TOWARDS THE TOTAL SYNTHESIS OF DAPHNIYUNNINE B

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TOWARDS THE TOTAL SYNTHESIS OF DAPHNIYUNNINE B
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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.
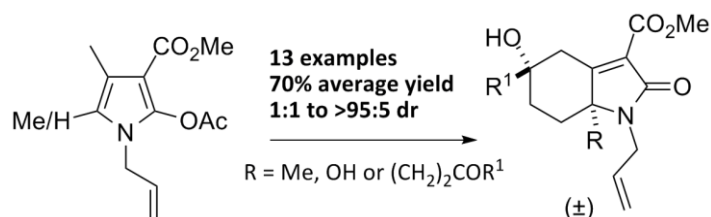
The enantioselective synthesis of the methyl-substituted core of Daphniyunnine B was achieved *via* an initial highly enantioselective organocatalytic Michael addition followed by a stereoselective organocatalytic intramolecular Michael addition.
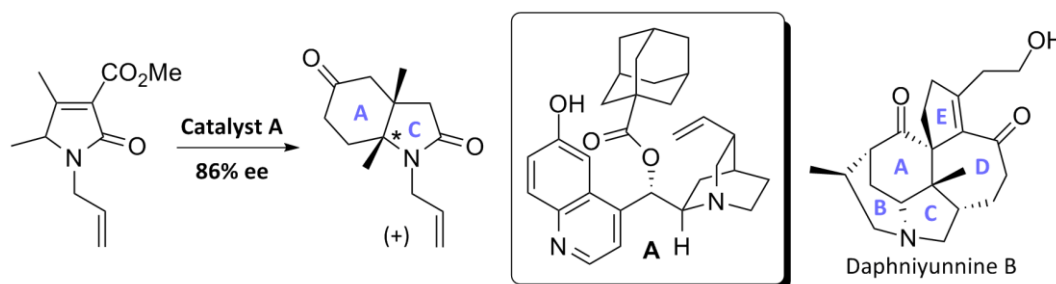
The stereocontrolled synthesis of the AC bicyclic core of (±) Daphniyunnine B was achieved *via* a quaternisation cyclisation approach.
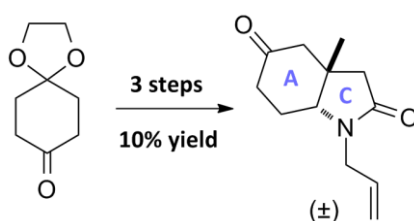
The stereocontrolled synthesis of the ACD tricyclic core of (±) Daphniyunnine B was achieved *via* an intramolecular Diels-Alder fragmentation reaction. Preliminary studies of an enantioselective variant are encouraging.
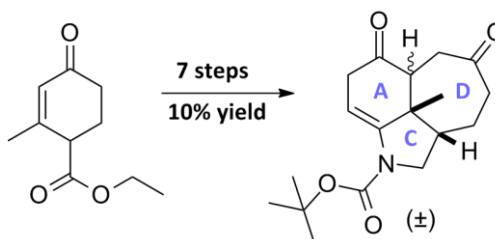
DECLARATION

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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ACKNOWLEDGEMENTS

ABBREVIATIONS

$^{\circ}$C	degrees Celsius
Å	angstrom
Ac	acetyl
Ar	aromatic group, (not phenyl)
BHT	butylated hydroxyl toluene
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	di-*tert*-butyl dicarbonate
bs	broad singlet
CDI	1,1'-carbonyldiimidazole
CI	chemical ionisation
cm	centimetre
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
d	doublet/day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
dd	doublet of doublets
dr	diastereomeric ratio
DEPT	distortionless enhancement by polarization transfer
DIBALH	di*iso*butyl aluminium hydride
DIAD	di*iso*propyl azodicarboxylate
DIPEA	*N,N*-di*iso*propylethylamine
DMAP	4-dimethylaminopyridine

DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electron impact
eq.	equivalents
equiv.	equivalents
ES	electrospray
Et	ethyl
EVK	ethyl vinyl ketone
EWG	electron withdrawing group
g	gram
h	hour(s)
HBMC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple-quantum coherence
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	Hertz
i	*iso*
IC_{50}	half maximal inhibitory concentration
IPA	isopropyl alcohol
IUPAC	International Union of Pure and Applied Chemistry
IR	Infrared

kJ	kiloJoule
LDA	lithium di*iso*propylamide
LHMDS	lithium hexamethyldisilazane
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet/minutes
m/z	mass-to-charge ratio
Me	methyl
mg	milligram
MHz	megahertz
m	minute(s)
mL	millilitre
µL	microlitre
mmol	millimole
MO	molecular orbital
Mol	mole
M.P.	melting point
MS	molecular sieves / mass spectrometry
MVK	methyl vinyl ketone
n	straight chain
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Np	naphthyl
Nu	nucleophile

p	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

TIPBA	2,4,6-tri*iso*propylbenzene sulfonic acid
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	p-toluenesulfonyl
TS	transition state
pTSA	toluene-4-sulfonic acid
µg	microgram

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. teijsmanni* and *D. humile*), and several other species (*D. calycinum*, *D. gracile*, *D. longeracemosum*, *D. yunnanense*, *D. longistylum*, *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, Yuzurimine, 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]
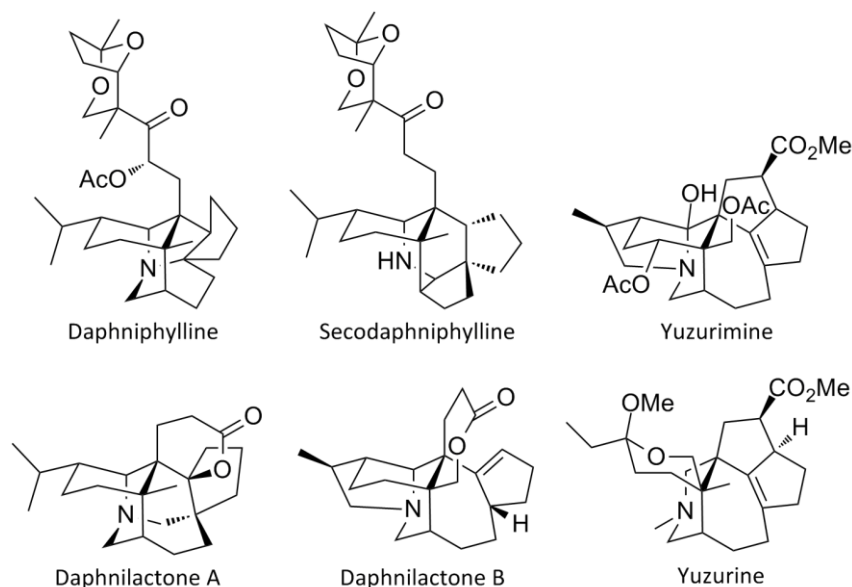
Figure 1.1 Orginal six *Daphniphyllum* alkaloids

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*).[2]
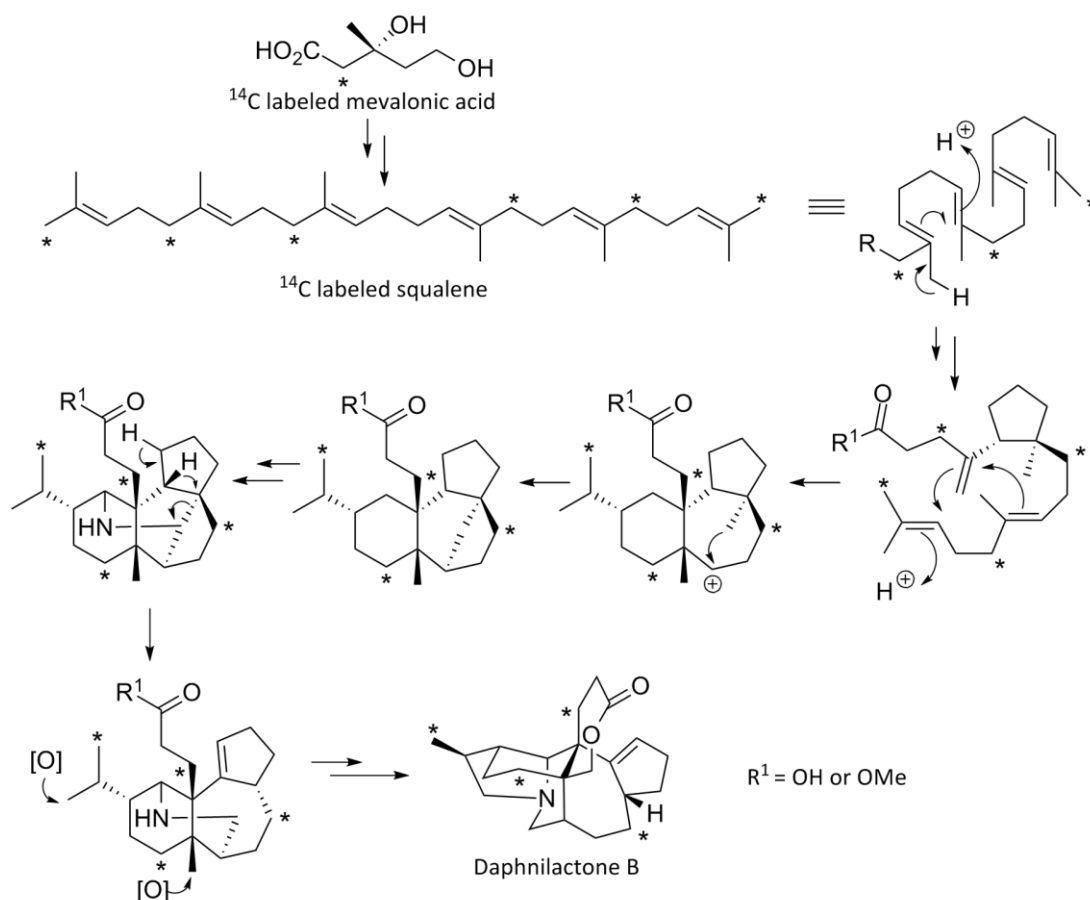
Scheme 1.1 Proposed biosynthesis of Daphnilactone B

While Yamamura outlined a biosynthetic route to the *Daphniyphyllum* 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 α,β-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]
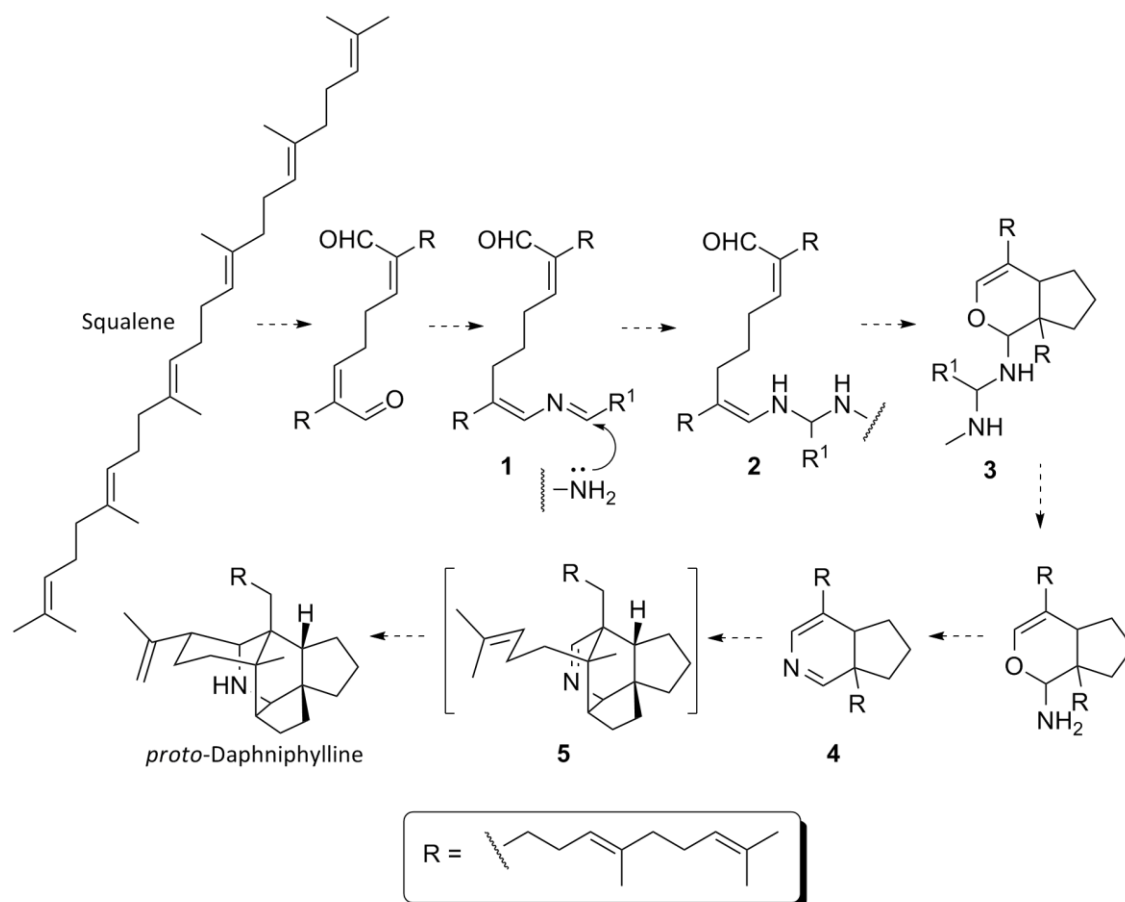
Scheme 1.2 Postulated biosynthetic pathways of *proto*-Daphniphlline

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**, α,β-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*).
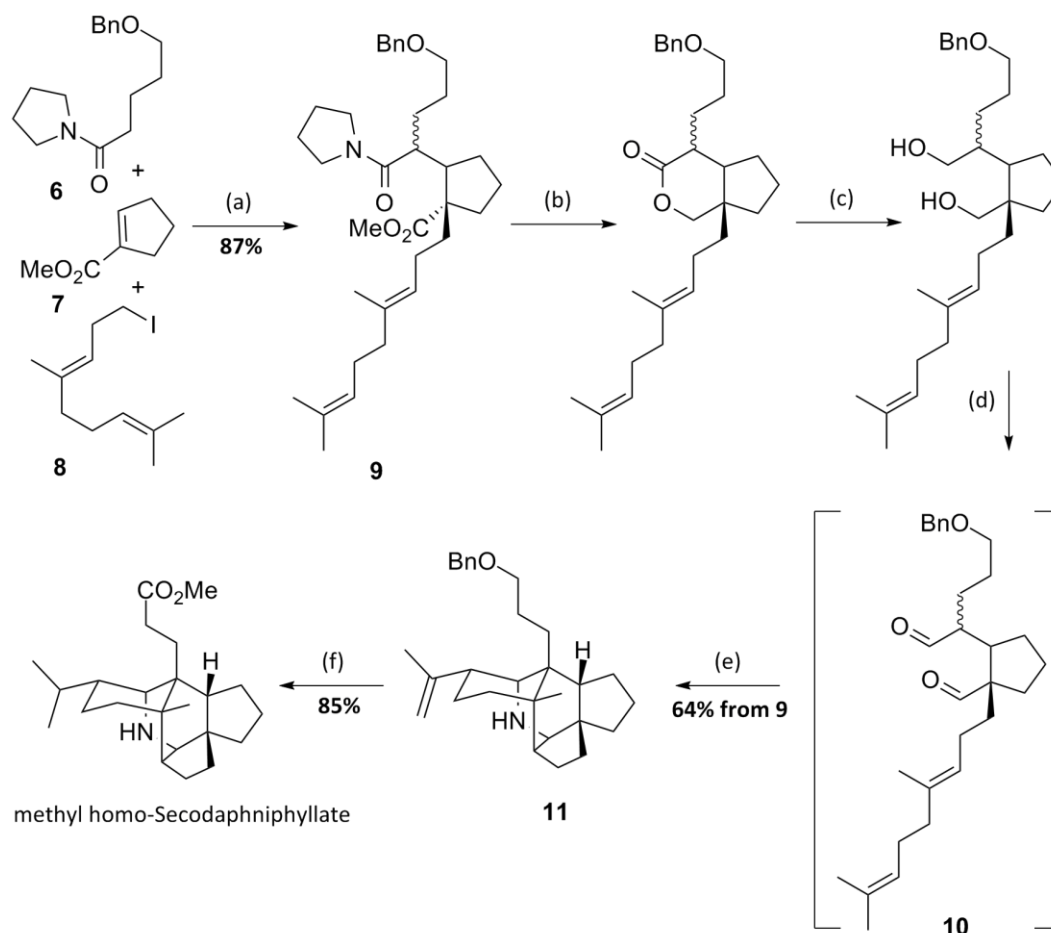
Scheme 1.3 Reagents and conditions (a) LDA, THF, -78 °C, **6**, then **7**, then **8** to RT; (b) DIBAL-H, NaOH, H_2O, EtOH; (c) LiALH$_4$; (d) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$; (e) NH$_3$, AcOH, CH$_2$Cl$_2$; (f) 1. Pd/C, H$_2$; 2. CrO$_3$, H_2SO_4, acetone; 3. MeOH, H_2SO_4

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-*proto*-Daphniphylline in 65% yield (*Scheme 1.4*).
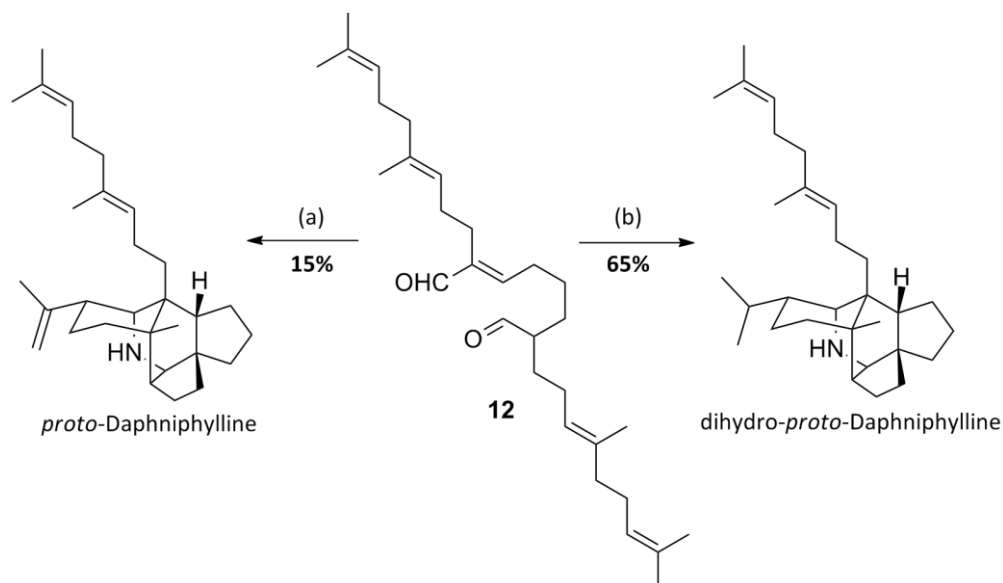
Scheme 1.4 Reagents and conditions (a) NH_3, AcOH, Heat; (b) $MeNH_2$, AcOH, Heat

The biomimetic mechanism for the synthesis of dihydro-*proto*-daphniphylline 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-*proto*-Daphniphylline (*Scheme 1.5*).
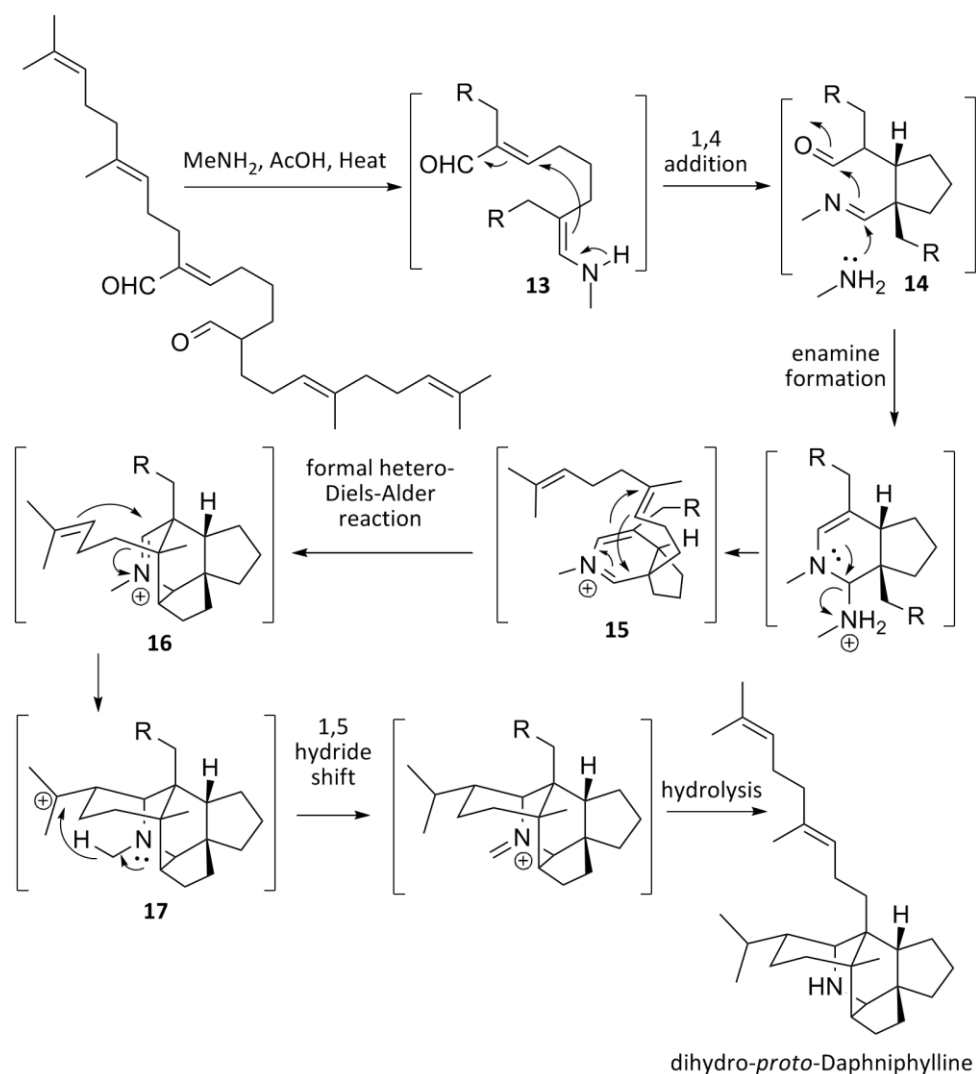
Scheme 1.5 Biomimetic mechanism

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.[5,6] Daphniyunnines A-E were evaluated in bioassays for antitumor activity according to standard protocols,[7] and pseudolaric acid B[8] 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 IC_{50} 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*).
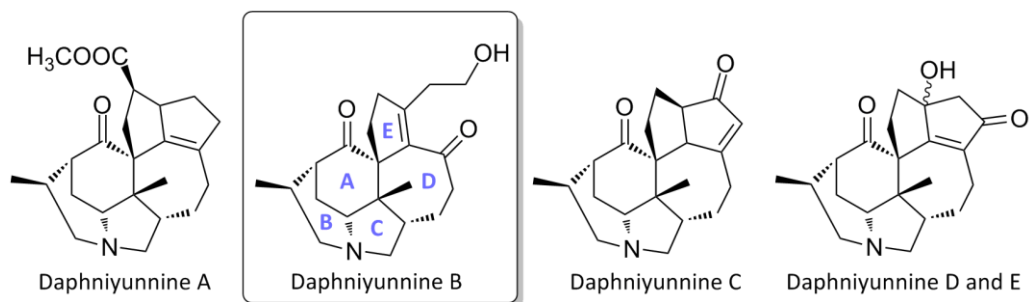
Figure 1.2 Family of Daphniyunnines

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]
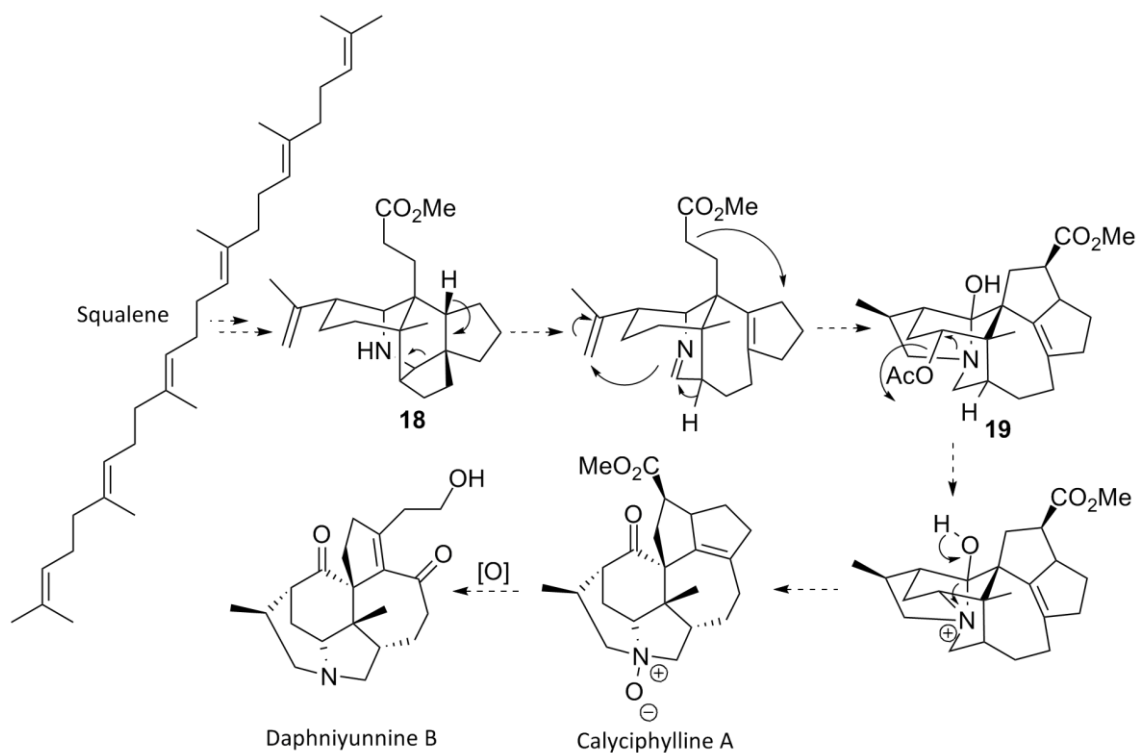
Scheme 1.6 Proposed biosynthesis of Daphniyunnine B

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.[11]

Daphniyunnine B   Calyciphylline A
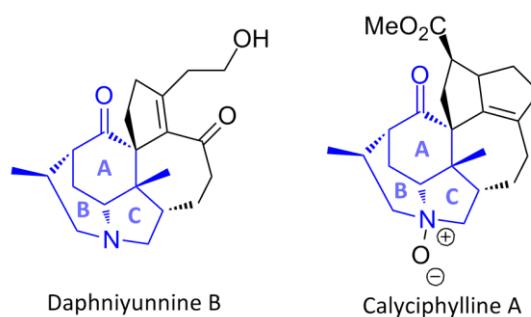
Figure 1.3 ABC tricyclic core of Daphniyunnine B and Calyciphylline A

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. Debenzylation 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*).
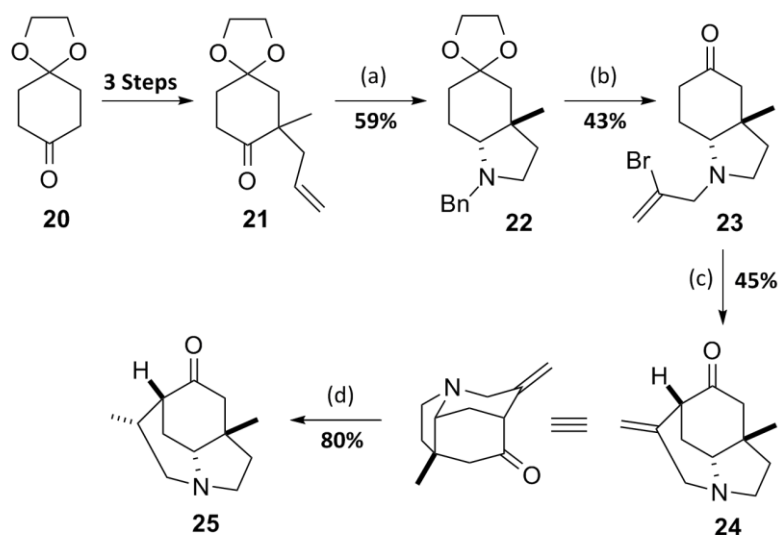
Scheme 1.7 Reagents and conditions (a) i) O_3, CH_2Cl_2 , ii) $NH_2Bn.HCl$, $NaBH_3CN$; (b) i) H_2, $Pd(OH)_2$, ii) $BrCH_2CBr=CH_2$, iii) 10% aq. HCl; (c) PhOK, $Pd(PPh_3)_4$, THF; (d) H_2, Pd-C

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*).
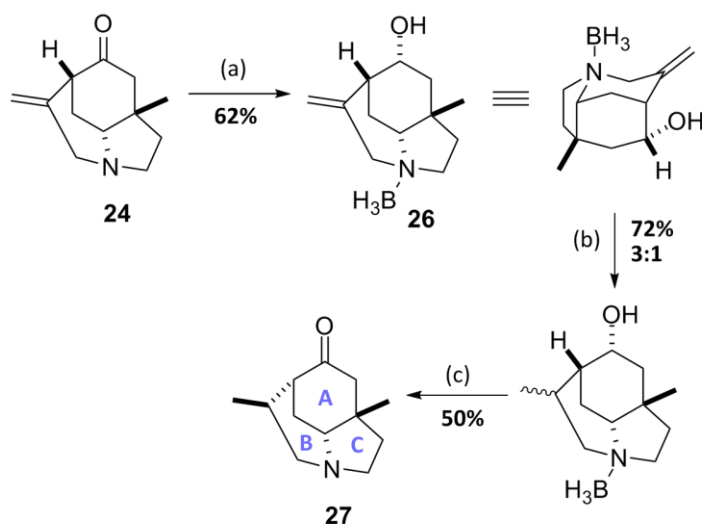
Scheme 1.8 Reagents and conditions (a) $NaBH_4$/ $CeCl_3$; (b) [Rh(NBD)(DIPHOS-4)]BF_4, H_2 (400 psi), NaH, THF; (c) i) DMSO, $(COCl)_2$, NEt_3, ii) 2N HCl

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]
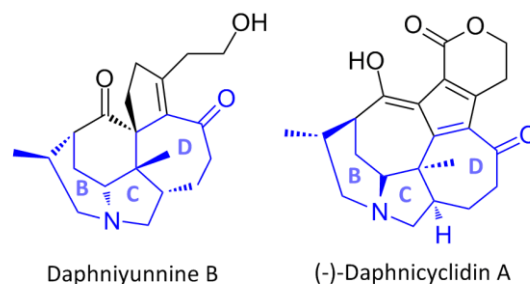
Figure 1.4 BCD tricyclic core of Daphniyunnine B and (-)-Daphnicyclidin A

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 tri*iso*propyl 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*).
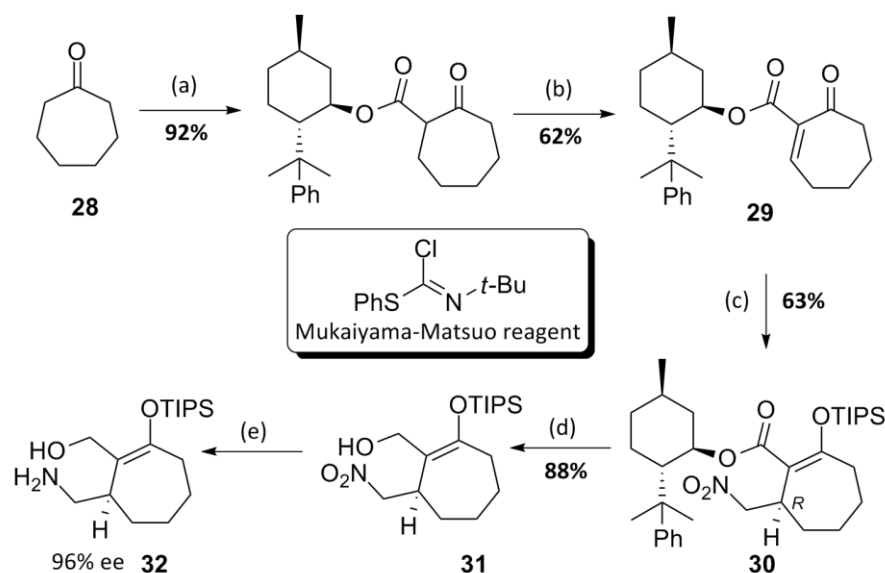
Scheme 1.9 Reagents and conditions (a) i) NaH, (MeCO)$_2$O, benzene, reflux, ii) (-)-8-phenylmenthol, DMAP, toluene, reflux (2 cycles); (b) LHMDS, Mukaiyama-Matsuo reagent, THF, -78 °C ; (c) n-BuLi, MeNO$_2$, THF, -78 °C, TIPSOTf, HMPA, -78 °C to 0 °C ; (d) DIBAL-H, toluene, -78 °C; (e) Fe, NH$_4$Cl, EtOH-H$_2$O, 80 °C, then pyridine, CH$_2$Cl$_2$

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 diastereocontrol. 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*).
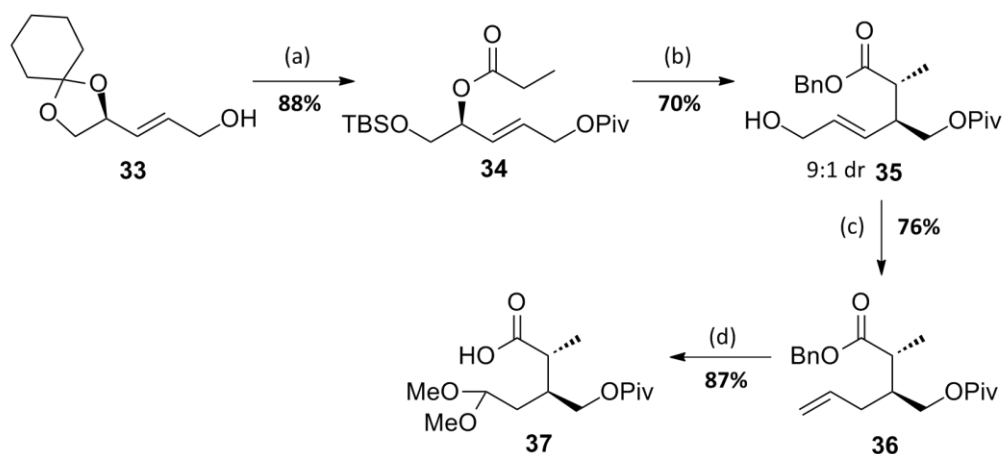
Scheme 1.10 Reagents and conditions (a) i) PivCl, Et$_3$N, ii) Dowex 50WX8, MeOH, iii) TBSCl, imidazole, iv) Propionic acid, EDCI, DMAP, CH$_2$Cl$_2$; (b) i) LHMDS, TBSCl, HMPA, 2-Me-THF/THF, -78 °C to RT, ii) 1-Me-imidazole, TsCl, BnOH, CH$_2$Cl$_2$, iii) PPTS, MeOH, 55 °C; (c) i) ClCO$_2$Me, pyridine, CH$_2$Cl$_2$, ii) Pd$_2$(dba)$_3$ CHCl$_3$, n-Bu$_3$P, HCO$_2$NH$_4$, DMF; (d) i) O$_3$, MeOH, Me$_2$S, p-TsOH, ii) H$_2$, Pd-C, AcOEt

.

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*).
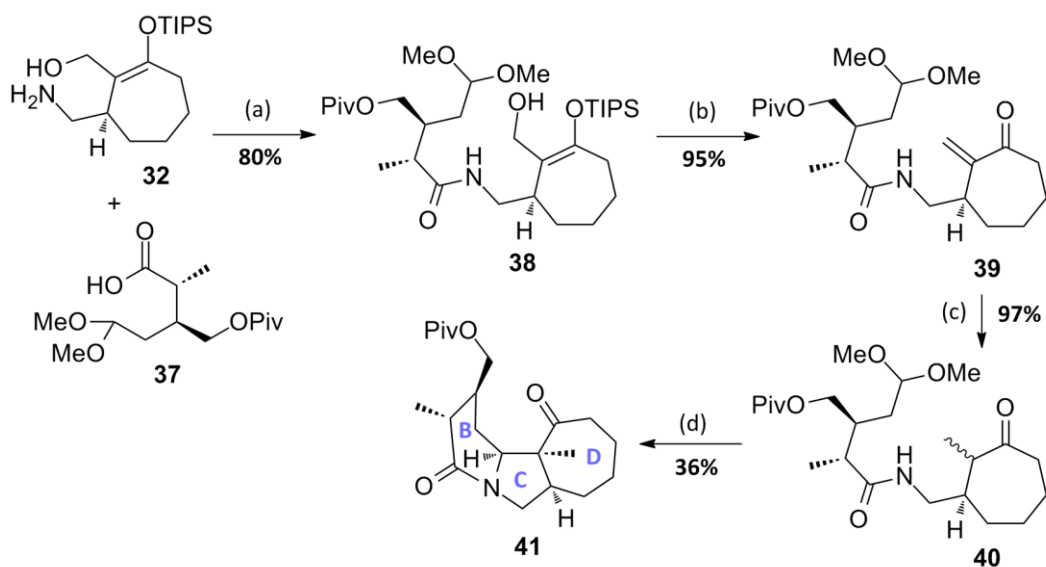
Scheme 1.11 Reagents and conditions (a) EDCI, DMAP, pyridine, CH$_2$Cl$_2$; (b) TsCl, Et$_3$N, Me$_3$N.HCl, CH$_2$Cl$_2$ the TBAF; (c) H$_2$, Pd-C, NaHCO$_3$, MeOH; (d) AcCl, *i*-PrOH, reflux

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*).
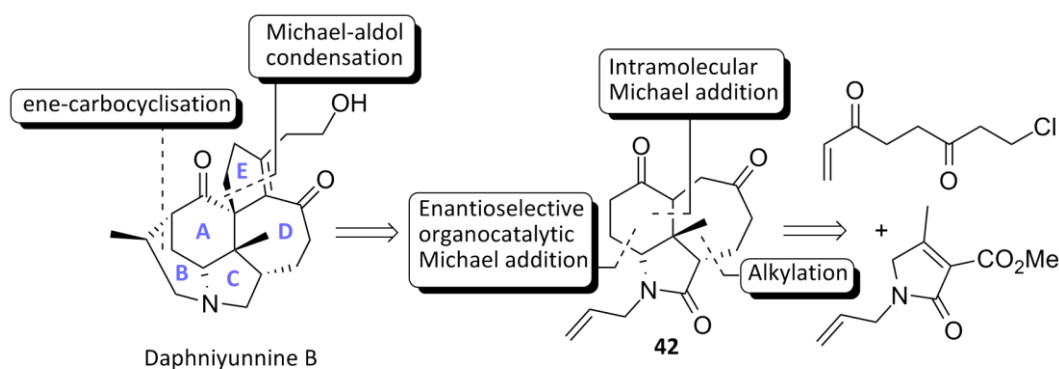
Scheme 2.1 Retrosynthetic analysis

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[13] and Claisen[14] and then developed by Arthur Michael[15] 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.[16-19]

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]
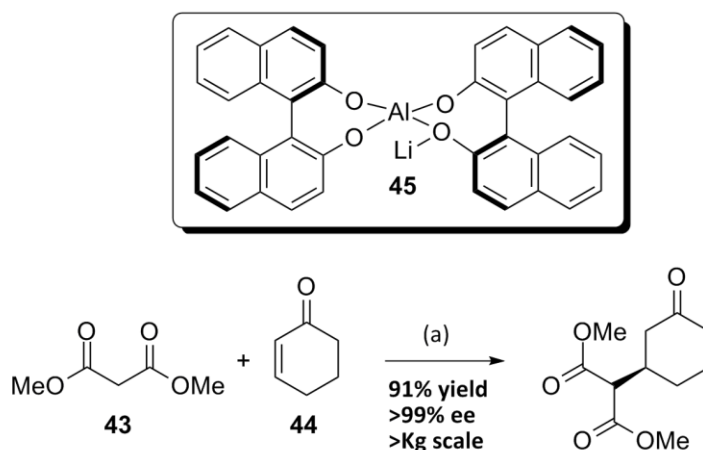
Scheme 2.2 Reagents and conditions (a) catalyst **45** (0.1 eq.), ^{t}BuOK (0.1 eq.), 4A Sieves, THF, 5 ^{o}C to RT

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.[23-26] 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]
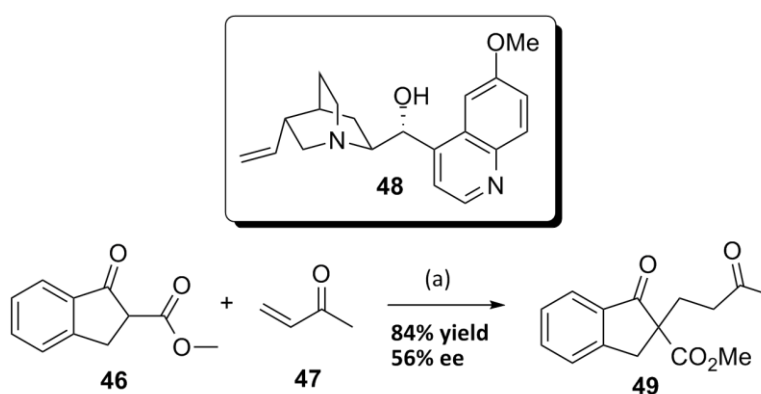
Scheme 2.3 Reagents and conditions (a) Quinine **48** (0.01 eq.), PhMe, RT

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]
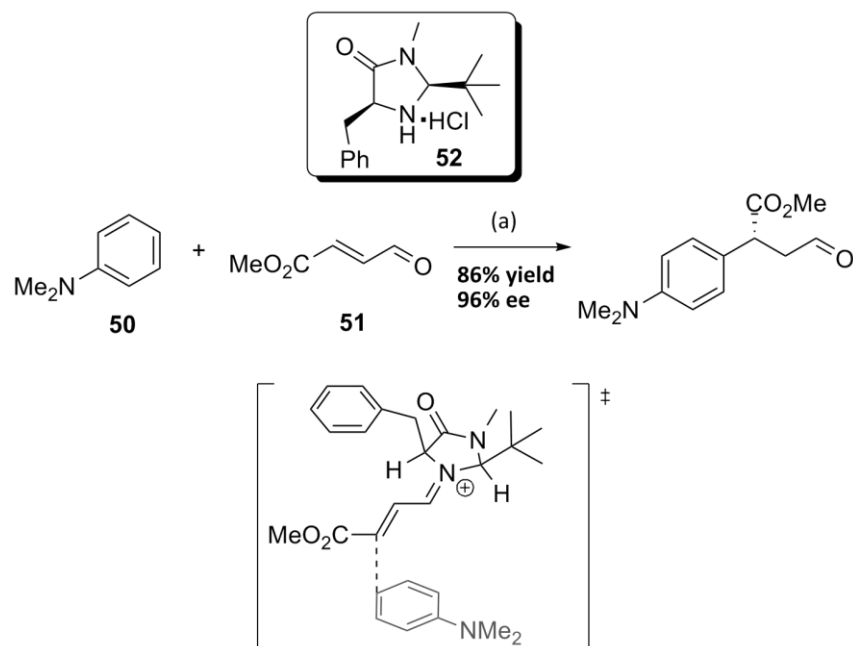
Scheme 2.4 Reagents and conditions (a) catalyst **52** (0.1 eq.), CHCl$_3$, -10 °C, 48h

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 diphenylsiloxymethyl group resulted in high enantio and diastereoselective control (*Scheme 2.5*).[29]
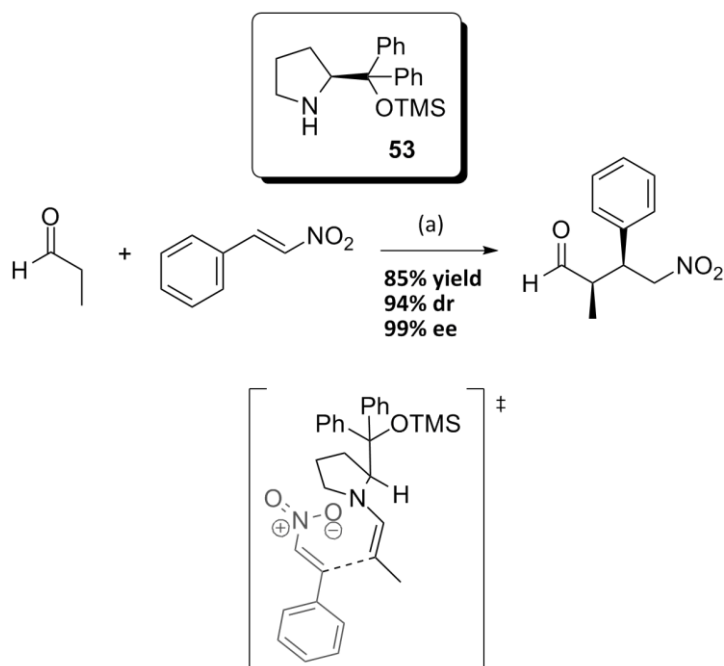
Scheme 2.5 Reagents and conditions (a) catalyst **53** (0.1 eq.), Hexane, 0 °C, 5h

