahydrofuran (10 mL) was added triethylamine (0.08 mL, 0.59 mmol) followed by drop-wise addition of tosyl chloride (110 mg, 0.59 mmol) in dichloromethane (4 mL) at 0 °C and stirred at this temperature until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate (10 mL). The aqueous was further extracted with ethyl acetate (3 x 10 mL), the organic layers were combined, dried (MgSO$_4$), filtered and concentrated in vacuo to afford 224 (41 mg, 62%) as a brown oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 5.91 (s, 1H, CH), 5.35 (s, 2H, C=CH$_2$), 2.72 (t, 2H, $J$ = 7.0Hz, COCH$_2$), 2.48 (m, 2H, COCH$_2$CH$_2$), 2.05 (s, 3H, CH$_3$) $^1$H NMR in agreement with the literature; MS m/z (ES+) 371 ([M+Na]$^+$)
**tert-Butyl furan-2-yl((6-methyl-1,4-dioxaspiro[4.5]dec-6-en-1-yl)methyl)carbamate;**

To a stirred solution of alcohol 221 (1.00 g, 5.43 mmol) in dry tetrahydrofuran (100 mL) was added triethylamine (0.83 mL, 5.97 mmol) followed by drop-wise addition of tosyl chloride (1.14 g, 5.97 mmol) in tetrahydrofuran (10 mL) at 0 °C. The reaction mixture was stirred for 1 hour at this temperature while the amidofuran 216 was prepared. To a stirred solution of amidofuran 216 (0.99 g, 5.43 mmol) in dry tetrahydrofuran (100 mL) was added 1.0 M solution of lithium hexamethyldisilazane in tetrahydrofuran (5.43 mL, 5.43 mmol) drop-wise at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes before being added drop-wise via cannula to the tosyl reaction mixture. The reaction mixture was warmed to room temperature before tetrabutylammonium bromide (1.74 g, 5.43 mmol) was added in one portion and then refluxed for 12 hours and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (100 mL). The aqueous layer was further extracted with ethyl acetate (3 x 100 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography (light petroleum ether : diethyl ether, 3 : 1) afforded 222 (0.68 g, 36%) as a yellow oil.

**IR** ν<sub>max</sub>(oil) 2961 (CH), 1566 (C=O); <sup>1</sup>H NMR (500 MHz, CDCl₃) δ<sub>H</sub> 7.16 (dd, 1H, J = 2.1 Hz and 0.9 Hz, 1'-CH<sub>2</sub>), 6.29 (dd, 1H, J = 3.1 Hz and 2.2 Hz, 3'-CH), 5.93 (bs, 1H, 2'-CH<sub>2</sub>), 4.21 (s, 2H, NCH<sub>2</sub>), 3.95 (s, 4H, OCH<sub>2</sub>CH<sub>2</sub>O), 2.21 (dt, 2H, J = 6.6 Hz and 2.0 Hz, 3'-CH<sub>2</sub>), 2.15 (s, 2H, 5'-CH<sub>2</sub>), 1.68 (t, 1H, J = 6.4 Hz, 2'-CH<sub>2</sub>), 1.47 (s, 3H, CH<sub>3</sub>), 1.43 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>); <sup>13</sup>C NMR (125 MHz, CDCl₃) δ<sub>C</sub> 154.6 (C=O), 148.5 (1'-C), 138.8 (4'-C), 128.9 (1-C), 125.4 (6-
C), 111.0 (2'-C), 102.7 (3'-C), 99.1 (4-C), 80.6 (CO(CH₃)₃), 49.5 (NCH₂), 48.4 (2 x OCH₂CH₂O), 40.5 (5-C), 30.0 (3-C), 28.9 (3 x CO(CH₃)₃), 25.7 (2-C), 20.1 (CH₃) **MS m/z** (ES+) 371 ([M+Na]+); **HRMS** Found [M+NH₄]+ 371.2227 (C₁₉H₃₁N₂O₅) requires (M) 367.2228

(±)-**tert-Butyl furan-2-yl((6-methyl-4-oxocyclohex-5-enyl)methyl)carbamate; 217**

![Chemical Structure](image)

To a stirred solution of 222 (100 mg, 0.29 mmol) in tetrahydrofuran (2 mL) was added 1.0 M hydrochloric acid (2 mL) and stirred for 12 hours and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated aqueous potassium carbonate solution (5 mL) and extracted with ethyl acetate (10 mL). The aqueous layer was further extracted with ethyl acetate (3 x 20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (light petroleum ether : diethyl ether, 1 : 1) afforded 217 (25 mg, 28%) as a colourless oil.

**IR** \( \nu_{\text{max}} \) (oil) 2977 (CH), 1714 (C=O), 1667 (C=O); **¹H-NMR** (500 MHz, CDCl₃) \( \delta_H \) 7.19 (s, 1H, 1'-CH), 6.36 (s, 1H, 3'-CH), 6.02 (bs, 1H, 2'-CH), 5.88 (s, 1H, 5-CH), 3.78-3.74 (m, 2H, NC₂H₂), 2.58 (dt, 1H, \( J = 9.0\text{Hz and} 4.8\text{Hz} \), 1-CH), 2.55-2.44 (m, 1H, 1 of 3-CH₂), 2.28 (td, 1H, \( J = 17.5\text{Hz and} 4.7\text{Hz} \), 1 of 3-CH₂), 2.1-1.98 (m, 2H, 2-CH₂), 1.96 (s, 3H, CH₃), 1.46 (s, 9H, C(CH₃)₃); **¹³C NMR** (125 MHz, CDCl₃) \( \delta_C \) 198.8 (C=O), 161.9 (6-C), 153.7 (CO₂C), 148.1 (1'-C), 138.1 (4'-C), 128.0 (5-C), 111.1 (2'-C), 101.2 (3'-C), 81.6 (OC(CH₃)₃), 48.4 (NCH₂), 39.2 (3-C), 33.1 (1-C), 28.1 (3 x OC(CH₃)₃), 24.5 (CH₃), 22.8 (2-C); **MS m/z** (ES+) 328 ([M+Na]⁺); **HRMS** Found [M+Na]⁺ 328.1520 (C₁₇H₂₃NNaO₄) requires (M) 328.1520
To a stirred solution of Hagemann’s ester 215 (10.2 g, 55.9 mmol) in methanol (300 mL) was added trimethylorthoformate (11.5 mL, 167.9 mmol) followed by para-toluene sulfonic acid (0.10 g, 0.56 mmol) in one portion and stirred for 12 hours at room temperature and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated aqueous potassium carbonate solution (100 mL) and extracted with ethyl acetate (200 mL). The aqueous layer was further extracted with ethyl acetate 3 x (100 mL), dried (MgSO$_4$) and concentrated in vacuo affording the crude acetal (11.8 g).