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.[30] A number of modes of action have been proposed,[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*).[32]
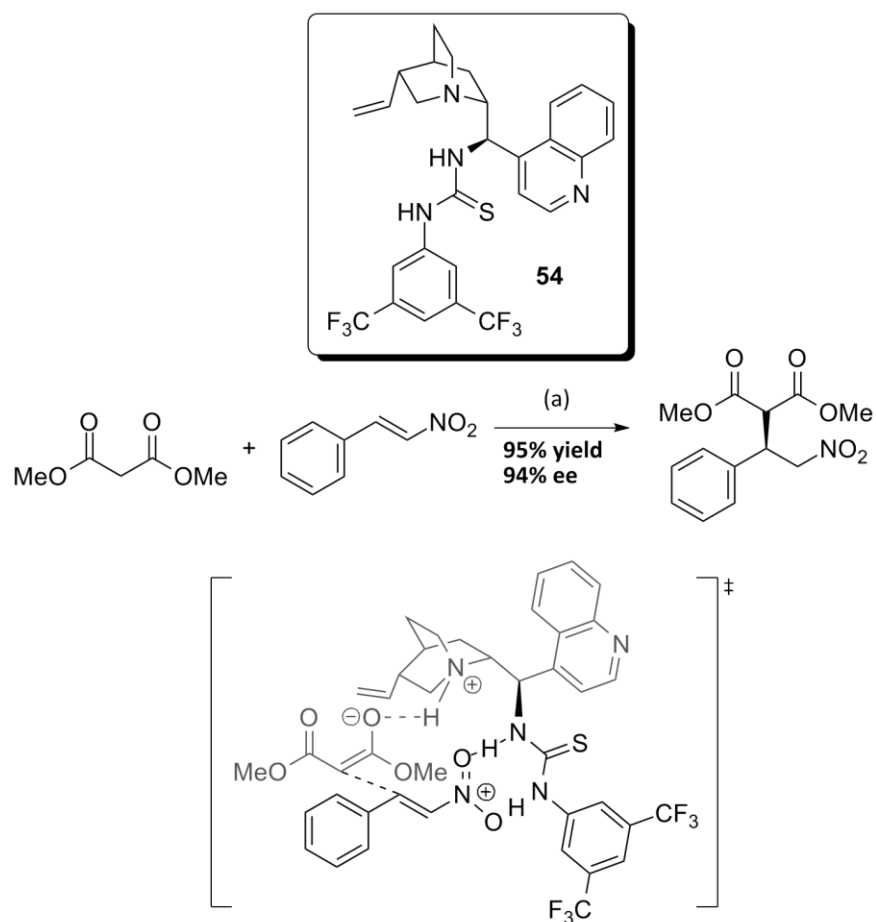
Scheme 2.6 Reagents and conditions (a) catalyst **54** (0.1 eq.), CH$_2$Cl$_2$, -20 $^{\circ}$C, 2h

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*).[33]
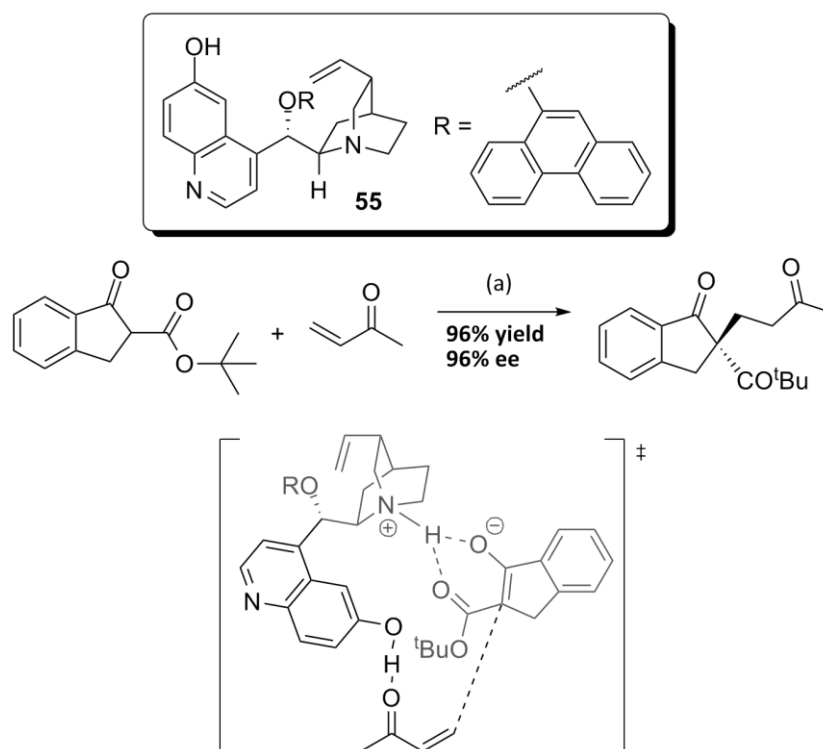
Scheme 2.7 Reagents and conditions (a) catalyst **55** (0.01 eq.), CH$_2$Cl$_2$, RT, 3h

Enantioselective organocatalytic Michael additions may initiate further transformations generating functionally dense multicyclic structures. The *M*ichael *I*nitiated *R*ing *C*losure 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 α,β-unsaturated ester or ketone to produce an enolate which subsequently undergoes intramolecular ring closure".[34]

2.3 MICHAEL INITIATED RING CLOSURE REACTIONS

Many different transformations have followed the initial Michael addition, including; alkylation[35], aldol condensation,[36] carbocyclisation[37] or a subsequent Michael addition.[38] 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.[39] Building on seminal work by Hajos, Parrish and Eder's,[36] Barbas and co-workers recently reported enantioselective Michael-aldol cascade reactions of

symmetrical cyclic ketones and α,β-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]
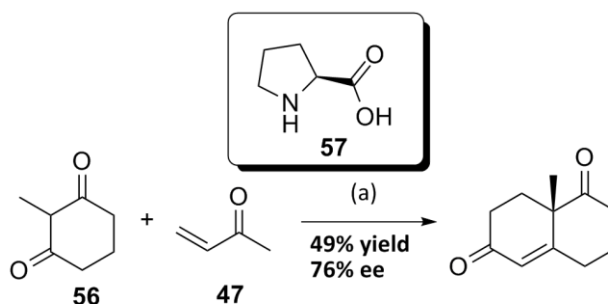
Scheme 2.8 Reagents and conditions (a) catalyst **57** (0.35 eq.), DMSO, 35 °C, 89h

2.3.2 MICHAEL-MICHAEL CASCADE

Deng and co-workers recently reported highly enantioselective Michael-Michael cascade reactions of α,β-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 α,β-unsaturated ketone **58** *via* reversible iminium formation with the organocatalyst **59**. Facially 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]
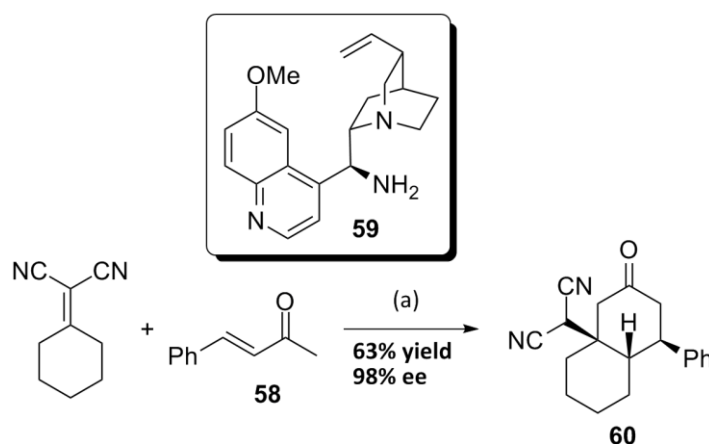
Scheme 2.9 Reagents and conditions (a) catalyst **59** (0.2 eq.), TFA (0.4 eq.), DIPEA (0.15 eq.), -20 °C, 96h

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*).[41]
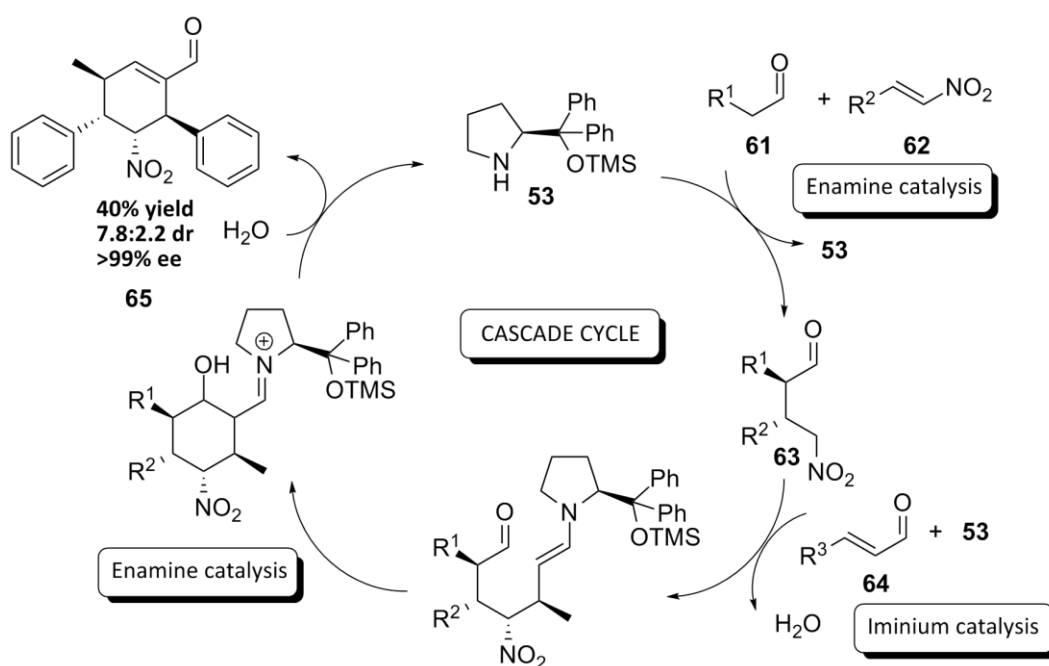
Scheme 2.10 Michael/Michael/aldol cascade

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*).
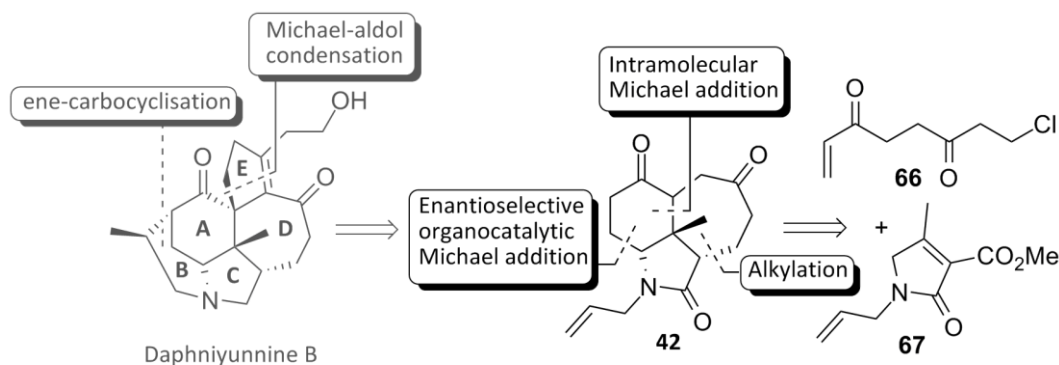
Scheme 2.11 Retrosynthetic analysis

Pyrrole-2-ones **67** are versatile synthetic intermediates owing to the presence of multiple reactive centers; the γ-methylene unit present in such a system will undergo various reactions including aldol condensations, Michael additions and Vilsmeier-Haack formylation.[42] 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*).
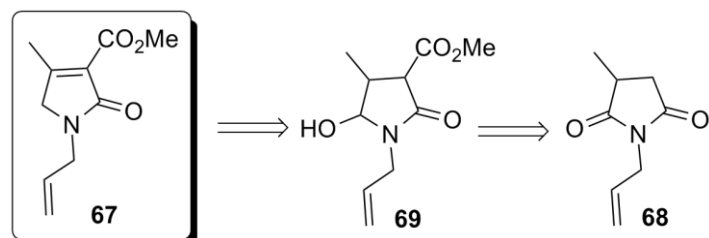
Scheme 2.12 Retrosynthesis of pyrrole-2-one **67**

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*).[43]
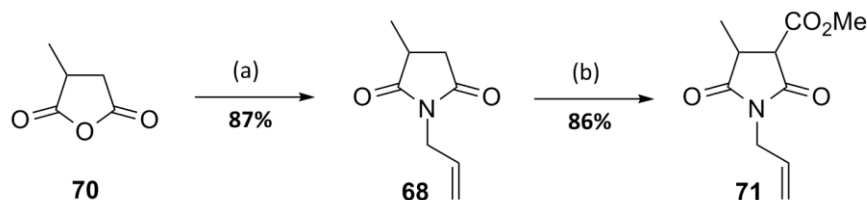
Scheme 2.13 Reagents and conditions (a) allylamine (1.1 eq.), CDI (1.1 eq.), CH_2Cl_2, RT to reflux; (b) $ClCO_2Me$ (2.0 eq.), LHMDS (2.0 eq.), THF, -78 °C, 5m

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 inseperable 3:1 mixture of regioisomers **72** (undesired) and **73** (desired) by inspection of the ^1H 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*).
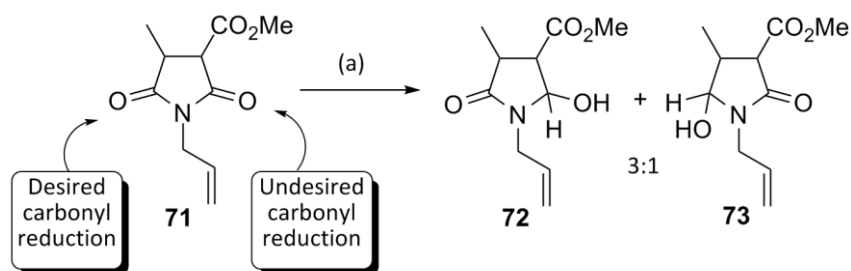
Scheme 2.14 Reagents and conditions (a) $NaBH_4$ (5.0 eq.), MeOH, 0 °C

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*).
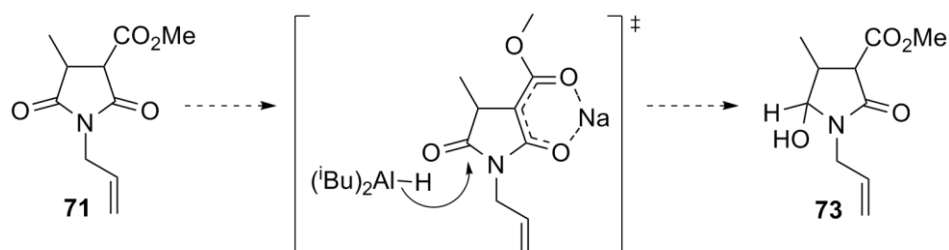
Scheme 2.15 Postulated protective deprotonation followed by reduction

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 di*iso*butylaluminium hydride at low temperature (*Scheme 2.16*).[44]
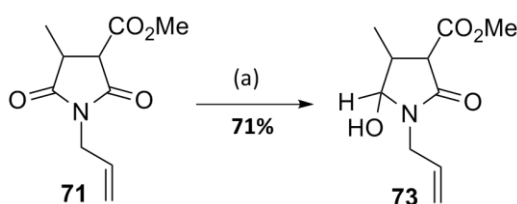
Scheme 2.16 Reagents and conditions (a) NaH (1.0 eq.), DIBALH (2.0 eq.), THF, -78 °C, 1h

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[45] 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*).
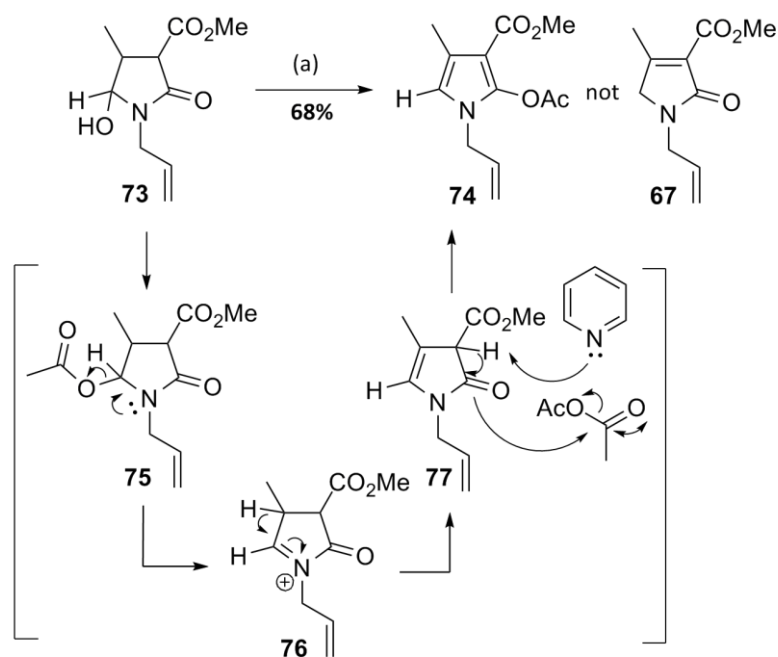
Scheme 2.17 Reagents and conditions (a) pyridine (30.0 eq.), acetic anhydride (15.0 eq.), THF, reflux, 2d

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*).
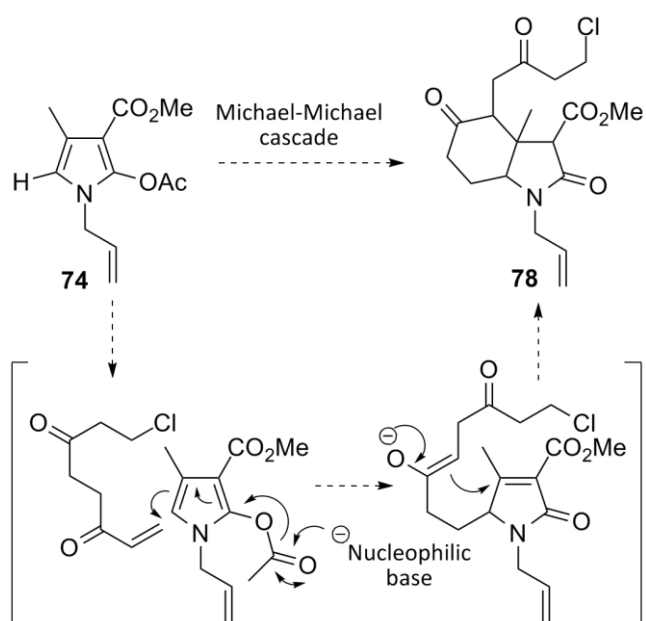
Scheme 2.18 Envisaged Michael-Michael cascade reaction

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 γ-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*).
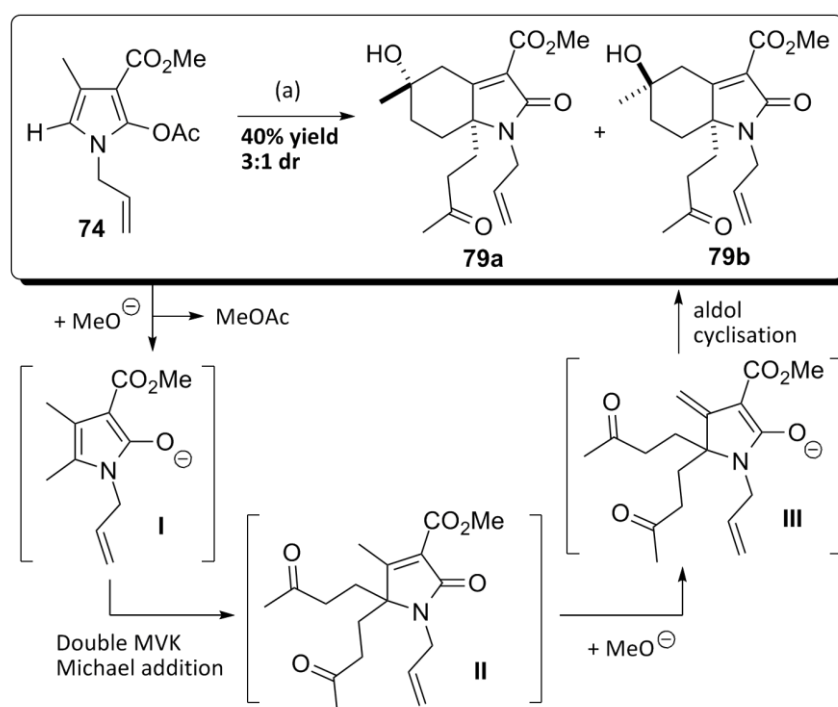
Scheme 2.19 Reagents and conditions (a) MVK (1.0 eq.), K_2CO_3 (0.2 eq.), MeOH, RT, 30m

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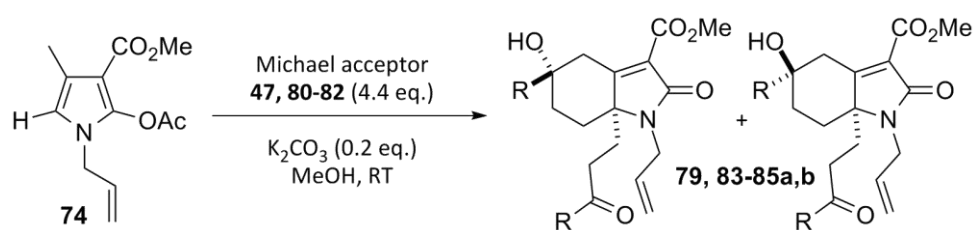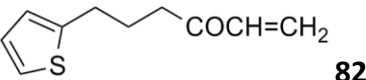
Table 2.1 Scope of reaction with respect to Michael acceptor

Entry	Michael acceptor	Product	Time (h)	Yield (%)	dr (**a:b**)[b]
1[a]	MeCOCH=CH$_2$ **47**	**79a,b**	0.5	76	3:1
2[a]	EtCOCH=CH$_2$ **80**	**83a.b**	0.5	75	3:1
3	COCH=CH$_2$ **81**	**84a,b**	0.5	65	3:1
4[a]	COCH=CH$_2$ **82**	**85a,b**	0.5	79	3:1

[a] Published results.[44] [b] determined by inspection of the ^{1}H NMR of the crude mixture

Double Michael-Dieckmann condensation cascade reactions have been reported[46] 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
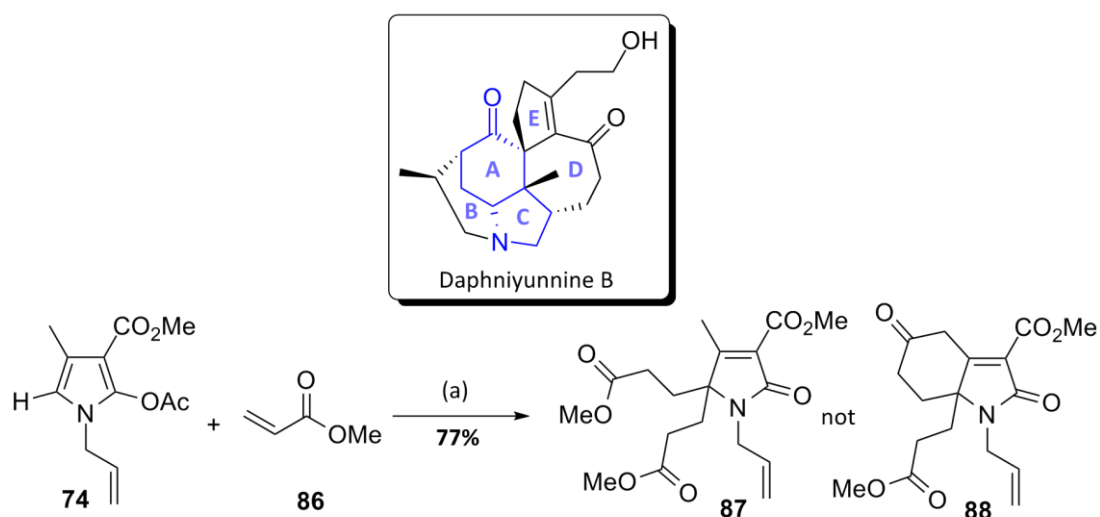
Scheme 2.20 Reagents and conditions (a) methyl acrylate 86 (4.4 eq.), K₂CO₃ (0.2 eq.), MeOH, RT, 30m

A brief study into the Dieckmann-type condensation was undertaken and the outcomes are shown in Table **2.2**.
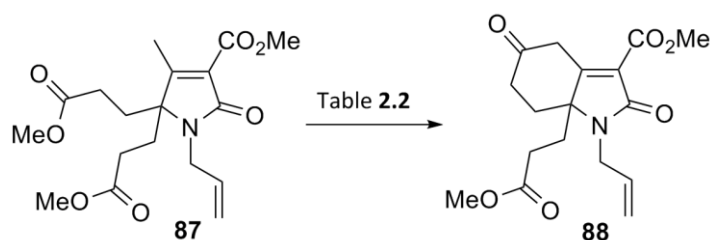
Table 2.2 Attempted Dieckmann-type condensation reaction conditions

Entry	Reaction conditions	Reaction outcome
1	^{t}BuOK/THF, room temperature and reflux	Recovery of starting materials
2	^{t}BuOK/DMF, room temperature and reflux	Recovery of starting materials
3	^{t}BuOK/$^-$BuOH, room temperature and reflux	Complex mixture of compounds
4	NaH/THF, room temperature and reflux	Recovery of starting materials
5	NaH/DMF, room temperature and reflux	Recovery of starting materials
6	LHMDS/DMF, room temperature and reflux	Recovery of starting materials

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*).
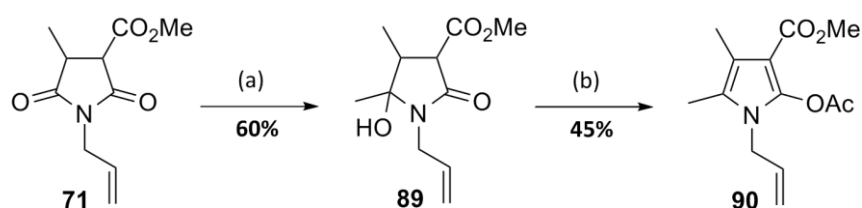
Scheme 2.21 Reagents and conditions (a) NaH (1.0 eq.), MeMgBr (4.5 eq.), THF, -78 °C to RT, 2h; (b) pyridine (30.0 eq.), acetic anhydride (15.0 eq.), THF, reflux, 2d

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-unstaturated 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*).
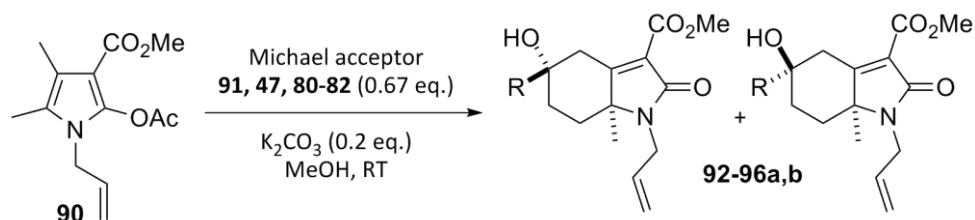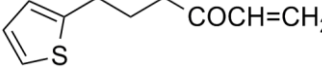
Table 2.3 Scope of reaction with respect to Michael acceptor

Entry[*]	Michael acceptor	Product	Time (h)	Yield (%)	Dr (**a:b**)
1	HCOCH=CH$_2$ **91**	**92a,b**	12	71	1:1
2	MeCOCH=CH$_2$ **47**	**93a,b**	0.5	74	2:1
3	EtCOCH=CH$_2$ **80**	**94a,b**	0.5	67	4:1
4	COCH=CH$_2$ **81**	**95a,b**	1	70	6:1
5	COCH=CH$_2$ **82**	**96a,b**	1	79	4:1

[a] Published results.[44] [b] determined by inspection of the ^{1}H NMR of the crude mixture

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*).
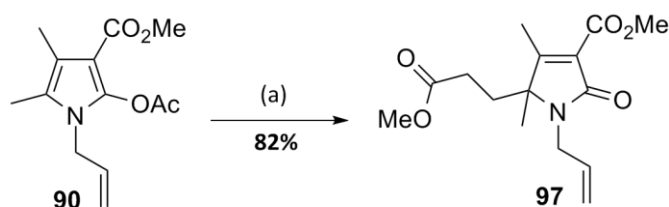
Scheme 2.22 Reagents and conditions (a) methyl acrylate **86** (2.2 eq.), K$_2$CO$_3$ (0.2 eq.), MeOH, RT, 30m

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*).
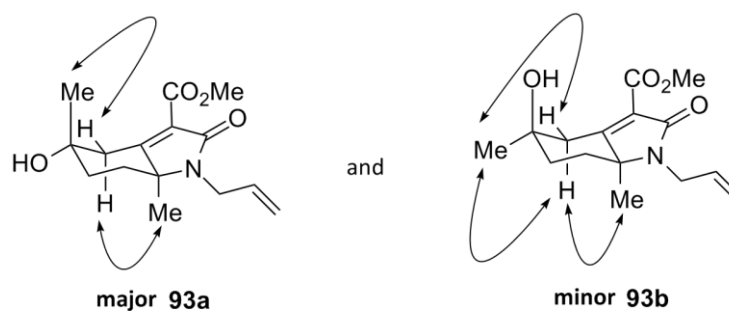
Figure 2.1 nOe experiments of **93a** and **93b**

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 diastereisomers. These data are consistent with stereoselectivity resulting from kinetic control in the aldol step (*Scheme 2.23*).
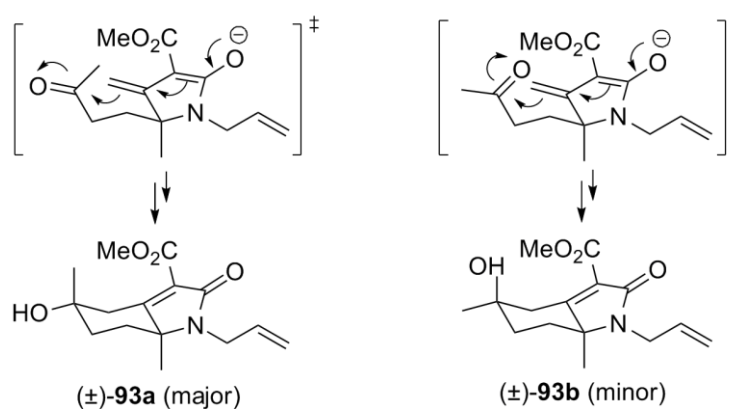
Scheme 2.23 Proposed transition structure models

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*).
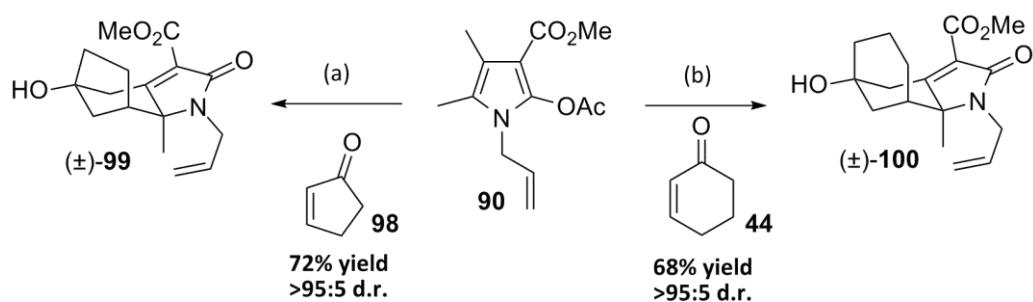
Scheme 2.24 Reagent and conditions (a) cyclopentenone **98** (0.67 eq.), K$_2$CO$_3$ (0.2 eq.), MeOH, RT, 12h; (b) cyclohexenone **44** (0.67 eq.), K$_2$CO$_3$ (0.2 eq.), MeOH, RT, 12h

The stereochemisty of **99** was established by nOe experiments. The high diastereoselectivity in the reaction is ascribed to an intial 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*).
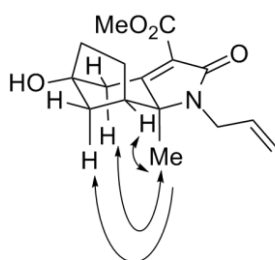
Figure 2.2 nOe experiments of **99**

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 ^{1}H NMR spectra of **99** (*Scheme 2.25*).
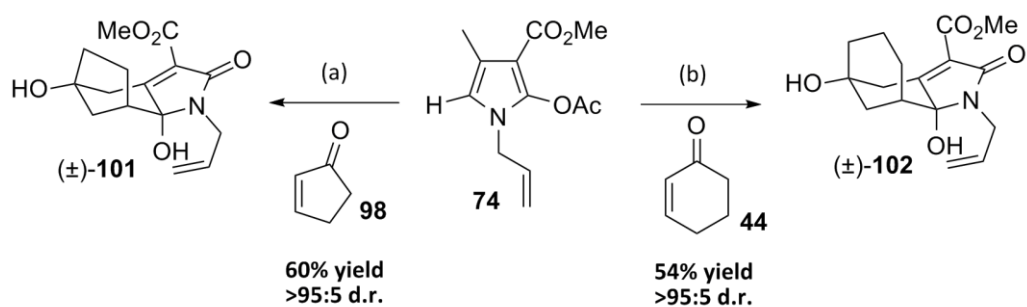
Scheme 2.25 Reagent and conditions (a) cyclopentenone **98** (0.67 eq.), K_2CO_3 (0.2 eq.), MeOH, RT, 12h; (b) cyclohexenone **44** (0.67 eq.), K_2CO_3 (0.2 eq.), MeOH, RT, 12h

There is insufficient data to determine the mechanism, however the oxygen oxidation of pyrrole-2-ones is well documented in the literature[47] 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 alkoxyl 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*).
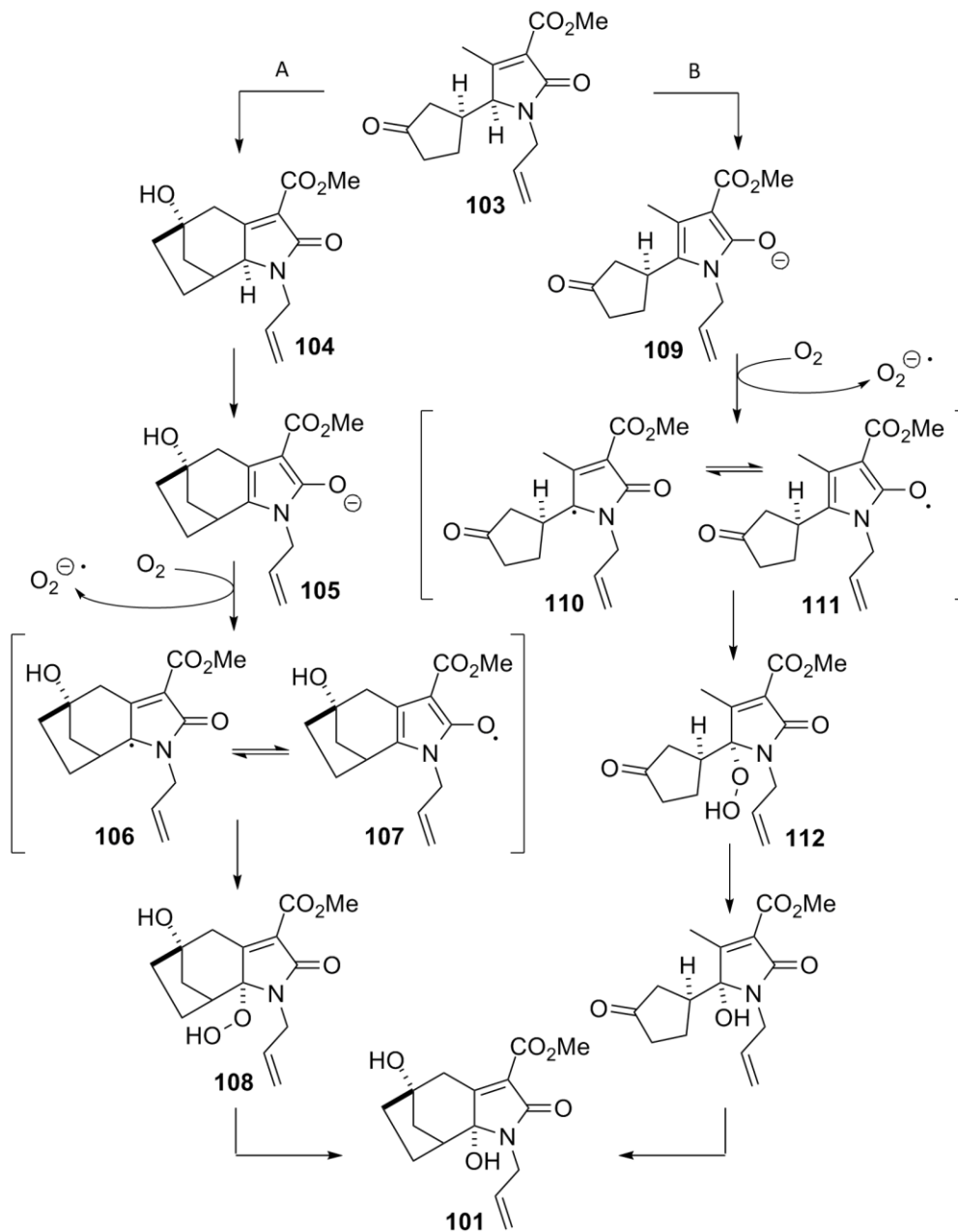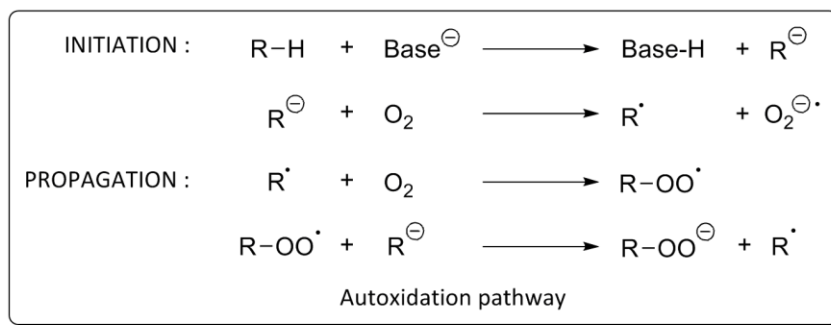
Scheme 2.26 Postulated mechanistic pathway for the formation of **101**

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*).
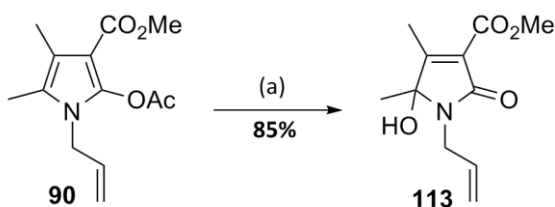
Scheme 2.27 Reagents and conditions (a) K_2CO_3 (0.2 eq.), MeOH, RT, air atmosphere

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*).
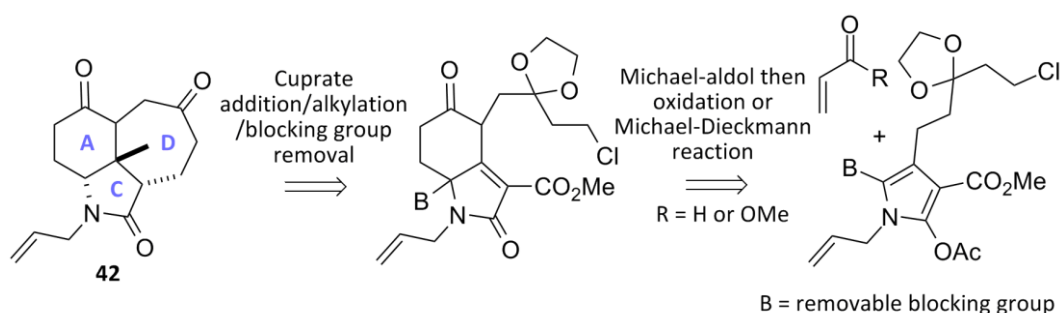
Scheme 2.28 Retrosynthetic analysis

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*).
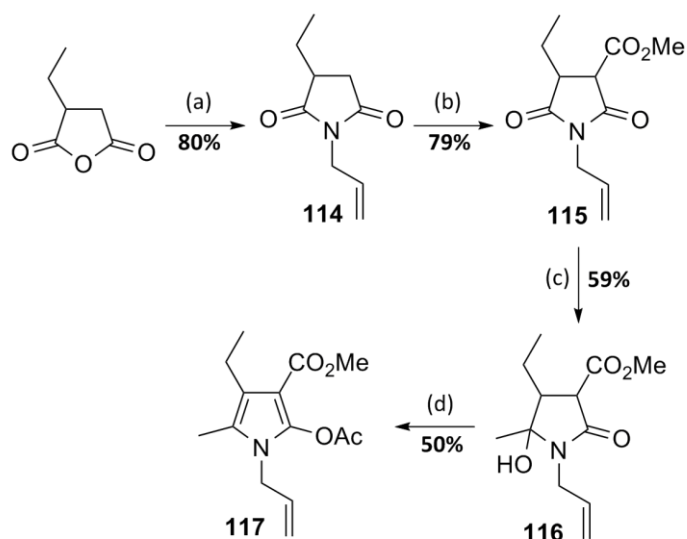
Scheme 2.29 Reagents and conditions (a) allylamine (1.1 eq.), CDI (1.1 eq.), CH_2Cl_2, RT to reflux; (b) MeCOCl (2.0 eq.), LHMDS (2.0 eq.), THF, -78 °C, 5m; (c) NaH (1.0 eq.), MeMgBr (4.5 eq.), THF, -78 °C to RT, 2h; (d) pyridine (30.0 eq.), acetic anhydride (15.0 eq.), THF, reflux, 2d

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*).
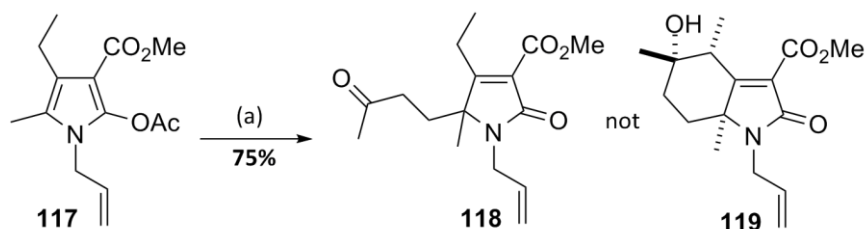
Scheme 2.30 Reagents and conditions (a) MVK (2.2 eq.), K_2CO_3 (0.2 eq.), MeOH, RT, 30m

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*).
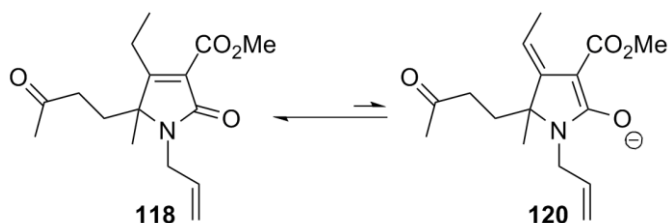
Scheme 2.31 Equilibrium between **118** and **120**

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*).
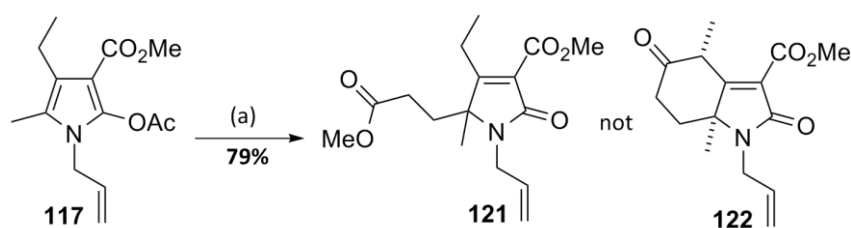
Scheme 2.32 Reagents and conditions (a) methyl acrylate (2.2 eq.), K_2CO_3 (0.2 eq.), MeOH, RT, 30m

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*).
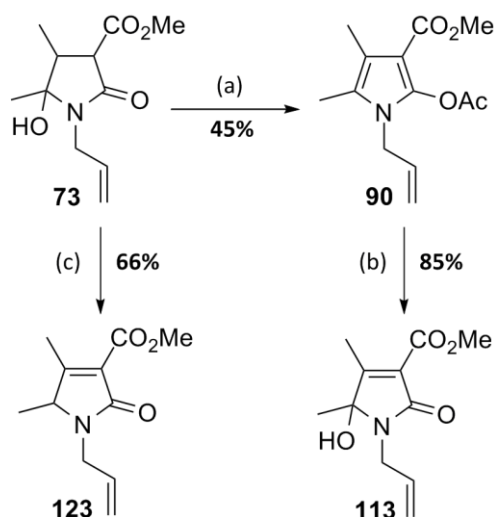
Scheme 2.33 Reagents and conditions (a) pyridine (30.0 eq.), acetic anhydride (15.0 eq.), THF, reflux, 2d; (b) K_2CO_3 (0.2 eq.), MeOH, RT; (c) 6M HCl:DCM (1:1), RT, 2h