To a stirred solution of lithium aluminium hydride (5.9 g, 155.3 mmol) in dry tetrahydrofuran (200 mL) was added the crude acetal (11.8 g, 51.8 mmol) in dry tetrahydrofuran (100 mL) drop-wise via cannula at 0 °C. The reaction mixture was stirred for 10 minutes and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with methanol, followed by addition of sodium sulphate decahydrate until the mixture became sluggish. The mixture was diluted with diethyl ether until stirring freely, then dried (MgSO$_4$), filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (neat diethyl ether) to afford 225 (7.11 g, 69%) as a light yellow oil.

**IR** $\nu_{\text{max}}$(oil) 3401 (OH), 2941 (CH); $^1$H **NMR** (400 MHz, CDCl$_3$) $\delta$H 4.12 (s, 2H, CH$_2$OH), 3.22 (s, 6H, (OC$_3$H$_7$)$_2$), 2.22 (s, 2H, 5-CH$_2$), 2.19 (m, 2H, 2-CH$_2$), 1.82 (m, 2H, 3-CH$_2$), 1.69 (s, 3H, CH$_3$); $^{13}$C **NMR** (125 MHz, CDCl$_3$) $\delta$C 129.1 (1-C), 127.4 (6-C), 99.9 (4-C), 62.5 (OCH$_2$), 50.7 (2 x OCH$_3$), 45.9 (5-C), 40.9 (3-C), 26.1 (2-C), 18.7 (CH$_3$); **MS** $m/z$ (ES+) 209 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 209.1149 (C$_{10}$H$_{18}$NaO$_3$) requires (M) 209.1148
tert-Butyl (4,4-dimethoxy-6-methylcyclohex-1-enyl)methyl(furan-2-yl)carbamate;

To a stirred solution of alcohol 225 (3 g, 16.1 mmol) in dry tetrahydrofuran (30 mL) was added a 1.6 M solution of n-butyl lithium in hexanes (10.1 mL, 16.1 mmol) drop-wise at -78 °C and stirred for 10 minutes before tosyl chloride (3.22 g, 16.9 mmol) in dry tetrahydrofuran (30 mL) was added drop-wise via cannula. The reaction mixture was warmed to 0 °C and stirred for 1 hour. Meanwhile, to a solution of amidofuran 216 (3.16 g, 17.26 mmol) in dry tetrahydrofuran (30 mL) was added a 0.5 M solution of potassium hexamethyldisilazane in toluene (34.5 mL, 17.3 mmol) drop-wise at 0 °C and stirred for 5 minutes. To the solution of tosylate at 0 °C was added the amidofuran reaction mixture drop-wise via cannula. The reaction mixture was warmed to room temperature and stirred until TLC confirmed complete consumption of starting material before saturated aqueous ammonium chloride (10 mL) was added and extracted with ethyl acetate (50 mL). The aqueous layer was further extracted with ethyl acetate (3 x 50 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography (light petroleum ether : diethyl ether, 3 : 1) afforded 226 (4.07 g, 72%) as a yellow oil.

IR νmax(oil) 2955 (CH), 1575 (C=O); ¹H NMR (300 MHz, CDCl₃) δH 7.15-7.13 (m, 1H, 1'-CH), 6.28-6.25 (m, 1H, 3'-CH₂), 5.89 (bs, 1H, 2'-CH), 4.18 (s, 2H, NCH₂), 3.18 (s, 6H, (OCH₃)₂), 2.12 (s, 2H, 5-C₄H₃), 2.04 (t, 2H, J = 6.6Hz, 2'-CH₂), 1.73 (t, 2H, J = 6.4Hz, 3-C₄H₃), 1.45 (s, 3H, C₃H₃), 1.41 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CD₂Cl₂) δC 154.7 (C=O), 148.5 (1'-C), 138.8 (4'-C), 128.5 (1-C), 125.8 (6-C), 111.1 (2'-C), 102.7 (3'-C), 99.7 (4-C), 81.1 (CO(CH₃)₃), 49.5 (NCH₂), 48.0 (2 x OCH₃), 40.9 (5-C), 30.1 (3-C), 29.1 (3 x CO(CH₃)₃).
25.8 (2-\(\text{C}\)), 19.8 (\(\text{CH}_3\)) \textbf{MS} \(m/z\) (ES+) 374 ([M+Na]\(^+\)); \textbf{HRMS} Found [M+H]\(^+\) 352.2120 (\(\text{C}_{19}\text{H}_{30}\text{NO}_5\)) requires (M) 352.2118

(\(\pm\)-\(\text{tert}\)-Butyl furan-2-yl\((6\text{-methyl-4-oxocyclohex-5-enyl})\text{methyl}\))carbamate; 217

\begin{align*}
\text{To a stirred solution of 226 (0.50 g, 1.42 mmol) in tetrahydrofuran (10 mL) was added} \\
0.1 \text{ M hydrochloric acid (10 mL) at room temperature and stirred for 10 minutes and} \\
\text{until TLC confirmed complete consumption of starting material. The reaction mixture} \\
\text{was quenched with a saturated aqueous potassium carbonate solution (10 mL) and} \\
\text{extracted with ethyl acetate (50 mL). The aqueous layer was further extracted with} \\
\text{ethyl acetate (3 x 50 mL), dried (MgSO}_4\), filtered and concentrated in vacuo to afford} \\
\text{the crude ketone 223 (0.43 g) as a yellow oil.}
\end{align*}