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*).
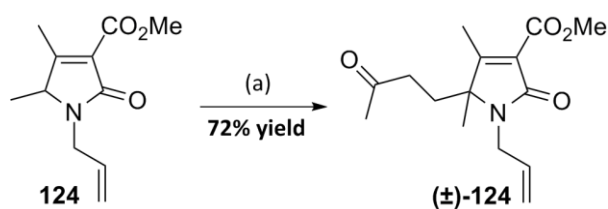
Scheme 2.34 Reagents and conditions (a) DABCO (0.2 eq.), MVK (4.0 eq.), CH_2Cl_2, RT, 5h

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*).
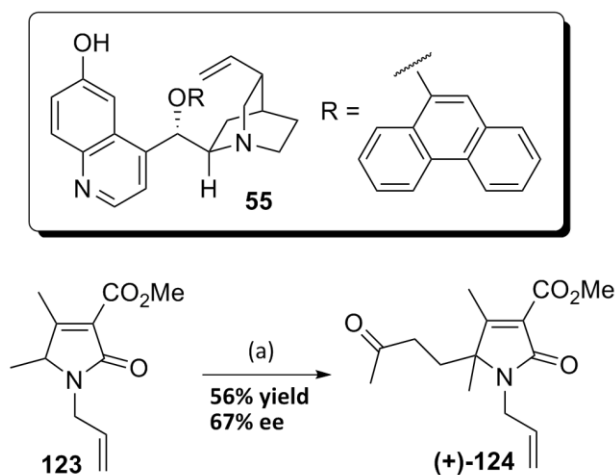
Scheme 2.35 Reagents and conditions (a) catalyst **55** (0.1 eq.), MVK (4.0 eq.), CH$_2$Cl$_2$, RT, 5h

A similar cinchona-derived organocatalyst **125*** has also been reported to undergo enantioselective Michael additions[48] and was included alongside **55** into our investigations under a variety of conditions (*Table 2.4*).
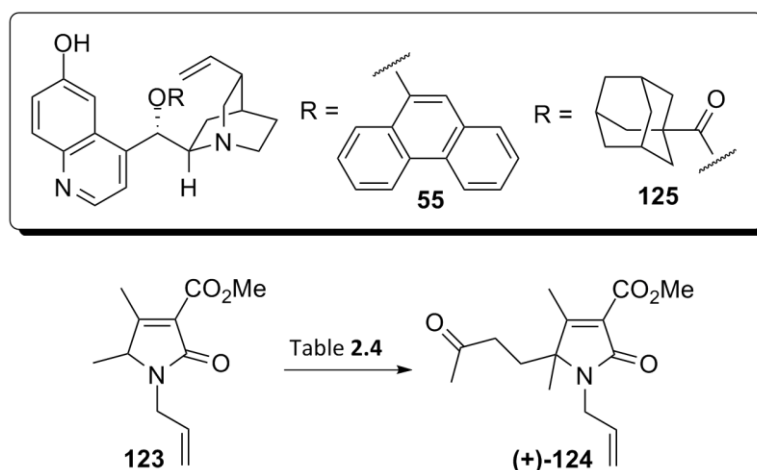
Table 2.4 Enantioselective organocatalytic Michael addition

Entry[*]	Catalyst	Solvent	Temperature	Time	Yield (%)	Ee (%)
1	**125**	CH_2Cl_2	RT	5h	67	73
2	**55**	CH_2Cl_2	-20 °C	20h	46	77
3	**125**	CH_2Cl_2	-20 °C	20h	60	85
4	**125**	MeOH	-20 °C	20h	50	11
5	**125**	TBME	-20 °C	20h	60	83
6	**125**	THF	-20 °C	20h	53	83
7	**125**	PhMe	-20 °C	20h	53	86

[*] **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 enantioselectivites 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 **47** is selectively delivered by hydrogen bonding of the quinoline phenol (6'-OH) (*Figure 2.3*).
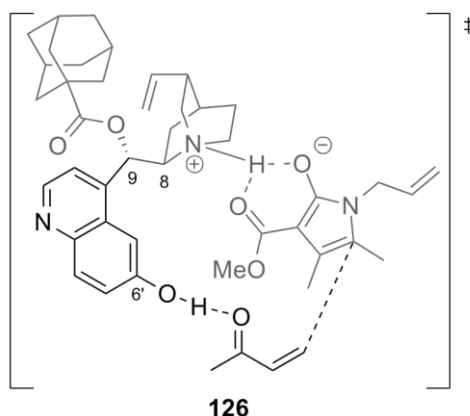
Scheme 2.3 Proposed transition structure for the enantioselective Michael addition

Ethyl vinyl ketone also underwent Michael addition with **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 **127** was not determined (*Scheme 2.36*).
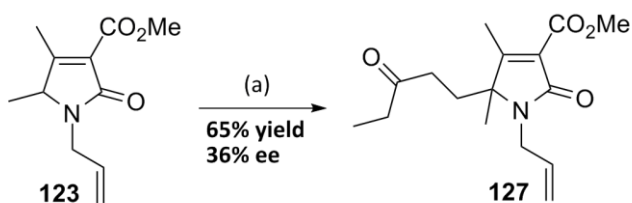
Scheme 2.36 Reagents and conditions (a) catalyst **125** (0.1 eq.), EVK (4.0 eq.) PhMe, -20 °C, 20h

2.4.7 RING CLOSING REACTIONS

The aldol reaction of the enantioenriched Michael adduct **(+)-124** (86% ee) was facilitated upon treatment with potassium carbonate in methanol to generate adduct **(+)-93a,b** in 92% yield and as a 2:1 mixture of diastereoisomers as observed previously in section **2.4.4**. The absolute stereochemistry was not determined (*Scheme 2.37*).
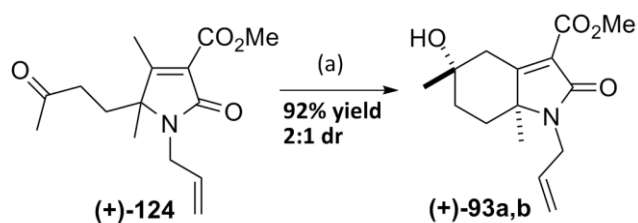
Scheme 2.37 Reagents and conditions (a) K_2CO_3 (0.2 eq.), MeOH, RT, 30m

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*).
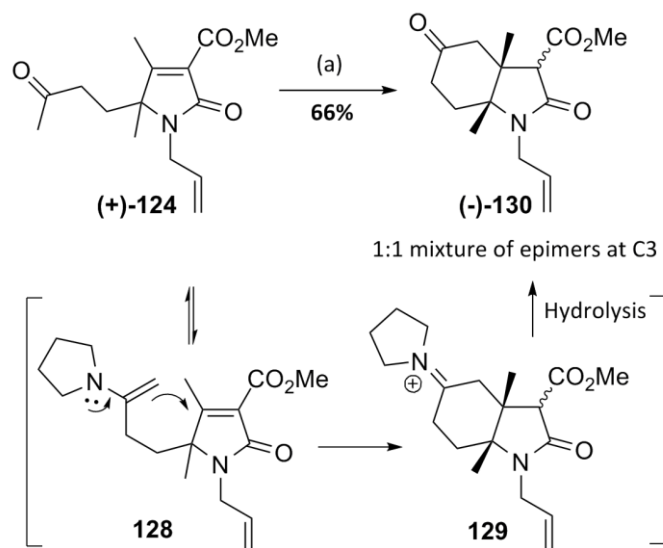
Scheme 2.38 Reagents and conditions (a) pyrrolidine (0.2 eq.), MeOH, RT, 18h

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*).
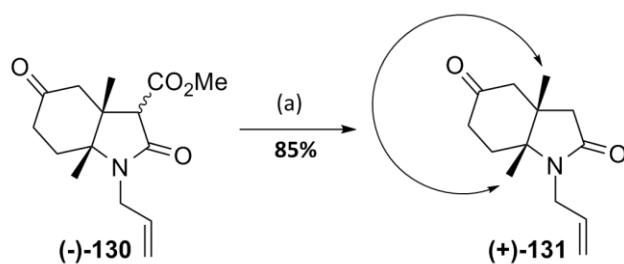
Scheme 2.39 Reagents and conditions (a) NaCl (1.5 eq.), H$_2$O, DMSO, 175 $^{\circ}$C, 2h

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 α,β-unsaturated carbonyl compounds in good yields and moderate to excellent diastereocontrol was discovered and developed (*Scheme 2.40*).
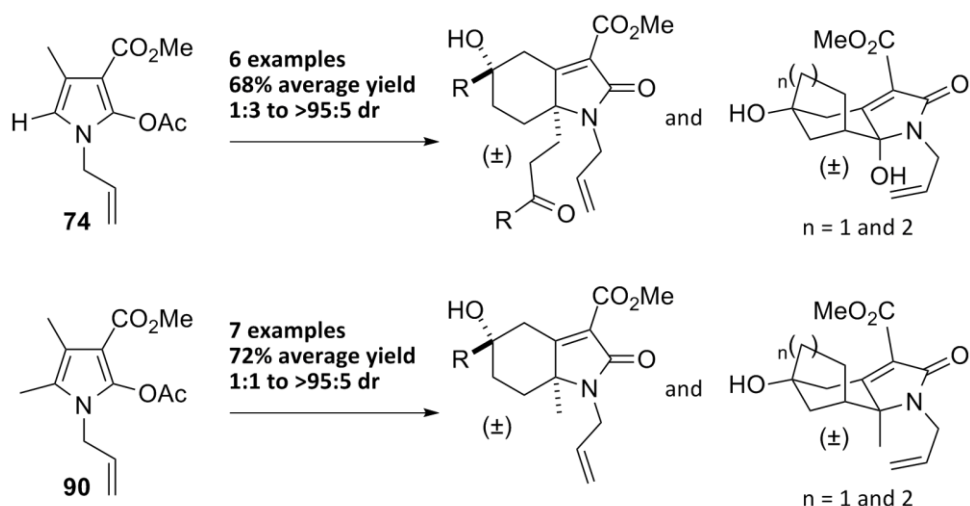
Scheme 2.40 Michael-aldol cascade reactions of **74** and **90**

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*).
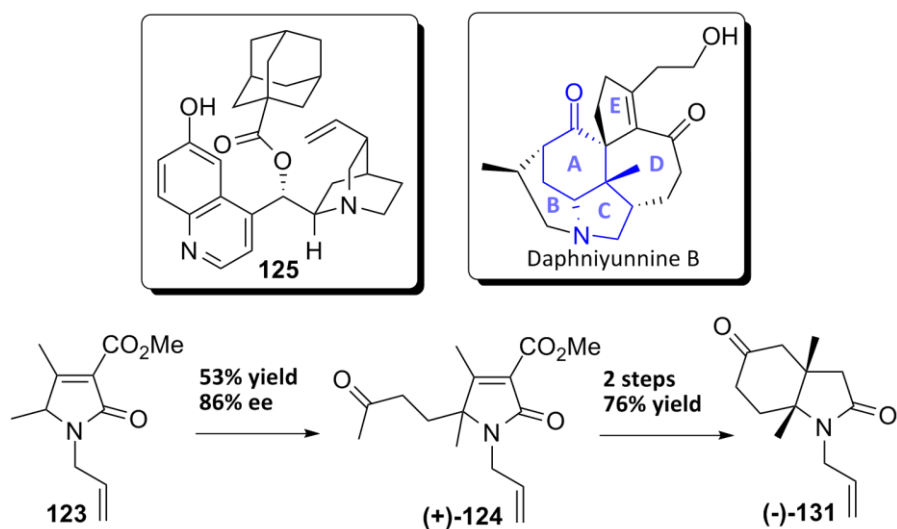
Scheme 2.41 Organocatalytic transformations to afford (-)-131

2.4.9 FUTURE WORK

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.[49] 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*).
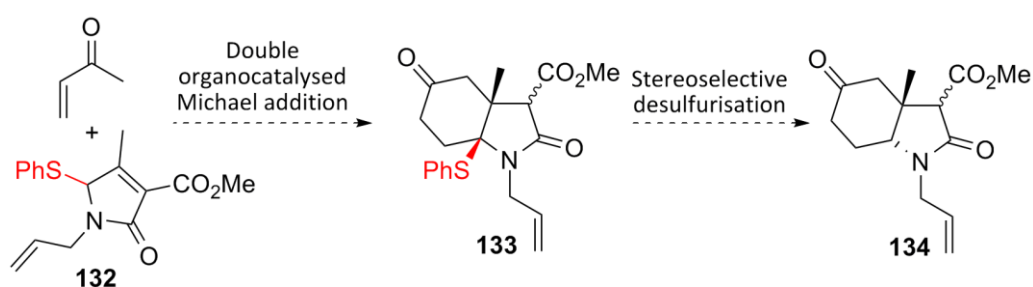
Scheme 2.42 Proposed enantioselective synthesis of the AC bicyclic core **134** of Daphniyunnine B

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*).

Scheme 2.43 Envisaged intramolecular Michael addition of **127**

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*).

Scheme 2.44 Proposed enantioselective synthesis of the ACD tricyclic core **42** of Daphniyunnine B

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.
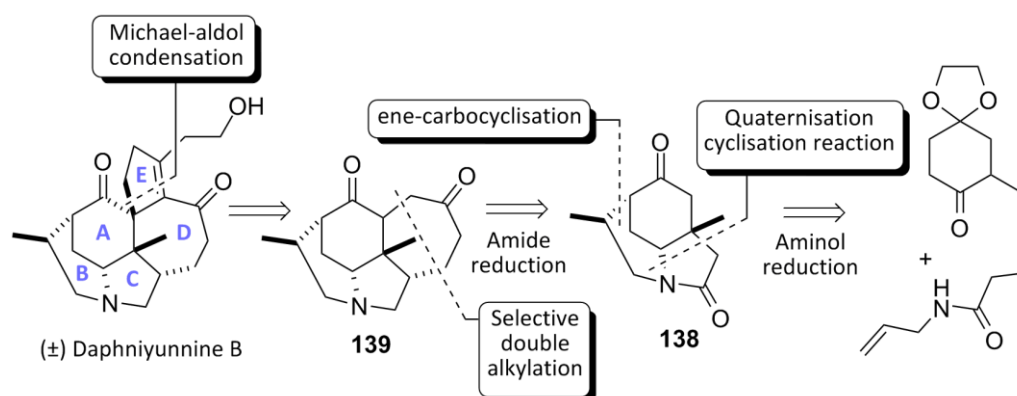
Scheme 3.1 Retrosynthetic analysis

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*).[50]
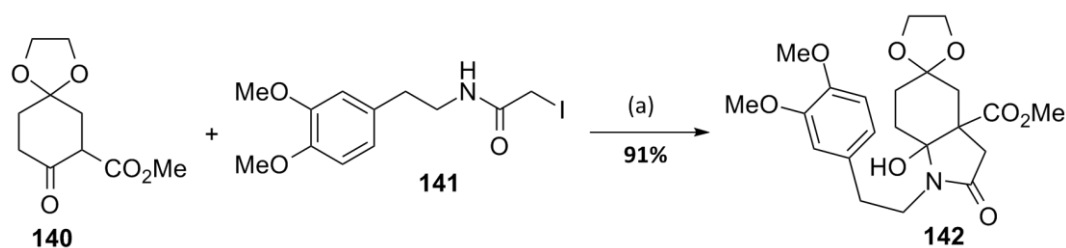
Scheme 3.2 Reagents and conditions (a) NaH (1.2 equiv.), THF, reflux then **141** (0.95 equiv.)

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 π-π bonding interactions (*Scheme 3.3*).[52]
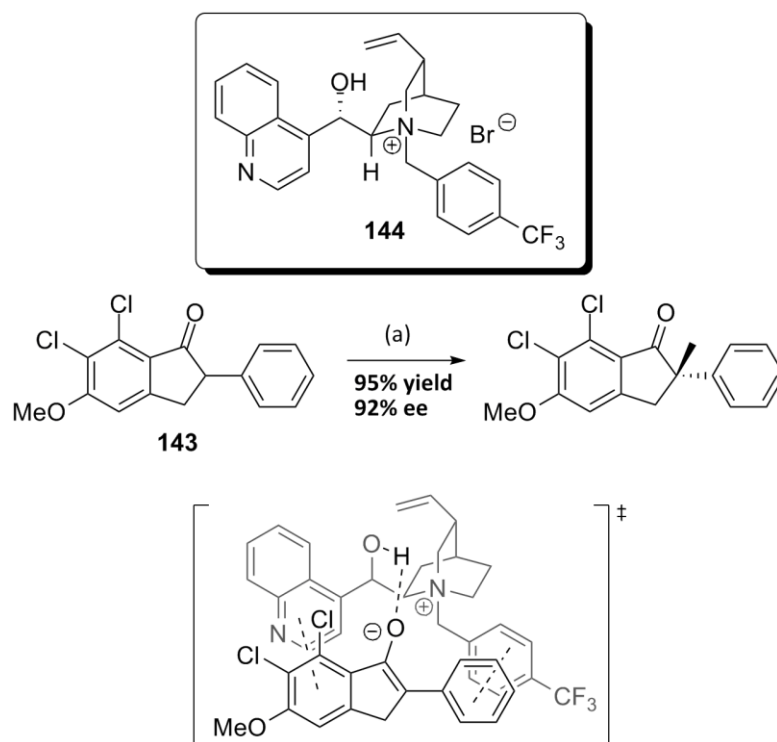
Scheme 3.3 Reagents and conditions (a) catalyst **144** (0.1 eq.), MeCl (1.0 equiv.), toluene/50% aq. NaOH, RT

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 pro-nucleophile is necessary to give high levels of enantioselectivity, presumably as this differentiates the two sides of the enolate (*Scheme 3.4*).[53]
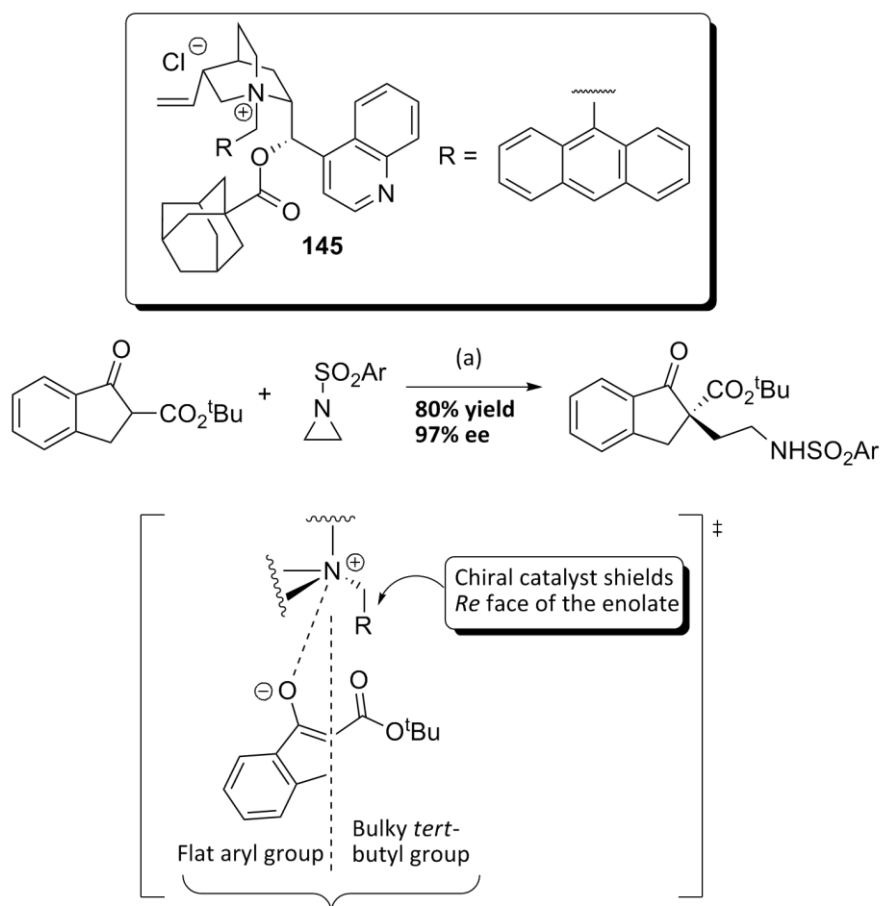
Scheme 3.4 Reagents and conditions (a) catalyst **145** (0.1 eq.), 50% aq. K_2HPO_4, toluene:$CHCl_3$ (9:1), -20 °C

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[54] and then developed by Conia and Perchec,[55] has received much attention in recent years.[56]

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,[55] strong mineral acid,[57] base,[54] or metal ion catalysis.[58] 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),[59] and copper(I)[60] species have proved to be efficient catalysts for the cyclisation of 1,3-dicarbonyls 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]
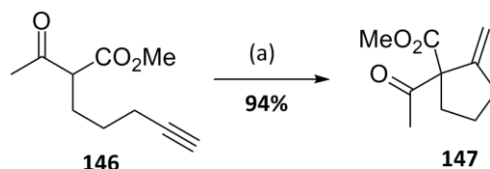
Scheme 3.5 Reagents and conditions (a) (PPh$_3$)AuCl (0.01 eq.), AgOTf (0.01 eq.), CH$_2$Cl$_2$, RT

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 protodemetallation 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 protodemetallation to produce the product **147** (*Scheme 3.6*).
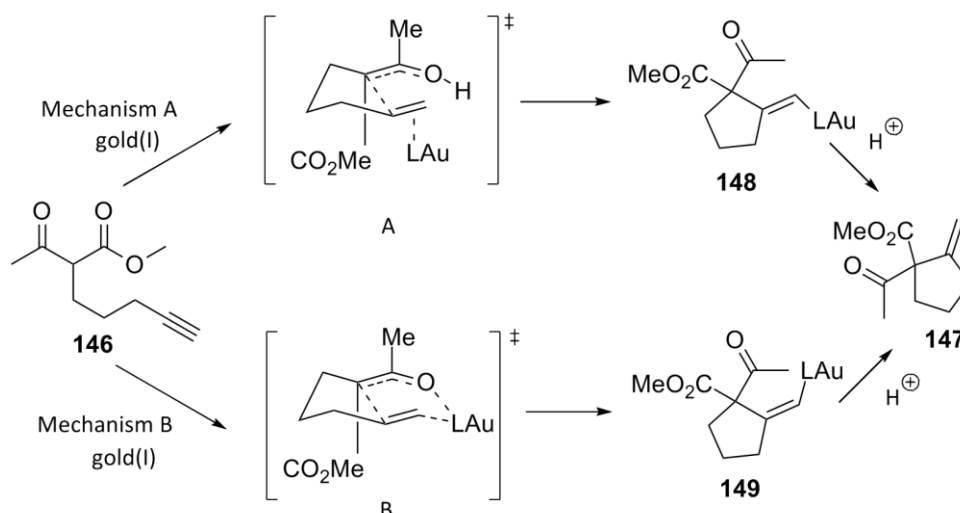
Scheme 3.6 Proposed mechanism for gold(I)-catalysed carbocyclisation reaction

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]
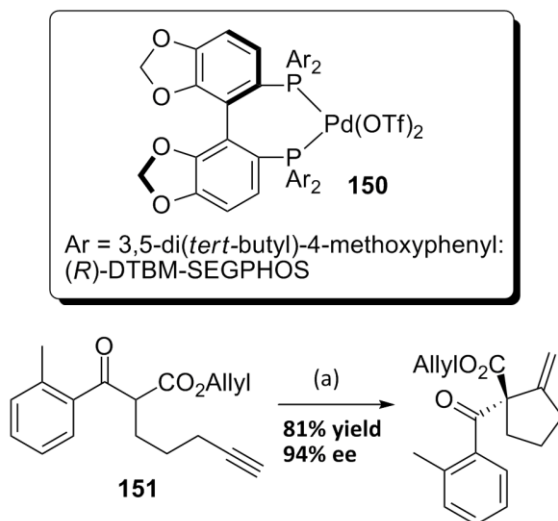
Scheme 3.7 Reagents and conditions (a) catalyst **150** (0.1 eq.), Yb(OTf)$_3$ (0.2 eq.), AcOH (10 equiv.), Et$_2$O, RT

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]
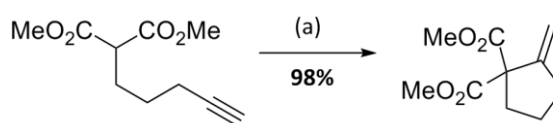
Scheme 3.8 Reagents and conditions (a) t-BuOK (0.15 eq.), CuI (0.1 eq.), THF, 30 °C

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*).[60]
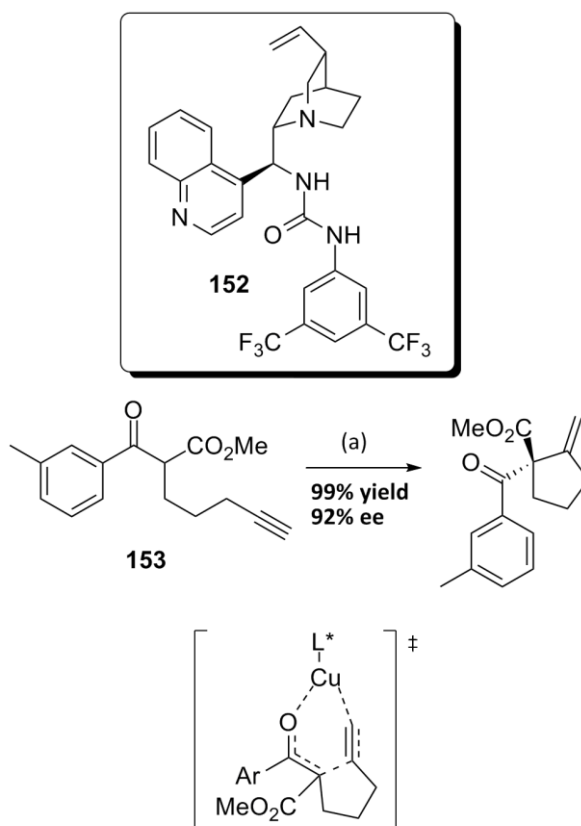
Scheme 3.9 Reagents and conditions (a) catalyst **152** (0.2 eq.), CuOTf$\cdot^1/_2$C$_6$H$_6$ (0.05 eq.),CH$_2$Cl$_2$, RT

The use of silyl enol ethers as π-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*).[63]
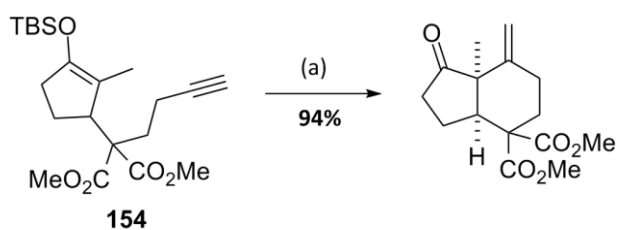
Scheme 3.10 Reagents and conditions (a) Ph$_3$PAuCl (0.1 eq.), AgBF$_4$ (0.1 eq.),CH$_2$Cl$_2$/H$_2$O (10:1), 40 ^{o}C

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]
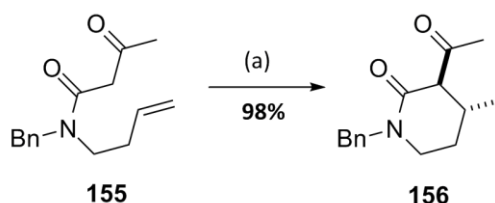
Scheme 3.11 Reagents and conditions (a) Au[P(t-Bu)$_2$(*o*-biphenyl)]Cl (0.05 eq.), AgOTf, (0.05 eq.), PhMe, 60 °C

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*).
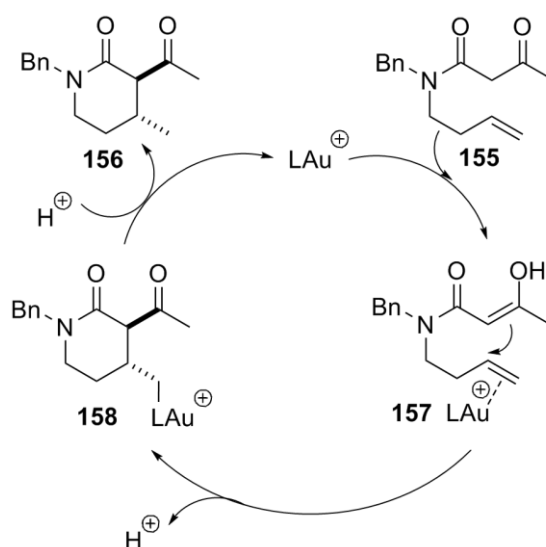
Scheme 3.12 Proposed ene-carbocyclisation reaction mechanism

The use of silyl enol ethers as π-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]
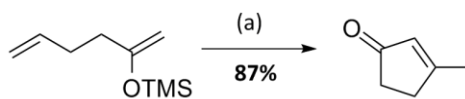
Scheme 3.13 Reagents and conditions (a) Pd(OAc)$_2$ (1.0 eq.), CH$_3$CN, RT

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*).
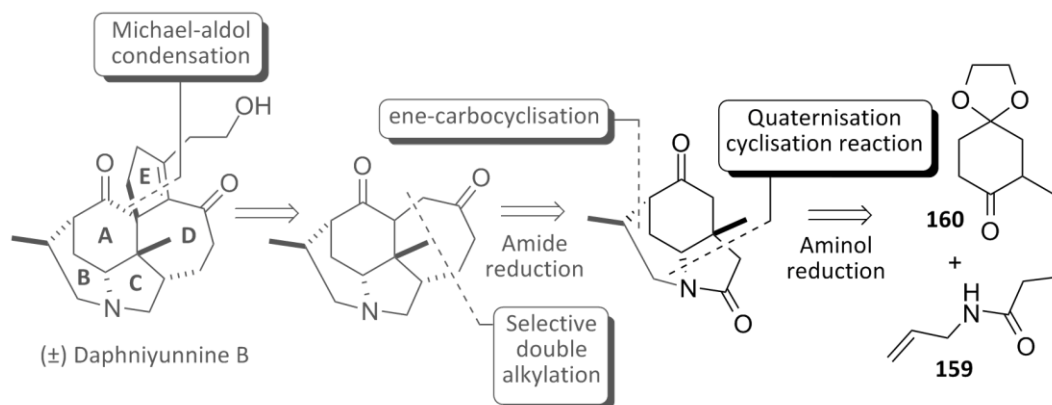
Scheme 3.14 Retrosynthetic analysis

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]
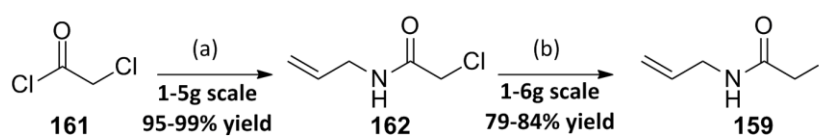
Scheme 3.15 Reagents and conditions (a) allylamine (1.07 eq.), triethylamine (1.0 eq.), THF, 0 °C to RT, 12h; (b) sodium iodide (1.1 eq.), acetone, 2h

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]
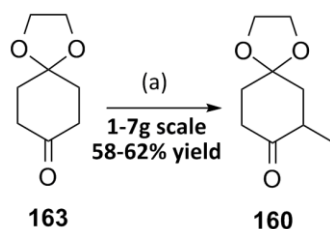
Scheme 3.16 Reagents and conditions (a) LDA (1.0 eq.), iodomethane (1.2 eq.), THF, -78 °C to RT

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*).
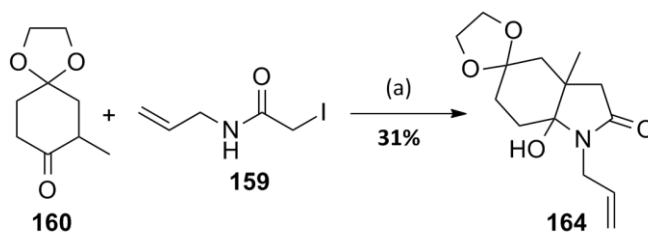
Scheme 3.17 Reagents and conditions (a) NaH (1.0 eq.), reflux, 2h, then; Iodoacetamide **159** (1.1 eq.), THF, -78 °C to RT

A variety of reaction conditions were investigated to improve the yield of this reaction and are shown in Table **3.1**.
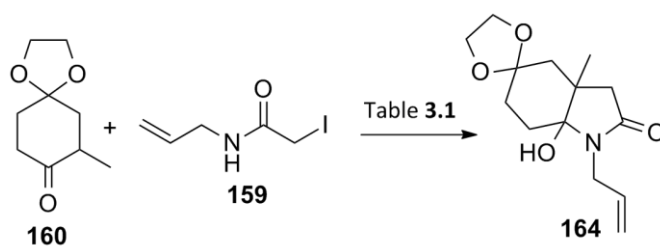
Table 3.1 Screen of reaction conditions

Entry[a]	Base (eq.)	Iodoacetamide **159** (eq.)	Isolated yield (%)	Yield brsm **160** (%)
1	NaH (1.0)	1.1	31	60
2	LHMDS (1.0)	1.1	34	67
3	LDA (1.0)	1.1	39	71
4	LDA (1.0)	3.0	33	64
5	LDA (2.0)	1.0	22	60

[a]Ketone **160** refluxed in tetrahydrofuran for 2h and then addition of iodoacetamide **159** at -78 $^{\circ}$C to RT

Replacing sodium hydride with lithium hexamethyldisilazane slightly increased the yield (*entry 2*) however lithium di*iso*propylamide 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.[68] 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*).
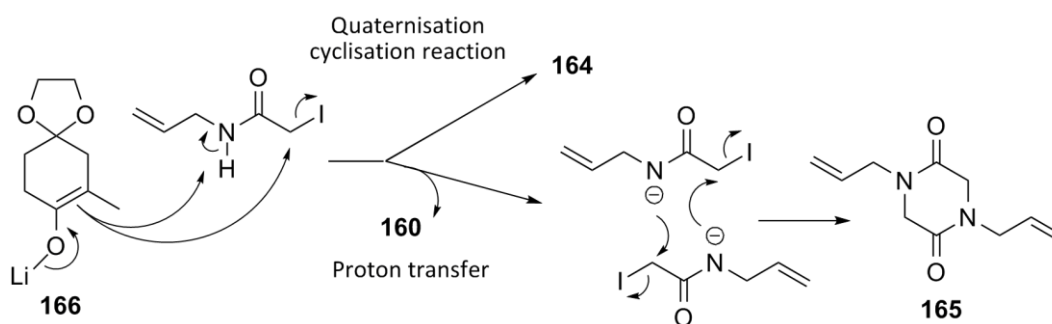
Scheme 3.18 Mechanistic rationale for poor yields and production of diketopiperazine **165**

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 diastereisomer.[69] Presumably, equatorial attack of the hydride of the silane onto the *N*-acyliminium ion was preferential as to avoid 1,3 diaxial interactions.[70] 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*).[69]
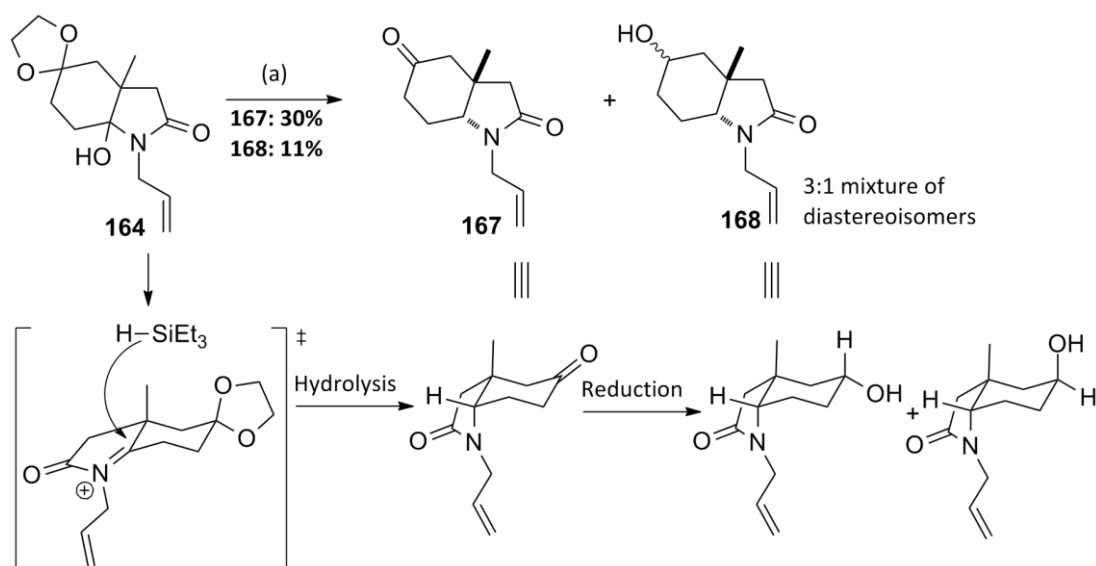
Scheme 3.19 Reagents and conditions (a) triethylsilane (10.0 eq.), BF$_3$.Et$_2$O (10.0 eq.), CH$_2$Cl$_2$, 0 °C, 10m

An investigation into this reaction found that generation of the *N*-acyliminium ion with one equivalent of trifluoroacetic acid rather than borontrifluoride 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*).
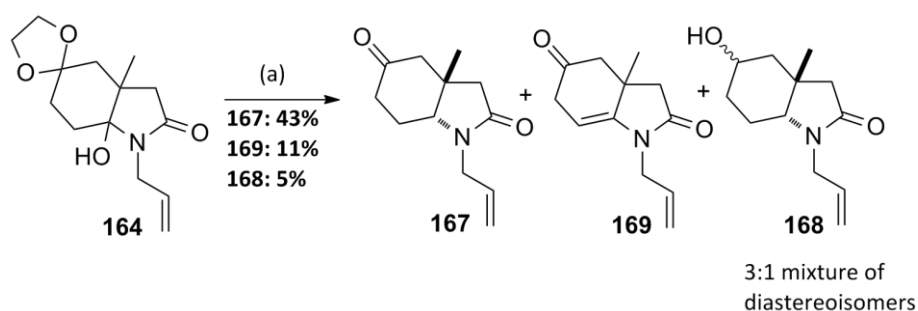
Scheme 3.20 Reagents and conditions (a) triethylsilane (1.0 eq.), TFA (1.0 eq.), CH$_2$Cl$_2$, -20 °C to 0 °C, 10m

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*).
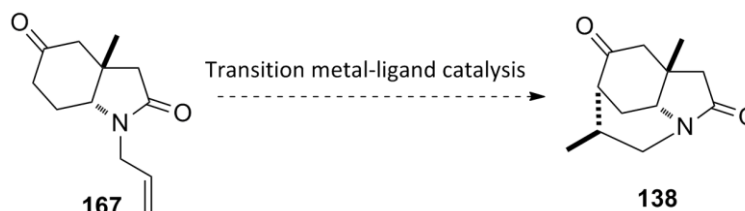
Scheme 3.21 Proposed ene-carbocyclisation of **167**

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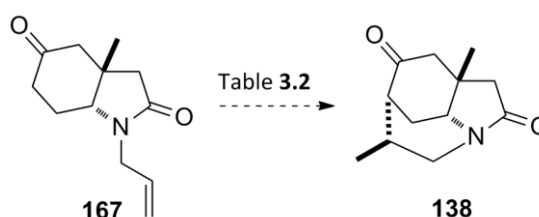
Table 3.2 Screen of ene-carbocyclisation reaction conditions

Entry[a]	Catalyst/pre-catalyst/additive (0.2 eq.)	Solvent	Reaction outcome[b]
1	(PPh$_3$)AuCl/AgOTf	PhMe or CH$_2$Cl$_2$	Recovery of starting material
2	(PPh$_3$)AuCl/AgOTf/pyrrolidine	PhMe or CH$_2$Cl$_2$	Recovery of starting material
3	(PPh$_3$)AuCl/AgOTf/*t*-BuOK (2.0 eq.)	PhMe or THF or dioxane	Recovery of starting material
4	Cu(OTf)$_2$/pyrrolidine	PhMe or CH$_2$Cl$_2$	Recovery of starting material
5	CuI/*t*-BuOK (2.0 eq.)	THF	Recovery of starting material
6	PdCl$_2$(CH$_3$CN)$_2$/CuCl$_2$/TMSCl (1.0 eq.)	Polyethylene glycol	Recovery of starting material

[a] All reactions began at room temperature and refluxed for 48h. [b] 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 **170** and thus low enol concentration did not perform the desired ene-carbocyclisation (*Scheme 3.22*).[64]
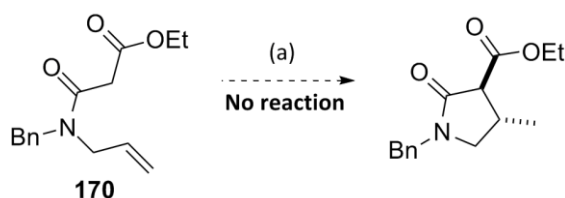
Scheme 3.22 Reagents and conditions (a) Au[P(t-Bu)$_2$(o-biphenyl)]Cl (0.05 eq.), AgOTf (0.05 eq.), Toluene, 50 °C

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*).
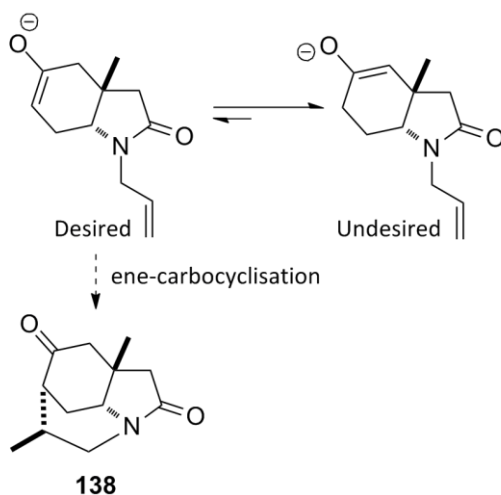
Scheme 3.23 Proposed equilibrium between desired and undesired enolates

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*).
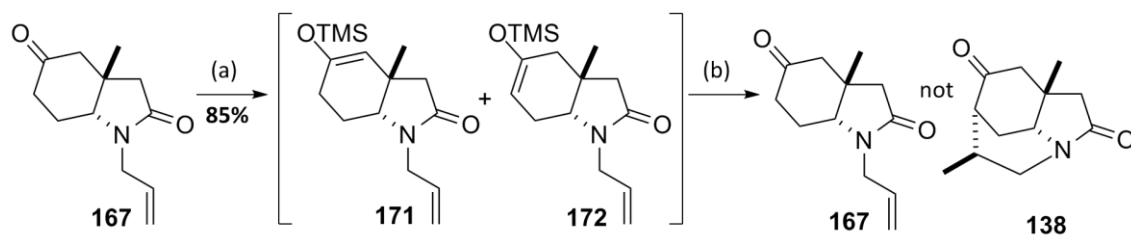
Scheme 3.24 Reagents and conditions (a) Et$_3$N (3.0 eq.), TMS-OTf (3.0 eq.), CH$_2$Cl$_2$, 0 °C; (b) Ph$_3$PAuCl (0.2 eq.), AgOTf (0.2 eq.), toluene, reflux

With the transition metal-ligand catalysis failing to achieve the ene-carbocyclisation, we envisaged that α-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 tricyclic core **138** (*Scheme 3.25*).[72]
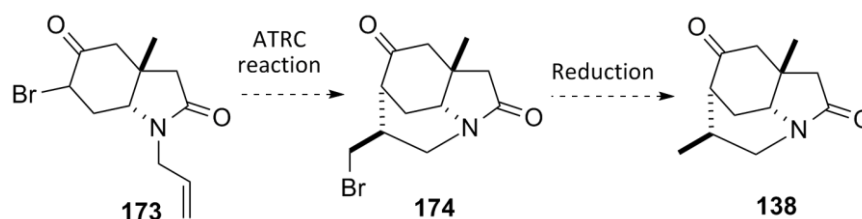
Scheme 3.25 Synthesis of **138** *via* ATRC reaction

The α-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 ^{1}H 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*).
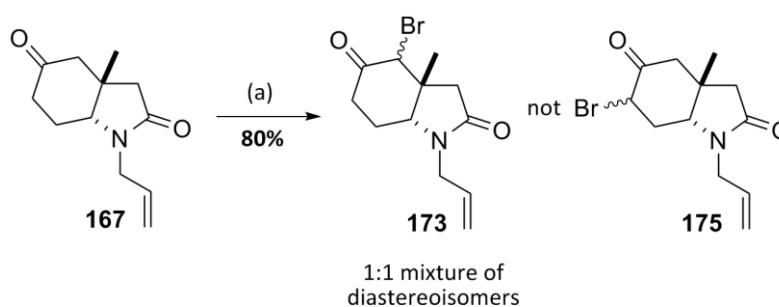
Scheme 3.26 Reagents and conditions (a) PTAP (1.2 eq.), THF, RT, 30m

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*).
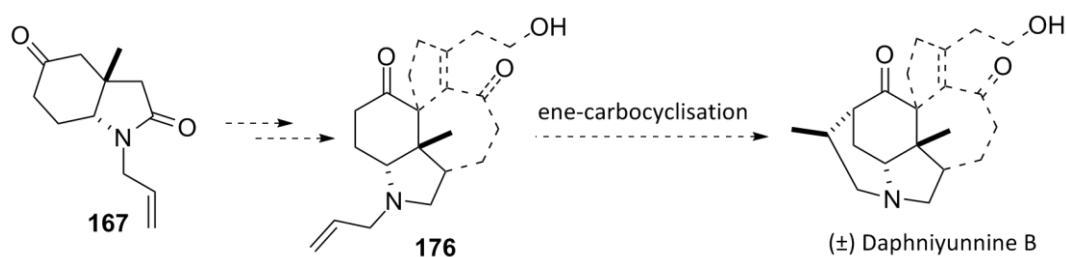
Scheme 3.27 Exploitation of the thermodynamic enolate to install right-hand side of Daphniyunnine B

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[75] and ii) β-keto esters undergo efficient alkylation reactions with acetamides.[50] One step ester reduction to the methyl group are precedented[76] however if required, step-wise ester and aminol reductions along with acetal hydrolysis could furnish enantiopure bicycle **167** (*Scheme 3.28*).
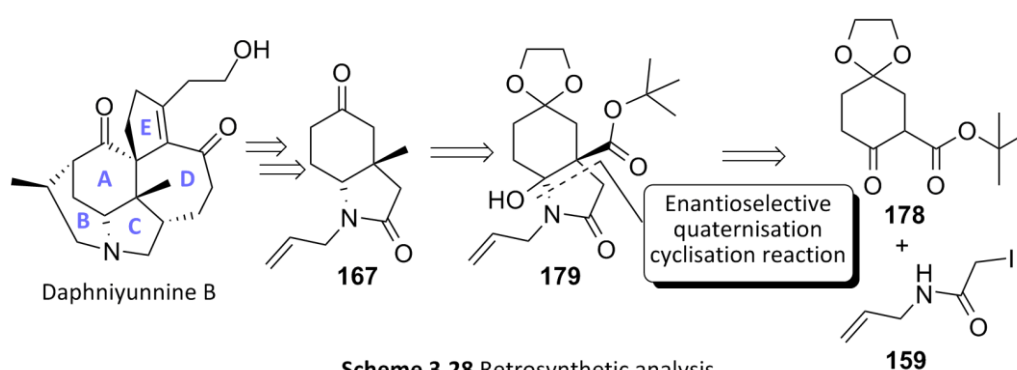
Scheme 3.28 Retrosynthetic analysis

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.[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. [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,[79] the commercially available and considerably less expensive[80] *tert*-butyl pyrrole-1-carboxylate **180**, was considered an attractive acylating agent. Treatment of the cyclic ketone **163** with a base followed by addition of *tert*-butyl pyrrole-1-carboxylate could afford the tetrahedral intermediate **181**. Heating would ensure decomposition of this intermediate to the *tert*-butyl ester **178** and relatively low toxicity side products (pyrrole) (*Scheme 3.29*).
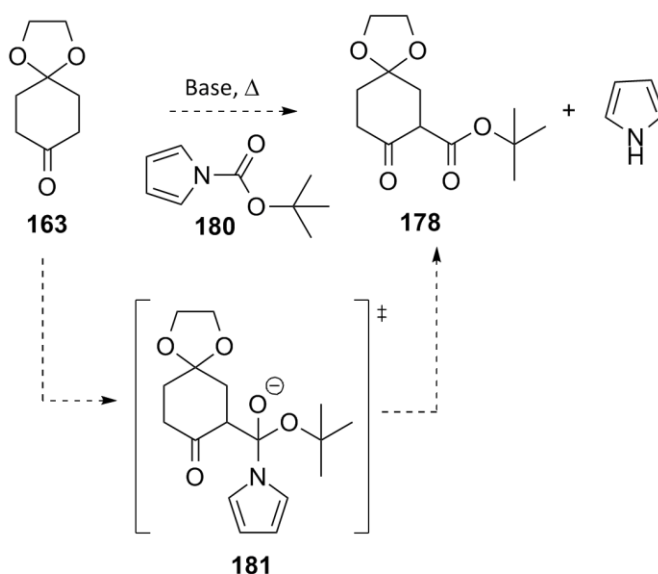
Scheme 3.29 Proposed preparation of *tert*-butyl ester **178**

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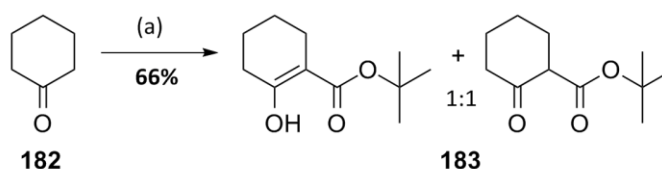
Scheme 3.30 Reagents and conditions (a) NaH (2.0 eq.), *tert* butyl pyrrole-1-carboxylate **180** (2.0 eq.), THF, reflux, 2h

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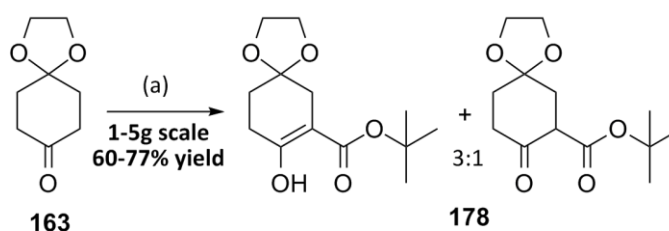
Scheme 3.31 Reagents and conditions (a) NaH (2.0 eq.), *tert* butyl pyrrole-1-carboxylate **180** (2.0 eq.), THF, reflux, 2h

This efficient, scalable acylation method has since been published by colleagues in the Dixon group for the preparation of *tert*-butyl ester starting materials.[75c] 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*).
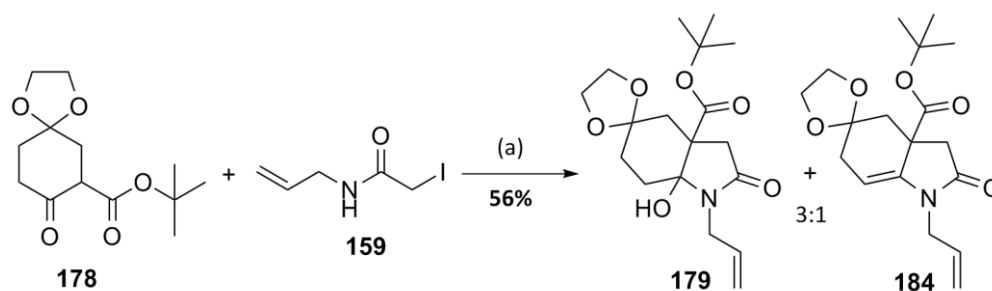
Scheme 3.32 Reagents and conditions (a) NaH (1.2 eq.), THF, reflux, 2h, then; Iodoacetamide **159** (0.95 eq.), THF, -78 °C to RT

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*).
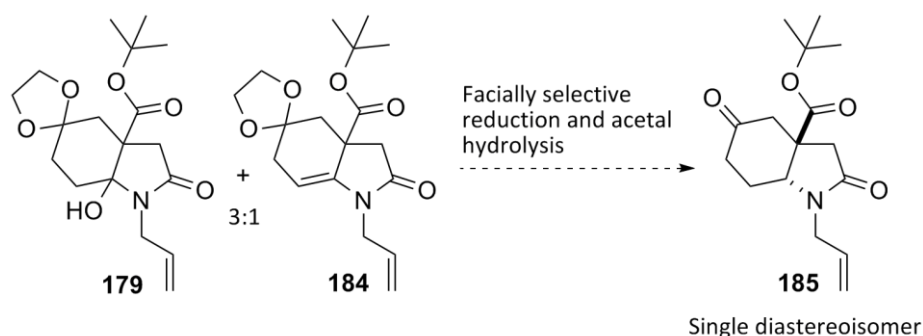
Scheme 3.33 Pathway to obtain HPLC analysis of racemate **185**

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**.
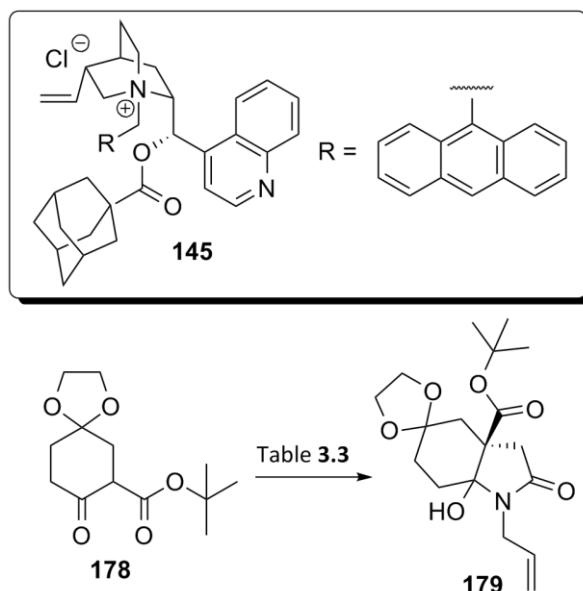
Table **3.3** Screen of enantioselective reaction conditions

Entry[*]	Base (eq.)	178 (eq.)	159 (eq.)	Solvent	T (°C)	Isolated yield (%)	Yield brsm 178 (%)
1	50% aq. K$_2$HPO$_4$ (3.0)	1.0	1.2	Toluene/CHCl$_3$ (9:1)	-20	19	57
2	50% aq. K$_2$HPO$_4$ (3.0)	1.0	1.2	Toluene/CHCl$_3$ (9:1)	RT	21	45
3	50% aq. K$_3$PO$_4$ (3.0)	1.0	1.2	Toluene/CHCl$_3$ (9:1)	RT	25	67
4	50% aq. K$_3$PO$_4$ (3.0)	1.0	1.2	CH$_2$Cl$_2$	RT	12	77
5	50% aq. K$_3$PO$_4$ (3.0)	1.0	1.2	THF	RT	15	71
6	50% aq. K$_3$PO$_4$ (3.0)	2.0	1.0	Toluene/CHCl$_3$ (9:1)	RT	17	-

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

None of the enamide **184** obtained previously was isolated from the enantioselective reactions.[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

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[*] 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*).
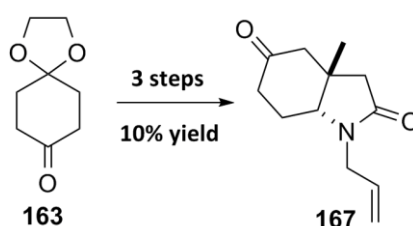
Scheme 3.34 Preparation of **167** as a single diastereoisomer

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*).

Mixture of keto/enol forms
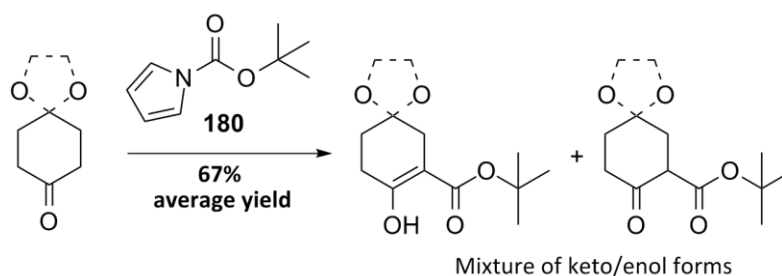
Scheme 3.35 Synthesis of *tert*-butyl esters using *tert*-butyl pyrrole-1-carboxylate **180**

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*).
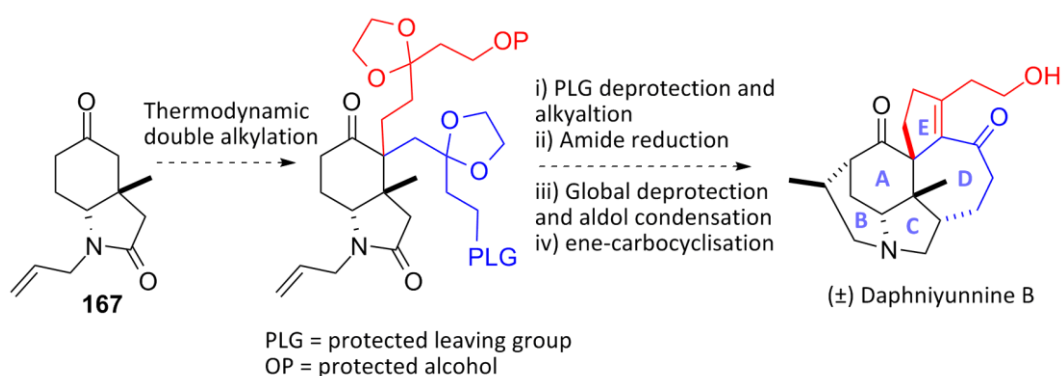
Scheme 3.36 Proposed forward synthesis of (±) Daphniyunnine B from **167**

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*).
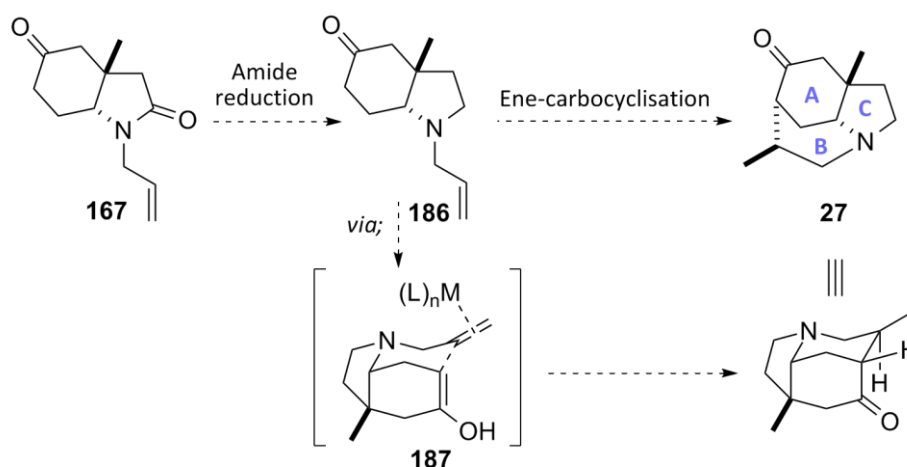
Scheme 3.37 Proposed ene-carbocyclisation of **186** to afford the ABC tricylclic core **27** of (±) Daphniyunnine B

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*).
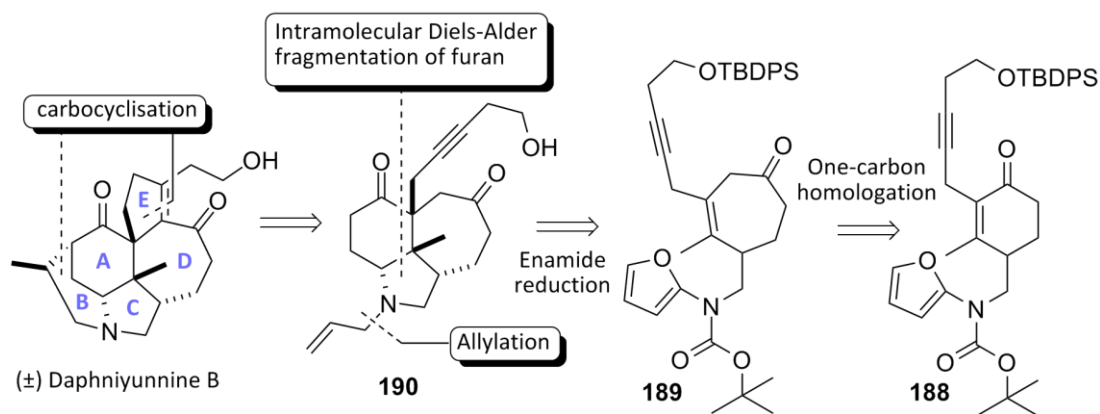
Scheme 4.1 Retrosynthetic analysis

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[81] and generally low yields of the desired product are obtained due to low regioselective control and frequent side reactions such as epoxide formation **191** and multiple carbon insertions **192** (*Scheme 4.2*).[82]
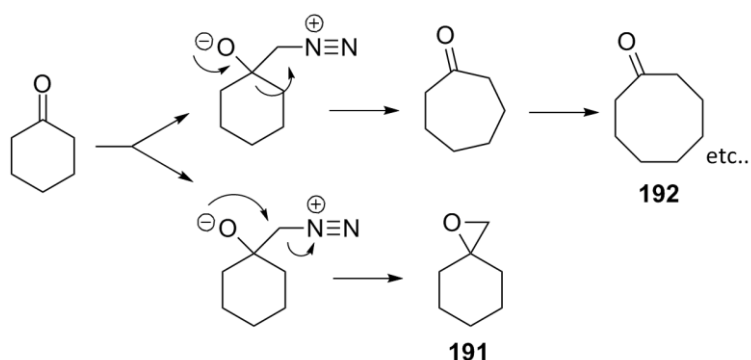
Scheme 4.2 Diazomethane one-carbon homologation

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*).[83]

	(a)	(b)
	10%	7%
	69%	Trace
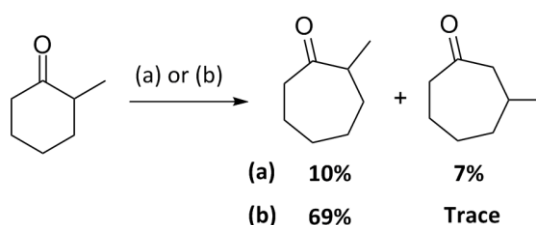
Scheme 4.3 Reagents and conditions (a) CH_2N_2, Et_2O; (b) $TMSCHN_2$, $BF_3 \cdot Et_2O$, CH_2Cl_2

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*).[84]
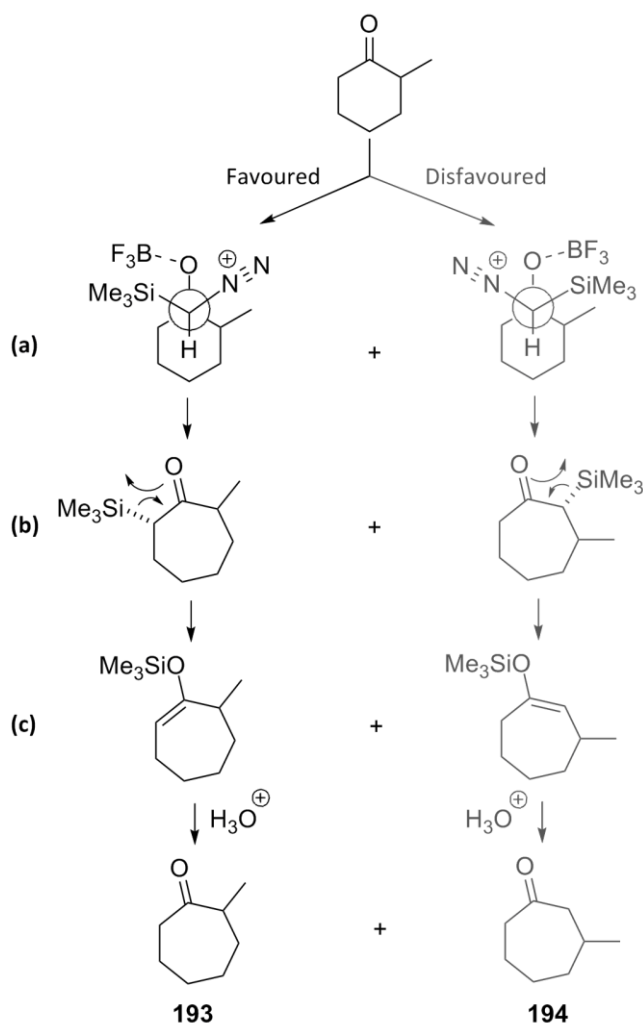
Scheme 4.4 Mechanism of one-carbon homologation

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. [85]

Cyclic α,β-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 α,β-unsaturated ketone **195** in their pursuit of the cyathin terpenoids (*Scheme 4.5*).[86]
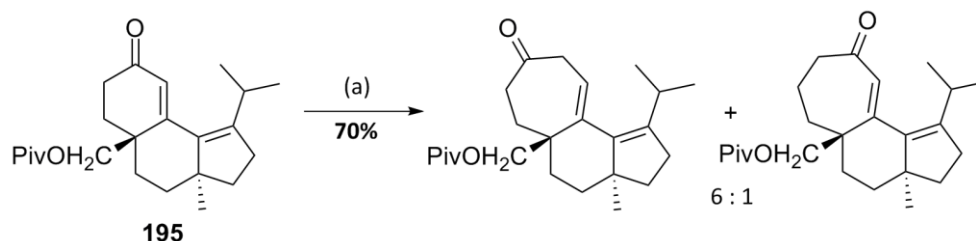
Scheme 4.5 Reagents and conditions (a) Me₃Al (5.0 eq.), TMSCHN₂ (5.0 eq.), CH₂Cl₂, RT, 4h then, 3M HCl, acetone, RT, 2h

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 β-OXIDO CARBENOID HOMOLOGATIONS

Nozaki and co-workers pioneered studies into β-oxido carbenoid homologations of symmetrical and unsymmetrical cyclic ketones (*Scheme 4.6*).[87]
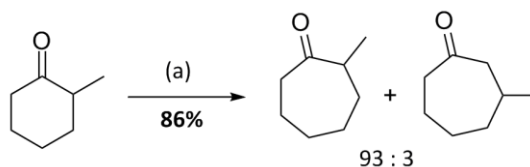
Scheme 4.6 Reagents and conditions (a) Br₂CH₂ (2.0 eq.), LDA (1.5 eq.), Et₂O, -95 °C, then, n-BuLi (4.0 eq.)

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*).
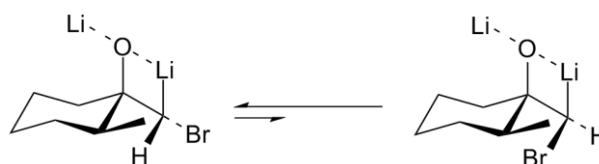
Scheme 4.7 Rationale for regioselectivity

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.[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[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.[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.[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[91] 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*).[92]
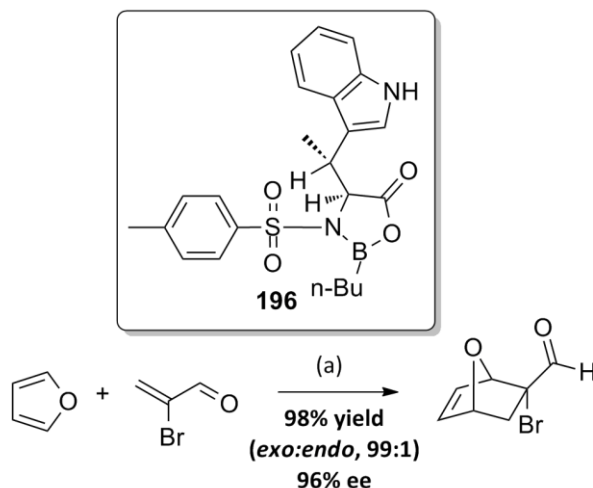
Scheme 4.8 Reagents and conditions (a) catalyst **196** (0.1 eq.), CH_2Cl_2, -78 ^oC, 5h

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.[91] 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.[91, 93] 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.[91]

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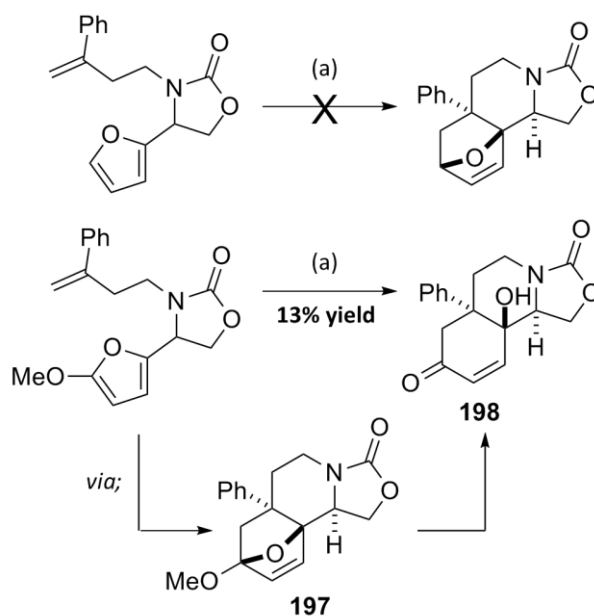
Scheme 4.9 Reagents and conditions (a) toluene, sealed tube, 250 °C

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]
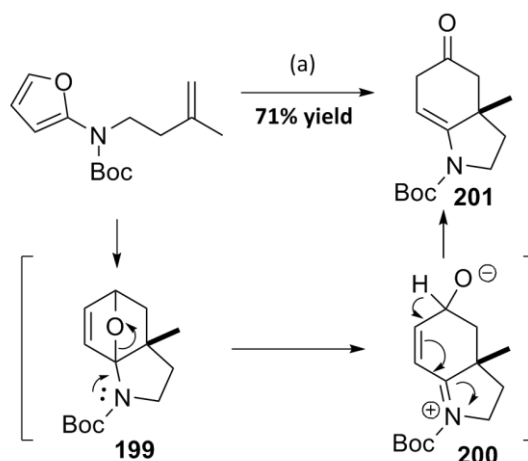
Scheme 4.10 Reagents and conditions (a) benzene, sealed tube, 165 °C

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*).[96]
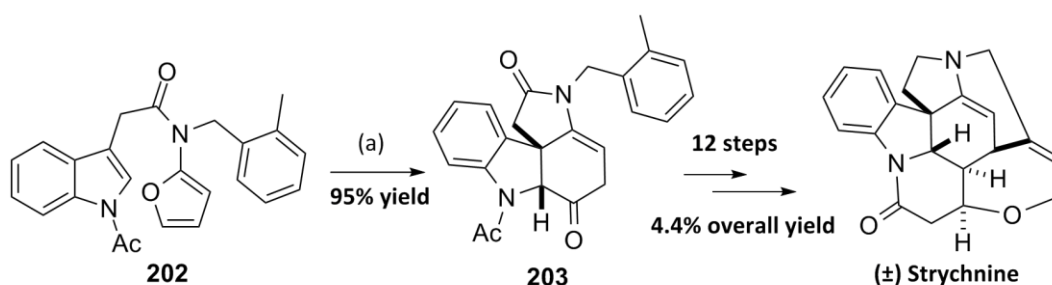
Scheme 4.11 Reagents and conditions (a) toluene, microwave reactor, MgI$_2$ (cat.), 150 °C

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.[69, 95] 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.[97] 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 α,β-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*).[98]
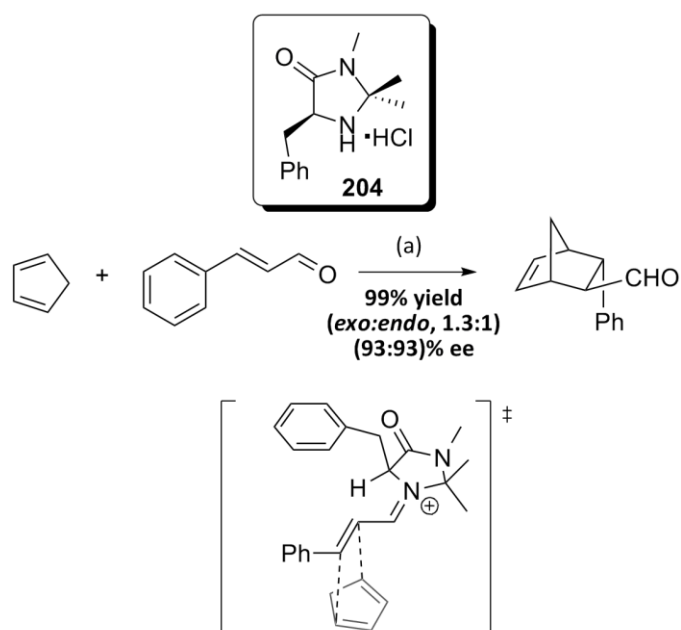
Scheme 4.12 Reagents and conditions (a) catalyst **204** (0.05 eq.), MeOH-H$_2$O, 23 $^{\circ}$C, 21h

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*).[99]
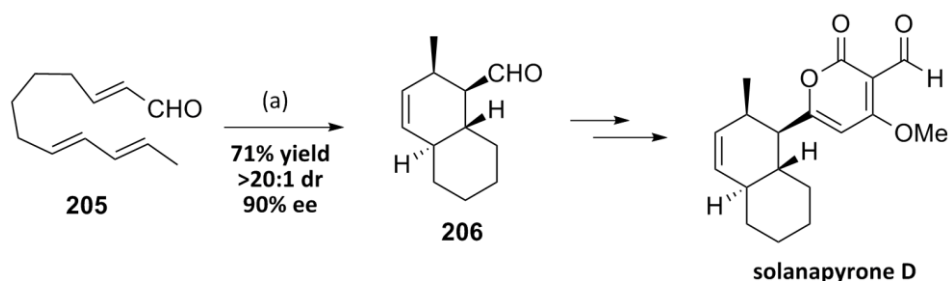
Scheme 4.13 Reagents and conditions (a) catalyst **204** (0.2 eq.), MeCN, 5 °C

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.

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*).[100]
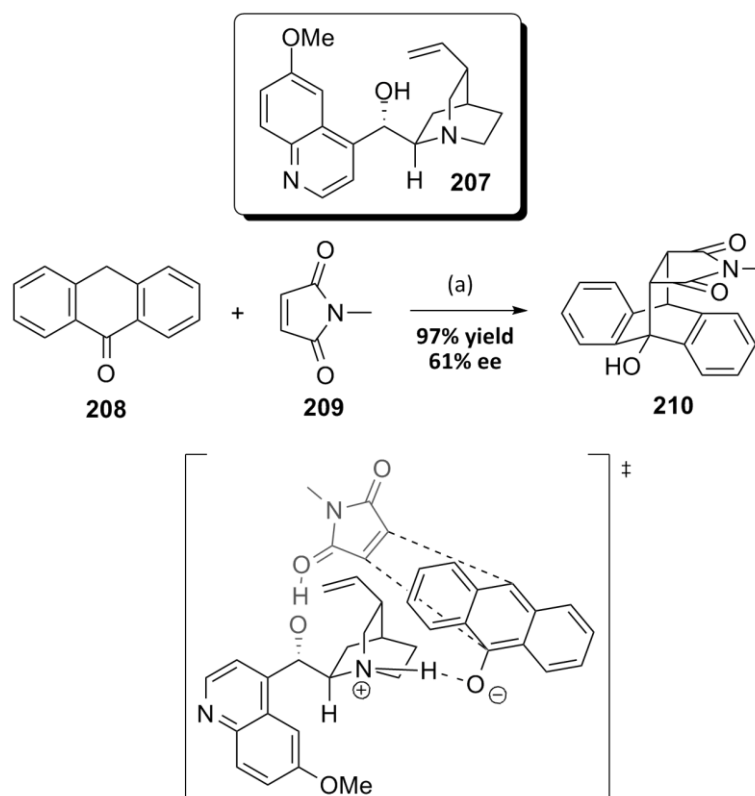
Scheme 4.14 Reagents and conditions (a) catalyst **207** (0.01 eq.), CHCl$_3$,- 50 °C

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*).[101]

Scheme 4.15 Reagents and conditions (a) catalyst **211** (0.05 eq.), Et$_2$O, RT

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 α,β-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]

Scheme 4.16 Reagents and conditions (a) catalyst **214** (0.05 eq.), CH$_2$Cl$_2$, -20 °C, 96h

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
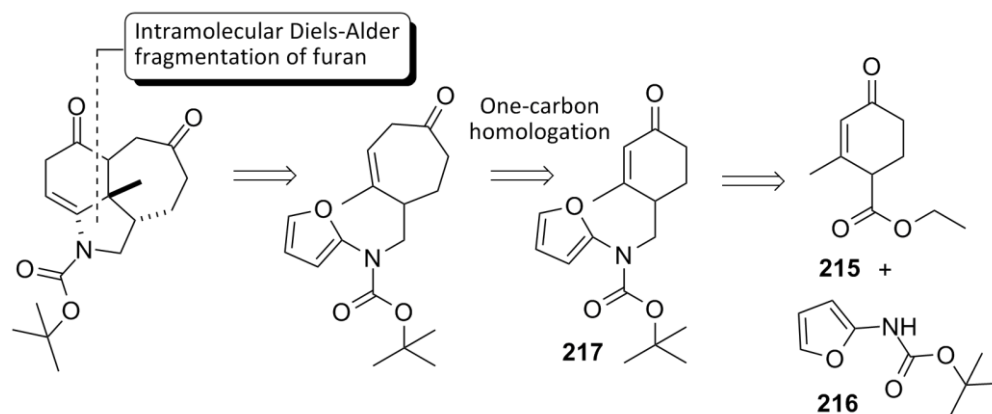
4.4.1 PREPARATION OF AMIDOFURAN 216

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
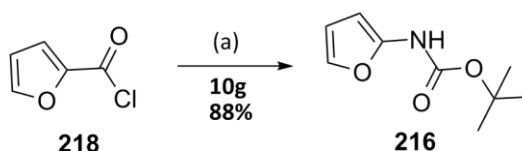
4.4.2 PREPARATION OF α,β-UNSATURATED CYCLIC KETONE 217

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]
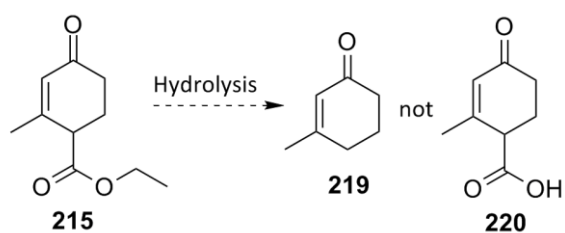
Scheme 4.19 Literature precedent for hydrolysis of **215**

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**.[105, 106] Acetal hydrolysis could form the β,γ-unsaturated ketone **223**, which was predicted to undergo tautomerism to the desired stable conjugated α,β-unsaturated cyclic ketone **217** (*Scheme 4.20*).
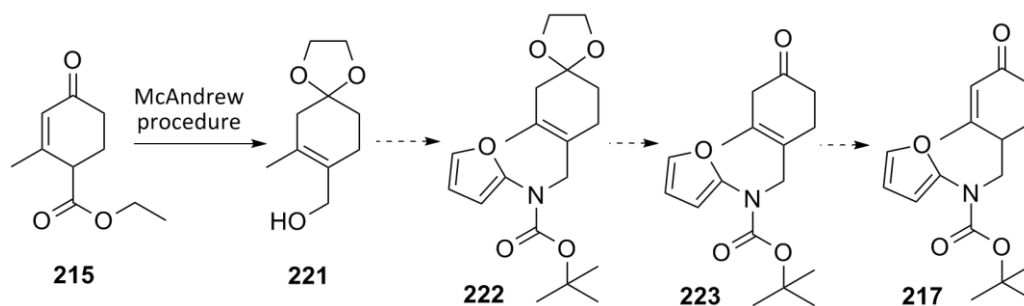
Scheme 4.20 Envisaged preparation of α,β-unsaturated ketone **217**

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 (*Scheme 4.21*).
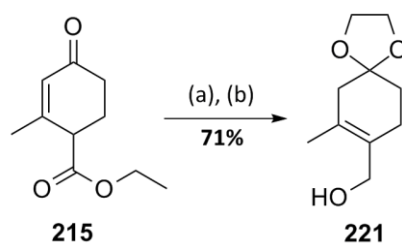
Scheme 4.21 Reagent and conditions (a) $CH(OCH_3)_3$ (3.0 eq.), p-TSA (0.1 eq.), ethylene glycol, RT, 12h; (b) $LiAlH_4$ (3.0 eq.), THF, 0 °C, 10m

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.[105] Mesylation and halogenation of the allylic alcohol **221** also gave products unstable upon isolation generating the diene **225** (*Scheme 4.22*).[106]
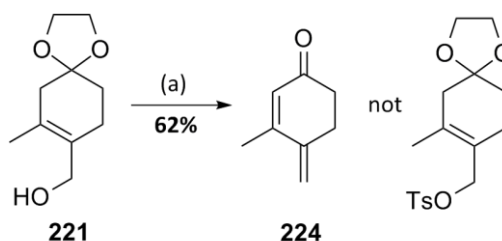
Scheme 4.22 Reagents and conditions (a) triethylamine (1.1 eq.), tosyl chloride (1.1 eq.), CH_2Cl_2, 0 °C, 1h

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*).
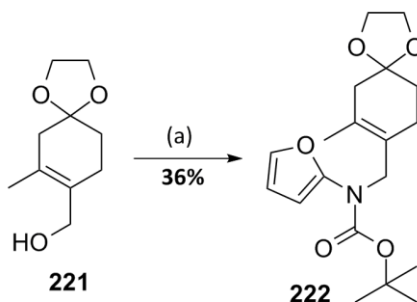
Scheme 4.23 Reagent and conditions (a) triethylamine (1.1 eq.), tosyl chloride (1.1 eq.), THF, 0 °C, 1h, then LHMDS (1.0 eq.), amidofuran **216** (1.0 eq.), THF, reflux, 12h

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*).[107]
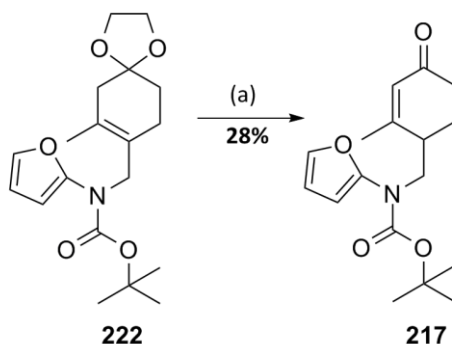
Scheme 4.24 Reagent and conditions (a) 1M HCl, THF, 12h

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*).
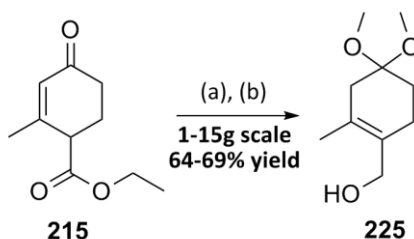
Scheme 4.25 Reagent and conditions (a) $CH(OCH_3)_3$ (3.0 eq.), p-TSA (0.2 eq.), MeOH, RT, 12h; (b) $LiAlH_4$ (3.0 eq.), THF, 0 °C, 10m

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*).
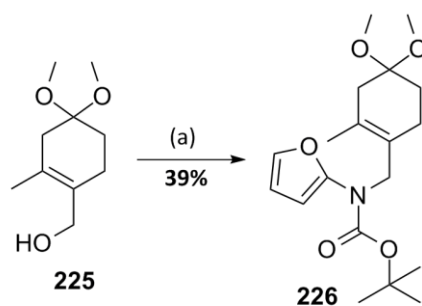
Scheme 4.26 Reagent and conditions (a) triethylamine (1.1 eq.), tosyl chloride (1.1 eq.), THF, 0 °C, 1h, then LHMDS (1.0 eq.), amidofuran **216** (1.0 eq.), THF, reflux, 12h

A range of reaction conditions were investigated to increase yields and are shown in Table **4.1**.
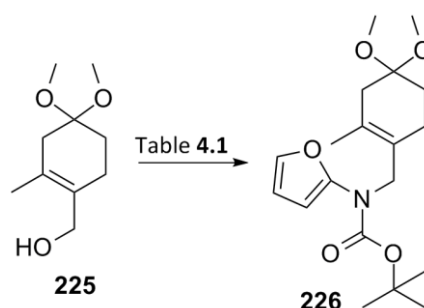
Table 4.1 Optimisation of nucleophilic substitution

Entry[a]	Activation of alcohol		Amidofuran **216**[b]	T (°C)	Time (h)	Yield (%)
	Base (1.1 eq.)	Activating reagent (1.1 eq.)	Base (1.5 eq.)			
1	Et$_3$N	Tosyl chloride	KHMDS	0 °C-RT	12	42
2	LHMDS	Tosyl chloride	LHMDS	-78 °C-reflux	12	45
3	LHMDS	Tosyl chloride	KHMDS	-78 °C-RT	6	51
4	n-BuLi	Tosyl chloride	KHMDS	-78 °C-RT	2	64

[a] Tetrahydrofuran was used as the solvent in each case; [b] 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*).
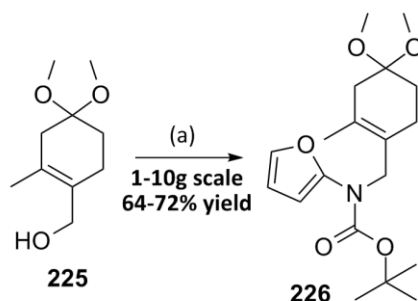
Scheme 4.27 Reagent and conditions (a) n-BuLi (1.0 eq.), tosyl chloride (1.05 eq.), then; amidofuran **216** (1.07 eq.), KHMDS (1.07 eq.), THF, -78 °C to RT

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*).
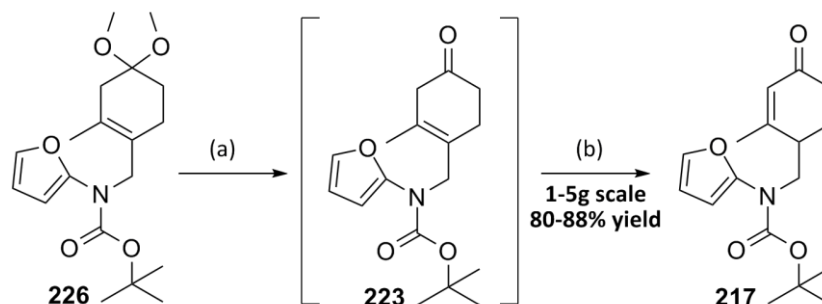
Scheme 4.28 Reagent and conditions (a) 0.1M HCl:THF (1:1), RT, 10m; (b) K_2CO_3 (0.2 eq.), MeOH, RT, 10m

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 hydroxyl toluene (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*). [69]
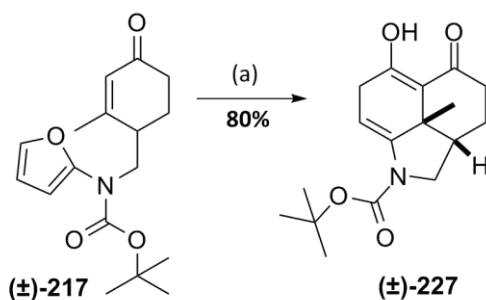
Scheme 4.29 Reagent and conditions (a) BHT (0.2 eq.), PhMe, reflux, 2d

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*).
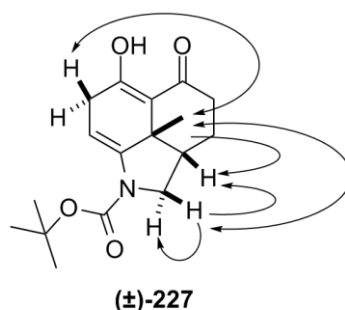
Figure 4.1 nOe experiments of **(±)-227**

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*).
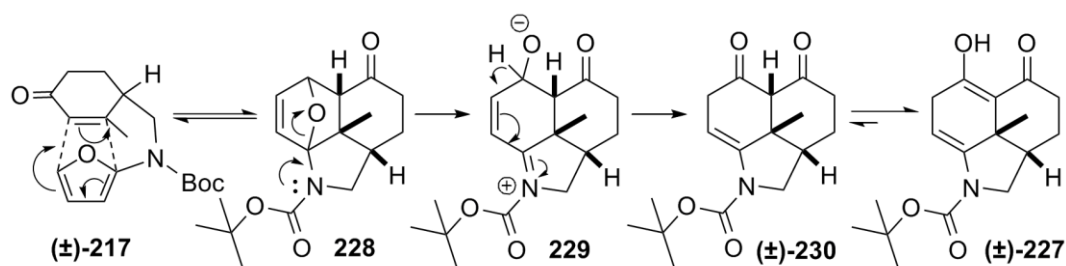
Scheme 4.30 Proposed origins of stereocontrol