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\begin{align*}
\text{Butyl furan-2-yl\((3\text{-methyl-4-oxocyclohex-1-enyl})\text{methyl}\))carbamate; 223 \\
\text{IR} \nu_{\text{max}}(\text{oil}) 2980 (\text{CH}), 1745 (\text{C=O}, 1665 (\text{C=O}); ^{1}H \text{NMR} (400 \text{ MHz, CDCl}_3) \delta_H 7.14 (s, 1H, 1'-\text{CH}) \\
6.28 (dd, 1H, J \approx 3.2\text{ Hz and } 2.1\text{Hz}, 3'-\text{CH}_3), 5.91 (bs, 1H, 2'-\text{CH}), 4.29 (s, 2H, \\
\text{NCH})_2, 2.72 (s, 2H, 5-\text{CH}_3), 2.38 (m, 4H, 2-\text{CH}_2 \text{ and } 3-\text{CH}_2), 1.55 (s, 3H, \text{CH}_3), 1.41 (s, 9H, \\
\text{C(CH}_3)_3); ^{13}C \text{NMR} (100 \text{ MHz, C}_6\text{D}_6) \delta_C 210.6 (\text{C}=O), 154.4 (\text{CO}_2\text{C}), 147.9 (1'-\text{C}), 138.5 \\
(4'-\text{C}), 129.1 (1'-\text{C}), 126.9 (6'-\text{C}), 110.8 (2'-\text{C}), 102.2 (3'-\text{C}), 81.3 (\text{OC(CH}_3)_3), 48.8 (\text{NCH})_2, \\
45.6 (5'-\text{C}), 38.7 (3'-\text{C}), 28.1 (\text{OC(CH}_3)_3), 26.9 (2'-\text{C}), 18.2 (\text{CH}_3); \textbf{MS} \(m/z\) (ES+): 328 \\
([\text{M+Na}]^+); \textbf{HRMS} \text{Found [M+Na]}^+ 328.1520 (\text{C}_{17}\text{H}_{23}\text{NNaO}_4) \text{requires (M) 328.1520}
\end{align*}

To a stirred solution of ketone 223 (0.43 g, 1.42 mmol) in methanol (10 mL) was added \\
potassium carbonate (0.19 g, 0.014 mmol) and stirred for 10 minutes and until TLC \\
confirmed complete consumption of starting material. The reaction mixture was
quenched with glacial acetic acid (0.84 mL, 0.014 mmol) and extracted with ethyl acetate (10 mL). The aqueous layer was further extracted with ethyl acetate (3 x 10 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash column chromatography (light petroleum ether : diethyl ether, 1 : 1) afforded 217 (0.38 g, 88%) as a colourless oil.

The $^1$H NMR was identical to 217 which was previously prepared from 222 using 1.0 M HCl in THF.

$^{(+)}$-tert-Butyl 1’-hydroxy-6-methyl-4-oxo-5,6,3,2,2’,3’-hexahydrobenzo[cd]indole-1(2H)-carboxylate; 227

![Chemical structure of 217 and 227](image)

To a stirred solution of enone 217 (100 mg, 0.32 mmol) in toluene (2 mL) was added butylated hydroxyl toluene (6 mg, 0.03 mmol) in one portion at room temperature and then refluxed for 2 days and until TLC confirmed complete consumption of starting material. The reaction mixture was concentrated in vacuo and purification by flash column chromatography (light petroleum ether : diethyl ether, 1 : 1) afforded 227 (80 mg, 80%) as a single diastereoisomer and a colourless oil at room temperature. Due to the rotameric nature of 227, some carbons in the $^{13}$C NMR at room temperature were indistinguishable. Therefore to allow full characterization, both the $^1$H NMR and $^{13}$C NMR were performed at 363K in deuterated dimethylsulfoxide.

**IR** $\nu_{\text{max}}$(oil) 3380 (OH), 2914 (CH), 2356 (H-C=C), 1713 (C=O), 1695 (C=O); **Enol form:** $^1$H NMR (400 MHz, d-DMSO, 363K) $\delta$H 14.08 (s, 1H, OH), 5.57 (d, 1H, $J = 5.2$Hz, 3’-CH), 4.00 (dd, 1H, $J = 11.5$Hz and 7.9Hz, NCH$_2$H$_8$), 3.42 (dd, 1H, $J = 11.5$Hz and 2.0Hz, NCH$_2$H$_8$),
3.21 (dd, 1H, J = 21.0Hz and 1.9Hz, 2’-CH\(_3\)H\(_8\)), 2.82 (dd, 1H, J = 21.0Hz and 6.4Hz, 2’-CH\(_3\)H\(_8\)), 2.36 (ddd, 1H, J = 17.3Hz, 13.2Hz and 4.1Hz, 1 of 3-CH\(_2\), 2-CH\(_2\)), 1.82 (m, 1H, 1-CH), 1.46 (s, 9H, C(CH\(_3\))\(_3\)), 1.19 (s, 3H, CH\(_3\)), 1.12 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, d-DMSO, 363K) δ\(_C\) 193.8 (C=O), 183.6 (1’-C), 151.5 (N\(_C\)=O), 146.7 (4’-C), 111.7 (5’-C), 99.0 (3’-C), 80.1 (C(CH\(_3\))\(_3\)), 53.3 (N\(_C\)H\(_2\)), 52.2 (1-\(\_\)C), 44.4, 40.9, 38.4, 38.3, 38.1, 36.1, 34.4, 31.6, 30.4, 27.9, 27.2, 25.5; Keto form observed: \(^1\)H NMR (400 MHz, d-DMSO, 363K) δ\(_H\) 5.75 (t, 1H, J = 7.3Hz and 3.8Hz, 3’-CH\(_2\)), 3.80 (dd, 1H, J = 11.1Hz and 5.5Hz, NCH\(_3\)H\(_8\)), 3.40 (s, 1H, 5-\(\_\)CH), 3.37 (dd, 1H, 11.2Hz and 5.9Hz, NCH\(_3\)H\(_8\)), 2.91 (dd, 1H, J = 22.4Hz and 4.4Hz, 2’-CH\(_3\)H\(_8\)), 2.76 (dd, 1H, 22.5Hz and 3.1Hz, 2’-CH\(_3\)H\(_8\)), 2.55 (dd, 1H, J = 13.5Hz and 4.8Hz, 1 of 3-CH\(_2\)), 2.47 (m, 1H, 1 of 3-CH\(_2\)); \(^{13}\)C NMR (100 MHz, d-DMSO, 363K) δ\(_C\) 205.9 (C=O), 205.1 (C=O), 152.0 (N\(_C\)=O), 140.5 (4’-C), 94.7 (3’-C), 66.6 (5’-C), 53.1 (NCH\(_2\)), 50.1 (1-\(\_\)C); MS m/z (ES+) 328 ([M+Na]+); HRMS Found [M+Na]+ 328.1522 (C\(_{17}\)H\(_{23}\)NNaO\(_4\)) requires (M) 328.1520.