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 ^{1}H 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*).
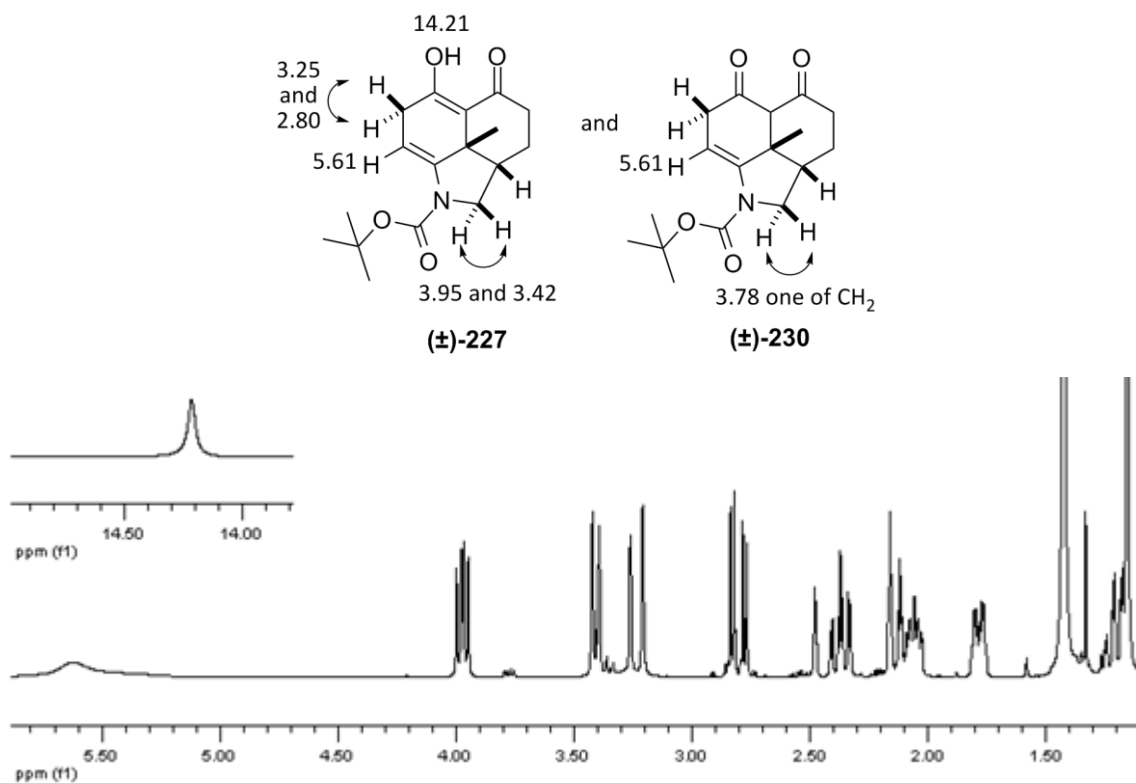
Figure 4.2 ^{1}H NMR in deuterated DMSO at room temperature of **(±)-227** and **(±)-230**
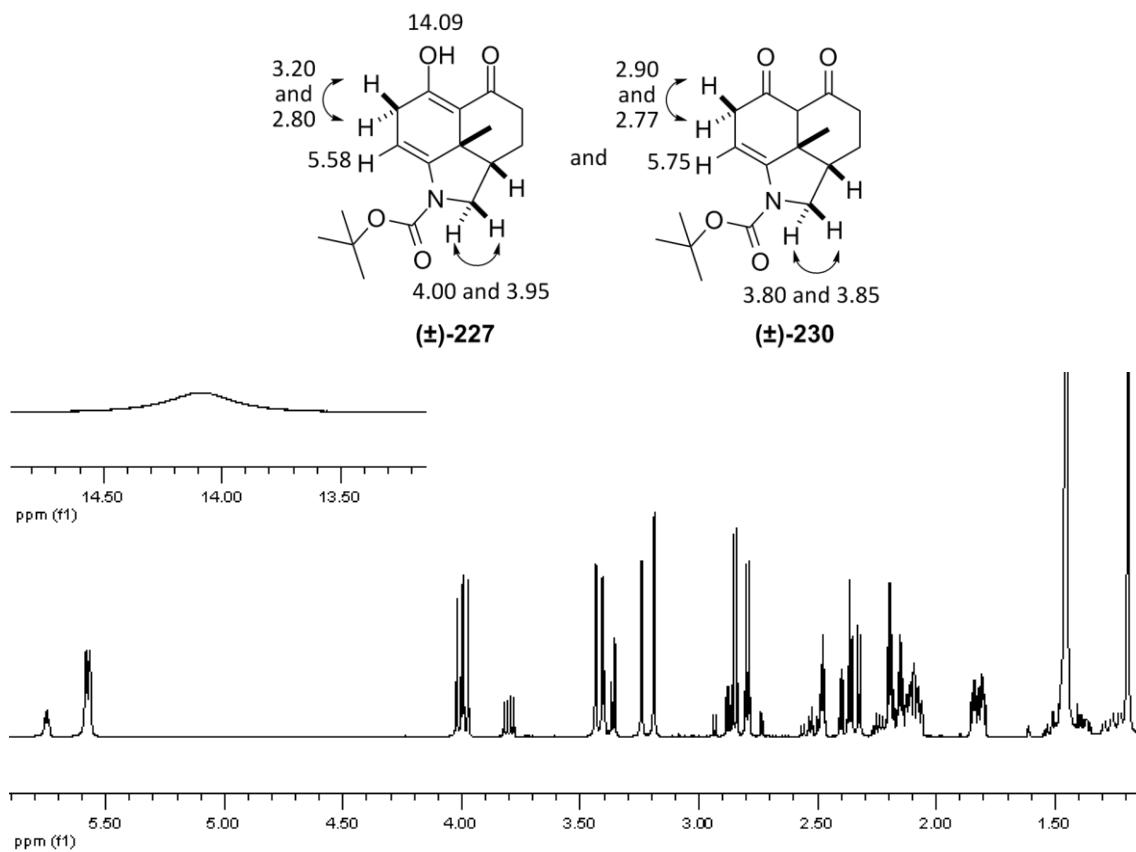
Figure 4.3 ^{1}H NMR in deuterated DMSO at 90°C of **(±)-227** and **(±)-230**

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*).
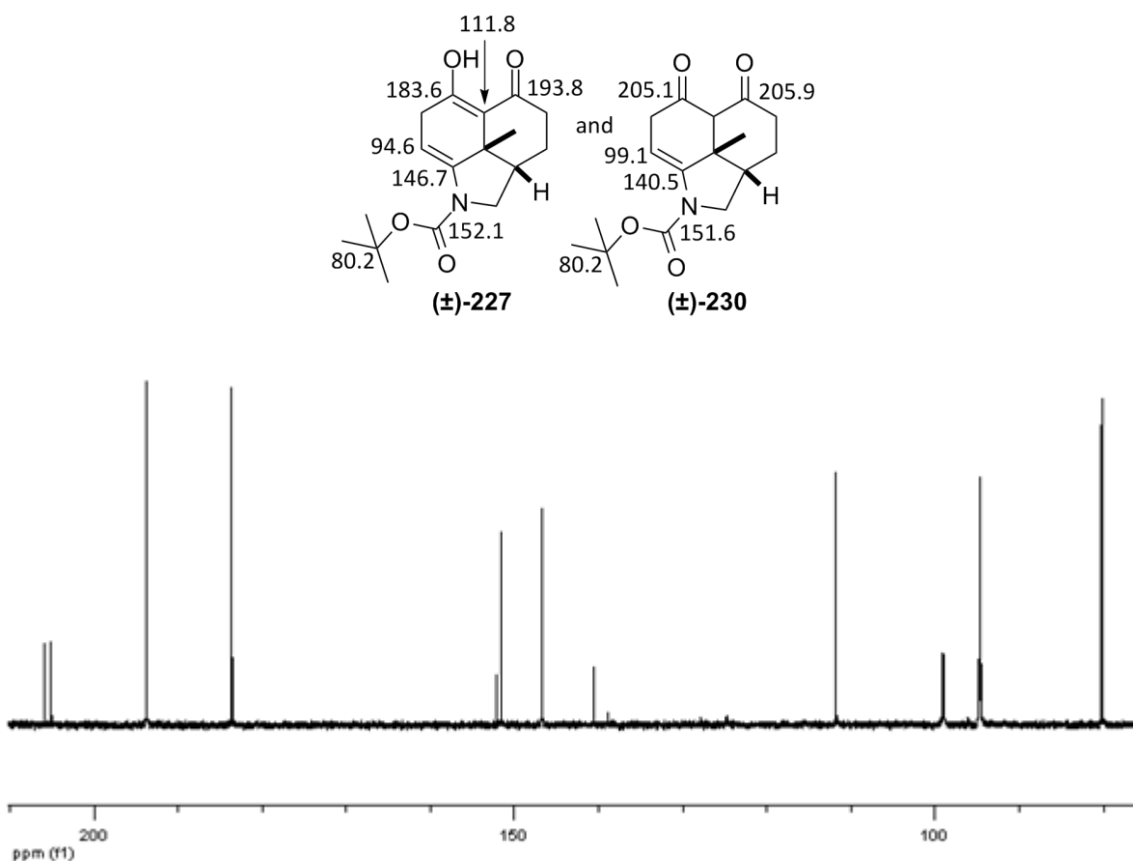
Figure 4.4 ^{13}C NMR in deuterated DMSO at 90°C of **(±)-227** and **(±)-230**

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*).
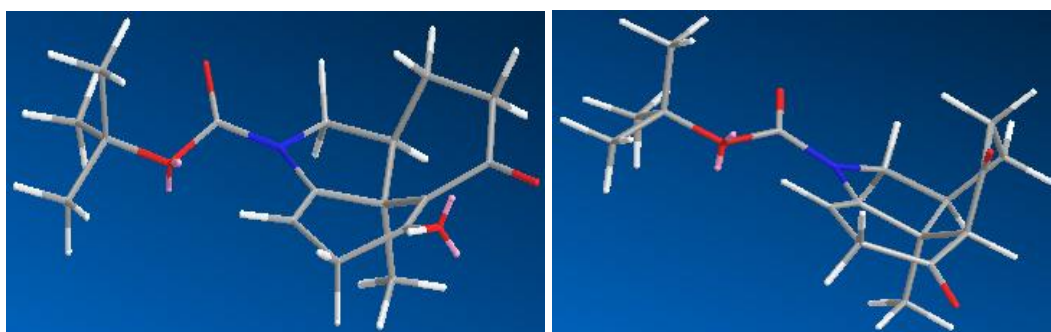
Figure 4.5 MM2 calculations of enol form **(±)-227** (left) and keto form **(±)-230** (right)

Having proven the intramolecular Diels-Alder fragmentation reaction was viable for furan (±)-217, to access the desired β,γ-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*).
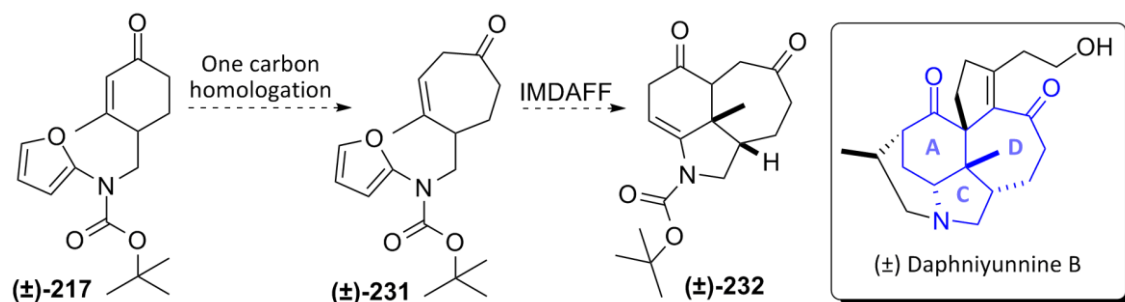
Scheme 4.31 Envisaged preparation of (±)-232

4.4.5 PREPARATION OF β,γ-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]
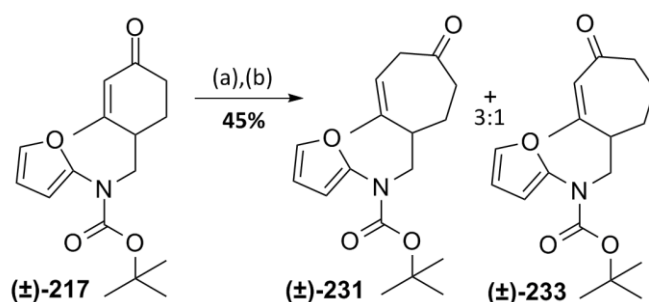
Scheme 4.32 Reagent and conditions (a) Me$_3$Al (2.0 eq.), TMSCHN$_2$ (2.0 eq.), CH$_2$Cl$_2$, -78 °C to RT, 1h; (b) 1M HCl:THF (1:1), RT, 30m

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**.
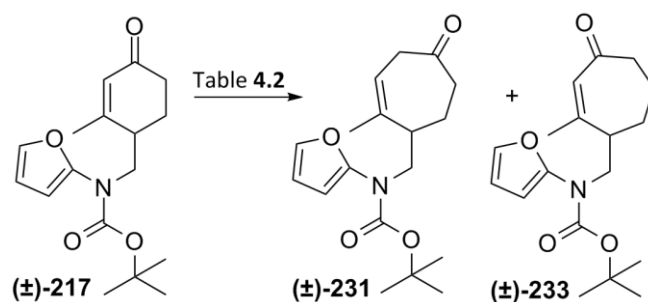
Table 4.2 Solvent screen and desilylation reaction conditions screen

Entry[a]	Solvent	Desilylation conditions	Yield **231** + **233** (%)	Ratio[b] (**231**:**233**)
1	CH_2Cl_2	TBAF, THF, -78 ^{o}C	36	3:1
2	CH_2Cl_2	HCl, MeOH, 0 ^{o}C	23	3:1
3	CH_2Cl_2	HCl, THF, RT	45	3:1
4	THF	As above	32	2:1
5	Et_2O	As above	29	2:1
6	PhMe	As above	40	3:1

[a] Two equivalents of trimethyldiazomethane and trimethylaluminium were used in each case; [b] Based on isolation

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*).
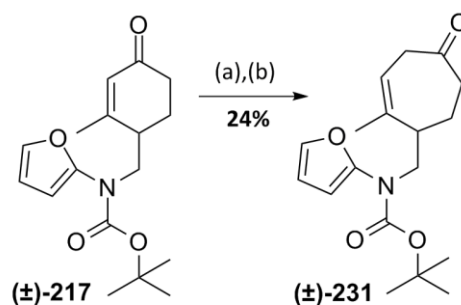
Scheme 4.33 Reagent and conditions (a) BF$_3$.Et$_2$O (2.0 eq.), TMSCHN$_2$ (2.0 eq.), CH$_2$Cl$_2$, -78 $^{\circ}$C to RT, 1h; (b) 1M HCl:THF (1:1), RT, 30m

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 β,γ-unsaturated cyclic ketone **(±)-231** and a sub-stoichiometric amount of butylated hydroxyl toluene under boiling toluene reaction conditions gave the desired 5,6,7 tricycle **(±)-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 **(±)-227** discussed previously in section **4.4.4** (*Scheme 4.34*). [69]
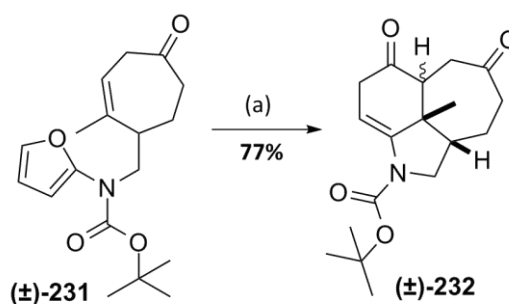
Scheme 4.34 Reagent and conditions (a) BHT (0.2 eq.), PhMe, reflux, 5d

Not too dissimilar to the mechanism proposed in section **4.4.4**, the stereochemistry of **(±)-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 **234** followed by subsequent hydrogen shift of the resulting zwitterion **235** could give the 1,4 diketone **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*).
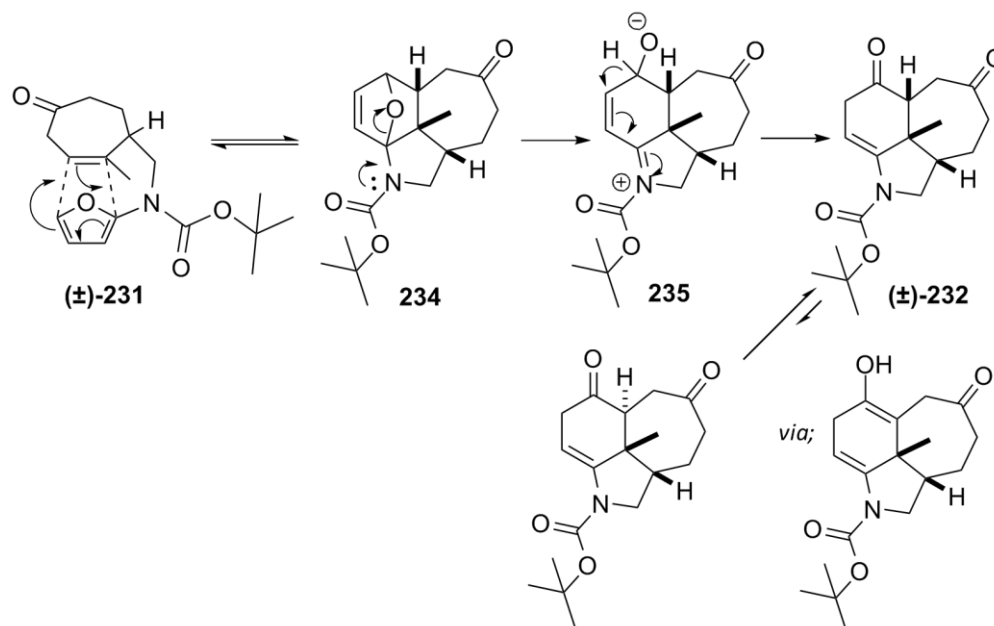
Scheme 4.35 Proposed origins of stereocontrol

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*).
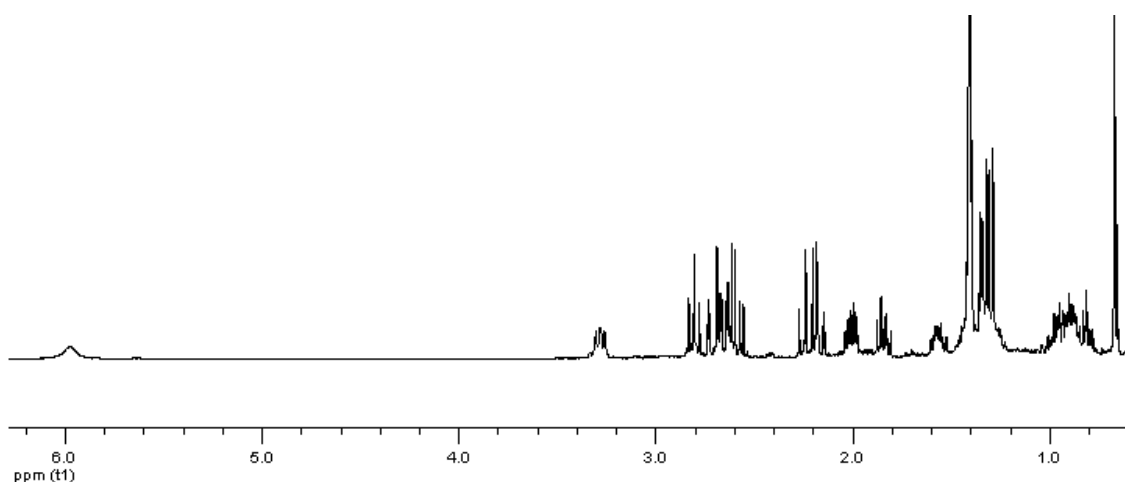
Figure 4.6 ^{1}H NMR of (±)-232 at 70°C in C$_6$D$_6$
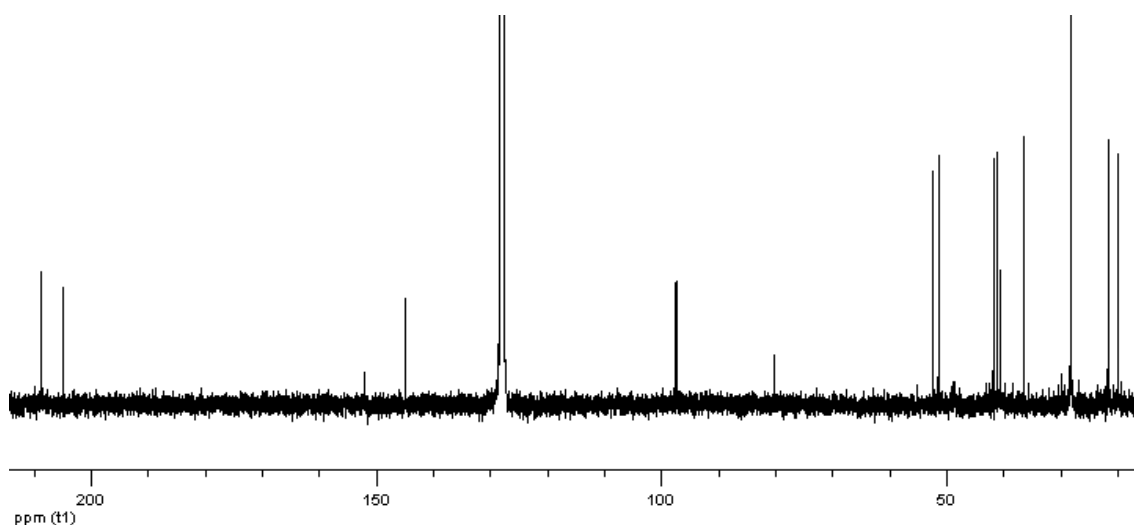
Figure 4.7 ^{13}C NMR of **(±)-232** at 70°C in C$_6$D$_6$

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*).
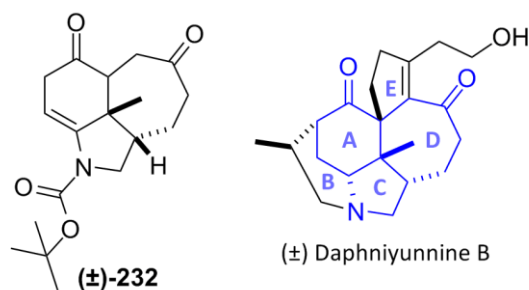
Figure 4.8 Comparison of synthesised ACD tricyclic core with that of (±) Daphniyunnine B

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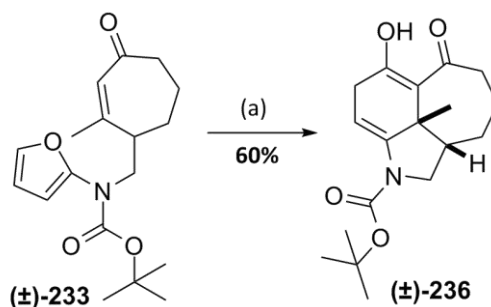
Scheme 4.36 Reagent and conditions (a) BHT (0.2 eq.), PhMe, reflux, 3d

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*).
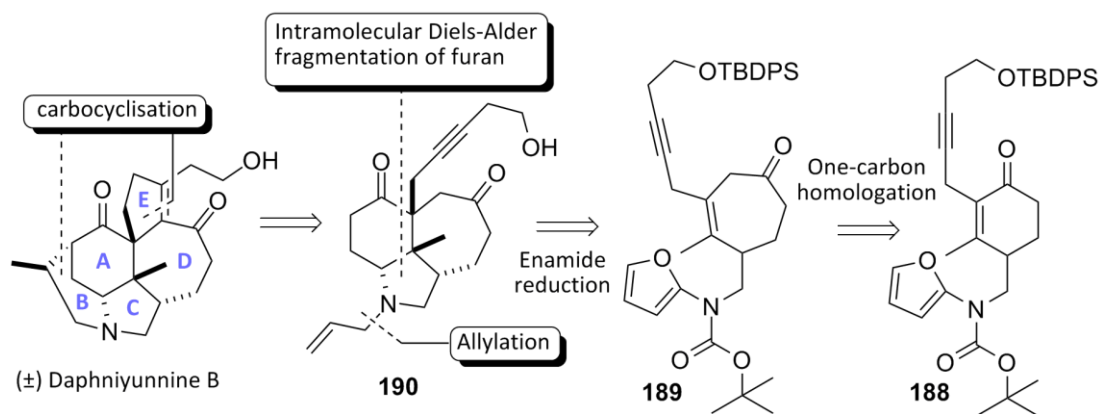
Scheme 4.37 Retrosynthetic analysis

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.[108] 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*).[109]
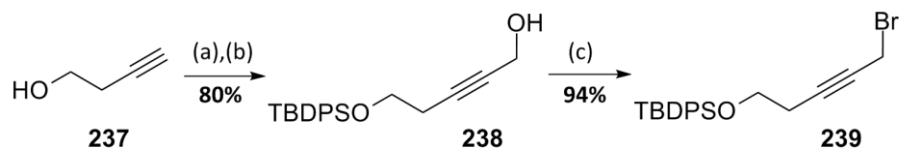
Scheme 4.38 Reagent and conditions (a) imidazole (1.5 eq.), DMAP (0.1 eq.), TBDPSCl (1.2 eq.), CH_2Cl_2, RT, 1h; (b) n-BuLi (1.3 eq.), $(CH_2O)n$ (2.4 eq.), THF, 0 °C to RT, 2h; (c) CBr_4 (1.2 eq.), PPh_3 (1.5 eq.), CH_2Cl_2, -78 °C to RT, 1h

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*).[110]
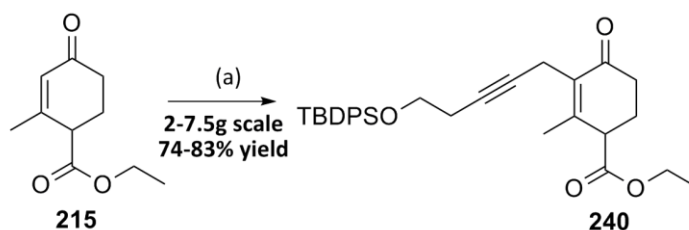
Scheme 4.39 Reagent and conditions (a) ^{t}BuOK (1.1 eq.), ^{t}BuOH, **239** (1.0 eq.), reflux, 1h

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*).
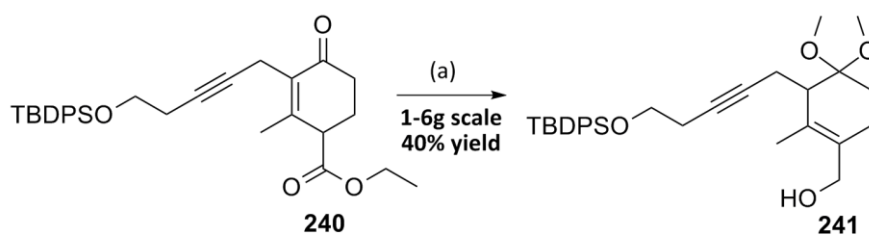
Scheme 4.40 Reagent and conditions (a) CH(OCH$_3$)$_3$ (3.0 eq.), p-TSA (0.1 eq.), THF:MeOH (3:1), RT, 12h; (b) LiAlH$_4$ (3.0 eq.), THF, 0 °C, 10m

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*).
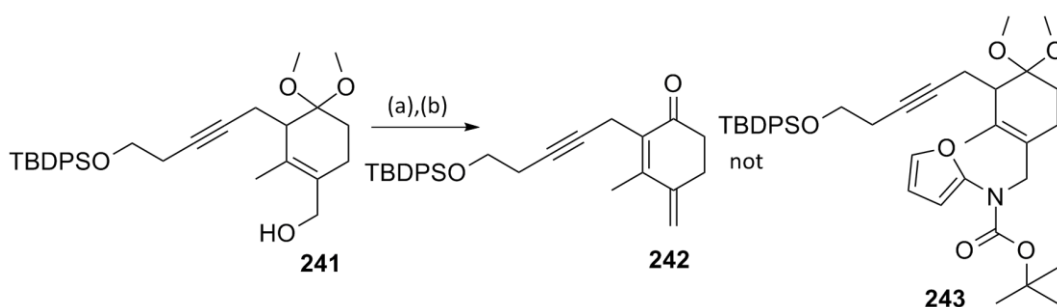
Scheme 4.41 Reagent and conditions (a) n-BuLi (1.0 eq.), tosyl chloride (1.05 eq.), amidofuran **216** (1.07 eq.), KHMDS (1.07 eq.), THF, -78 °C to RT

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*).
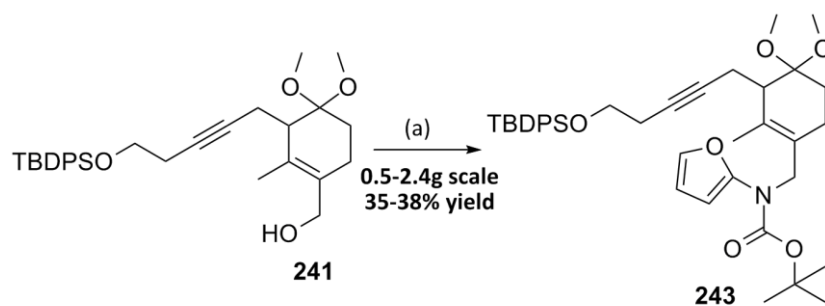
Scheme 4.42 Reagent and conditions (a) PPh$_3$ (3.0 eq.), amidofuran **216** (3.0 eq.), DIAD (3.0 eq.), THF, RT, 1h

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*).
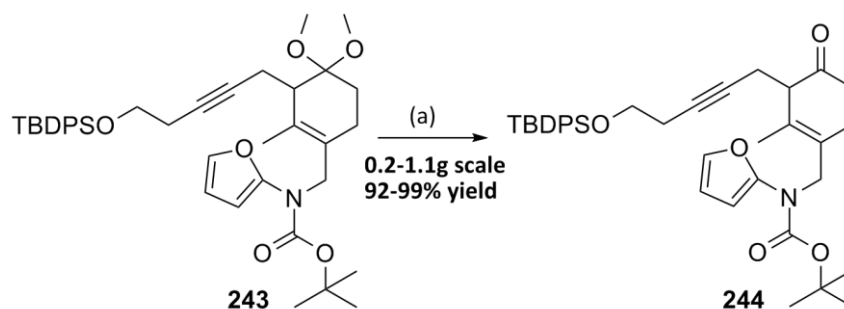
Scheme 4.43 Reagent and conditions (a) 1M HCl:THF (1:1), RT, 12h

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*).
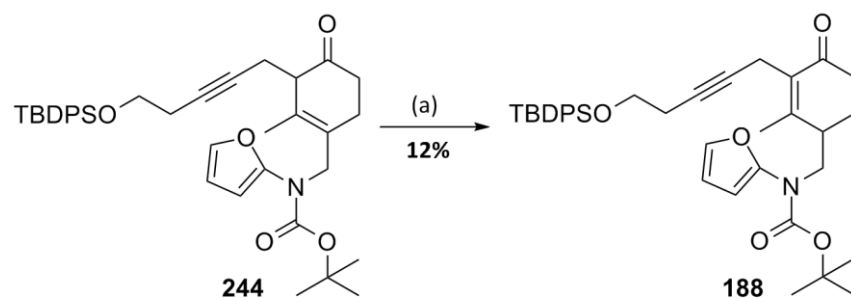
Scheme 4.44 Reagent and conditions (a) K$_2$CO$_3$ (0.1 eq.), MeOH, RT

A range of reaction conditions were attempted to obtain the desired α,β-unsaturated cyclic ketone **188** in greater yield and are shown in Table **4.3**.
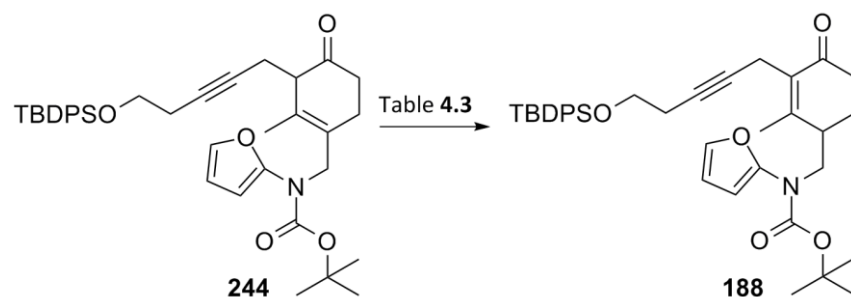
Table 4.3 Optimisation of alkene isomerism

Entry	Reaction conditions	Yield (%)
1	Pyrrolidine (0.4 eq.), MeOH, RT, 12h	16
2	Triethylamine (0.4 eq.), THF, RT, 12h	63
3	N, N-Diisopropylethylamine (0.4 eq.), THF, RT, 12h	71
4	1,8-Diazabicycloundec-7-ene (0.4 eq.), THF, RT, 12h	80

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*).
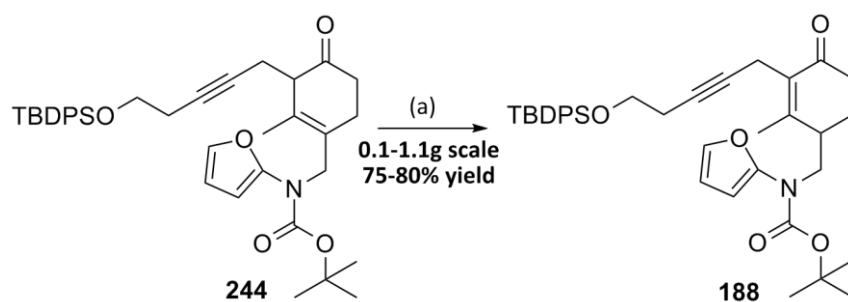
Scheme 4.45 Reagent and conditions (a) DBU (0.4 eq.), THF, RT, 12h

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**.
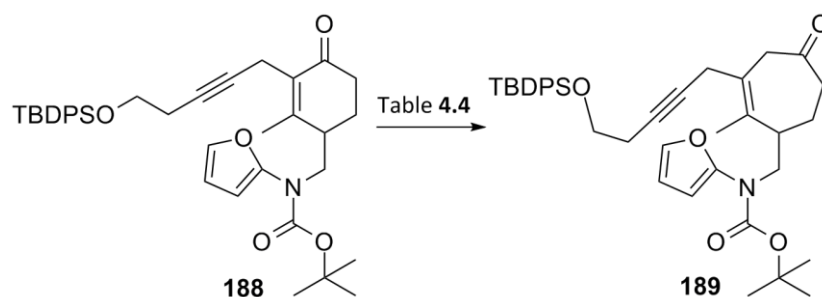
Entry	Reaction conditions	Outcome
1	Me$_3$Al (2.0 eq.), TMSCHN$_2$ (2.0 eq.), CH$_2$Cl$_2$, -78 ^{o}C to RT	Complex mixture of products
2	BF$_3$.Et$_2$O (2.0 eq.), TMSCHN$_2$ (2.0 eq.), CH$_2$Cl$_2$, -78 ^{o}C to RT	Complex mixture of products
3	CH$_2$Br$_2$ (2.0 eq.), LDA (2.0 eq.), THF, then BuLi (2.0 eq.), -78 ^{o}C to RT	Complex mixture of products
4	CH$_2$Br$_2$ (2.0 eq.), LDA (2.0 eq.), THF, -78 ^{o}C to RT	Complex mixture of products

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 α,β-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*).
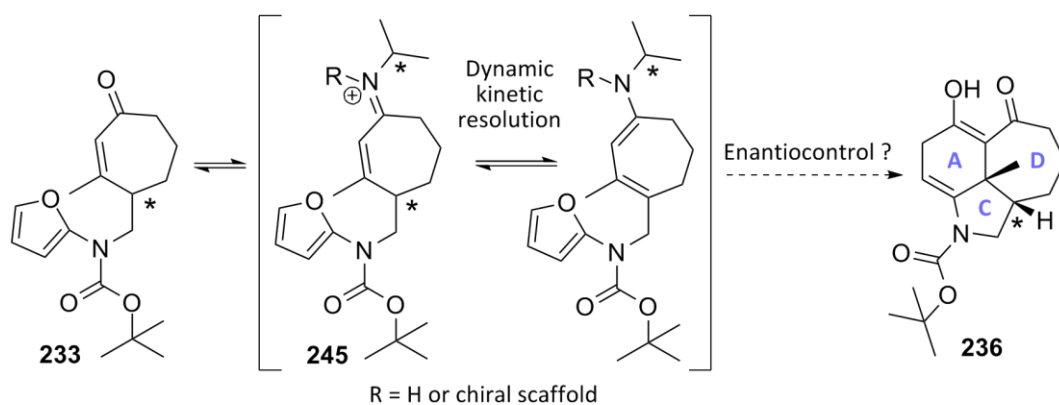
Scheme 4.46 Envisaged enantioselective intramolecular Diels-Alder fragmentation reaction

The 7-ring α,β-unsaturated ketone **233** is the minor product, obtained in only 11% yield, from the one-carbon homolgation of the 6-ring α,β-unsaturated ketone **(±)-217**. Therefore preliminary studies were performed with this easily accessible one-carbon lower homologue **(±)-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*).
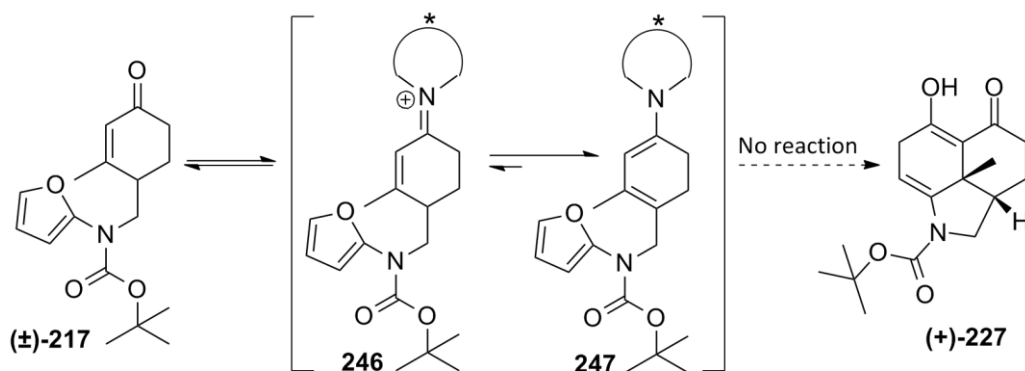
Scheme 4.47 Rationale for lack of reactivity under secondary amine catalysis

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**.
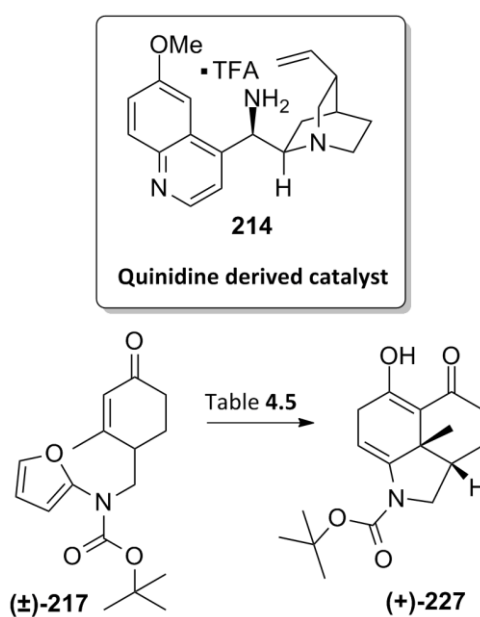
Table 4.5 Solvent screen

Entry	Solvent	Conversion by ^{1}H NMR (%)[*]	ee (%)
1	CH$_2$Cl$_2$	~20	16
2	1,4-dioxane	~30	26
3	THF	~30	81
4	EtOH	~10	0

[*]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*).[111]
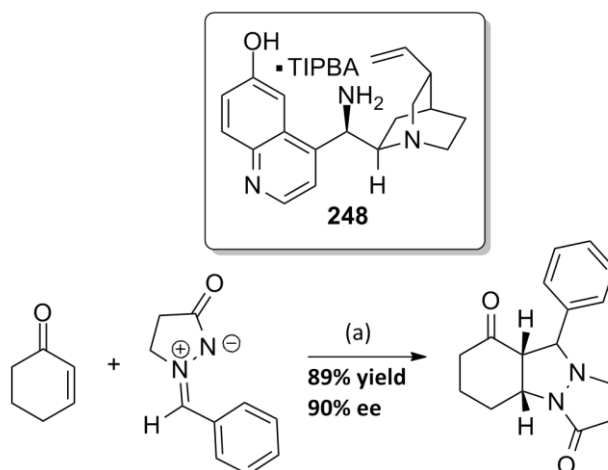
Scheme 4.48 Reagents and conditions (a) catalyst **248** (0.1 eq.), TIPBA (0.2 eq.), THF, 40 °C, 36h

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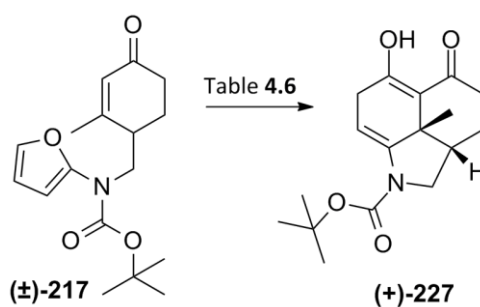
Table 4.6 Attempt to achieve full conversion

Entry	Catalyst **214** loading (mol%)	Temperature (^{o}C)	Conversion by ^{1}H NMR (%)^a	Yield (%)	ee (%)
1	40	23	~45	-	81
2	20	50	~60	-	81
3	40	50	~80^b	-	81
4	40	50	100^c	25	81

^{a} i) Based on consumption of starting material **(±)-217**; ii) After 72h; ^{b} 96h; ^{c} 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*).
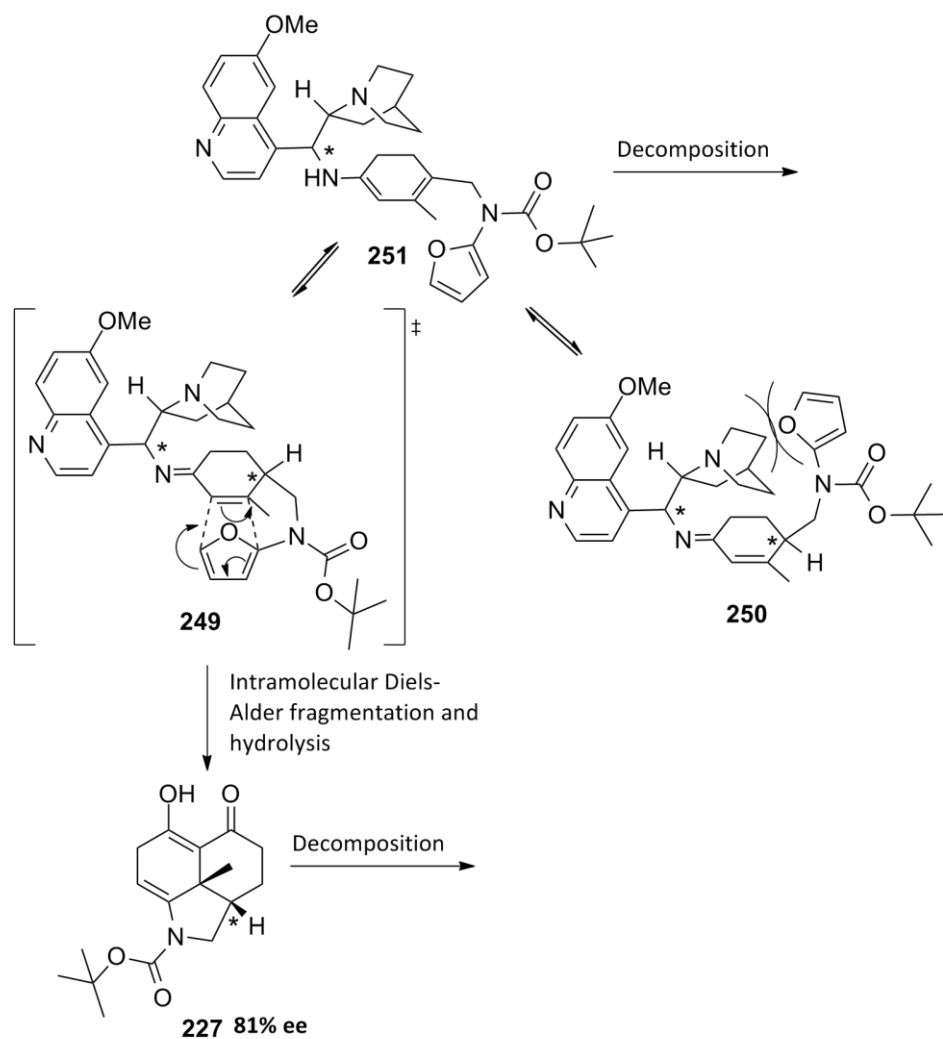
Scheme 4.49 Proposed mode of action for enantioselective intramolecular Diels-Alder fragmentation

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*).
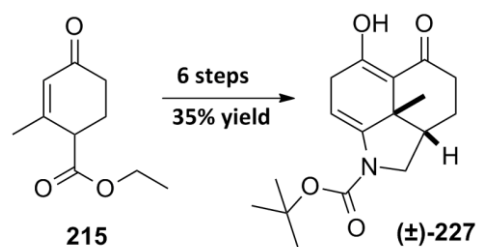
Scheme 4.50 Synthesis of 5,6,6 tricycle **(±)-227**

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*).
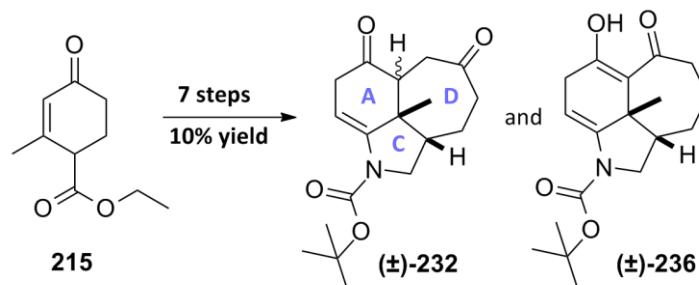
Scheme 4.51 Synthesis of ACD tricyclic core **(±)-232** and **(±)-236** of (±) Daphniyunnine B