(±)-\(\_\)tert-Butyl furan-2-yl((7-methyl-4-oxocyclohept-6-enyl)methyl)carbamate; 231 and (±)-\(\_\)tert-Butyl furan-2-yl((7-methyl-5-oxocyclohept-6-enyl)methyl)carbamate; 233

To a solution of enone 217 (100 mg, 0.33 mmol) in dichloromethane (12 mL) at -78 °C was added a 2.0 M solution of trimethylaluminium in toluene (0.33 mL, 0.66 mmol) drop-wise, followed by a 2.0 M solution of trimethylsilyldiazomethane in hexanes (0.33 mL, 0.66 mmol) drop-wise. The reaction mixture was stirred at -78 °C for 10 minutes, warmed to room temperature and stirred for 1 hour and until TLC confirmed complete consumption of starting material. A saturated solution of sodium hydrogen carbonate (5 mL) was added and extracted with dichloromethane (20 mL). The aqueous layer
was further extracted with dichloromethane (3 x 20 mL) and the combined organic layers were dried (Na₂SO₄), filtered and concentrated in vacuo. To a stirred solution of the crude residue in tetrahydrofuran (2 mL) at room temperature was added 1.0 M hydrochloric acid (2 mL) and stirred for 30 minutes and until TLC confirmed consumption of starting material. A saturated solution of sodium hydrogen carbonate (5 mL) was added to quench and extracted with diethyl ether (30 mL). The aqueous layer was further extracted with diethyl ether (3 x 30 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. Purification by column chromatography (light petroleum ether : diethyl ether, 3:1) afforded separation of the two regioisomers 231 (34 mg, 33%) and 233 (11 mg, 10%) as colourless oils.

(±)-tert-Butyl furan-2-yl(7-methyl-4-oxocyclohept-6-enyl)methylcarbamate; 231

IR νₘₐₓ(oil) 2967 (CH), 1751 (C=O), 1649 (C=O); ¹H NMR (500 MHz, CDCl₃) δH 6.96 (s, 1H, 1'-CH), 6.13 (s, 1H, 3'-CH), 5.79 (bs, 1H, 2'-CH), 5.13 (t, 1H, J = 6.1Hz, 6-CH), 3.64-3.41 (m, 2H, NCH₂), 2.89 (ddd, 2H, J = 20.0Hz, 14.3Hz and 5.0Hz, 5-CH₂), 2.38-2.28 (m, 2H, 3-CH₂), 2.21 (ddd, 1H, J = 17.0Hz, 8.7Hz and 3.4Hz, 1-CH), 1.82 (ddd, 1H, J = 13.0Hz, 8.3Hz and 4.1Hz, 1 of 2-CH₂), 1.77-1.68 (m, 1H, 1 of 2-CH₂), 1.50 (s, 3H, CH₃), 1.23 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δC 209.8 (C=O), 148.3 (CO₂C), 138.7 (1'-C), 138.1 (4'-C), 117.3 (7-C), 117.3 (6-C), 111.0 (2'-C), 101.5 (3'-C), 81.4 (OC(CH₃)₃), 50.1 (NCH₂), 43.9 (5-C), 41.9 (3-C), 40.0 (1-C), 28.1 (3 x OC(CH₃)₃), 24.6 (2-C), 24.1 (CH₃); MS m/z (ES+): 342 ([M+Na]+); HRMS Found [M+NH₄]+ 337.2115 (C₁₈H₂₉O₄N₂) requires (M) 337.2122.

(±)-tert-Butyl furan-2-yl(7-methyl-5-oxocyclohept-6-enyl)methylcarbamate; 233

IR νₘₐₓ(oil) 2967 (CH), 1705 (C=O), 1599 (C=O); ¹H NMR (400 MHz, CDCl₃) δH 7.13 (dd, 1H, J = 2.0Hz and 0.8Hz, 1'-CH), 6.34-6.25 (m, 1H, 3'-CH), 5.96 (bs, 1H, 2'-CH), 5.82 (s, 1H, 6-CH), 3.68 (ddd, 2H, J = 18.3Hz, 14.1Hz and 7.2Hz, NCH₂), 2.61-2.50 (m, 2H, 1-CH and 1 of 4-CH₂), 2.45-2.08 (m, 3H, 1 of 4-CH₂ and 3-CH₂), 1.95 (td, 2H, J = 6.7Hz and 4.36Hz, 2-CH₂), 1.53 (s, 3H, CH₃), 1.40 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δC 196.5 (C=O), 160.6 (7-C), 154.9 (CO₂C), 148.0 (1'-C), 137.9 (4'-C), 128.7 (6-C), 111.0 (2'-C), 101.3 (3'-C), 80.8 (OC(CH₃)₃), 48.1 (NCH₂), 40.0 (4-C), 35.7 (1-C), 28.3 (3 x OC(CH₃)₃),
25.2 (CH₃), 23.4 (3-Ç) 22.7 (2-Ç); MS m/z (ES+): 342 ([M+Na]⁺); HRMS Found [M+H]⁺ 320.1859 (C₁₈H₂₆O₄N) requires (M) 320.1856.

(±)-tert-Butyl 7-methyl-1',4-dioxo-1,2,3,5,6,2',3',4'-octahydro-1H-cyclohepta[cd]indole-4'(7H)-carboxylate; 232

To a stirred solution of 231 (100 mg, 0.31 mmol) in toluene (5 mL) was added butylated hydroxyl toluene (14 mg, 0.06 mmol) in one portion at room temperature and then refluxed for 5 days and until TLC confirmed complete consumption of starting material. The reaction mixture was concentrated in vacuo and purification by flash column chromatography (light petroleum ether : diethyl ether, 1 : 1) afforded 232 (77 mg, 77%) as a light yellow foam as a 2:1 mixture of diastereoisomers. Not too dissimilar to 227, compound 232 is rotameric and therefore the ¹H NMR and ¹³C NMR were performed at 343K in deuterated benzene.

IR νmax(oil) 2955 (CH), 1767 (C=O), 1711 (C=O), 1647 (C=O); Major 232a: ¹H NMR (400 MHz, C₆D₆, 343K) δH 5.97 (bs, 1H, 3'-CH₃), 3.28 (dd, 1H, J = 10.0Hz and 7.7Hz, NCH₂H₈), 2.81 (t, 1H, J = 10.7Hz, NCH₂H₈), 2.71 (dd, 1H, J = 17.3Hz and 2.5Hz, 2'-CH₃H₈), 2.65 (ddd, 1H, J = 13.7Hz, 3.0Hz and 0.8Hz, 6-CH₂), 2.59 (dd, 1H, J = 17.3Hz and 7.0Hz, 2'-CH₃H₈), 2.20 (td, 2H, J = 16.3Hz and 13.1Hz, 5-CH₃), 2.06-1.96 (m, 1H, 1 of 3-CH₂), 1.84 (td, 1H, J = 11.6Hz, 8.0Hz, 1 of 3-CH₂), 1.62-1.52 (m, 1H, 1-CH), 1.41 (s, 9H, C(CH₃)₃), 0.94-0.86 (m, 2H, 2-CH₂), 0.67 (s, 3H, CH₃); ¹³C NMR (100 MHz, C₆D₆, 343K) δC 208.7 (C=O), 204.8 (C=O), 152.6 (NC=O), 144.8 (4'-Ç), 97.4 (3'-Ç), 80.3 (OC(CH₃)₃), 52.5 (6-Ç), 51.7 (NCH₂), 48.7 (7-Ç), 41.8 (2'-Ç), 41.1 (3-Ç), 40.6 (5-Ç), 38.6 (1-Ç), 28.3 (3 x OC(CH₃)₃), 21.8 (CH₃), 21.6 (CH₃), 20.0 (2-Ç); Minor 232b observed: ¹H NMR (400
MHZ, C₆D₆, 343K) δ_H 6.06 (bs, 1H, 3'-CH), 3.44 (dd, 1H, J = 5.8Hz and 11.4Hz, NCH₂H₈), 3.09 (d, 1H, J = 11.4Hz, NCH₃H₈), 2.78-2.75 (m, 1H, 2'-CH₃H₈), 2.56-2.53 (m, 1H, 2'-CH₃H₈), 0.73 (s, 3H, CH₃); ¹³C NMR (100 MHz, C₆D₆, 343K) δ_C 207.0 (C=O), 206.5 (C=O), 152.1 (N=O), 145.1 (4'-C), 98.2 (3'-C), 80.5 (OCH₃H₃), 54.6 (6-C), 51.4 (NCH₂), 47.5 (7-C), 41.7 (2'-C), 41.2 (3-C), 40.3 (5-C), 35.2 (1-C), 27.8 (3 x OCH₃H₃), 20.2 (2-C); MS m/z (ES+): 342 ([M+Na]+); HRMS Found [M+H]+ 320.1852 (C₁₈H₂₆O₄N) requires (M) 320.1856.

(t)-tert-Butyl 1'-hydroxy-7-methyl-5-oxo-1,2,3,4,6,2'-hexahydro-1H-cyclohepta(cd)indole-4'(7H)-carboxylate; 236

To a stirred solution of 233 (100 mg, 0.32 mmol) in toluene (5 mL) was added butylated hydroxyl toluene (14 mg, 0.71 mmol) in one portion at room temperature and then refluxed for 3 days and until TLC confirmed complete consumption of starting material. The reaction mixture was concentrated in vacuo and purification by flash column chromatography (light petroleum ether : diethyl ether, 3 : 1) afforded 236 (60 mg, 60%) as a single diastereoisomer and a light yellow foam.

Compound 236 was assigned based on IR, ¹H NMR and mass spectrometry data. A ¹³C NMR was performed, however significant decomposition was observed during the experiment at 343K. IR ν_max(oil) 3352 (OH), 2842 (CH), 1724 (C=O), 1677 (C=O); ¹H NMR (400 MHz, C₆D₆) δ_H 14.12 (bs, 1H, OH), 5.66 (bs, 1H, 3'-CH), 3.74 (dd, 1H, J = 11.3Hz and 7.6Hz, NCH₃H₈), 3.25 (dd, 1H, J = 14.0Hz and 7.6Hz, NCH₃H₈), 2.97 (m, 1H, 1 of 2'-CH₃H₈), 2.73 (m, 1H, 2'-CH₃H₈), 2.45 (m, 1H, 1 of 4-CH₃), 2.08 (m, 1H, 1 of 4-CH₃), 1.98 (m, 1H, 1 of 2-CH₃), 1.84 (m, 1H, 1 of 2-CH₃), 1.59 (m, 2H, 3-CH₂), 1.48 (m, 1H, 1-
To a solution of 3-butyne-1-ol 237 (3.54 g, 50.0 mmol) in dichloromethane (80 mL) was added imidazole (5.11 g, 75.0 mmol), 4-dimethylaminopyridine (0.06 g, 0.50 mmol) and tert-butylidiphenylchlorosilane (16.5 g, 60.0 mmol) at room temperature. The reaction mixture was stirred for 1 hour and until TLC confirmed complete consumption of starting material before water (80 mL) was added and extracted with dichloromethane (2 x 80 mL), washed with brine (80 mL), dried (MgSO$_4$), filtered and concentrated in vacuo affording the crude alkyne (15.4 g).