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*).
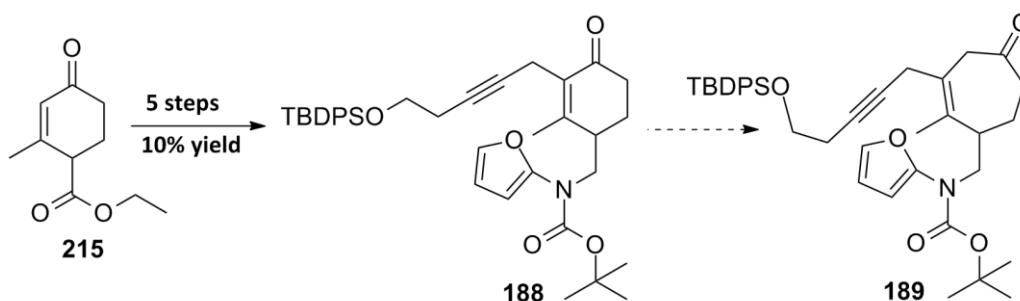
Scheme 4.52 Synthesis of the α,β-unsaturated ketone **188**

A novel, enantioselective intramolecular Diels-Alder fragmentation reaction of furan **(±)-217** using a primary amine organocatalyst **214** was discovered (*Scheme 4.53*).
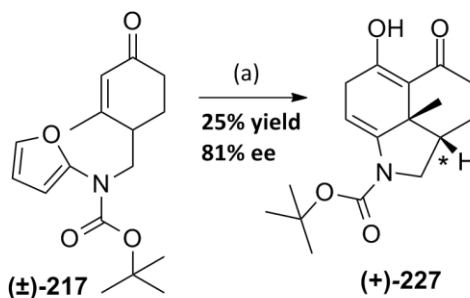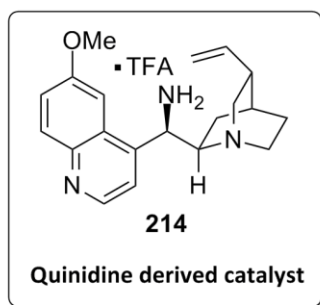
Scheme 4.53 Reagents and conditions (a) catalyst **214** (0.4 eq.), THF, 50 °C, 120h

4.4.9 FUTURE WORK

One-carbon homologation of **188** could allow the preparation of the β,γ-unsaturated cyclic ketone **189** which after a further 4 steps could rapidly complete the synthesis of (±) Daphniyunnine B (*Scheme 4.54*).
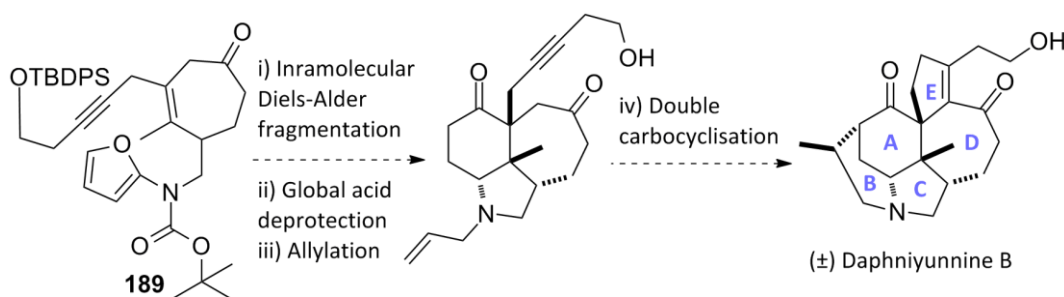
Scheme 4.54 Anticipated completion of (±) Daphniyunnine B

The encouraging preliminary results obtained with the enantioselective intramolecular Diels-Alder fragmentation reaction of α,β-unsaturated cyclic ketone **(±)-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 **(±)-233** to potentially give enantioenriched **236** (*Scheme 4.55*).
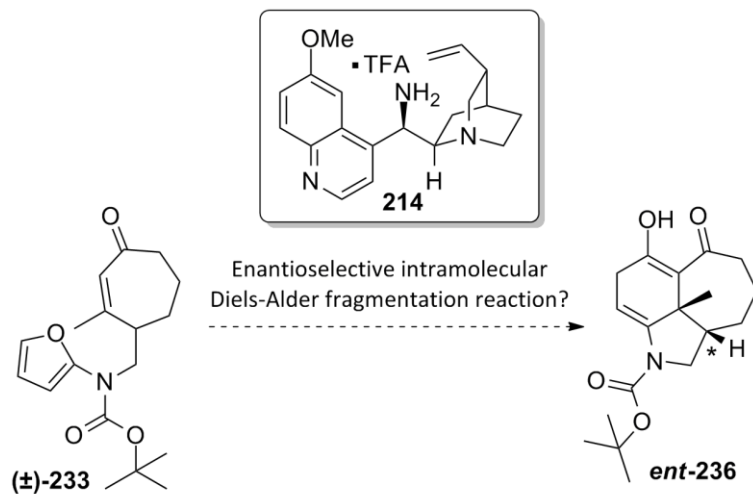
Scheme 4.55 Postulated enantioselective synthesis of *ent*-236

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 α,β-unsaturated ketones affording highly functionalized perhydroindole bicyclic and tricyclic compounds in good yields and moderate to excellent diastereocontrol (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 ^{o}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} degcm^{-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 (^{o}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 (ν_{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 (δ_H) are quoted in parts per million (ppm ± 0.01 ppm) downfield of tetramethylsilane, relative to the residual protiosolvent (δ_H (C**H**Cl$_3$) = 7.26 ppm) against an internal deuterium lock. Coupling constants (*J*) are given in Hertz (Hz ± 0.5 Hz). The ^{1}H NMR spectra are reported as follows: δ / 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]
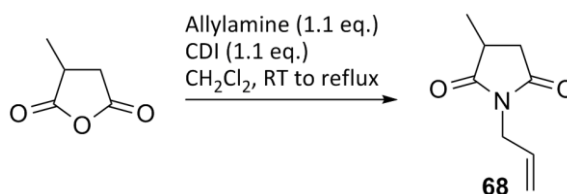
A solution of methyl succinic anhydride (1.61 mL, 17.0 mmol) and allylamine (1.42 mL, 17.0 mmol) in dichloromethane (160 mL) was stirred for 12 hours before 1, 1'-

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 (MgSO$_4$), filtered and concentrated *in vacuo* to afford essentially pure **68** (2.24 g, 87%) as a light yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ$_H$ 5.78 (ddt, 1H, *J* = 17.1Hz, 10.2Hz and 5.8Hz, NCH$_2$C$\underline{H}$), 5.20-5.18 (m, 2H, NCH$_2$CHC$\underline{H}_2$), 4.09 (td, 2H, *J* = 5.9Hz and 1.4Hz, NC$\underline{H}_2$), 2.93 (dd, 1H, *J* = 17.7Hz and 9.1Hz, 1 of COC$\underline{H}_2$CH), 2.86 (m, 1H, COC$\underline{H}$CH$_3$), 2.33 (dd, 1H, *J* = 17.7Hz and 4.2Hz, 1 of COC$\underline{H}_2$CH), 1.35 (d, 3H, *J* = 7.2Hz, CHC$\underline{H}_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ$_c$ 180.1 (N$\underline{C}$=O), 176.0 (N$\underline{C}$=O), 130.7 (allyl-$\underline{C}$), 118.1 (allyl-$\underline{C}$), 40.8 (N$\underline{C}$H$_2$), 36.4 (CO$\underline{C}$HCH$_3$), 34.6 (CO$\underline{C}$H$_2$CH), 16.8 ($\underline{C}$H$_3$). *^{1}H NMR and ^{13}C NMR in agreement with the literature*

(±)-Methyl 1-allyl-4-methyl-2,5-dioxopyrrolidine-3-carboxylate; 71
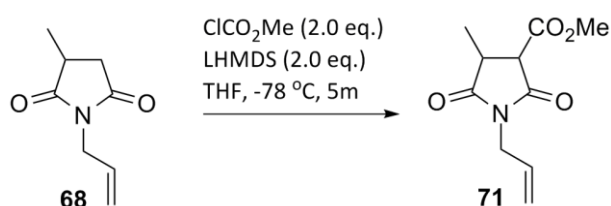
To a stirred solution of **68** (1.03 g, 6.73 mmol) and methyl chloroformate (1.27 mL, 13.5 mmol) in dry tetrahydrofuran (10 mL) at -78 °C was added a 1M solution of lithium hexamethyldisilazane in tetrahydrofuran (12.7 mL, 13.5 mmol) drop-wise. The reaction mixture was stirred at -78 °C for 5 minutes 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 (MgSO$_4$), filtered and concentrated *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 ν_{max} (oil): 2959 (CH), 1785 (C=O), 1735 (C=O) and 1702 (C=O); **Major: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.79-5.66 (m, 1H, NCH$_2$C*H*), 5.19-5.06 (m, 2H, NCH$_2$CHC*H$_2$*), 4.06 (m, 2H, NC*H$_2$*), 3.78 (s, 3H, CO$_2$C*H$_3$*), 3.37 (d, 1H, *J* = 5.4Hz, C*H*CO$_2$Me), 3.22-3.14 (m, 1H, C*H*CH$_3$), 1.35 (d, 3H, *J* = 7.5Hz, CHC*H$_3$*); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ_C 177.9 (*C*=O), 170.9 (*C*=O), 168.0 (*C*=O), 130.0 (allyl-*C*), 118.4 (allyl-*C*), 54.1 (CO$_2$*C*H$_3$), 53.2 (*C*HCO$_2$Me), 41.3 (allyl-*C*), 39.1 (*C*HCH$_3$), 15.4 (CH*C*H$_3$); **Minor observed: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 3.76 (s, 3H, CO$_2$C*H$_3$*), 3.14-3.08 (m, 1H, C*H*CH$_3$), 1.24 (d, 3H, *J* = 7.5Hz, CHC*H$_3$*); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ_C 177.7 (*C*=O), 171.8 (*C*=O), 167.3 (*C*=O), 118.1 (allyl-*C*), 52.5 (CO$_2$*C*H$_3$), 51.2 (*C*HCO$_2$Me), 41.2 (allyl-*C*), 37.4 (*C*HCH$_3$) and 11.1 (CH*C*H$_3$); **MS *m/z*** (ES+): 234 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 234.0735 (C$_{10}$H$_{13}$NNaO$_4$) requires (M) 234.0737.

(±)-Methyl 1-allyl-5-hydroxy-4-methyl-2-oxopyrrolidine-3-carboxylate; 73
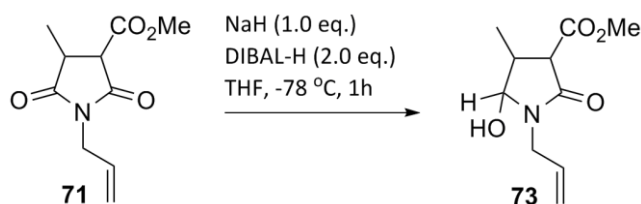
A solution of **71** (2.0 g, 9.48 mmol) in dry tetrahydrofuran (80 mL) was added drop-wise *via* cannula to a stirred suspension of 60% sodium hydride in oil (0.23 g, 9.48 mmol) in dry tetrahydrofuran (80 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 minutes and then cooled to −78 °C before a 1.0 M solution of di*iso*butylaluminium 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 × 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 ν_{max} (oil): 3369 (OH), 2958 (CH), 1741 (C=O), 1681 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.74 (ddt, 1H, J = 17.1Hz, 10.1Hz, and 5.3Hz, NCH$_2$C$\underline{H}$), 5.24-5.20 (m, 2H, NCH$_2$CHC$\underline{H_2}$), 5.11 (t, 1H, J = 5.8Hz, C$\underline{H}$OH), 4.17 (dt, 2H, J = 5.3Hz and 1.6Hz, NC$\underline{H_2}$), 3.8 (s, 3H, OC$\underline{H_3}$), 3.27 (d, 1H, J = 10.4Hz, COC$\underline{H}$CO$_2$Me), 2.8 (dqd, 1H, J = 10.2Hz, 7.0Hz and 5.8Hz, C$\underline{H}$CH$_3$), 2.38 (d, 1H, J = 5.9Hz, O$\underline{H}$), 1.18 (d, 3H, J = 7.0Hz, CHC$\underline{H_3}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 170.0 ($\underline{C}$=O), 169.9 ($\underline{C}$=O), 132.4 (allyl-$\underline{C}$), 118.6 (allyl-$\underline{C}$), 82.9 ($\underline{C}$HOH), 53.5 ($\underline{C}$HCO$_2$Me), 52.7 (CO$_2\underline{C}$H$_3$), 43.3($\underline{C}$HCH$_3$), 37.3 (allyl-$\underline{C}$), 12.7 (CHC$\underline{H_3}$); **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
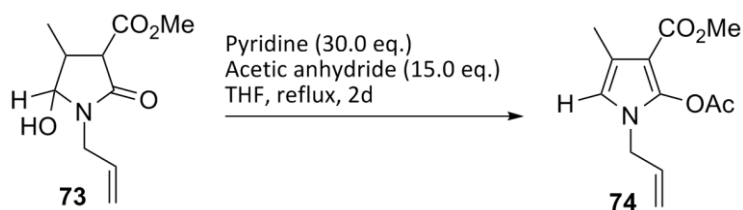
To a stirred solution of **73** (0.24 g, 0.94 mmol) in dry tetrahydrofuran (15 mL) was added dry pyridine (2.23 mL, 28.2 mmol) and acetic anhydride (1.41 mL, 14.1 mmol) consecutively at room temperature. The reaction mixture was refluxed for 2 days and until TLC confirmed complete consumption of starting 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** ν_{max}(solid) 2950 (CH), 1787 (C=O), 1702 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 6.15 (s, 1H, pyrrole-$\underline{H}$), 5.82 (ddt, 1H, J = 16.5Hz, 10.2Hz and 5.6Hz, NCH$_2$C$\underline{H}$), 5.19 (d, 1H, J = 10.2Hz, 1 of NCH$_2$CHC$\underline{H_2}$), 5.11 (d, 1H, J = 16.5Hz, 1 of NCH$_2$CHC$\underline{H_2}$), 4.23 (d, 2H, J = 5.6Hz, NC$\underline{H_2}$), 3.74 (s, 3H, CO$_2$C$\underline{H_3}$), 2.32 (s, 3H, acetate-C$\underline{H_3}$) and 2.19 (s, 3H, C$\underline{H_3}$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 168.4 ($\underline{C}$=O), 164.4 ($\underline{C}$=O), 139.4 (pyrrole-$\underline{C}$), 132.5

(allyl-$\underline{C}$), 119.1 (pyrrole-$\underline{C}$), 118.0 (allyl-$\underline{C}$), 113.9 (pyrrole-$\underline{C}$), 101.1 (pyrrole-$\underline{C}$), 50.6 ($CO_2\underline{C}H_3$), 47.4 (allyl-$\underline{C}$), 20.4 (acetate-$\underline{C}H_3$), 12.6 ($\underline{C}H_3$); **MS *m/z*** (CI+): 260 ($[M+Na]^+$); **HRMS** Found $[M+H]^+$ 238.1067 ($C_{12}H_{16}NO_4$) requires (M) 238.1074. Analysis calculated for $C_{12}H_{16}NO_4$: 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 K_2CO_3 (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
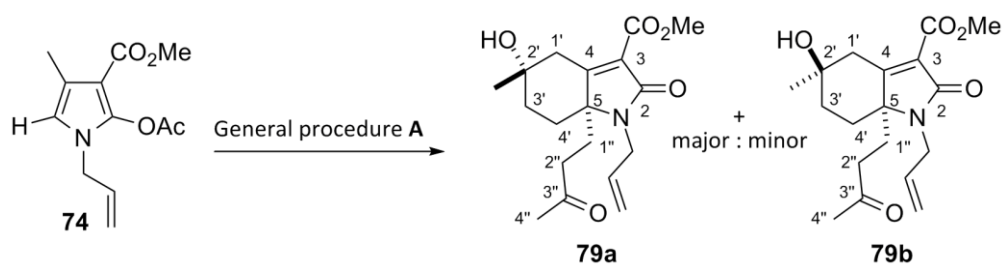
Following the general procedure **A** described above with α,β-unsaturated ketone **47**, the Michael-Michael-aldol product **79a,b** was obtained following purification by column chromatography (diethyl ether : light petroleum ether, 4:1) as a 3:1 mixture of diastereoisomers and a yellow oil (112 mg, 76%).

IR ν_{max} (oil) 3550-3200 (OH), 2953 (CH), 1760 (C=O), 1715 (C=O) 1686 (C=O); **Major 79a: ^{1}H NMR** (500 MHz; CDCl$_3$) δ$_H$ 5.87-5.77 (m, 1H, NCH$_2$C$\underline{H}$), 5.22 (d, 1H, *J* = 17.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.11 (d, 1H, *J* = 10.0Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.06 (dd, 1H, *J* = 15.3Hz and 5.4Hz, NC$\underline{H}_A$H$_B$), 3.86 (s, 3H, CO$_2$C$\underline{H}_3$), 3.74 (dd, 1H, *J* = 15.3Hz and 6.7Hz, NCH$_A$$\underline{H}_B$), 3.59 (d, 1H, *J* = 12.6Hz, 1'-C$\underline{H}_A$H$_B$), 2.34 (dd, 1H, *J* = 13.8Hz and 8.4Hz, 1''-C$\underline{H}_A$H$_B$), 2.31 (d, 1H,

J = 12.6Hz, 1'-CH$_A$$\underline{H}_B$), 2.20-2.18 (m, 2H, 4'-C$\underline{H}_2$), 2.10-1.96 (m, 2H, 2''-C$\underline{H}_A$H$_B$ and 1''-CH$_A$$\underline{H}_B$), 2.05 (s, 3H, 4''-C$\underline{H}_3$), 1.89 (dd, 1H, J = 15.0Hz and 10.3Hz, 2''-CH$_A$$\underline{H}_B$), 1.77-1.67 (m, 1H, 3'-C$\underline{H}_A$H$_B$), 1.40 (s, 3H, 2'-C$\underline{H}_3$) and 1.31 (dt, 1H, J = 14.0Hz and 4.4Hz, 3'-CH$_A$$\underline{H}_B$); **^{13}C NMR** (125 MHz; CDCl$_3$) δ_C 206.9 (3''-$\underline{C}$=O), 170.3 (4-$\underline{C}$), 166.2 (2-$\underline{C}$=O), 162.8 ($\underline{C}$O$_2$CH$_3$), 133.5 (allyl-$\underline{C}$), 123.7 (3-$\underline{C}$), 118.2 (allyl-$\underline{C}$), 74.9 (2'-$\underline{C}$), 66.0 (5-$\underline{C}$), 52.0 (CO$_2$$\underline{C}H_3$), 42.3 (allyl-$\underline{C}$), 39.7 (1'-$\underline{C}H_2$), 36.5 (4''-$\underline{C}H_3$), 35.6 (2''-$\underline{C}H_2$), 34.2 (3'-$\underline{C}H_2$), 30.2 (4'-$\underline{C}H_2$), 25.9 (2'-$\underline{C}H_3$), 25.7 (1''-$\underline{C}H_2$); **Minor 79b observed: ^{1}H NMR** (500 MHz; CDCl$_3$) δ_H 3.50 (d, 1H, J = 13.8Hz, 1'-C$\underline{H}_A$H$_B$), 2.23 (d, 1H, J = 13.8Hz, 1'-CH$_A$$\underline{H}_B$), 2.03 (s, 3H, 4''-C$\underline{H}_3$) and 1.13 (s, 3H, 2'-C$\underline{H}_3$); **^{13}C NMR** (125 MHz; CDCl$_3$) δ_C 133.7 (allyl-$\underline{C}$), 118.0 (allyl-$\underline{C}$), 74.0 (2'-$\underline{C}$); **MS** m/z (ES+): 358 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 358.1617 (C$_{18}$H$_{25}$NaO$_5$) 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 ν_{max}(oil) 3700-3300 (OH), 2940 (CH), 1760 (C=O), 1710 (C=O) 1690 (C=O); **Major 83a:** **^{1}H NMR** (300 MHz, CDCl$_3$) δ_H 5.92-5.71 (m, 1H, NCH$_2$C$\underline{H}$), 5.20 (d, 1H, J = 17.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.09 (d, 1H, J = 10.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.04 (dd, 1H, J = 15.4Hz and 6.4Hz, NC$\underline{H}_A$H$_B$), 3.84 (s, 3H, CO$_2$C$\underline{H}_3$), 3.75 (dd, 1H, J = 14.4Hz and 6.4Hz, NCH$_A$$\underline{H}_B$), 3.63 (d, 1H, J = 13.5Hz, 1'-C$\underline{H}_A$H$_B$), 2.31-2.27 (m, 4H, 2''-C$\underline{H}_2$ and 4''-C$\underline{H}_2$), 2.26-2.23 (m, 1H,
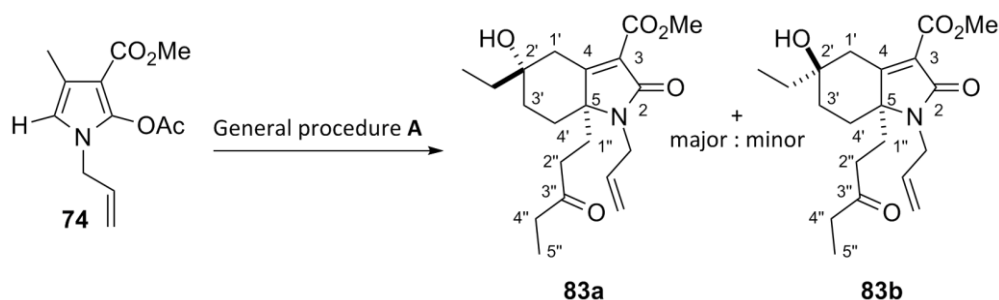
1'-CH$_A$$\underline{H}$$_B$), 2.12-1.55 (m, 5H, 3'-C$\underline{H}$$_AH_B$, 1''-C$\underline{H}$$_2$ and 4'-C$\underline{H}$$_2$), 1.44-1.27 (m, 2H, 2'-C$\underline{H}$$_2CH_3$), 1.26-1.12 (m, 1H, 3'-CH$_A$$\underline{H}$$_B$) and 0.96 (t, 6H, J = 7.4Hz, 2 × CH$_2$C$\underline{H}$$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ$_C$ 209.8 (3''-$\underline{C}$=O), 171.4 (4-$\underline{C}$), 166.2 (2-$\underline{C}$=O), 163.5 ($\underline{C}$O$_2$CH$_3$), 133.7 (allyl-$\underline{C}$), 125.0 (3-$\underline{C}$), 118.1 (allyl-$\underline{C}$), 76.6 (2'-$\underline{C}$), 66.5 (5-$\underline{C}$), 52.1 (CO$_2$$\underline{C}H_3$), 42.3 (allyl-$\underline{C}$), 37.9 (4''-$\underline{C}H_2$), 36.2 ($\underline{C}H_2CH_3$), 35.2 ($\underline{C}H_2$), 34.8 ($\underline{C}H_2$), 32.0 ($\underline{C}H_2$), 29.6 (2'-$\underline{C}H_2CH_3$), 26.2 ($\underline{C}H_2$), 7.7 (5''-CH$_2$$\underline{C}H_3$) and 6.8 (CH$_2$$\underline{C}H_3$); **Minor 83b observed:** ^{1}H NMR (300 MHz, CDCl$_3$) δ$_H$ 3.46 (d, 1H, J = 15.1Hz, 1'-C$\underline{H}$$_AH_B$), 2.16 (d, 1H, J = 13.5Hz, 1'-CH$_A$$\underline{H}$$_B$) and 0.84 (t, 6H, J = 7.4Hz, 2 × CH$_2$C$\underline{H}$$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ$_C$ 209.6 (3''-$\underline{C}$=O), 170.3 (4-$\underline{C}$), 162.8 ($\underline{C}$O$_2$CH$_3$), 133.6 (allyl-$\underline{C}$), 123.9 (3-$\underline{C}$), 117.9 (allyl-$\underline{C}$), 76.4 (2'-$\underline{C}$), 66.1 (5-$\underline{C}$), 52.0 (CO$_2$$\underline{C}H_3$), 42.2 (allyl-$\underline{C}$), 36.5 (4''-$\underline{C}H_2$), 35.7 ($\underline{C}H_2CH_3$), 35.0 ($\underline{C}H_2$), 32.9 ($\underline{C}H_2$), 25.2 ($\underline{C}H_2$); **MS** *m/z* (ES+): 364 ([M+H]$^{+}$); **HRMS** Found [M+H]$^{+}$ 364.2129 (C$_{20}$H$_{30}$NO$_5$) requires (M) 364.2118.

(±)-Methyl-1-allyl-2'-hydroxy-2-oxo-5-((E)-3''-oxohex-4''-enyl)-2'-((E)-prop-1'''-enyl)-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 84a,b

Following the general procedure **A** described above with α,β-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 ν$_{max}$(oil) 3423 (OH), 2931 (CH), 1741 (C=O), 1713 (C=O), 1686 (C=O); **Major 84a:** ^{1}**H NMR** (400 MHz, CDCl$_3$) δ$_H$ 6.82-6.71 (m, 1H, 5''-C$\underline{H}$), 6.05-5.96 (m, 1H, 4''-C$\underline{H}$), 5.91-5.73 (m, 1H, NCH$_2$C$\underline{H}$CH$_2$), 5.78 (m, 1H, 1'''-C$\underline{H}$), 5.64 (m, 1H, 2'''-C$\underline{H}$), 5.23 (d, 1H, J = 17.1Hz, 1 of NCH$_2$CHC$\underline{H}$$_2$), 5.11 (d, 1H, J = 10.1Hz, 1 of NCH$_2$CHC$\underline{H}$$_2$), 4.08 (m, 1H, NC$\underline{H}$$_AH_B$), 3.87
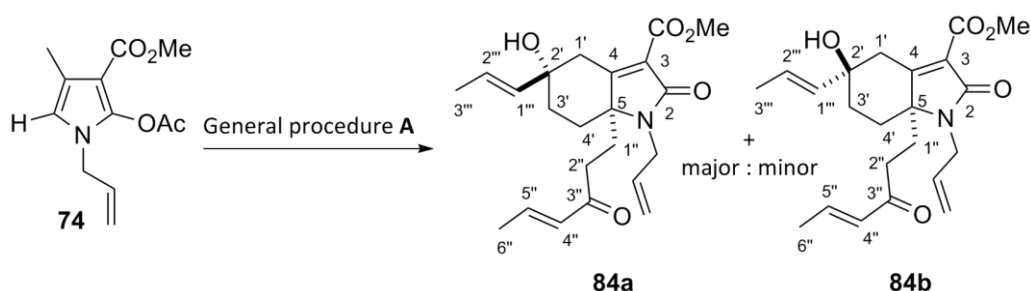
(s, 3H, CO$_2$C$\underline{H}_3$), 3.74 (m, 1H, NCH$_A\underline{H}_B$CHCH$_2$), 3.50 (m, 1H, 1'-C$\underline{H}_A$H$_B$), 2.55 (ddd, 2H, J = 15.5Hz, 7.8Hz and 5.9Hz, 2''-C$\underline{H}_2$), 2.37-2.20 (m, 2H, 1'-CH$_A\underline{H}_B$ and 1''-C$\underline{H}$), 2.20-1.88 (m, 4H, 4'-C$\underline{H}_2$ and 3'-C$\underline{H}_2$) 1.86 (dd, 3H, J = 6.8Hz and 1.5Hz, C$\underline{H}_3$) and 1.11 (dd, 3H, J = 6.1Hz and 2.0Hz, C$\underline{H}_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ$_C$ 207.9 (3''$\underline{C}$=O), 198.1 (N$\underline{C}$=O), 143.6 ($\underline{C}$O$_2$), 136.9 (quat. $\underline{C}$=C), 133.8 (5''-$\underline{C}$H), 131.5 (4''-$\underline{C}$H), 124.5 (1'''-$\underline{C}$H), 118.2 (allyl-$\underline{C}$), 117.9 (2'''-$\underline{C}$H), 73.0 (2'-$\underline{C}$), 66.1 (5-$\underline{C}$), 56.2 (CO$_2\underline{C}$H$_3$), 55.6, 52.1, 42.2 (N$\underline{C}$H$_2$), 37.4, 36.8, 35.6, 33.3, 25.0, 18.9, 17.6; **Minor 84b observed:** ^{13}C NMR (100 MHz, CDCl$_3$) δ$_C$ 207.8 (3''$\underline{C}$=O), 75.6 (2'-$\underline{C}$), 66.0 (5-$\underline{C}$), 56.1 (CO$_2\underline{C}$H$_3$); **MS** m/z (ES+): 410 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 410.1939 (C$_{22}$H$_{29}$NNaO$_5$) requires (M) 410.1937.

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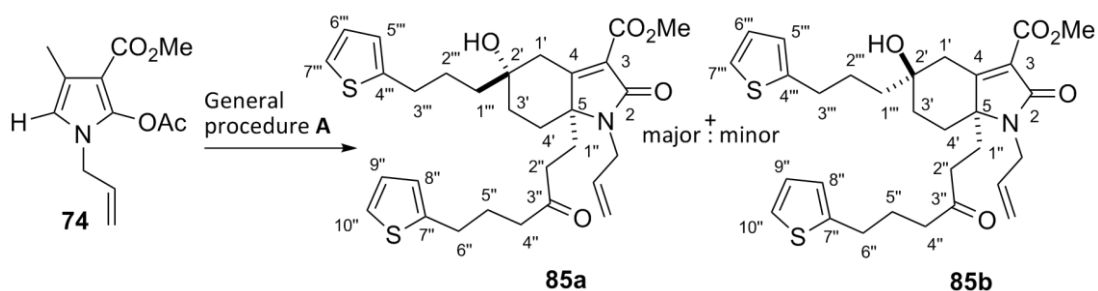
Following the general procedure **A** described above with α,β-unsaturated ketone **82**, the Michael-Michael-aldol product **85a,b** was obtained following purification by column chromatography (neat diethyl ether) as a 3:1 mixture of diastereoisomers and a light yellow oil (176 mg, 79%). The diastereoisomers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

85a: IR ν$_{max}$(oil) 3600-3100 (OH), 2948 (CH), 1736, (C=O), 1714 (C=O), 1677 (C=O); ^{1}H NMR (500 MHz, CDCl$_3$) δ$_H$ 7.11 (dd, 1H, J = 5.1Hz and 1.0Hz, thiophene-$\underline{H}$), 6.90 (ddd, 1H, J = 5.1Hz and 3.4Hz, thiophene-$\underline{H}$), 6.89 (dd, 1H, J = 5.1Hz and 3.4Hz, thiophene-$\underline{H}$), 6.75 (d, 2H, J = 3.4Hz, thiophene-$\underline{H}$), 5.81 (ddt, 1H, J = 17.0Hz, 10.1Hz and 6.5Hz, NCH$_2$C$\underline{H}$), 5.22 (dd, 1H, J = 17.0Hz and 1.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.11 (d, 1H, J = 10.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.05 (dd, 1H, J = 15.4Hz and 6.2Hz, NC$\underline{H}_A$H$_B$), 3.85 (s, 3H, CO$_2$C$\underline{H}_3$),

3.72 (dd, 1H, J = 15.4Hz and 6.8Hz, NCH$_A$$\underline{H}_B$), 3.66 (d, 1H, J = 12.8Hz, 1'-C$\underline{H}_A$H$_B$), 2.78 (dd, 4H, J = 14.8Hz and 7.5Hz, 3'''-C$\underline{H}_2$ and 6''-C$\underline{H}_2$), 2.34 (t, 4H, J = 7.4Hz, 2''-C$\underline{H}_2$ and 4''-C$\underline{H}_2$), 2.25 (d, 1H, J = 12.8Hz, 1'-CH$_A$$\underline{H}_B$), 2.16-2.08 (m, 1H, 3'-C$\underline{H}_A$H$_B$), 2.04-1.95 (m, 1H, 4'-C$\underline{H}_A$H$_B$), 1.87 (m, 4H, 1''-C$\underline{H}_2$ and 4''-C$\underline{H}_2$), 1.85-1.73 (m, 1H, 4'-CH$_A$$\underline{H}_B$), 1.71-1.58 (m, 4H, 2'''-C$\underline{H}_2$ and 5''-C$\underline{H}_2$), 1.40 (m, 2H, 1'''-C$\underline{H}_2$) and 1.24 (ddd, 1H, J = 13.2Hz, 7.6Hz and 4.7Hz, 3'-CH$_A$$\underline{H}_B$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ$_C$ 208.5 (3''$\underline{C}$=O), 169.7 (4-$\underline{C}$), 166.0 (2-$\underline{C}$=O), 162.7 ($\underline{C}$O$_2$CH$_3$), 144.7 (thiophene-$\underline{C}$), 144.0 (thiophene-$\underline{C}$), 133.5 (allyl-$\underline{C}$), 126.8 (thiophene-$\underline{C}$), 126.7 (thiophene-$\underline{C}$), 124.5 (thiophene-$\underline{C}$), 124.2 (3-$\underline{C}$), 124.1 (thiophene-$\underline{C}$), 123.3 (thiophene-$\underline{C}$), 123.1 (thiophene-$\underline{C}$), 118.1 (allyl-$\underline{C}$), 76.3 (2'-$\underline{C}$), 65.9 (5-$\underline{C}$), 52.0 (CO$_2$$\underline{C}H_3$), 42.3 (allyl-$\underline{C}$), 41.8 (4''-$\underline{C}H_2$), 38.1 (1''-$\underline{C}H_2$), 36.3 (2'''-$\underline{C}H_2$), 35.3 (3''-$\underline{C}H_2$), 35.0 (6'''-$\underline{C}H_2$), 33.5 (3'-$\underline{C}H_2$), 29.9 (4'-$\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 26.0 ($\underline{C}H_2$), 25.3 ($\underline{C}H_2$) and 25.0 (1'''-$\underline{C}H_2$); **MS** *m/z* (ES+): 578 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 578.2016 (C$_{30}$H$_{37}$NNaO$_5$S$_2$) requires (M) 578.2005.

85b: IR ν$_{max}$(oil) 3600-3100 (OH), 2952 (CH), 1735, (C=O), 1721 (C=O), 1673 (C=O); ^{1}**H NMR** (500 MHz, CDCl$_3$) δ$_H$ 7.12 (dd, 1H, J = 5.3Hz and 0.8Hz, thiophene-$\underline{H}$), 6.92 (dd, 1H, J = 5.3Hz and 3.6Hz, thiophene-$\underline{H}$), 6.90 (dd, 1H, J = 5.3Hz and 3.6Hz, thiophene-$\underline{H}$), 6.79 (d, 1H, J = 3.6Hz, thiophene-$\underline{H}$), 5.83 (ddt, 1H, J = 17.0Hz, 10.0Hz and 6.5Hz, NCH$_2$C$\underline{H}$), 5.22 (d, 1H, J = 17.0Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.10 (d, 1H, J = 10.0Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.04 (dd, 1H, J = 15.4Hz and 6.5Hz, NC$\underline{H}_A$H$_B$), 3.86 (s, 3H, CO$_2$C$\underline{H}_3$), 3.76 (dd, 1H, J = 15.4Hz and 6.5Hz, NCH$_A$$\underline{H}_B$), 3.48 (d, 1H, J = 13.6Hz, 1'-C$\underline{H}_A$H$_B$), 2.87 (t, 2H, J = 7.3Hz, 6''-C$\underline{H}_2$), 2.79 (t, 2H, J = 7.3Hz, 3'''-C$\underline{H}_2$), 2.33 (t, 2H, J = 7.3Hz, 2''-C$\underline{H}_2$), 2.26-2.18 (m, 1H, 3'-CH$_A$$\underline{H}_B$), 2.17 (d, 1H, J = 13.6Hz, 3'-C$\underline{H}_A$H$_B$), 2.11-2.06 (m, 2H, 4''-C$\underline{H}_2$), 1.98-1.89 (m, 2H, 4'-C$\underline{H}_2$), 1.88 (t, 2H, J = 7.3Hz, 2'''-C$\underline{H}_2$), 1.85-1.74 (m, 3H, 5''-C$\underline{H}_2$) and 1.73-1.62 (m, 5H, 1'''-C$\underline{H}_2$, 3'-CH$_A$$\underline{H}_B$ and 1''-C$\underline{H}_2$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ$_C$ 208.6 (3''-$\underline{C}$=O), 170.8 (4-$\underline{C}$), 166.0 (2-$\underline{C}$=O), 163.5 ($\underline{C}$O$_2$CH$_3$), 144.6 (thiophene-$\underline{C}$), 144.0 (thiophene-$\underline{C}$), 133.7 (allyl-$\underline{C}$), 126.8 (thiophene-$\underline{C}$), 125.2 (3-$\underline{C}$), 124.5 (thiophene-$\underline{C}$), 124.4 (thiophene-$\underline{C}$), 123.3 (thiophene-$\underline{C}$), 123.1 (thiophene-$\underline{C}$), 117.9 (allyl-$\underline{C}$), 76.1 (2'-$\underline{C}$), 66.4 (5-$\underline{C}$), 52.1 (CO$_2$$\underline{C}H_3$), 42.8 (allyl-$\underline{C}$), 42.2 , 41.8 (4''-$\underline{C}H_2$), 36.9 (2'''-$\underline{C}H_2$), 35.7 (3''-$\underline{C}H_2$ and 6'''-$\underline{C}$H$_2$), 32.4 (3'-$\underline{C}$H$_2$), 30.0 (4'-$\underline{C}$H$_2$), 28.9 ($\underline{C}$H$_2$), 25.6 ($\underline{C}$H$_2$), 25.3 ($\underline{C}$H$_2$) and 25.0 (1'''-$\underline{C}$H$_2$); **MS** *m/z* (ES+): 578 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 578.2012 (C$_{30}$H$_{37}$NNaO$_5$S$_2$) requires (M) 578.2005.

Dimethyl 3,3'-(1-allyl-4-(methoxycarbonyl)-3-methyl-5-oxo-2,5-dihydro-1H-pyrrole-2,2-diyl)dipropanoate; 87

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 K_2CO_3 (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 ν_{max} /cm^{-1} (oil) 1738 (C=O), 1695 (C=O) and 1437 (C=C); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.92-5.79 (m, 1H, NCH$_2$C*H*), 5.25 (d, 1H, *J* = 17.0Hz, 1 of NCH$_2$CHC*H$_2$*), 5.10 (d, 1H, *J* = 10.0Hz, 1 of NCH$_2$CHC*H$_2$*), 4.02 (m, 2H, NC*H$_2$*), 3.82 (s, 3H, CO$_2$C*H$_3$*), 3.58 (s, 6H, 2 × OC*H$_3$*), 2.15 (td, 2H, *J* = 11.6Hz and 4.8Hz, COC*H$_2$*CH$_2$), 2.14 (s, 3H, C*H$_3$*), 2.03-1.95 (m, 2H, COC*H$_2$*CH$_2$), 1.89 (ddd, 2H, *J* = 16.1Hz, 10.9Hz and 5.0Hz, COCH$_2$C*H$_2$*), 1.74 (ddd, 2H, *J* = 16.1Hz, 10.9Hz and 5.0Hz, COCH$_2$C*H$_2$*); **^{13}C NMR** (125 MHz, CDCl$_3$) 172.4 (2 × $\underline{C}$O$_2$), 168.1 (N$\underline{C}$=O), 166.4 ($\underline{C}$O$_2$), 162.5 (quat. $\underline{C}$=C), 132.5 (allyl-$\underline{C}$), 126.2 (quat. C=$\underline{C}$), 118.7 (allyl-$\underline{C}$), 69.5 (N$\underline{C}$), 51.8 (3 × O$\underline{C}$H$_3$), 42.3 (N$\underline{C}$H$_2$), 29.4 (2 × CO$\underline{C}$H$_2$), 27.2 (2 × COCH$_2$$\underline{C}H_2$), 12.2 ($\underline{C}H_3$) **MS** *m/z* (ES+): 390 ([M+Na]$^+$); Found [M+H]$^+$ 368.1708 (C$_{18}$H$_{26}$NO$_7$) requires (M) 368.1704.

(±)-Methyl 1-allyl-5-hydroxy-4,5-dimethyl-2-oxopyrrolidine-3-carboxylate; 89
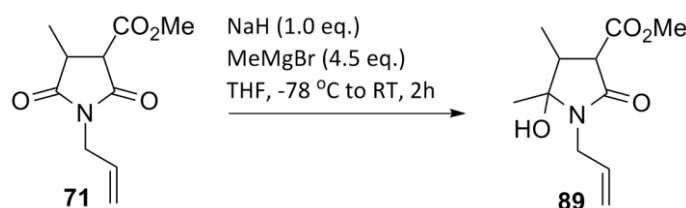
A solution of **71** (2.94 g, 14.0 mmol) in dry tetrahydrofuran (115 mL) was added dropwise *via* cannula to a stirred suspension of 60% sodium hydride in oil (0.56 g, 14.0 mmol) in dry tetrahydrofuran (115 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 minutes and 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 (MgSO$_4$), 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_{max} (oil); 3600-3200 (OH), 1742 (C=O), 1690 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.84 (ddt, 1H, J = 17.1Hz, 10.6Hz and 5.9Hz, NCH$_2$C$\underline{H}$), 5.22 (d, 1H, J = 17.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.15 (d, 1H, J = 10.6Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 3.82-3.97 (m, 2H, NC$\underline{H}_2$), 3.79 (s, 3H, CO$_2$C$\underline{H}_3$), 3.30 (d, 1H, J = 10.7Hz, C$\underline{H}$CO$_2$Me), 3.02-2.78 (bs, 1H, O$\underline{H}$), 2.57 (dq, 1H, J = 10.7Hz and 6.9Hz, C$\underline{H}$CH$_3$), 1.51 (s, 3H, C$\underline{H}_3$), 1.14 (d, 3H, J = 6.9Hz, CHC$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 170.1 ($\underline{C}$=O), 170.0 ($\underline{C}$=O), 134.0 (allyl-$\underline{C}$), 117.3 (allyl-$\underline{C}$), 89.8 (quat. $\underline{C}$), 53.6 ($\underline{C}$HCO$_2$Me), 52.7 (CO$_2$$\underline{C}H_3$), 42.8 ($\underline{C}HCH_3$), 42.1 (allyl-$\underline{C}$), 24.7 (C$\underline{C}H_3$) and 11.9 (CH$\underline{C}H_3$); **MS** *m/z* (ES+): 250.3 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 250.1054 (C$_{11}$H$_{17}$NNaO$_4$) 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 (MgSO$_4$), 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** ν_{max}(solid) 2985 (CH), 2950 (C=CH), 1788 (C=O), 1690 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.78 (ddt, 1H, J = 17.0Hz, 10.1Hz and 4.8Hz, NCH$_2$C*H*), 5.14 (d, 1H, J = 10.1Hz, 1 of NCH$_2$CHC*H$_2$*), 4.92 (d, 1H, J = 17.0Hz, 1 of NCH$_2$CHC*H$_2$*), 4.28-4.25 (m, 2H, NC*H*), 3.73 (s, 3H, CO$_2$C*H$_3$*), 2.32 (s, 3H, acetate-C*H$_3$*), 2.16 (s, 3H, NCC*H$_3$*) and 2.04 (s, 3H, C*H$_3$*); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 168.8 (*C*=O), 164.6 (*C*=O), 138.7 (pyrrole-*C*), 132.5 (allyl-*C*), 120.3 (pyrrole-*C*), 116.8 (allyl-*C*), 114.3 (pyrrole-*C*), 100.1 (pyrrole-*C*), 50.6 (CO$_2$*C*H$_3$), 44.5 (allyl-*C*), 20.5 (acetate-*C*H$_3$), 10.8 (*C*H$_3$) and 8.9 (*C*H$_3$); **MS *m/z*** (CI+): 252 ([M+H]$^+$); **HRMS** Found [M+H]$^+$ 252.1223 (C$_{13}$H$_{18}$NO$_4$) requires (M) 252.1230. Analysis calculated for C$_{13}$H$_{18}$NO$_4$: 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 K_2CO_3 (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, NCH₂C*H*), 5.21 (d, 1H, *J* = 17.2Hz, 1 of NCH₂CHC*H*₂), 5.12 (d, 1H, *J* = 10.0Hz, 1 of NCH₂CHC*H*₂), 4.40 (bs, 1H, O*H*), 4.11 (dd, 1H, *J* = 15.8Hz and 5.8Hz, NC*H*_AH_B), 3.92 (dd, 1H, *J* = 15.9Hz and 6.4Hz, NCH_A*H*_B), 3.85 (s, 3H, CO₂C*H*₃), 3.70 (dt, 1H, *J* = 14.2Hz and 2.6Hz, 1'-C*H*_AH_B), 3.4-3.28 (m, 1H, 2'-C*H*OH), 2.48 (dd, 1H, *J* = 14.2Hz and 3.2 Hz, 1'-CH_A*H*_B), 2.02-2.04 (m, 1H, 1 of 3'-C*H*₂), 1.90-1.66 (m, 3H, 1 of 3'-C*H*₂ and 4'-C*H*₂) and 1.37 (s, 3H, 5-C*H*₃); **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 (O*C*H₃), 42.1 (N*C*H₂), 35.0 (1'-*C*), 33.0 (4'-*C*), 29.7 (3'-*C*), 21.1 (*C*H₃); **Minor 92b observed: ¹H NMR** (500 MHz, CDCl₃) δ_H 3.75-3.72 (m, 1H, 1'-C*H*_AH_B), 2.30 (dd, 1H, *J* = 10.9Hz and 12.6Hz, 1'-CH_A*H*_B), 2.20-2.15 (m, 1H, 1 of 3'-C*H*₂), 2.03-1.97 (m

1H, 1 of 3'-C$\underline{H}_2$), 1.90-1.66 (m, 2H, 1 of 3'-C$\underline{H}_2$ and 1 of 4'-C$\underline{H}_2$), 1.64-1.54 (m, 1H, 1 of 4'-C$\underline{H}_2$) and 1.33 (s, 3H, 5-C$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ$_C$ 171.1 (2-$\underline{C}$=O), 165.5 ($\underline{C}$=O), 134.4 (allyl-$\underline{C}$), 121.9 (3-$\underline{C}$), 117.1 (allyl-$\underline{C}$), 68.7 (2'-$\underline{C}$), 63.5 (5-$\underline{C}$), 52.0 (O$\underline{C}$H$_3$), 42.0 (N$\underline{C}$H$_2$), 34.7 (1'-$\underline{C}$), 30.4 (4'-$\underline{C}$), 28.4 (3'-$\underline{C}$), 20.4 ($\underline{C}$H$_3$); **MS** *m/z* (ES+): 266 ([M+H]$^+$); **HRMS** Found [M+H]$^+$ 266.1385 (C$_{14}$H$_{20}$NO$_4$) requires (M) 266.1387.

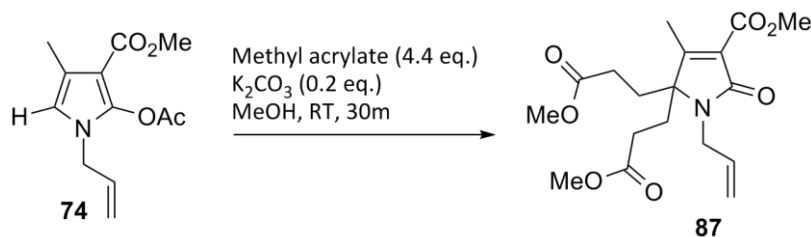## (±)-Methyl-1-allyl-2'-hydroxy-2',5-dimethyl-2-oxo-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 93a,b

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 ν$_{max}$ (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$_2$C$\underline{H}$), 5.20 (d, 1H, *J* = 17.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.11 (d, 1H, *J* = 10.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.10 (dd, 1H, *J* = 15.6Hz and 6.6Hz, NC$\underline{H}_A$H$_B$), 3.89 (dd, 1H, *J* = 15.6Hz and 6.6Hz, NCH$_A$$\underline{H}_B$), 3.84 (s, 3H, CO$_2C\underline{H}_3$), 3.61 (d, 1H, *J* = 12.8Hz, 1'-C$\underline{H}_A$H$_B$), 2.47 (d, 1H, *J* = 12.8Hz, 1'-CH$_A$$\underline{H}_B$), 2.12 (dt, 1H, *J* = 13.3Hz and 2.9Hz, 3'-C$\underline{H}_A$H$_{Bm}$), 1.82 (dt, 1H, *J* = 14.1Hz and 4.1Hz, 4'-C$\underline{H}_A$H$_B$), 1.76-1.66 (m, 1H, 4'-CH$_A$$\underline{H}_B$), 1.37 (s, 3H, 5-C$\underline{H}_3$), 1.28-1.22 (m, 1H, 3'-CH$_A$$\underline{H}_B$), 1.12 (s, 3H, 2'-C$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ$_C$ 172.6 (3-$\underline{C}$), 172.0 (4-$\underline{C}$), 165.6 ($\underline{C}$=O), 163.1 ($\underline{C}$O$_2$CH$_3$), 134.3 (allyl-$\underline{C}$), 117.2 (allyl-$\underline{C}$), 74.7 (2'-$\underline{C}$), 63.8 (5-$\underline{C}$), 51.9 (CO$_2$$\underline{C}H_3$), 42.2 (allyl-$\underline{C}$), 39.5 (1'-$\underline{C}$), 35.6 (3'-$\underline{C}$), 35.5 (4'-$\underline{C}$), 25.8 (5-C$\underline{C}H_3$), 21.1(2'-C$\underline{C}H_3$); **Minor 93a observed: ^{1}H NMR** (500 MHz, CDCl$_3$) δ$_H$ 3.54 (d, 1H, *J* = 13.9Hz, 1'-C$\underline{H}_A$H$_B$), 2.34 (d, 1H, *J* = 13.9Hz, 1'-CH$_A$$\underline{H}_B$), 2.04-2.00 (m, 1H, 3'-C$\underline{H}_A$H$_B$), 1.40 (s, 3H, 2'-C$\underline{H}_3$), 1.31 (s, 3H, 5-C$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ$_C$ 165.5 ($\underline{C}$=O), 163.8 ($\underline{C}$O$_2$CH$_3$), 134.4 (allyl-$\underline{C}$), 117.1 (allyl-$\underline{C}$), 73.8 (2'-$\underline{C}$),

52.0 ($CO_2\underline{C}H_3$), 42.1 (allyl-$\underline{C}$), 38.4 (1'-$\underline{C}$), 35.3 (3'-$\underline{C}$), 34.4 (4'-$\underline{C}$), 30.7 (5-C$\underline{C}H_3$), 20.5 (2'-C$\underline{C}H_3$); **MS** *m/z* (ES+): 302 ([M+Na]$^+$); **HRMS** Found [M+H]$^+$ 280.1549 ($C_{15}H_{22}NO_4$) 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 ν_{max}(oil) 3550-3200 (OH), 2900, 2800 (CH), 1720 (C=O), 1685 (C=O); **Major 94a: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.86-5.76 (m, 1H, NCH$_2$C$\underline{H}$), 5.19 (d, 1H, *J* = 17.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.10 (d, 1H, *J* = 10.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.09 (dd, 1H, *J* = 15.8Hz and 5.9Hz, NC$\underline{H}_A$H$_B$), 3.87 (dd, 1H, *J* = 15.8Hz and 6.7Hz, NCH$_A\underline{H}_B$), 3.83 (s, 3H, OC$\underline{H}_3$), 3.67 (d, 1H, *J* = 13.0Hz, 1'-C$\underline{H}_A$H$_B$), 2.41 (d, 1H, *J* = 13.0Hz, 1'-CH$_A\underline{H}_B$), 2.08 (dt, 1H, *J* = 13.3Hz and 4.0Hz, 3'-C$\underline{H}_A$H$_B$), 1.83-1.76 (m, 1H, 4'-C$\underline{H}_A$H$_B$), 1.73 (dt, 1H, *J* = 14.0Hz and 4.0Hz, 4'-CH$_A\underline{H}_B$), 1.43-1.37 (m, 2H, C$\underline{H}_2$CH$_3$), 1.37 (s, 3H, 5-C$\underline{H}_3$), 1.34 (q, 1H, *J* = 7.4Hz, 1 of C$\underline{H}_2$CH$_3$), 1.19 (m, 1H, 3'-CH$_A\underline{H}_B$), 0.85 (t, 3H, *J* = 7.4Hz, CH$_2$C$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 173.0 (3-$\underline{C}$), 172.0 (4-$\underline{C}$), 165.6 ($\underline{C}$=O), 163.1 ($\underline{C}O_2$CH$_3$), 134.3 (allyl-$\underline{C}$), 117.2 (allyl-$\underline{C}$), 76.4 (2'-$\underline{C}$), 64.1 (5-$\underline{C}$), 51.8 (CO$_2\underline{C}$H$_3$), 42.1 (allyl-$\underline{C}$), 37.6 (1'-$\underline{C}$), 34.8 (3'-$\underline{C}$), 32.8 (4'-$\underline{C}$), 29.4 ($\underline{C}$H$_2$CH$_3$), 21.4 (5-$\underline{C}$H$_3$), 6.7 (CH$_2\underline{C}$H$_3$); **Minor 94b observed: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 3.84 (s, 3H, OC$\underline{H}_3$), 3.51 (d, 1H, *J* = 13.8Hz, 1'-C$\underline{H}_A$H$_B$), 2.28 (d, 1H, *J* = 13.9Hz, 1'-CH$_A\underline{H}_B$), 1.64 (q, 1H, *J* = 7.6Hz, 1 of C$\underline{H}_2$CH$_3$), 1.53 (m, 1H, 4'-CH$_A\underline{H}_B$), 1.30 (s, 3H, 5-C$\underline{H}_3$), 0.97 (t, 3H, *J* = 7.5Hz, CH$_2$C$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 163.9

($\underline{C}O_2CH_3$), 134.4 (allyl-$\underline{C}$), 117.0 (allyl-$\underline{C}$), 76.1 (2'-$\underline{C}$), 63.8 (5-$\underline{C}$), 52.0 (CO$_2\underline{C}H_3$), 36.3 (1'-$\underline{C}$), 36.0 ($\underline{C}H_2CH_3$), 35.4 (3'-$\underline{C}$), 32.0 (4'-$\underline{C}$), 20.3 (5-$\underline{C}H_3$), 7.7 (CH$_2\underline{C}H_3$); **MS** *m/z* (ES+): 294 ([M+H]$^+$); **HRMS** Found [M+H]$^+$ 294.1705 (C$_{16}$H$_{24}$NO$_4$) requires (M) 294.1700.

(±)-(E)-Methyl-1-allyl-2'-hydroxy-5-methyl-2-oxo-2'-(prop-1''-enyl)-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 95a,b

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 ν$_{max}$ (oil) 3600-3300 (OH), 2948 (CH), 1741 (C=O), 1714 (C=O), 1679 (C=O); **Major 95a:** ^{1}**H NMR** (400 MHz, CDCl$_3$) δ$_H$ 5.92-5.75 (m, 2H, NCH$_2$C$\underline{H}$ and 1''-C$\underline{H}$), 5.65 (dd, 1H, *J* = 15.5Hz and 1.5Hz, 2''-C$\underline{H}$), 5.26-5.19 (m, 1H, 1 of NCH$_2$CHC$\underline{H_2}$), 5.12 (dd, 1H, *J* = 10.1Hz and 1.3Hz, 1 of NCH$_2$CHC$\underline{H_2}$), 4.11 (ddt, 1H, *J* = 15.7Hz, 5.8Hz and 1.5Hz, NC$\underline{H}_A$H$_B$), 3.98-3.89 (m, 1H, NCH$_A\underline{H}_B$), 3.87 (s, 3H, CO$_2$C$\underline{H_3}$), 3.55 (dd, 1H, *J* = 13.9Hz and 2.1Hz, 1'-C$\underline{H}_A$H$_B$), 2.44 (d, 1H, *J* = 13.9Hz, 1'-CH$_A\underline{H}_B$), 2.20-2.03 (m, 1H, 3'-C$\underline{H}_A$H$_B$), 1.73 (dd, 3H, *J* = 6.4Hz and 1.5Hz, 3''-C$\underline{H_3}$), 1.71-1.58 (m, 3H, 3'-CH$_A\underline{H}_B$, 4'-C$\underline{H_2}$), 1.39 (s, 3H, 5-C$\underline{H_3}$), and 1.34 (s, 3H, 5-C$\underline{H_3}$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ$_C$ 172.7 (3-$\underline{C}$), 172.0 (4-$\underline{C}$), 165.5 (2-$\underline{C}$=O), 163.9 ($\underline{C}$O$_2$CH$_3$), 137.1 (1''-$\underline{C}$H), 134.6 (allyl-$\underline{C}$), 127.6 (2''-$\underline{C}$H), 117.1 (allyl-$\underline{C}$), 75.4 (2'-$\underline{C}$), 63.7 (5-$\underline{C}$), 52.1 (CO$_2\underline{C}$H$_3$), 42.1 (allyl-$\underline{C}$), 37.3 (1'-$\underline{C}$H$_2$), 35.3 (3'-$\underline{C}$H$_2$), 33.5 (4'-$\underline{C}$H$_2$), 20.4 (5-$\underline{C}$H$_3$) and 17.6 (3''-$\underline{C}$H$_3$); **Minor 95b observed:** ^{1}**H NMR** (400 MHz, CDCl$_3$) δ$_H$ 2.53 (d, 1H, *J* = 13.1Hz, 1'-CH$_A\underline{H}_B$); **MS** *m/z* (ES+): 328 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 328.1527 (C$_{17}$H$_{23}$NNaO$_4$) requires (M) 328.1519

(±)-Methyl 1-allyl-2'-hydroxy-5-methyl-2-oxo-2'-(3''-(thiophen-2-yl)propyl)-2,1',2',3',4',5-hexahydro-1H-indole-3-carboxylate; 96a,b
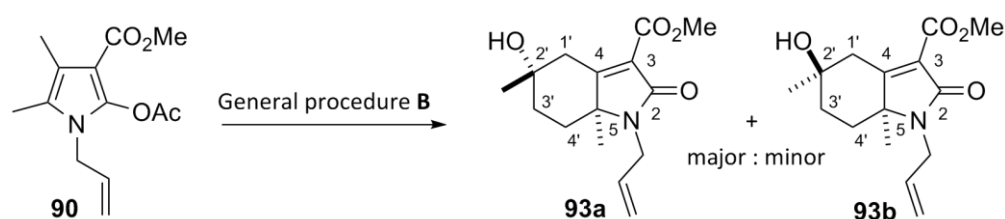

Following the general procedure **B** described above with α,β-unsaturated ketone **82**, the Michael-aldol product **96a,b** was obtained following purification by column chromatography (diethyl ether : light petroleum ether, 4:1) as a 4:1 mixture of diastereoisomers and a yellow oil (72 mg, 69%).

IR ν_{max} (oil) 3700-3200 (OH), 2948, (CH), 1736 (C=O), 1690 (C=O); **Major 96a: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.10 (d, 1H, J = 5.1Hz, 7''-C$\underline{H}$), 6.75 (d, 1H, J = 2.8Hz, 5''-C$\underline{H}$), 5.83 (ddt, 1H, J = 16.9Hz, 10.2Hz and 6.0Hz, NCH$_2$C$\underline{H}$), 5.21 (d, 1H, J = 16.9Hz, 1 of NCH$_2$CHC$\underline{H_2}$), 5.13 (d, 1H, J = 10.2Hz, 1 of NCH$_2$CHC$\underline{H_2}$), 4.11 (dd, 1H, J = 16.1Hz and 6.0Hz, NC$\underline{H_A}$H$_B$), 3.90 (dd, 1H, J = 16.1Hz and 6.0Hz, NCH$_A$$\underline{H_B}$), 3.85 (s, 3H, CO$_2C\underline{H_3}$), 3.71 (d, 1H, J = 13.0Hz, 1'-C$\underline{H_A}$H$_B$), 2.84-2.71 (m, 2H, 3''-C$\underline{H_2}$), 2.40 (d, 1H, J = 13.0Hz, 1'-CH$_A$$\underline{H_B}$), 2.09 (dt, 1H, J = 13.3Hz and 3.5Hz, 3'-C$\underline{H_A}$H$_B$), 1.88-1.77 (m, 3H, 4'-C$\underline{H_2}$ and 2''-C$\underline{H_A}$H$_B$), 1.73 (dt, 1H, J = 14.1Hz and 4.0Hz, 2''-CH$_A$$\underline{H_B}$), 1.48-1.36 (m, 2H, 1''-C$\underline{H_2}$), 1.39 (s, 3H, 5-C$\underline{H_3}$) and 1.20 (dt, 1H, J = 12.6Hz and 5.1Hz, 3'-CH$_A$$\underline{H_B}$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ_C 172.1 (3-$\underline{C}$), 171.5 (4-$\underline{C}$), 165.6 (2-$\underline{C}$=O), 163.1 ($\underline{C}$O$_2$CH$_3$), 144.7 (4''-$\underline{C}$), 134.4 (allyl-$\underline{C}$), 126.7 (6''-$\underline{C}$H), 124.2 (5''-$\underline{C}$H), 123.1 (7''-$\underline{C}$H), 117.3 (allyl-$\underline{C}$), 76.4 (2'-$\underline{C}$), 63.7 (5-$\underline{C}$), 52.0 (CO$_2$$\underline{C}H_3$), 42.2 (allyl-$\underline{C}$), 37.9 (1'-$\underline{C}H_2$), 36.3 (5-$\underline{C}H_3$), 35.0 (C3'-$\underline{C}H_2$), 33.6 (4'-$\underline{C}H_2$), 29.9 (3''-$\underline{C}H_2$), 25.0 (2''-$\underline{C}H_2$), 21.4 (1''-$\underline{C}H_2$); **Major 96b observed: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.12 (d, 1H, J = 5.1Hz, 7''-C$\underline{H}$), 6.92 (dd, 1H, J = 5.1Hz and 3.5Hz, 6''-C$\underline{H}$), 6.89 (dd, 1H, J = 5.1Hz and 3.4Hz, 6''-C$\underline{H}$), 6.80 (d, 1H, J = 2.8Hz, 5''-C$\underline{H}$), 4.09 (dd, 1H, J = 16.1Hz and 6.0Hz, NC$\underline{H_A}$H$_B$), 3.93 (dd, 1H, J = 16.1Hz and 6.0Hz, NCH$_A$$\underline{H_B}$), 3.86 (s, 3H, CO$_2C\underline{H_3}$), 3.54 (d, 1H, J = 13.8Hz, 1'-C$\underline{H_A}$H$_B$), 2.87 (t, 2H, J = 7.3Hz, 3''-C$\underline{H_2}$), 2.30 (d, 1H, J = 13.8Hz, 1'-CH$_A$$\underline{H_B}$), 1.31 (s, 3H, 5-C$\underline{H_3}$); 126.8 (6''-$\underline{C}$H), 124.3 (5''-$\underline{C}$H), 123.2 (7''-$\underline{C}$H),

42.1 (allyl-$\underline{C}$), 36.8 (1'-$\underline{C}H_2$), 35.5 (3'-$\underline{C}H_2$); **MS** *m/z* (ES+): 412 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 412.1540 ($C_{21}H_{27}NNaO_4S$) requires (M) 412.1553.

(±)-Methyl-1-allyl-5-(3-methoxy-3-oxopropyl)-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate; 97
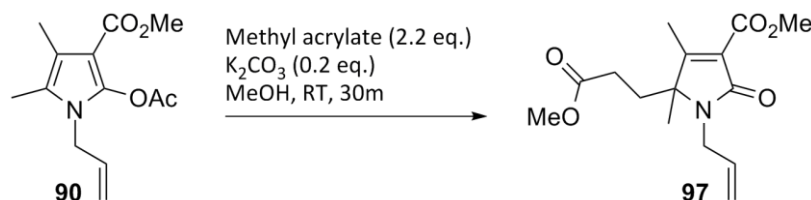
To a stirred solution of **90** (100 mg, 0.42 mmol) in MeOH (2 mL) was added methyl acrylate (0.08 mL, 0.93 mmol) and K_2CO_3 (12 mg, 0.08 mmol) at room temperature. The reaction was stirred until TLC confirmed complete consumption of starting material before quenched by addition of acetic acid (10 μL, 0.17 mmol) and concentrated *in vacuo*. Purification by column chromatography (neat diethyl ether) gave **97** (101 mg, 82%) as a yellow oil.

IR ν_{max} /cm^{-1} (oil) 2954 (CH), 1750 (C=O), 1700 (C=O), 1436 (C=C); **^{1}H NMR** (500 MHz, CDCl$_3$) δ$_H$ 5.87-5.75 (m, 1H, NCH$_2$C$\underline{H}$), 5.20 (d, 1H, *J* = 17.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.09 (d, 1H, *J* = 10.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 3.98 (d, 1H, *J* = 15.6Hz, 1 of NC$\underline{H}_2$), 3.82 (s, 3H, CO$_2$C$\underline{H}_3$), 3.79 (m, 1H, 1 of NC$\underline{H}_2$), 3.59 (s, 3H, OC$\underline{H}_3$), 2.18 (s, 3H, C$\underline{H}_3$), 2.12 (m, 1H, 1 of COC$\underline{H}_2$), 1.97 (m, 1H, 1 of COC$\underline{H}_2$), 1.89 (ddd, 1H, *J* = 15.9Hz, 10.5Hz and 5.1Hz, 1 of COCH$_2$C$\underline{H}_2$), 1.73 (ddd, 1H, *J* = 15.9Hz, 10.5Hz and 5.1Hz, 1 of COCH$_2$C$\underline{H}_2$), 1.29 (s, 3H, C$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ$_C$ 172.6 (N$\underline{C}$=O), 170.3 ($\underline{C}$O$_2$), 165.9 ($\underline{C}$O$_2$), 163.1 (quat. $\underline{C}$=C), 133.5 (allyl-$\underline{C}$), 124.6 (quat. C=$\underline{C}$), 117.6 (allyl-$\underline{C}$), 67.0 (N$\underline{C}$), 51.8 (2 × O$\underline{C}$H$_3$), 42.1 (N$\underline{C}$H$_2$), 29.5 (CO$\underline{C}$H$_2$CH$_2$), 27.6 (COCH$_2$$\underline{C}H_2$), 23.2 ($\underline{C}H_3$), 12.2 ($\underline{C}H_3$); **MS** *m/z* (ES+): 318 ([M+Na]$^+$); **HRMS** Found [M+H]$^+$ 296.1503 ($C_{15}H_{22}NO_5$) requires (M) 296.1492.

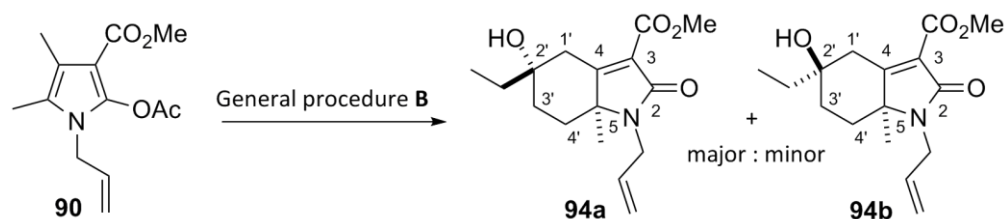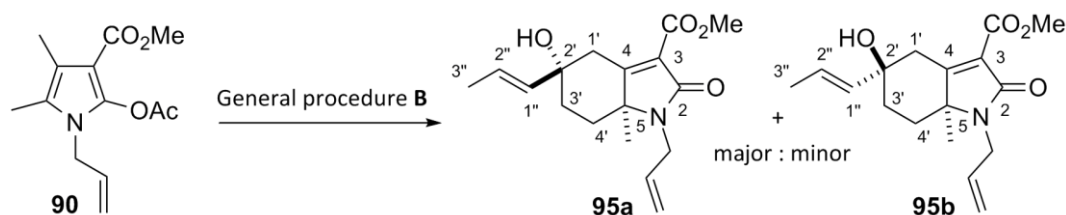**(±)-Methyl 8-hydroxy-2-methyl-4-oxo-3-(prop-2-en-1-yl)-3-azatricyclo[6.2.1.0²,⁶]undec-5-ene-5-carboxylate; 99**

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%).

IR ν_{max}(oil) 3325 (OH), 2928 (CH), 1741, (C=O), 1730 (C=O), 1684 (C=O); **¹H NMR** (400 MHz, CDCl₃) δ_H 5.79 (dddd, 1H, J = 17.2Hz, 10.0Hz, 7.2Hz and 5.8Hz, NCH₂C*H*), 5.23 (dd, 1H, J = 17.1Hz and 1.4Hz, 1 of NCH₂CHC*H₂*), 5.12 (dd, 1H, J = 10.1Hz and 1.2Hz, 1 of NCH₂CHC*H₂*), 4.16 (ddt, 1H, J = 15.5Hz, 5.8Hz and 1.5Hz, NC*H*ₐH_B), 3.87 (s, 3H, OC*H₃*), 3.75 (dd, 1H, J = 15.5Hz and 7.2Hz, NCHₐ*H_B*), 3.57 (dd, 1H, J = 13.3Hz and 3.0Hz, 1 of 1'-C*H*ₐH_B), 2.69 (d, 1H, J = 13.3Hz, 1 of 1'-CHₐ*H_B*) 2.44 (t, 1H, J = 5.0Hz, 4'-C*H*), 2.02-1.86 (m, 2H, 3'-C*H₂*), 1.66-1.62 (m, 1H, 1 of 2''-C*H₂*), 1.55-1.49 (m, 2H, 1''-C*H₂*), 1.42 (s, 3H, 5-C*H₃*), 1.16-1.08 (m, 1H, 1 of 2''-C*H₂*); **¹³C NMR** (125 MHz; CDCl₃) δ_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 (O*C*H₃), 42.6 (3'-*C*), 42.5 (N*C*H₂), 41.1 (1''-*C*), 40.9 (1'-*C*), 35.7 (4'-*C*), 23.1 (*C*H₃), 22.0 (3'-*C*); **MS** m/z (ES+): 314 ([M+Na]⁺); **HRMS** Found [M+H]⁺ 292.1541 (C₁₆H₂₂NO₄) requires M 292.1543

(±)-Methyl 8-hydroxy-2-methyl-4-oxo-3-(prop-2-en-1-yl)-3-azatricyclo[6.3.1.0²,⁶]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_{max}(oil) 3390 (OH), 2919 (CH), 1736, (C=O), 1713 (C=O), 1674 (C=O); **¹H NMR** (400 MHz, CDCl₃) δ_H 5.94 (ddt, 1H, J = 16.6Hz, 10.1Hz and 6.5Hz, NCH₂C$\underline{H}$), 5.24 (dd, 1H, J = 17.1Hz and 1.4Hz, 1 of NCH₂CHC$\underline{H}_2$), 5.14 (dd, 1H, J = 10.1Hz and 1.2Hz, 1 of NCH₂CHC$\underline{H}_2$), 4.02 (ddt, 1H, J = 15.3Hz, 6.3Hz and 1.3Hz, NC$\underline{H}_A$H$_B$), 3.91 (dd, 1H, J = 15.4Hz and 6.5Hz, NCH$_A$$\underline{H}_B$), 3.86 (s, 3H, OC$\underline{H}_3$), 3.70 (dd, 1H, J = 14.8Hz and 2.7Hz, 1'-C$\underline{H}_A$H$_B$), 2.65 (dd, 1H, J = 14.8Hz and 1.8Hz, 1 of 1'-CH$_A$$\underline{H}_B$), 2.41 (m, 1H, 4'-C$\underline{H}$), 2.13 (ddd, 1H, J = 13.1Hz, 5.2Hz and 2.8Hz, 1 of 3'-C$\underline{H}_2$), 1.85 (dd, 1H, J = 11.9Hz and 2.8Hz, 1 of 3'-C$\underline{H}_2$), 1.68 (td, 1H, J = 13.1Hz and 3.0Hz, 1 of 3''-C$\underline{H}_2$), 1.63-1.48 (m, 2H, 1 of 1''-C$\underline{H}_2$ and 1 of 3''-C$\underline{H}_2$), 1.46 (s, 3H, 5-C$\underline{H}_3$), 1.35 (m, 3H, 1 of 1''-C$\underline{H}$ and 2''-C$\underline{H}_2$); **¹³C NMR** (125 MHz; CDCl₃) δ_C 174.5 (2-C=O), 166.8 (C=O), 163.3 (4-$\underline{C}$), 133.9 (allyl-$\underline{C}$), 121.5 (3-$\underline{C}$), 117.7 (allyl-$\underline{C}$), 72.7 (2'-$\underline{C}$), 67.2 (5-$\underline{C}$), 51.9 (O$\underline{C}$H₃), 42.8 (N$\underline{C}$H₂), 40.9 (1''-$\underline{C}$), 40.5 (1'-$\underline{C}$), 39.0 (3'-$\underline{C}$), 38.8 (4'-$\underline{C}$), 25.8 (3''-$\underline{C}$), 25.2 (2''-$\underline{C}$), 20.8 ($\underline{C}$H₃); **MS** m/z (ES+): 328 ([M+Na]⁺); **HRMS** Found [M+Na]⁺ 328.1520 (C₁₇H₂₃NNaO₄) requires (M) 328.1519

## (±)-Methyl 2,8-dihydroxy-4-oxo-3-(prop-2-en-1-yl)-3-azatricyclo[6.2.1.0^{2,6}]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, (C=O), 1690 (C=O); **^{1}H NMR** (500 MHz, MeOD) δ_H 5.70 (dddd, 1H, *J* = 17.3Hz, 10.2Hz 7.4Hz and 5.3Hz, NCH$_2$C*H*), 5.15 (dd, 1H, *J* = 17.1Hz and 1.3Hz, 1 of NCH$_2$CHC*H$_2$*), 5.01 (dd, 1H, *J* = 10.1Hz and 0.9Hz, 1 of NCH$_2$CHC*H$_2$*), 3.95 (ddt, 1H, *J* = 15.7Hz, 5.6Hz and 1.6Hz, NC*H$_A$*H$_B$), 3.74 (s, 3H, OC*H$_3$*), 3.70 (dd, 1H, *J* = 14.7Hz and 7.7Hz, NCH$_A$*H$_B$*), 3.26 (dd, 1H, *J* = 13.1Hz and 3.0Hz, 1'-C*H$_A$*H$_B$), 2.63 (dd, 1H, *J* = 13.1Hz and 1.8Hz, 1'-CH$_A$*H$_B$*), 2.48 (dd, 1H, *J* = 6.6Hz and 5.2Hz, 4'-C*H*), 2.13 (d, 1H, *J* = 11.4Hz, 3'-C*H$_A$*H$_B$), 1.69 (ddd, 1H, *J* = 11.4Hz, 5.0Hz and 3.1Hz, 3'-CH$_A$*H$_B$*), 1.67-1.58 (m, 1H, 1 of 2''-C*H$_2$*), 1.46 (ddt, 1H, *J* = 12.8Hz, 5.1Hz and 1.9Hz 1 of 1''-C*H$_2$*), 1.40-1.33 (m, 1H, 1 of 1''-C*H$_2$*), 0.84 (m, 1H, 1 of 2''-C*H$_2$*); **^{13}C NMR** (125 MHz, MeOD) δ_C 171.2 (2-C=O), 170.7 (C=O), 166.5 (quat. C=C), 137.6 (H*C*=CH$_2$), 126.3 (quat. C=C), 120.4 (HC=*C*H$_2$), 93.9 (5-C), 83.0 (2'-OH), 54.9 (OCH$_3$), 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 (C$_{15}$H$_{19}$NNaO$_5$) 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); **^{1}H NMR** (400 MHz, MeOD) δ_H 5.83 (dddd, 1H, J = 17.4Hz, 10.1Hz, 7.4Hz and 5.6Hz, NCH$_2$C$\underline{H}$), 5.18 (dd, 1H, J = 17.1Hz and 1.4Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.03 (dd, 1H, J = 10.1Hz and 1.3Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 3.84 (m, 2H, NC$\underline{H}_2$), 3.74 (s, 3H, OC$\underline{H}_3$), 3.38 (dd, 1H, J = 14.5Hz and 2.7Hz, 1'-C$\underline{H}_A$H$_B$), 2.61 (dd, 1H, J = 14.5Hz and 1.6Hz, 1'-CH$_A\underline{H}_B$), 2.46-2.41 (m, 1H, 2'-O$\underline{H}$), 2.30 (ddd, 1H, J = 12.4Hz, 4.9Hz and 3.0Hz, 1 of 3'-C$\underline{H}_2$), 1.72-1.65 (m, 1H, 1 of 1''-C$\underline{H}_2$), 1.53-1.22 (m, 7H, 3'-C$\underline{H}$, 4'-C$\underline{H}$, 1''-C$\underline{H}$, 2'' and 3''-C$\underline{H}_2$); **^{13}C NMR** (125 MHz, MeOD) δ_C 172.1 (2-C=O), 168.6 (C=O), 164.2 (quat. C=C), 135.3 (H$\underline{C}$=CH$_2$), 121.8 (quat. C=C), 118.1 (HC=$\underline{C}$H$_2$), 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
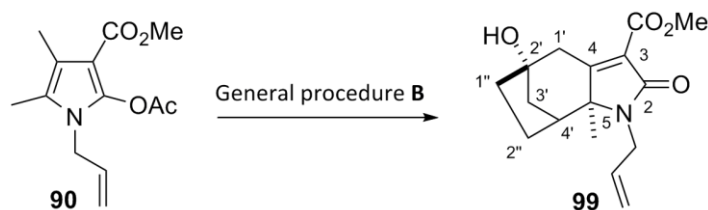
(±)-Methyl 1-allyl-5-hydroxy-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate; 113

To a stirred solution of **90** (100 mg, 0.42 mmol) in MeOH (2 mL) was added K_2CO_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 ν_{max} (oil); 3322 (OH), 2925 (CH), 1741 (C=O), 1715 (C=O), 1690 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ$_H$ 5.84 (m, 1H, NCH$_2$C*H*), 5.21 (dd, 1H, *J* = 17.2Hz and 1.3Hz, 1 of NCH$_2$CHC*H*$_2$), 5.13 (dd, 1H, *J* = 10.2Hz and 1.2Hz, 1 of NCH$_2$CHC*H*$_2$), 4.02 (ddt, 1H, *J* = 15.8Hz, 5.2Hz, and 1.4Hz, 1 of NC*H*$_2$CHCH$_2$), 3.94 (dd, 1H, *J* = 16.0Hz and 6.6Hz, 1 of NC*H*$_2$CHCH$_2$), 3.84 (s, 3H, OC*H*$_3$), 3.30 (s, 1H, O*H*), 2.30 (s, 3H, (OH)C*H*$_3$), 1.45 (s, 3H, CC*H*$_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ$_C$ 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 (*C*OH), 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-ethylpyrrolidine-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 v_{max} /cm^{-1} (oil) 1700 (C=O), 1428 (C=O) and 1395 (C=C); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.78 (ddt, 1H, J = 16.1Hz, 10.3Hz and 5.8Hz, NCH$_2$C$\underline{H}$), 5.21 (d, 1H, J = 16.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.17 (d, 1H, J = 10.3Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.10 (d, 2H, J = 5.8Hz, NC$\underline{H}_2$), 2.84 (dd, 1H, J = 17.7Hz and 9.0Hz, 1 of COC$\underline{H}_2$CH), 2.78 (dt, 1H, J = 9.0Hz and 4.1Hz, COC$\underline{H}$CH$_2$CH$_3$), 2.40 (dd, 1H, J = 17.7Hz and 4.1Hz, 1 of COC$\underline{H}_2$CH), 1.93 (dqd, 1H, J = 14.9Hz, 7.4Hz and 4.1Hz, 1 of C$\underline{H}_2$CH$_3$), 1.67-1.57 (m, 1H, 1 of C$\underline{H}_2$CH$_3$), 0.98 (t, 3H, J = 7.4Hz, C$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_c 179.4 (N$\underline{C}$=O), 176.2 (N$\underline{C}$=O), 130.8 (allyl-$\underline{C}$), 118.2 (allyl-$\underline{C}$), 41.1 (N$\underline{C}$H$_2$), 40.8 (CO$\underline{C}$HCH$_2$CH$_3$), 33.8 (CO$\underline{C}$H$_2$CH), 24.4 (COCH$\underline{C}$H$_2$CH$_3$), 10.8 ($\underline{C}$H$_3$); **MS** m/z (ES+): 190 ([M+Na]$^+$);

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

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 ν_{max} /cm^{-1} (oil) 2967 (CH), 1700 (C=O), 1428 (C=O) and 1395 (C=C); **^{1}H NMR** (300 MHz, CDCl$_3$) δ_H 5.77 (ddt, 1H, *J* = 17.0Hz, 10.2Hz and 5.7Hz, NCH$_2$C*H*), 5.24-5.15 (m, 2H, NCH$_2$CHC*H$_2$*), 4.11 (d, 2H, *J* = 5.7Hz, NC*H$_2$*), 3.82 (s, 3H, CO$_2$C*H$_3$*), 3.47 (d, 1H, *J* = 5.0Hz, C*H*CO$_2$CH$_3$), 3.14 (dt, 1H, *J* = 9.8Hz and 5.0Hz, C*H*CH$_2$CH$_3$), 1.98 (qd, 1H, *J* = 14.1Hz and 7.5Hz, 1 of C*H$_2$*CH$_3$), 1.67 (qd, 1H, *J* = 14.1Hz and 7.4Hz, 1 of C*H$_2$*CH$_3$), 0.99 (t, 3H, *J* = 7.5Hz, C*H$_3$*); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 177.1 (*C*=O), 171.2 (*C*=O), 168.3 (*C*O$_2$), 130.1 (allyl-*C*), 118.3 (allyl-*C*), 53.3 (*C*HCO$_2$CH$_3$), 51.8 (CO$_2$*C*H$_3$), 45.6 (N*C*H$_2$), 41.2 (*C*HCH$_2$CH$_3$), 23.5 (*C*H$_2$CH$_3$), 10.7 (CH$_2$*C*H$_3$); **MS** *m/z* (ES+): 248 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 248.0895 (C$_{11}$H$_{15}$NNaO$_4$) 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 (MgSO$_4$), 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_{max} /cm^{-1} (oil) 3700-3200 (OH), 1744 (C=O), 1680 (C=O); **Major: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.88-5.76 (m, 1H, NCH$_2$C*H*), 5.19 (d, 1H, *J* = 15.4Hz, 1 of NCH$_2$CHC*H*$_2$), 5.13 (d, 1H, *J* = 10.2Hz, 1 of NCH$_2$CHC*H*$_2$), 3.92-3.87 (m, 2H, NC*H*$_2$), 3.77 (s, 3H, CO$_2$C*H*$_3$), 3.33 (dd, 1H, *J* = 10.1Hz and 2.6Hz, COC*H*CO$_2$CH$_3$), 2.47 (ddt, 1H, *J* = 10.1Hz, 4.8Hz and 1.8Hz, C*H*CH$_2$CH$_3$), 1.57-1.46 (m, 2H, C*H*$_2$CH$_3$), 1.52 (s, 3H, C*H*$_3$), 0.92 (dt, 3H, *J* = 7.4Hz and 1.6Hz, C*H*$_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ_C 170.9 (C=O), 170.3 (*C*O$_2$), 133.8 (allyl-*C*), 117.3 (allyl-*C*), 90.0 (N*C*OH), 53.0 (CO$_2$*C*H$_3$), 49.6 (N*C*H$_2$), 41.9 (CO*C*HCO$_2$CH$_3$), 25.6 (*C*HCH$_2$CH$_3$), 23.9 (C*C*H$_3$) 21.5 (CH*C*H$_2$CH$_3$), 10.3 (CHCH$_2$*C*H$_3$); **Minor observed: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 3.27 (d, 1H, *J* = 5.6Hz, COC*H*CO$_2$CH$_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ_C 130.5 (allyl-*C*), 117.0 (allyl-*C*), 86.1 (N*C*OH), 52.6 (CO$_2$*C*H), 42.0 (CO*C*HCO$_2$CH$_3$), 26.8 (*C*HCH$_2$CH$_3$), 12.2 (CHC*H*$_2$CH$_3$); **MS *m/z*** (ES+): 264 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 264.1207 (C$_{12}$H$_{19}$NNaO$_4$) 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 tetrahyrdofuran (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$_4$), 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_{max} /cm^{-1} (oil) 1789 (C=O), 1703 (C=O) and 1540 (C=C); **^{1}H NMR** (500 MHz) δ_H 5.85 (ddd, 1H, J = 17.0Hz, 10.4Hz and 5.6Hz, NCH$_2$C$\underline{H}$), 5.20 (d, 1H, J = 10.4Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.12 (d, 1H, J = 17.0Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.27 (d, 2H, J = 5.6Hz, NC$\underline{H}_2$), 3.75 (s, 3H, CO$_2$C$\underline{H}_3$), 2.68 (q, 2H, J = 7.4Hz, C$\underline{H}_2$CH$_3$), 2.33 (s, 3H, C$\underline{H}_3$), 2.09 (s, 3H, NCCC$\underline{H}_3$) 1.16 (t, 3H, J = 7.4, CH$_2$C$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 168.5 ($\underline{C}$=O), 164.3 ($\underline{C}$O$_2$), 139.6 (pyrrole-$\underline{C}$), 132.6 (allyl-$\underline{C}$), 126.0 (pyrrole-$\underline{C}$), 118.1 (allyl-$\underline{C}$), 112.6 (pyrrole-$\underline{C}$), 100.5 (pyrrole-$\underline{C}$), 50.6 (CO$_2\underline{C}$H$_3$), 47.6 (N$\underline{C}$H$_2$), 20.5 (acetate-$\underline{C}$H$_3$), 20.2 ($\underline{C}$H$_2$CH$_3$), 13.7 (CH$_2\underline{C}$H$_3$), 11.1 ($\underline{C}$H$_3$); **MS *m/z*** (ES+): 288 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 288.1209 (C$_{14}$H$_{19}$NNaO$_4$) requires (M) 288.1207.

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

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$_2$CO$_3$ (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_{max} /cm^{-1} (oil) 1742 (C=O), 1715 (C=O), 1684 (C=C); **^{1}H NMR** (300 MHz, CDCl$_3$) δ_H 5.85 (ddt, 1H, J = 17.1Hz, 10.1Hz and 6.3Hz, NCH$_2$C$\underline{H}$), 5.22 (dd, 1H, J = 17.1Hz and 1.3Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.12 (dd, 1H, J = 10.1Hz and 1.3Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.00 (dd, 1H, J = 15.6Hz and 6.3Hz, 1 of NC$\underline{H}_2$), 3.88 (s, 3H, CO$_2$C$\underline{H}_3$), 3.76 (dd, 1H, J = 15.6Hz and 6.3Hz, 1 of NC$\underline{H}_2$), 2.71 (dq, 1H, J = 13.3Hz and 7.6Hz, 1 of C$\underline{H}_2$CH$_3$), 2.39 (dq, 1H, J = 13.3Hz and 7.6Hz, 1 of C$\underline{H}_2$CH$_3$), 2.17-1.86 (m, 4H, CO$\underline{H}_2$C$\underline{H}_2$), 2.05 (s, 3H, C$\underline{H}_3$), 1.35 (m,

3H, C$\underline{H}_3$), 1.18 (t, 3H, J = 7.5, CH$_2$C$\underline{H}_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ_C 206.7 ($\underline{C}$=O), 175.4 (N$\underline{C}$=O), 166.3 ($\underline{C}$O$_2$), 163.2 (quat. $\underline{C}$=C), 133.5 (allyl-$\underline{C}$), 117.7 (allyl-C), 117.6 (quat. C=$\underline{C}$), 67.4 (N$\underline{C}$), 52.0 (CO$_2\underline{C}$H$_3$), 42.1 (N$\underline{C}$H$_2$), 37.0 (CO$\underline{C}$H$_2$), 30.2 (CO$\underline{C}$H$_3$), 28.2 (COCH$_2\underline{C}$H$_2$), 23.0 (NC$\underline{C}$H$_3$), 20.0 ($\underline{C}$H$_2$CH$_3$), 13.1 (CH$_2\underline{C}$H$_3$); **MS *m/z*** (ES+): 316 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 316.1514 (C$_{16}$H$_{23}$NNaO$_4$) 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 K$_2$CO$_3$ (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 ν_{max} /cm^{-1} (oil) 2952 (CH), 1740 (C=O), 1714 (C=O), 1694 (C=O); ^{1}**H NMR** (500 MHz, CDCl$_3$) δ_H 5.86 (ddt, 1H, J = 16.8Hz, 10.1Hz and 6.4Hz, NCH$_2$C$\underline{H}$), 5.24 (d, 1H, J = 16.8Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.13 (d, 1H, J = 10.1Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.04 (dd, 1H, J = 15.6Hz and 6.4Hz, 1 of NC$\underline{H}_2$), 3.87 (s, 3H, CO$_2$C$\underline{H}_3$), 3.80 (dd, 1H, J = 15.6Hz and 6.4Hz, 1 of NC$\underline{H}_2$), 3.63 (s, 3H, CO$_2$C$\underline{H}_3$), 2.73 (dq, 1H, J = 15.1Hz and 7.6Hz, 1 of C$\underline{H}_2$CH$_3$), 2.41 (dq, 1H, J = 15.1Hz and 7.5Hz, C$\underline{H}_2$CH$_3$), 2.17 (ddd, 1H, J = 15.9Hz, 11.0Hz and 5.3Hz, 1 of COC$\underline{H}_2$), 2.08 (ddd, 1H, J = 15.9Hz, 10.5Hz and 5.4Hz, 1 of COC$\underline{H}_2$), 1.94 (ddd, 1H, J = 15.9Hz, 10.5Hz and 5.3Hz, 1 of COCH$_2$C$\underline{H}_2$), 1.80 (ddd, 1H, J = 16.5Hz, 11.0Hz and 5.4Hz, 1 of COCH$_2$C$\underline{H}_2$), 1.36 (s, 3H, C$\underline{H}_3$), 1.20 (t, 3H, J = 7.6Hz, CH$_2$C$\underline{H}_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ_C 175.1 (N$\underline{C}$=O), 172.8 ($\underline{C}$O$_2$), 166.2 ($\underline{C}$O$_2$), 163.1 (quat. $\underline{C}$=C), 133.5 (allyl-$\underline{C}$), 124.6

(quat. C=$\underline{C}$), 117.7 (allyl-$\underline{C}$), 67.5 (N$\underline{C}$), 52.0 (2 × CO$_2$$\underline{C}H_3$), 42.1 (N$\underline{C}H_2$), 29.8 (CO$\underline{C}H_2$), 27.9 (COCH$_2$$\underline{C}H_2$), 23.0 ($\underline{C}H_3$), 20.0 ($\underline{C}H_2CH_3$), 13.1 (CH$_2$$\underline{C}H_3$); **MS *m/z*** (ES+): 332 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 332.1473 (C$_{16}$H$_{23}$NNaO$_5$) requires (M) 332.1468
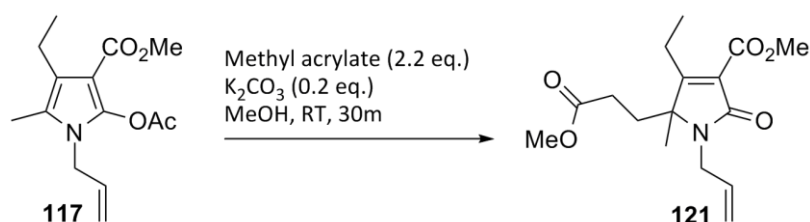
(±)-Methyl 1-allyl-4,5-dimethyl-2-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate; 123

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 × 10 mL). The organic layers were combined, dried (MgSO$_4$) and concentrated *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}H NMR and mass spectrometry data.