To a stirred solution of the crude alkyne (15.4 g, 50.0 mmol) in tetrahydrofuran (120 mL) at -78 °C was added 1.6 M solution of n-butyl lithium in hexanes (40.6 mL, 65.0 mmol) and kept at -78 °C for 0.5 hours before para-formaldehyde (3.60 g, 120.0 mmol) was added in one portion. The reaction mixture was warmed to room temperature and stirred at this temperature for 2 hours and until TLC confirmed complete consumption of starting material. Water (10 mL) was added and extracted with diethyl ether (2 x 40 mL), washed with brine (10 mL), dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash column chromatography (light petroleum ether : ethyl acetate, 5 : 1) afforded 238 (13.5 g, 80%) as a colourless oil.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.72 (m, 4H, Ar-H), 7.42 (m, 6H, Ar-H), 4.33 (t, 2H, $J = 2.1$Hz, $CH_2$OH), 3.61 (q, 2H, $J = 6.2$Hz, $CH_2$OSi), 2.40 (tt, 2H, $J = 6.1$Hz and 2.1Hz, $CH_2$OSi).
To a stirred solution of alcohol 238 (13.5 g, 39.9 mmol) and tetrabromomethane (15.9 g, 47.9 mmol) in dichloromethane (1 L) at -78 °C was added a solution of triphenylphosphine (15.7 g, 59.9 mmol) in dichloromethane (1 L) drop-wise. The reaction mixture was warmed to room temperature and stirred at this temperature for 0.5 hours and until TLC confirmed complete consumption of starting material before filtering through a pad of silica and concentrating in vacuo. Purification by flash column chromatography (light petroleum ether : ethyl acetate, 10 : 1) afforded 239 (15 g, 94%) as a light-orange oil.

\( ^1H \text{ NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) 7.71 (m, 4H, Ar-H), 7.41 (m, 6H, Ar-H), 4.31 (t, 2H, \( J = 2.1 \text{Hz}, \ CH_2Br \)), 3.33 (t, 2H, \( J = 7.4 \text{Hz}, \ CH_2OSi \)), 2.71 (tt, 2H, \( J = 7.4 \text{Hz and 2.1Hz}, \ CH_2CH_2OSi \)), 1.05 (s, 9H, C(CH\(_3\)\(_3\)\)) \( ^1H \text{ NMR in agreement with the literature; MS m/z (ES+): 401 ([M+H]^+) } \)
(±)-Ethyl 5-(5''-(tert-butyldiphenylsilyloxy)pent-2-ynyl)-6-methyl-4-oxocyclohex-1-enecarboxylate; 240

To a stirred solution of potassium tert-butoxide (4.62 g, 41.3 mmol) in tert-butanol (200 mL) was added a solution of Hagemann’s ester 215 (7.50 g, 41.3 mmol) in tert-butanol (100 mL) at room temperature. The reaction mixture was stirred for 1 hour until a solution of 239 (15.0 g, 37.5 mmol) in tert-butanol (200 mL) was added and refluxed for 1 hour and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (100 mL) and the resultant mixture was extracted with diethyl ether (2 x 100 mL), washed with brine (100 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography (light petroleum ether : ethyl acetate, 5 : 1) afforded 240 (17.2 g, 83%) as an orange oil.

IR \(\nu_{\text{max}}\) (oil) 2981 (CH), 1705 (C=O), 1666 (C=O); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta_H\) 7.59 (td, 4H, \(J = 7.8\)Hz and \(1.4\)Hz, Ar-\(H\)), 7.38-7.27 (m, 6H, Ar-\(H\)), 4.10 (q, 2H, \(J = 7.1\)Hz, CO₂CH₂CH₃), 3.64 (t, 2H, \(J = 7.1\)Hz, 5''-CH₂), 3.28 (td, 1H, \(J = 16.8\)Hz and 2.2Hz, 1 of 1''-CH₃H₈), 2.50 (ddd, 2H, \(J = 13.6\)Hz, 11.2Hz and 5.2Hz, 3-CH₂), 2.36-2.27 (m, 2H, 4''-CH₂), 2.22-2.05 (m, 2H, 2-CH₂), 1.98 (s, 3H, CH₃), 1.18 (t, 3H, \(J = 7.1\)Hz, CO₂CH₂CH₃), 0.96 (s, 9H, C(CH₃)₃); \(^1^3\)C NMR (125 MHz, CDCl₃) \(\delta_C\) 195.9 (C=O), 171.9 (CO₂C), 152.4 (6-\(C\)), 135.5 (6 x Ar-\(C\)), 133.6 (5-\(C\)), 129.6 (2 x Ar-\(C\)), 127.6 (4 x Ar-\(C\)), 77.9 (3''-\(C\)), 76.4 (2''-\(C\)), 62.7 (OCH₂CH₃), 61.3 (5''-\(C\)), 47.7 (1-\(C\)), 34.3 (3-\(C\)), 26.7 (3 x C(CH₃)₃), 25.3, 22.9, 20.7, 19.2, 14.6, 14.1; MS \(m/z\) (ES+): 525 ([M+Na]⁺); HRMS Found [M+Na]⁺ 525.2437 (C₃₁H₃₈NaO₄Si) requires (M) 525.2432
(5′′-(tert-Butyldiphenylsilyloxy)pent-2-ynyl)-4,4-dimethoxy-6-methylcyclohex-1-enyl)methanol; 241

To a stirred solution of 240 (6.00 g, 11.9 mmol) in tetrahydrofuran (150 mL) and methanol (50 mL) was added trimethylorthoformate (3.93 mL, 35.9 mmol) followed by para-toluene sulfonic acid (0.23 g, 1.19 mmol) in one portion. The reaction mixture was stirred for 12 hours at room temperature and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated aqueous potassium carbonate solution (100 mL) and the organic layer was extracted with ethyl acetate (200 mL). The aqueous layer was further extracted with ethyl acetate (3 x 100 mL), dried (MgSO₄) and concentrated in vacuo to afford the crude acetal (6.5 g).

To a stirred solution of lithium aluminium hydride (1.42 g, 35.9 mmol) in dry tetrahydrofuran (50 mL) was added crude acetal (6.50 g, 11.9 mmol) in dry tetrahydrofuran (50 mL) drop-wise via cannula at 0 °C. The reaction mixture was stirred for 10 minutes and until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with methanol, followed by addition of sodium sulphate decahydrate until the mixture became sluggish. The mixture was diluted with diethyl ether until stirring freely, then dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography (diethyl ether : light petroleum ether, 4 : 1) afforded 241 (2.4 g, 40%) as a colourless oil.

IR νmax(oil) 3425 (OH), 2931 (CH); ¹H NMR (300 MHz, CD₂Cl₂) δH 7.61-7.55 (m, 4H, Ar-H), 7.38-7.24 (m, 6H, Ar-H), 3.92 (s, 2H, CH₂OH), 3.62 (t, 2H, J = 7.1Hz, 5''-CH₂), 3.06 (s, 3H, OCH₃), 3.04 (s, 3H, OCH₃), 2.46-2.35 (m, 1H, 5-CH), 2.30 (tt, 1H, J = 7.3Hz and 2.3Hz, 1'')...
C₃H₃H₂, 2.20-2.13 (m, 2H, 4''-CH₂), 2.09-1.95 (m, 1H, 1''-CH₆H₆), 1.82-1.72 (m, 3H, 2-CH₂ and 1 of 3-CH₂), 1.69 (s, 3H, CH₃), 1.65-1.54 (m, 1H, 1 of 3-CH₂), 0.95 (s, 9H, C(CH₃)₃); ¹³C NMR (75 MHz, CD₂Cl₂) δC 135.9 (6 x Ar-Ç), 134.1 (1-Ç), 130.9 (6-Ç), 130.1 (2 x Ar-Ç), 128.0 (4 x Ar-Ç), 101.7 (4-Ç), 80.6 (3''-Ç), 78.8 (2''-Ç), 63.4 (OCH₂), 62.7 (5''-Ç), 48.1 (OCH₃), 48.0 (OCH₃), 46.3 (5-Ç), 27.0 (2-Ç), 26.3 (3 x C(CH₃)₃), 25.0 (4''-Ç), 23.3 (C(CH₃)₃), 21.0, 19.4, 18.7; MS m/z (ES+): 529 ([M+Na⁺]); HRMS Found [M+Na⁺] 529.2743 (C₃₁H₄₂NaO₄Si) requires (M) 529.2745.

tert-Butyl (5''-(5''-tert-butyldiphenylsilyloxy)pent-2-ynyl)-4,4-dimethoxy-6-methylcyclohex-1-enyl)methyl(furan-2-yl)carbamate; 243

To a stirred solution of alcohol 241 (2.40 g, 4.74 mmol) in dry tetrahydrofuran (12.5 mL) was added triphenylphosphine (3.73 g, 14.2 mmol), amidofuran 216 (2.61 g, 14.2 mmol) and diisopropyl azodicarboxylate (2.88 g, 14.2 mmol) successively at room temperature. The reaction mixture was stirred at this temperature until TLC confirmed complete consumption of starting material and then filtered through a pad of silica and concentrated in vacuo. Purification by flash column chromatography (light petroleum ether : diethyl ether, 4 : 1) afforded 243 (1.2 g, 38%) as a yellow oil.

IR νmax(oil) 2957 (CH), 1582 (C=O); ¹H NMR (400 MHz, CD₂Cl₂) δH 7.60-7.56 (m, 4H, Ar-H), 7.36-7.27 (m, 6H, Ar-H), 7.06 (dd, 1H, J = 2.0Hz and 0.9Hz, 1'-CH), 6.19 (dd, 1H, J = 3.2Hz and 2.1Hz, 3''-CH), 5.86 (bs, 1H, 2'-CH), 4.06 (s, 2H, NCH₂), 3.62 (t, 2H, J = 7.0Hz, 5''-CH₂), 3.05 (s, 3H, OCH₃), 3.02 (s, 3H, OCH₃), 2.38-2.26 (m, 3H, 5-CH and 4''-CH₂), 2.14-2.08 (m, 1H, 1 of 2-CH₂), 1.91 (d, 2H, J = 7.8Hz, 1''-CH₂), 1.87-1.79 (m, 1H, 1 of 2-CH₂), 1.78-1.70 (m, 2H, 3-CH₂), 1.50 (s, 3H, CH₃), 1.32 (s, 9H, OC(CH₃)₃), 0.95 (s, 9H,
SiC(CH₃)₃; ¹³C NMR (75 MHz, CD₂Cl₂) δC 154.6 (CO₂C), 148.4 (1’-C), 138.8 (4’-C), 135.9 (4 x Ar-C), 134.1 (5-C), 130.0 (2 x Ar-C), 128.0 (6 x Ar-C), 125.8 (1-C), 111.1 (2’-C), 102.8 (3’-C), 101.5 (4-C), 81.1 (3’’-C), 81.0 (C(CH₃)₃), 78.4 (2”-C), 63.3 (5”-C), 49.5 (NCH₂), 48.1 (OCH₃), 48.0 (OCH₃), 46.8 (5-C), 28.3 (3 x OC(CH₃)₃), 26.9 (3 x SiC(CH₃)₃), 26.1, 24.8, 23.3, 21.4, 19.4, 18.8; MS m/z (ES+): 694 ([M+Na⁺]); HRMS Found [M+NH₄⁺] 689.3981 (C₄₀H₅₇N₂O₆Si) requires (M) 689.3981.

tert-Butyl (5-(5’-(tert-butyldiphenylsilyloxy)pent-2-ynyl)-6-methyl-4-oxocyclohex-1-enyl)methyl(furan-2-yl)carbamate; 244

To a stirred solution of 243 (1.20 g, 1.79 mmol) in tetrahydrofuran (5 mL) was added 1.0 M hydrochloric acid (5 mL) at room temperature. The reaction mixture was stirred at this temperature until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated aqueous potassium carbonate solution (5 mL) and extracted with ethyl acetate (10 mL). The aqueous layer was further extracted with ethyl acetate (3 x 10 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by flash column chromatography (light petroleum ether : diethyl ether, 3 : 1) afforded 244 (1.1 g, 99%) as a colourless oil.

IR νmax(oil) 2995 (CH), 1750 (C=O), 1660 (C=O); ¹H NMR (400 MHz, CD₂Cl₂) δH 7.60-7.55 (m, 4H, Ar-H), 7.38-7.28 (m, 6H, Ar-H), 7.08 (dd, 1H, J = 2.0Hz and 0.9Hz, 1’-CH₃), 6.21 (dd, 1H, J = 3.2Hz and 2.1Hz, 3’-CH₃), 5.88 (d, 1H, J = 2.7Hz, 2’-CH₃), 4.19 (q, 2H, J = 14.5Hz, NCH₂), 3.59 (t, 2H, J = 7.1Hz, 5”-CH₂), 2.56-2.46 (m, 1H, 5-CH), 2.44-2.15 (m, 8H, 4”-CH₂, 1’’-CH₂, 2-CH₂ and 3-CH₂), 1.48 (s, 3H, CH₃), 1.34 (s, 9H, OCH(CH₃)₃), 0.95 (s, 9H, SiC(CH₃)₃); ¹³C NMR (125 MHz, CD₂Cl₂) δC 209.9 (C=O), 153.3 (NC=O), 147.2 (1’-C),...
137.7 (4'-C), 134.7 (4 x Ar-C), 132.8 (6-C), 128.8 (2 x Ar-C), 128.4 (1-C), 126.9 (6 x Ar-C), 110.0 (2'-C), 101.5 (3'-C), 80.2 (2''-C), 78.1 (O(CH3)3), 77.0 (3''-C), 62.0 (5''-C), 48.3 (NCH3), 37.0 (5-C), 28.9 (3 x OCH3), 27.1 (3 x Si(C3H3))3, 27.0, 25.8, 22.0, 21.9, 19.2, 18.2; **MS m/z** (ES+): 648 ([M+Na]+); **HRMS** Found [M+Na]+ 648.3118 (C38H47NNaO5Si) requires (M) 648.3116 (±)tert-Butyl (5-(5''-(tert-butyldiphenylsilyloxy)pent-2-ynyl)-6-methyl-4-oxocyclohex-5-enyl)methyl(furan-2-yl)carbamate; 188

To a stirred solution of 244 (1.10 g, 1.78 mmol) in tetrahydrofuran (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.11 g, 0.72 mmol) and stirred for 12 hours and until TLC confirmed complete consumption of starting material. The reaction mixture was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (light petroleum ether : diethyl ether, 3:1) to afford 188 (0.88 g, 80%) as a light yellow oil.

**IR** νmax(oil) 2981 (CH), 1705 (C=O), 1666 (C=O); **1H NMR** (400 MHz, CD2Cl2) δH 7.60-7.54 (m, 4H, Ar-H), 7.35-7.24 (m, 6H, Ar-H), 7.10 (dd, 1H, J = 1.9Hz and 0.7Hz, 1'-CH), 6.27 (dd, 1H, J = 3.0Hz and 2.1Hz, 3'-CH), 5.94 (bs, 1H, 2'-CH), 3.68 (dd, 1H, J = 14.0Hz and 10.6Hz, 1 of NCH3), 3.61 (t, 2H, J = 6.9Hz, 5''-CH2), 3.58-3.50 (m, 1H, 1 of NCH3), 3.02 (dd, 2H, J = 51.6Hz and 16.7Hz, 1''-CH2), 2.51-2.36 (m, 2H, 3-CH2), 2.29 (tt, 2H, J = 6.8Hz and 2.1Hz, 4''-CH2), 2.18 (td, 1H, J = 17.5Hz and 4.0Hz, 1-CH), 1.89 (s, 3H, CH3), 1.89-1.75 (m, 2H, 2-CH2), 1.35 (s, 9H, O(CH3)3), 0.94 (s, 9H, Si(CH3)3); **13C NMR** (100 MHz, CD2Cl2) δc 196.4 (C=O), 157.4 (N=O), 148.8 (1'-C), 138.5 (4'-C) 135.9 (2 x Ar-C), 134.1 (6-C), 133.5 (5-C), 130.0 (6 x Ar-C), 128.0 (4 x Ar-C), 111.4 (2'-C), 101.4 (3'-C), 81.9
(OC(CH₃)₃), 78.7 (3''-C), 76.4 (2''-C), 63.2 (5''-C), 48.4 (NCH₂), 41.3 (3-C), 33.2 (1-C), 28.3 (3 x OC(CH₃)₃), 26.9 (3 x SiC(CH₃)₃), 23.8, 23.2, 20.3, 19.4, 14.8; **MS m/z** (ES+): 648 ([M+Na⁺]; **HRMS** Found [M+Na⁺] 648.3117 (C₃₈H₄₇NNaO₅Si) requires (M) 648.3116

(+)-**tert-Butyl 1'-hydroxy-6-methyl-4-oxo-5,6,3,2,2',3'-hexahydrobenzo[cd]indole-1(2H)-carboxylate; 227**

To a stirred solution of organocatalyst 214 (20 mg, 0.03 mmol) in dry tetrahydrofuran (2 mL) was added a solution of enone 217 (50 mg, 0.16 mmol) in dry tetrahydrofuran (1 mL) and warmed to 50 °C. The reaction mixture was stirred at this temperature until TLC confirmed complete consumption of starting material. The reaction mixture was then concentrated *in vacuo* and the crude residue was purified by flash column chromatography (light petroleum ether : diethyl ether, 1 : 1) to afford 227 (13 mg, 25% yield, 81% ee) as a colourless oil. [Chiralpak AS, Hexanes / IPA 95:5, 1.0 mL / min, λ 230 nm, t (minor) = 6.131 min, t (major) = 6.519 min].

The **¹H NMR** was identical to 227 which was previous prepared from 217 using a catalytic amount of butylated hydroxy toluene in boiling toluene. [α]₀°: +15 (c 0.26, CHCl₃).
CHAPTER SEVEN: REFERENCES

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CHAPTER EIGHT: APPENDIX

8.1 NOE DATA FOR 93a

Data obtained at The University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK

Data includes:
1) Irradiation at 1.22 ppm
2) Irradiation at 1.30 to 1.37 ppm
3) Irradiation at 1.43 ppm
4) Irradiation at 1.72 to 1.91 ppm
5) Irradiation at 1.99 to 2.12 ppm
6) Irradiation at 2.50 to 2.53 ppm
7) Irradiation at 3.68 to 3.70 ppm
8) Model structure with annotation
8.2 NOE DATA FOR 93b

Data obtained at The University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK

Data includes:

1) Irradiation at 1.40 ppm
2) Irradiation at 1.49 ppm
3) Irradiation at 2.06 to 2.11 ppm
4) Irradiation at 2.40 to 2.47 ppm
5) Irradiation at 3.59 to 3.65 ppm
6) Model structure with annotation
8.3 NOE DATA FOR 99

Data obtained at AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire, LE11 5RH, UK

Data includes: 1) Irradiation at 1.42 ppm
2) Irradiation at 2.41 to 2.46 ppm
3) Irradiation at 2.73 ppm
8.4 NOE DATA FOR 227

Data obtained at AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, Leicestershire, LE11 5RH, UK

Data includes:
1) Irradiation at 1.16 ppm
2) Irradiation at 3.19 to 3.28 ppm
3) Irradiation at 3.93 to 4.03 ppm