^{1}H NMR (500 MHz, CDCl$_3$) δ_H 5.72 (m, 1H, NCH$_2$C$\underline{H}$), 5.15 (m, 2H, NCH$_2$CHC$\underline{H}_2$), 4.44 (dd, 1H, *J* = 4.7Hz and 15.6Hz, NC$\underline{H}_A$H$_B$), 3.95 (q, 1H, *J* = 7.0Hz, NC$\underline{H}$CH$_3$), 3.81 (s, 3H, CO$_2$C$\underline{H}_3$), 3.61 (dd, 1H, *J* = 7.5Hz and 15.7Hz, NCH$_A$$\underline{H}_B$), 2.28 (s, 3H, CC$\underline{H}_3$), 1.28 (d, 3H, *J* = 7.0Hz, NCHC$\underline{H}_3$); **MS *m/z*** (ES+): 232 ([M+Na]$^+$).

(+)-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 v_{max}(oil) 2949 (CH), 1742 (C=O), 1715 (C=O), 1690 (C=O); **[α]$_D^{26}$**: +10 (c 1.25, CHCl$_3$); **^{1}H NMR** (500 MHz; CDCl$_3$) δ_H 5.88-5.78 (m, 1H, NCH$_2$C$\underline{H}$), 5.21 (d, 1H, *J* = 17.2Hz, 1 of

NCH$_2$CHCH$_2$), 5.10 (d, 1H, J = 10.1Hz, 1 of NCH$_2$CHCH$_2$), 3.97 (dd, 1H, J = 15.7Hz and 6.3Hz, NCH$_A$H$_B$), 3.86 (s, 3H, OCH$_3$), 3.80 (dd, 1H, J = 15.7Hz and 6.3Hz, NCH$_A$H$_B$), 2.18 (s, 3H, COCH$_3$), 2.13-1.98 (m, 2H, CH$_2$CH$_2$CO), 2.04 (s, 3H, COCH$_3$), 1.96-1.81 (m, 2H, CH$_2$CH$_2$CO), 1.31 (s, 3H, CH$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) δ_C 206.7 (C=O), 170.8 (quat. C=C), 166.1 (NC=O), 163.2 (CO$_2$CH$_3$), 133.5 (allyl-C), 124.4 (quat. C=C), 117.7 (allyl-C), 67.0 (NCH$_2$), 51.9 (OCH$_3$), 42.1 (allyl-C), 36.7 (CH$_2$C=O), 30.1 (COCH$_3$), 28.0 (CH$_2$CH$_2$C=O), 23.2 (CH$_3$), 12.3 (CH$_3$); **MS** *m/z* (ES+) 302 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 302.1364 (C$_{15}$H$_{21}$NNaO$_4$) requires (M) 302.1363.

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

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 ν_{max}/cm^{-1} (oil) 2978 (CH), 1744 (C=O), 1711 (C=O), 1638 (C=O); ^{1}**H NMR** (500 MHz) δ_H 5.84 (ddt, 1H, J = 16.8Hz, 10.1Hz and 6.3Hz, NCH$_2$CH), 5.22 (dd, 1H, J = 17.1Hz and 1.3Hz, 1 of NCH$_2$CHCH$_2$), 5.11 (dd, 1H, J = 10.1Hz and 1.3Hz, 1 of NCH$_2$CHCH$_2$), 3.99 (dd, 1H, J = 15.6Hz and 6.3Hz, 1 of NCH$_2$), 3.87 (s, 3H, CO$_2$CH$_3$), 3.81 (dd, 1H, J = 15.6Hz and 6.3Hz, 1 of NCH$_2$), 2.30 (q, 2H, J = 7.3, COCH$_2$CH$_3$), 2.20 (s, 3H, CH$_3$), 2.15-2.07 (m, 1H, 1 of COCH$_2$CH$_2$), 2.06-1.92 (m, 2H, 1 of COCH$_2$CH$_2$ and 1 of COCH$_2$CH$_2$), 1.84 (ddd, 1H, J = 13.2Hz, 10.5Hz and 3.6Hz, 1 of COCH$_2$CH$_2$), 1.32 (s, 3H, CH$_3$), 0.99 (t, 3H, J = 7.3Hz, COCH$_2$CH$_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ_C 209.5 (C=O), 171.0 (NC=O), 166.1 (CO$_2$), 163.3 (quat. C=C), 133.6 (allyl-C), 124.5 (quat. C=C), 117.7 (allyl-C), 67.1 (NC), 52.0

(CO$_2$CH$_3$), 42.1 (NCH$_2$), 36.2 (COCH$_2$CH$_3$), 35.4 (COCH$_2$CH$_2$), 28.1 (COCH$_2$CH$_2$), 23.2 (CH$_3$), 12.3 (CH$_3$), 7.7 (COCH$_2$CH$_3$); **MS *m/z*** (ES+) 318 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 318.1676 (C$_{16}$H$_{25}$NNaO$_4$) 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 K$_2$CO$_3$ (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 ^{1}H 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]$_D^{25}$: +85 (c 1.25, CHCl$_3$).

(-)-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 v_{max}(oil) 2954 (CH), 1722 (C=O), 1716 (C=O), 1682 (C=O); **[α]$_D$^{25}**: -30 (c 0.48, CHCl$_3$); **130a: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.90 (ddt, 1H, J = 16.2Hz, 10.3Hz and 6.0Hz, NCH$_2$C*H*), 5.27 (ddd, 1H, J = 17.2Hz, 3.8Hz and 1.4Hz, 1 of NCH$_2$CHC*H$_2$*), 5.17 (ddd, 1H, J = 10.2Hz, 5.0Hz and 1.2Hz, 1 of NCH$_2$CHC*H$_2$*), 3.98 (ddd, 1H, J = 15.7Hz, 5.9Hz and 1.3Hz, NC*H$_A$*H$_B$), 3.88-3.77 (m, 1H, NCH$_A$*H$_B$*), 3.75 (s, 3H, CO$_2$C*H$_3$*), 3.36 (s, 1H, 3-C*H*), 2.78 (d, 1H, J = 14.4Hz, 1'-C*H$_A$*H$_B$), 2.56 (d, 1H, J = 14.8Hz, 1'-C*H$_A$*H$_B$), 2.31-2.14 (m, 2H, 4'-C*H$_2$* and 3'-C*H$_2$*), 1.39 (s, 3H, 5-C*H$_3$*), 1.21 (s, 3H, C*H$_3$*); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 208.8 (*C*=O), 169.2 (N*C*=O), 168.5 (*C*O$_2$Me), 134.1 (allyl-*C*), 117.8 (allyl-*C*), 64.5 (5-*C*), 58.8 (3-*C*H), 52.4 (O*C*H$_3$), 51.6 (1'-*C*H$_2$), 47.2 (N*C*H$_2$), 44.4 (4'-*C*H$_2$), 36.3 (3'-*C*H$_2$), 33.0 (4-*C*), 22.1 (*C*H$_3$), 21.9 (*C*H$_3$); **130b observed: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 3.74 (s, 3H, CO$_2$C*H$_3$*), 3.23 (s, 1H, 3-C*H*), 2.12-1.88 (m, 4H, 4'-C*H$_2$* and 3'-C*H$_2$*), 1.24 (s, 3H, 5-C*H$_3$*), 1.12 (s, 3H, C*H$_3$*); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 208.6 (*C*=O), 169.1 (N*C*=O), 168.2 (*C*O$_2$Me), 133.7 (allyl-*C*), 117.4 (allyl-*C*), 63.6 (5-*C*), 57.8 (3-*C*H), 46.9 (N*C*H$_2$), 42.9 (4'-*C*H$_2$), 35.5 (3'-*C*H$_2$), 32.1 (4-*C*), 21.8 (*C*H$_3$), 20.9 (*C*H$_3$); **MS m/z** (ES+) 302 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 302.1364 (C$_{15}$H$_{21}$NNaO$_4$) requires (M) 302.1368.

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

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 ^{o}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 ν_{max}(oil) 2971 (CH), 1715 (C=O), 1681 (C=O); **[α]$_D$^{25}:** +31 (c 1.3, CHCl$_3$); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.82 (ddt, 1H, *J* = 17.1Hz, 10.2Hz and 6.1Hz, NCH$_2$C*H*), 5.16 (qd, 1H, *J* = 17.2Hz and 1.4Hz, 1 of NCH$_2$CHC*H*$_2$), 5.09 (qd, 1H, *J* = 10.1Hz and 1.3Hz, 1 of NCH$_2$CHC*H*$_2$), 3.81 (d, 2H, *J* = 5.9Hz, NC*H*$_2$) 2.40 (d, 1H, *J* = 14.4, 1'-C*H*$_A$H$_B$) 2.22 (m, 5H, 1'-C*H*$_A$H$_B$, 3-C*H*$_2$ and 3'-C*H*$_2$) 2.05 (td, 1H, *J* = 15.0Hz and 5.5Hz, 4'-C*H*$_A$H$_B$) 1.89 (ddd, 1H, *J* = 15.0Hz, 11.2Hz and 5.1Hz, 4'-CH$_A$*H*$_B$) 1.19 (s, 3H, 5-C*H*$_3$) 1.08 (s, 3H, C*H*$_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_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

N-Allyl-2-chloroacetamide; 162[66]

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$_4$), filtered and concentrated *in vacuo* to afford essentially pure **159** (5.87 g, 99%) as an orange oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ$_H$ 6.71 (bs, 1H, N*H*), 5.84 (dq, 1H, *J* = 10.7Hz and 5.6Hz, NCH$_2$C*H*), 5.19 (dd, 2H, *J* = 20.8Hz and 13.7Hz, NCH$_2$CHC*H*$_2$), 4.07 (s, 2H, COC*H*$_2$Cl), 3.93 (t, 2H, *J* = 5.7Hz, NC*H*$_2$) *^{1}H NMR in agreement with literature*; **MS *m/z*** (EI/CI): 134 ([M +H]$^+$).

N-Allyl-2-iodoacetamide; 159[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$_2$SO$_4$), filtered and concentrated *in vacuo* to afford **159** (8.3 g, 84%) as a white solid.

M.P. 57-60 ^{o}C; **^{1}H NMR** (500 MHz, CDCl$_3$) δ$_H$ 6.13 (s, 1H, N*H*), 5.85 (ddd, 1H, *J* = 22.6Hz, 10.7Hz and 5.6Hz, NCH$_2$C*H*), 5.21 (dd, 2H, *J* = 27.6Hz and 14.2Hz, NCH$_2$CHC*H*$_2$), 3.91 (dt, 2H, *J* = 5.7Hz and 1.2Hz, NC*H*$_2$), 3.73 (s, 2H, COC*H*$_2$Cl) *^{1}H NMR in agreement with literature*; **MS *m/z*** (EI/CI): 225 ([M +H]$^+$)

(±)-7-Methyl-1,4-dioxaspiro[4.5]decan-8-one; 160[113]

To a stirred solution of di*iso*propylamine (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 (MgSO$_4$), 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; **^{1}H NMR** (500 MHz, CDCl$_3$) δ$_H$ 3.88 (m, 4H, OCH_2CH_2O), 2.59 (m, 1H, COCH), 2.49 (ddt, 1H, *J* = 14.0Hz, 6.2Hz and 0.9Hz, CHCH_AH$_B$), 2.22 (ddd, 1H, *J* = 14.3Hz, 5.1Hz and 2.9Hz, CHCH$_A$$H_B$), 1.90 (dtd, 2H, *J* = 14.7Hz, 6.1Hz and 3.6Hz, COCH_2), 1.82 (dd, 1H, *J* = 13.6Hz and 5.0Hz, 1 of COCH$_2$CH_2), 1.58 (t, 1H, *J* = 13.2Hz, 1 of COCH_2CH$_2$), 0.87 (d, 3H, *J* = 6.6Hz, CHCH_3) *^{1}H NMR in agreement with literature*; **MS *m/z*** (ES+): 193 ([M +Na]$^+$)

(±)-1'-Allyl-5-hydroxy-4-methylhexahydrospiro[[1,3]dioxolane-2,2'-indol]-2'(1'H)-one; 164
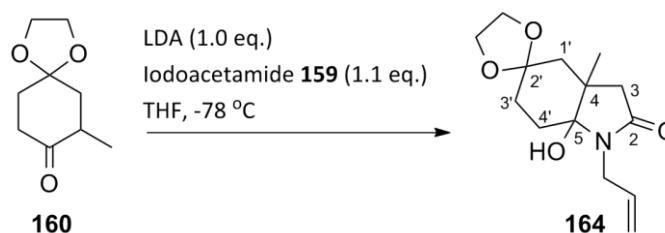
To a stirred solution of di*iso*propylamine (0.87 mL, 6.17 mmol) in dry tetrahydrofuran (15 mL) at -78 °C was added a 1.6 M solution of n-butyl lithium in hexanes (3.67 mL, 5.88 mmol) *via* syringe. The resultant colourless solution was stirred at -78 °C for 5 minutes, warmed to 0 °C and then to room 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 (MgSO$_4$), 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_{max}(oil) 3358 (OH), 2937 (CH), 1671 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.90 (ddt, 1H, *J* = 16.6Hz, 10.1Hz and 6.4Hz, NCH$_2$C*H*), 5.25 (dd, 1H, *J* = 17.2Hz and 1.4Hz, 1 of NCH$_2$CHC*H$_2$*), 5.15 (dd, 1H, *J* = 10.1Hz and 1.2Hz, 1 of NCH$_2$CHC*H$_2$*), 4.07 (dd, 1H, *J* = 15.9Hz and 6.6Hz, NC*H$_A$*H$_B$), 3.92 (m, 4H, OC*H$_2$*C*H$_2$*O), 3.74 (dd, 1H, *J* = 15.5Hz and 6.5Hz, NCH$_A$*H$_B$*), 2.28 (q, 2H, *J* = 16.3Hz, 3-C*H$_2$*), 1.45-2.04 (m, 6H, 1', 3' and 4'-C*H$_2$*),

1.23 (s, 3H, C$\underline{H}_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ_c 175.0 (N$\underline{C}$=O), 134.8 (allyl-$\underline{C}$), 117.4 (allyl-$\underline{C}$), 108.6 (2'-$\underline{C}$), 94.6 (5-$\underline{C}$), 64.4 (2 x O$\underline{C}$H$_2$$\underline{C}H_2$O), 46.8 (N$\underline{C}H_2$), 43.5 (1'-$\underline{C}$), 42.0 (3-$\underline{C}$), 37.2 (3'-$\underline{C}$), 31.1 (4-$\underline{C}$), 25.5 (4'-$\underline{C}$), 20.8 ($\underline{C}H_3$); **MS m/z** (ES+): 268 ([M+H]$^+$); **HRMS**: Found [M+H]$^+$ 268.1550 (C$_{14}$H$_{22}$NO$_4$) requires (M) 268.1543

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

<center>**1,4-Diallylpiperazine-2,5-dione; 165**[68a]</center>

<center>**165**</center>

Compound **165** was assigned based on ^{1}H NMR and mass spectrometry data. No further data was collected. ^{1}**H NMR** (300 MHz, CDCl$_3$) δ_H 5.87-5.83 (m, 2H, NCH$_2$C$\underline{H}$), 5.27-5.11 (m, 4H, NCH$_2$CHC$\underline{H}_2$), 4.09 (s, 4H, NC$\underline{H}_2$CO), 3.98 (m, 4H, NC$\underline{H}_2$CH); **MS m/z** (ES+): 217 ([M+Na]$^+$);

<center>**(±)-1-Allyl-4-methyltetrahydro-1H-indole-2,2'(3H,6H)-dione; 167**</center>

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

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 (MgSO$_4$), 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); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.75 (tdd, 1H, *J* = 17.4Hz, 10.3Hz and 5.1Hz, NCH$_2$C*H*), 5.24 (dd, 2H, *J* = 12.3Hz and 5.7Hz, NCH$_2$CHC*H$_2$*), 4.37 (dd, 1H, *J* = 15.4Hz and 5.0Hz, NC*H$_A$*H$_B$), 3.53 (dd, 1H, *J* = 15.4Hz and 7.4Hz, NCH$_A$*H$_B$*), 2.46 (d, 1H, *J* = 15.1Hz, 1 of 3-C*H$_A$*H$_B$), 3.47 (t, 1H, *J* = 4.7Hz, 5-C*H*), 2.31 (s, 2H, 1'-C*H$_2$*), 2.35 (d, 1H, *J* = 15.1Hz, 1 of 3-CH$_A$*H$_B$*), 2.27-2.24 (m, 2H, 3'-C*H$_2$*), 2.05 (2H, m, 4'-C*H$_2$*), 1.23 (s, 3H, C*H$_3$*); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_c 210.0 (*C*=O), 172.9 (N*C*=O), 132.3 (allyl-*C*), 118.5 (allyl-*C*), 62.2 (5-*C*), 49.8 (1'-*C*), 45.3 (3-*C*), 43.3 (N*C*H$_2$), 36.6 (3'-*C*), 34.3 (4-*C*), 28.6 (4'-*C*), 23.9 (*C*H$_3$); **MS *m/z*** (ES+): 230 ([M+Na]$^+$); **HRMS:** Found [M+Na]$^+$ 230.1157 (C$_{12}$H$_{17}$NNaO$_2$) 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); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.67 (tdd, 1H, *J* = 21.9Hz, 10.7Hz and 5.5Hz, NCH$_2$C*H*), 5.12 (m, 2H, NCH$_2$CHC*H$_2$*), 4.83 (t, 1H, *J* = 3.8Hz, 4'-C*H*), 4.16 (dd, 1H, *J* = 16.0Hz and 5.3Hz, NC*H$_A$*H$_B$), 3.97 (dd, 1H, *J* = 16.0Hz and 5.7Hz, NCH$_A$*H$_B$*), 2.59 (d, 1H, *J*

= 14.8Hz, 1'-C$\underline{H}_A$H$_B$), 2.95-2.92 (m, 2H, 3'-C$\underline{H}_2$), 2.51 (d, 1H, J = 14.8Hz, 1'-CH$_A\underline{H}_B$), 2.47 (d, 1H, J = 16.7Hz, 1 of 3-C$\underline{H}_2$), 2.35 (d, 1H, J = 16.7Hz, 1 of 1 of 3-C$\underline{H}_2$), 1.12 (s, 3H, C$\underline{H}_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ$_c$ 207.5 ($\underline{C}$=O), 173.0 (N$\underline{C}$=O), 146.5 (5-$\underline{C}$), 131.2 (allyl-$\underline{C}$), 121.3 (4'-$\underline{C}$), 117.5 (allyl-$\underline{C}$), 51.2 (1'-$\underline{C}$), 44.5 (N$\underline{C}$H$_2$), 42.3 (3'-$\underline{C}$), 37.6 (3-$\underline{C}$), 37.5 (4-$\underline{C}$), 25.9 ($\underline{C}$H$_3$); **MS** *m/z* (ES+): 228 ([M+Na]$^+$); **HRMS**: Found [M+H]$^+$ 206.1177 (C$_{12}$H$_{16}$NO$_2$) requires (M) 206.1175

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

168

168 (7 mg, 5%) was isolated as an inseperable 3:1 mixture of diastereoisomers and a colourless oil. **IR** ν$_{max}$(oil) 3399 (OH), 2928 (CH), 1670 (C=O); **Major:** ^{1}**H NMR** (500 MHz, CDCl$_3$) δ$_H$ 5.65 (tdd, 1H, J = 15.3Hz, 10.1Hz, 7.7Hz and 5.1Hz, NCH$_2$C$\underline{H}$), 5.14 (m, 2H, NCH$_2$CHC$\underline{H}_2$), 4.27 (m, 1H, NC$\underline{H}_A$H$_B$), 4.19 (s, 1H, O$\underline{H}$), 3.78 (dt, 1H, J = 8.1Hz and 3.9Hz, 2'-C$\underline{H}$OH), 3.37 (dd, 1H, J = 15.2Hz and 7.6Hz, NCH$_A\underline{H}_B$), 3.05 (m, 1H, 5-C$\underline{H}$), 2.32 (d, 1H, J = 16.3Hz, 3-C$\underline{H}_A$H$_B$), 2.05-2.20 (m, 2H, 3'-C$\underline{H}_2$), 1.93 (d, 1H, J = 16.3Hz, 3-CH$_A\underline{H}_B$), 1.86 (dd, 1H, J = 13.8Hz and 2.9Hz, 1'-C$\underline{H}_A$H$_B$), 1.79-1.47 (m, 2H, 4'-C$\underline{H}_2$) 1.32 (dd, 1H, J = 13.8Hz and 9.2Hz, 1'-CH$_A\underline{H}_B$), 1.12 (s, 3H, C$\underline{H}_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ$_c$ 174.2 (N$\underline{C}$=O), 132.7 (allyl-$\underline{C}$), 118.3 (allyl-$\underline{C}$), 66.7 (2'-$\underline{C}$), 60.6 (5-$\underline{C}$), 47.1 (1'-$\underline{C}$), 43.2 (3-$\underline{C}$), 42.6 (N$\underline{C}$H$_2$), 37.7 (3'-$\underline{C}$), 29.6 (4'-$\underline{C}$), 28.7 ($\underline{C}$H$_3$), 23.7 (4-$\underline{C}$); **Minor observed:** ^{1}**H NMR** (500 MHz, CDCl$_3$) δ$_H$ 3.67 (m, 1H, 2'-C$\underline{H}$OH), 3.17 (t, 1H, J = 3.3Hz, 5-C$\underline{H}$), 1.12 (s, 3H, C$\underline{H}_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ$_c$ 173.6 (N$\underline{C}$=O), 132.8 (allyl-$\underline{C}$), 117.9 (allyl-$\underline{C}$), 66.6 (2'-$\underline{C}$), 61.8 (5-$\underline{C}$), 43.4 (1'-$\underline{C}$), 42.9 (3-$\underline{C}$), 42.4 (N$\underline{C}$H$_2$), 36.9 (3'-$\underline{C}$), 30.2 (4'-$\underline{C}$), 24.4 ($\underline{C}$H$_3$), 21.6 (4-$\underline{C}$); **MS** *m/z* (ES+): 232 ([M +Na]$^+$), **HRMS**: Found [M+Na]$^+$ 232.1311 (C$_{12}$H$_{19}$NNaO$_2$) requires (M) 232.1309

(±)-1-Allyl-1'-bromo-4-methyltetrahydro-1H-indole-2,2'(3H,6H)-dione; 173

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 (MgSO$_4$), 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 ^{1}H NMR and mass spectrometry data. No further data was collected. **173a: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.73 (m, 1H, NCH$_2$C*H*), 5.25 (m, 2H, NCH$_2$CHC*H*$_2$), 4.68 (s, 1H, 1'-C*H*), 4.35 (ddd, 1H, *J* = 15.5Hz, 13.5Hz and 5.0Hz, 1 of NC*H*$_2$), 3.71 (t, 1H, *J* = 4.2Hz, 5-C*H*), 3.58-3.45 (m, 1H, 1 of NC*H*$_2$), 2.60-2.33 (m, 4H, 3'-C*H*$_2$, 1 of 3-C*H*$_2$, 1 of 4'-C*H*$_2$), 2.23 (d, 1H, *J* = 18.0Hz, 1 of 3-C*H*$_2$), 2.14 (m, 1H, 1 of 4'-C*H*$_2$), 1.49 (s, 3H, C*H*$_3$); **173b observed: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 4.49 (s, 1H, 1'-C*H*), 3.58-3.45 (m, 1H, 5-C*H*), 2.60-2.33 (m, 2H, 3-C*H*$_2$), 2.14 (m, 1H, 1 of 4'-C*H*$_2$), 2.07 (m, 1H, 1 of 4'-C*H*$_2$), 1.34 (s, 3H, C*H*$_3$); **MS *m/z*** (ES+): 308 ([M +Na]$^+$).

(±)-*tert*-Butyl 2-oxocyclohexanecarboxylate; 183[114]

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 a 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 (MgSO$_4$), 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: ^{1}H NMR (500 MHz, CDCl$_3$) δ_H 12.40 (bs, 1H, O$\underline{H}$), 2.35-2.33 (m, 2H, 2-C$\underline{H}_2$), 2.23 (t, 2H, J = 6.4Hz, 5-C$\underline{H}_2$), 1.91 (m, 2H, 4-C$\underline{H}_2$), 1.66 (m, 2H, 3-C$\underline{H}_2$), 1.47 (s, 9H, OC(C$\underline{H}_3$)$_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_c 172.7 (6-$\underline{C}$), 169.3 ($\underline{C}$O$_2$C), 98.9 (1-$\underline{C}$), 80.7 (O$\underline{C}$(CH$_3$)$_3$), 29.9 (5-$\underline{C}$), 29.2 (2-$\underline{C}$), 28.0 (3 x OC($\underline{C}$H$_3$)$_3$), 27.2, 22.5; **183b: ^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 3.26 (ddd, 1H, J = 1.0Hz, 8.8Hz and 5.6Hz, 1'-C$\underline{H}$), 2.49 (m, 2H, 5'-C$\underline{H}_2$), 2.14 (m, 2H, 2'-C$\underline{H}_2$), 2.03 (m, 2H, 4'-C$\underline{H}_2$), 1.82 (m, 2H, 3'-C$\underline{H}_2$), 1.49 (s, 9H, OC(C$\underline{H}_3$)$_3$); 206.9 (6'-$\underline{C}$), 171.3 ($\underline{C}$O$_2$C), 81.9 (O$\underline{C}$(CH$_3$)$_3$), 57.9 (1'-$\underline{C}$), 41.5 (5'-$\underline{C}$), 28.3 (3 x OC($\underline{C}$H$_3$)$_3$), 23.1, 22.8, 22.0. *^{1}H and ^{13}C NMR in agreement with the literature*

(±)-*tert*-Butyl 3-oxo-1,4-dioxaspiro[4.5]decane-1-carboxylate; 178

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 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 (300 mL) and partitioned between ethyl acetate (200 mL). The aqueous phase was further extracted with ethyl acetate (2 x 150 mL) and the combined organic layers were dried (MgSO$_4$), 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$_{max}$(oil) 2976 (CH), 1737 (C=O), 1651 (C=O); **Major 178a:** ^{1}**H NMR** (500 MHz, CDCl$_3$) δ$_H$ 12.40 (bs, 1H, O$\underline{H}$), 4.00 (m, 8H, OC$\underline{H}_2$C$\underline{H}_2$O), 2.47 (t, 2H, *J* = 6.8Hz, 5-C$\underline{H}_2$), 2.42 (s, 2H, 2-C$\underline{H}_2$), 1.82 (t, 2H, *J* = 6.8Hz, 4-C$\underline{H}_2$), 1.48 (s, 9H, OC(C$\underline{H}_3$)$_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ$_c$ 171.9 (6-$\underline{C}$), 168.6 ($\underline{C}$O$_2$C), 107.4 (3-$\underline{C}$), 96.4 (1-$\underline{C}$), 81.2 (O$\underline{C}$(CH$_3$)$_3$), 64.7 (O$\underline{C}$H$_2$CH$_2$O), 64.6 (OCH$_2$$\underline{C}H_2$O), 34.5 (2-$\underline{C}$), 33.2 (4-$\underline{C}$), 30.2, 27.9 (3 x OC($\underline{C}H_3$)$_3$); **Minor 178b observed:** ^{1}**H NMR** (500 MHz, CDCl$_3$) δ$_H$ 3.50 (dd, 1H, *J* = 6.0Hz and 10.1Hz, 1'-C$\underline{H}$), 2.61 (m, 2H, 5'-C$\underline{H}_2$), 2.38 (m, 1H, 1 of 2'-C$\underline{H}_2$), 2.10 (dd, 1H, *J* = 6.0Hz and 13.6Hz, 1 of 2'-C$\underline{H}_2$), 2.03 (m, 2H, 4'-C$\underline{H}_2$), 1.47 (s, 9H, OC(C$\underline{H}_3$)$_3$); ^{13}**C NMR** (125 MHz, CDCl$_3$) δ$_c$ 205.4 (6'-$\underline{C}$), 170.2 ($\underline{C}$O$_2$C), 106.8 (3'-$\underline{C}$), 81.8 (O$\underline{C}$(CH$_3$)$_3$), 54.7 (1'-$\underline{C}$), 38.1 (2'-$\underline{C}$), 36.4 (4'-$\underline{C}$), 28.3 (3 x OC($\underline{C}$H$_3$)$_3$), 27.8; **MS *m/z*** (ES+): 274 ([M +NH$_4$]$^+$); **HRMS**: Found [M+Na]$^+$ 279.1203 (C$_{13}$H$_{20}$NaO$_5$) 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
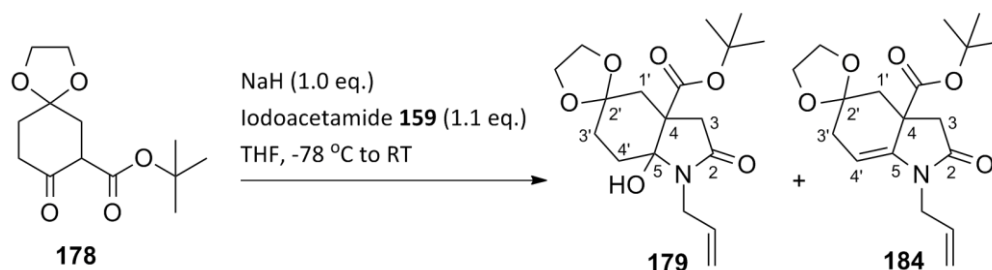
To a stirred solution of **178** (100 mg, 0.39 mmol) in dry tetrahydrofuran (4 mL) was added 60% sodium hydride in oil (190 mg, 0.47 mmol) portion-wise and stirred at room temperature for 0.5 hours. A solution of *N*-allyl-2-iodoacetamide **159** (83 mg, 0.37 mmol) in dry tetrahydrofuran (3 mL) was added 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 (MgSO$_4$), 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 ^{1}H NMR, ^{13}C 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: ^{1}H NMR** (500 MHz, CDCl$_3$) δ$_H$ 5.85 (ddt, 1H, *J* = 16.5Hz, 10.2Hz and 6.2Hz NCH$_2$C*H*), 5.22 (d, 1H, *J* = 17.1Hz, 1 of NCH$_2$CHC*H$_2$*), 5.12 (d, 1H, *J* = 10.2Hz, 1 of NCH$_2$CHC*H$_2$*), 5.00 (bs, 1H, O*H*), 3.92 (m, 6H, OC*H$_2$*C*H$_2$*O and NC*H$_2$*), 2.74 (d, 1H, *J* = 16.2Hz, 3-C*H$_A$*H$_B$), 2.36 (d, 1H, *J* = 16.2Hz, 3-CH$_A$*H$_B$*), 2.26 (dd, 1H, *J* = 2.3Hz and 14.1Hz, 1'- C*H$_A$*H$_B$), 2.21 (d, 1H, *J* = 4.6Hz, 1 of 3'-C*H$_2$*), 2.11 (td, 1H, *J* = 14.7Hz and 4.6Hz, 1 of 3'-C*H$_2$*), 1.73 (d, 1H, *J* = 14.1Hz, 1 of 1'-CH$_A$*H$_B$*), 1.56-1.63 (m, 2H, 4'-C*H$_2$*), 1.48 (s, 9H,

OC(C$\underline{H}_3$)$_3$); **184 observed:** **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.74 (ddd, 1H, J = 22.6Hz, 10.7Hz and 5.6Hz, NCH$_2$C$\underline{H}$), 5.23 (d, 1H, J = 17.8Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 5.15 (d, 1H, J = 10.2Hz, 1 of NCH$_2$CHC$\underline{H}_2$), 4.93 (t, 1H, J = 3.8Hz, 4'-C$\underline{H}$), 4.22 (dd, 1H, J = 16.0Hz, and 5.3Hz 1 of NC$\underline{H}_2$), 2.65 (d, 1H, J = 21.4Hz, 3-C$\underline{H}_A$H$_B$), 2.41-2.56 (m, 3H, 3-CH$_A\underline{H}_B$ and 3'-C$\underline{H}_2$), 1.39 (s, 9H, OC(C$\underline{H}_3$)$_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_c 174.7 ($\underline{C}$O$_2$C), 172.6 (N$\underline{C}$=O), 140.4 (5-C), 132.3 (allyl-$\underline{C}$), 118.2 (allyl-$\underline{C}$), 108.2 (2'-$\underline{C}$), 65.1 (2 x O$\underline{C}$H$_2$$\underline{C}H_2$O), 49.6 (1'-$\underline{C}$), 43.7, 35.8, 28.4 (3 x CO$_2$C($\underline{C}$H$_3$)$_3$), 43.5, 42.3 (N$\underline{C}$H$_2$), 31.4; **MS m/z** (ES+): 354 ([**179** M+H$^+$]$^+$) and 358 ([**184** M+Na$^+$]$^+$).

(±)-*tert*-Butyl 1-allyl-5-hydroxy-2'-oxooctahydrospiro[[1,3]dioxolane-2,2'-indole]-4-carboxylate; 179

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 ν_{max}(oil) 3417 (OH), 2975 (CH), 1713 (C=O), 1702 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 5.85 (ddt, 1H, *J* = 16.5Hz, 10.2Hz and 6.2Hz NCH$_2$C*H*), 5.22 (d, 1H, *J* = 17.1Hz, 1 of NCH$_2$CHC*H$_2$*), 5.12 (d, 1H, *J* = 10.2Hz, 1 of NCH$_2$CHC*H$_2$*), 5.00 (bs, 1H, O*H*), 3.92 (m, 6H, OC*H$_2$*C*H$_2$*O and NC*H$_2$*), 2.74 (d, 1H, *J* = 16.2Hz, 3-C*H$_A$*H$_B$), 2.36 (d, 1H, *J* = 16.2Hz, 3-CH$_A$*H$_B$*), 2.26 (dd, 1H, *J* = 2.3Hz and 14.1Hz, 1'- C*H$_A$*H$_B$), 2.21 (d, 1H, *J* = 4.6Hz, 1 of 3'-C*H$_2$*), 2.11 (td, 1H, *J* = 14.7Hz and 4.6Hz, 1 of 3'-C*H$_2$*), 1.73 (d, 1H, *J* = 14.1Hz, 1 of 1'-CH$_A$*H$_B$*), 1.56-1.63 (m, 2H, 4'-C*H$_2$*), 1.48 (s, 9H, OC(C*H$_3$*)$_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_c 174.0 (*C*O$_2$C), 173.7 (N*C*=O), 134.4 (allyl-*C*), 116.9 (allyl-*C*), 106.9 (2'-*C*), 90.1 (5-*C*), 83.0 (O*C*(CH$_3$)$_3$), 64.7 (O*C*H$_2$CH$_2$O), 64.6 (OCH$_2$*C*H$_2$O), 50.2 (1'-*C*), 41.7 (N*C*H$_2$), 40.8 (3-*C*), 40.2, 31.5, 30.8, 27.9 (3 x CO$_2$C(*C*H$_3$)$_3$); **MS *m/z*** (ES+): 354 ([M+H$^+$]$^+$), **HRMS**: Found [M+Na]$^+$ 376.1733 (C$_{18}$H$_{27}$NNaO$_6$) requires (M) 376.1730

6.4 EXPERIMENTAL FOR CHAPTER FOUR

tert-Butyl furan-2-ylcarbamate; 216[103]

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$_3$) δ_H 7.06 (dd, 1H, J = 2.0Hz and 1.0Hz, NCCHCHC*H*), 6.58 (bs, 1H, NCCHC*H*CH), 6.34 (dd, 1H, J = 3.0Hz and 2.2Hz, NCC*H*CH), 6.04 (bs, 1H, N*H*), 1.50 (s, 9H, C(C*H*$_3$)$_3$), *^{1}H NMR in agreement with the literature*; **MS m/z** (ES+) 206 ([M+Na]$^+$).

(6-Methyl-1,4-dioxaspiro[4.5]dec-6-en-1-yl)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 *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 *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 ν_{max}(oil) 3408 (OH), 2945 (CH); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 4.05 (s, 2H, C*H*$_2$OH), 3.15 (s, 4H, OC*H*$_2$C*H*$_2$O), 2.22 (s, 2H, 5-C*H*$_2$), 2.20 (m, 2H, 2-C*H*$_2$), 1.82 (m, 2H, 3-C*H*$_2$), 1.70 (s, 3H, C*H*$_3$), *^{1}H NMR in agreement with the literature*; **MS m/z** (ES+) 207 ([M+Na]$^+$).

3-Methyl-4-methylenecyclohex-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 ^{o}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$_3$) δ_H 5.91 (s, 1H, C*H*), 5.35 (s, 2H, C=C*H*$_2$), 2.72 (t, 2H, *J* = 7.0Hz, COC*H*$_2$), 2.48 (m, 2H, COCH$_2$C*H*$_2$), 2.05 (s, 3H, C*H*$_3$) *^{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; 222

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 ^{o}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 ^{o}C. The reaction mixture was stirred at 0 ^{o}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 (MgSO$_4$), 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_{max}(oil) 2961 (CH), 1566 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 7.16 (dd, 1H, _J_ = 2.1Hz and 0.9Hz, 1'-C_H_), 6.29 (dd, 1H, _J_ = 3.1Hz and 2.2Hz, 3'-C_H_), 5.93 (bs, 1H, 2'-C_H_), 4.21 (s, 2H, NC_H_$_2$), 3.95 (s, 4H, OC_H_$_2$C_H_$_2$O), 2.21 (dt, 2H, _J_ = 6.6Hz and 2.0Hz, 3-C_H_$_2$), 2.15 (s, 2H, 5-C_H_$_2$), 1.68 (t, 1H, _J_ = 6.4Hz, 2-C_H_$_2$), 1.47 (s, 3H, C_H_$_3$), 1.43 (s, 9H, C(C_H_$_3$)$_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 154.6 (_C_=O)**,** 148.5 (1'-_C_), 138.8 (4'-_C_), 128.9 (1-_C_), 125.4 (6-

$\underline{C}$), 111.0 (2'-$\underline{C}$), 102.7 (3'-$\underline{C}$), 99.1 (4-$\underline{C}$), 80.6 ($\underline{C}O(CH_3)_3$), 49.5 (N$\underline{C}H_2$), 48.4 (2 x O$\underline{C}H_2\underline{C}H_2O$), 40.5 (5-$\underline{C}$), 30.0 (3-$\underline{C}$), 28.9 (3 x CO($\underline{C}H_3)_3$), 25.7 (2-$\underline{C}$), 20.1 ($\underline{C}H_3$) **MS *m/z*** (ES+) 371 ([M+Na]$^+$); **HRMS** Found [M+NH$_4$]$^+$ 371.2227 ($C_{19}H_{31}N_2O_5$) requires (M) 367.2228

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

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 (MgSO$_4$), 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 ν_{max}(oil) 2977 (CH), 1714 (C=O), 1667 (C=O); **^{1}H-NMR** (500 MHz, CDCl$_3$) δ_H 7.19 (s, 1H, 1'-C$\underline{H}$), 6.36 (s, 1H, 3'-C$\underline{H}$), 6.02 (bs, 1H, 2'-C$\underline{H}$), 5.88 (s, 1H, 5-C$\underline{H}$), 3.78-3.74 (m, 2H, NC$\underline{H}_2$), 2.58 (dt, 1H, *J* = 9.0Hz and 4.8Hz, 1-C$\underline{H}$), 2.55-2.44 (m, 1H, 1 of 3-C$\underline{H}_2$), 2.28 (td, 1H, *J* = 17.5Hz and 4.7Hz, 1 of 3-C$\underline{H}_2$), 2.1-1.98 (m, 2H, 2-C$\underline{H}_2$), 1.96 (s, 3H, C$\underline{H}_3$), 1.46 (s, 9H, C(C$\underline{H}_3)_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 198.8 ($\underline{C}$=O), 161.9 (6-$\underline{C}$), 153.7 ($\underline{C}O_2C$), 148.1 (1'-$\underline{C}$), 138.1 (4'-$\underline{C}$), 128.0 (5-$\underline{C}$), 111.1 (2'-$\underline{C}$), 101.2 (3'-$\underline{C}$), 81.6 (O$\underline{C}(CH_3)_3$), 48.4 (N$\underline{C}H_2$), 39.2 (3-$\underline{C}$), 33.1 (1-$\underline{C}$), 28.1 (3 x OC($\underline{C}H_3)_3$), 24.5 ($\underline{C}H_3$), 22.8 (2-$\underline{C}$); **MS *m/z*** (ES+) 328 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 328.1520 ($C_{17}H_{23}NNaO_4$) requires (M) 328.1520

(4,4-Dimethoxy-6-methylcyclohex-1-enyl)methanol; 225

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 ν_{max}(oil) 3401 (OH), 2941 (CH); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 4.12 (s, 2H, C$\underline{H}_2$OH), 3.22 (s, 6H, (OC$\underline{H}_3$)$_2$), 2.22 (s, 2H, 5-C$\underline{H}_2$), 2.19 (m, 2H, 2-C$\underline{H}_2$), 1.82 (m, 2H, 3-C$\underline{H}_2$), 1.69 (s, 3H, C$\underline{H}_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 129.1 (1-$\underline{C}$), 127.4 (6-$\underline{C}$), 99.9 (4-$\underline{C}$), 62.5 (O$\underline{C}$H$_2$), 50.7 (2 x O$\underline{C}$H$_3$), 45.9 (5-$\underline{C}$), 40.9 (3-$\underline{C}$), 26.1 (2-$\underline{C}$), 18.7 ($\underline{C}$H$_3$); **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; 226

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 (MgSO$_4$), 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 ν$_{max}$(oil) 2955 (CH), 1575 (C=O); **^{1}H NMR** (300 MHz, CDCl$_3$) δ$_H$ 7.15-7.13 (m, 1H, 1'-C_H_), 6.28-6.25 (m, 1H, 3'-C_H_), 5.89 (bs, 1H, 2'-C_H_), 4.18 (s, 2H, NC_H_$_2$), 3.18 (s, 6H, (OC_H_$_3$)$_2$), 2.12 (s, 2H, 5-C_H_$_2$), 2.04 (t, 2H, _J_ = 6.6Hz, 2-C_H_$_2$), 1.73 (t, 2H, _J_ = 6.4Hz, 3-C_H_$_2$), 1.45 (s, 3H, C_H_$_3$), 1.41 (s, 9H, C(C_H_$_3$)$_3$); **^{13}C NMR** (100 MHz, CD$_2$Cl$_2$) δ$_C$ 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 (_C_O(CH$_3$)$_3$), 49.5 (N_C_H$_2$), 48.0 (2 x O_C_H$_3$), 40.9 (5-_C_), 30.1 (3-_C_), 29.1 (3 x CO(_C_H$_3$)$_3$),

25.8 (2-$\underline{C}$), 19.8 ($\underline{C}H_3$) **MS** *m/z* (ES+) 374 ([M+Na]$^+$); **HRMS** Found [M+H]$^+$ 352.2120 ($C_{19}H_{30}NO_5$) requires (M) 352.2118

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

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

tert-Butyl furan-2-yl((3-methyl-4-oxocyclohex-1-enyl)methyl)carbamate; 223

IR ν_{max}(oil) 2980 (CH), 1745 (C=O), 1665 (C=O); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.14 (s, 1H, 1'-C$\underline{H}$), 6.28 (dd, 1H, *J* = 3.2Hz and 2.1Hz, 3'-C$\underline{H}$), 5.91 (bs, 1H, 2'-C$\underline{H}$), 4.29 (s, 2H, NC$\underline{H}_2$), 2.72 (s, 2H, 5-C$\underline{H}_2$), 2.38 (m, 4H, 2-C$\underline{H}_2$ and 3-C$\underline{H}_2$), 1.55 (s, 3H, C$\underline{H}_3$), 1.41 (s, 9H, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, C$_6$D$_6$) δ_C 210.6 ($\underline{C}$=O), 154.4 ($\underline{C}O_2$C), 147.9 (1'-$\underline{C}$), 138.5 (4'-$\underline{C}$), 129.1 (1-$\underline{C}$), 126.9 (6-$\underline{C}$), 110.8 (2'-$\underline{C}$), 102.2 (3'-$\underline{C}$), 81.3 (O$\underline{C}$(CH$_3$)$_3$), 48.8 (N$\underline{C}H_2$), 45.6 (5-$\underline{C}$), 38.7 (3-$\underline{C}$), 28.1 (OC($\underline{C}H_3$)$_3$), 26.9 (2-$\underline{C}$), 18.2 ($\underline{C}H_3$); **MS** *m/z* (ES+): 328 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 328.1520 ($C_{17}H_{23}NNaO_4$) requires (M) 328.1520

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

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 v_{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) δ_H 14.08 (s, 1H, O*H*), 5.57 (d, 1H, *J* = 5.2Hz, 3'-C*H*), 4.00 (dd, 1H, *J* =11.5Hz and 7.9Hz, NC*H$_A$*H$_B$), 3.42 (dd, 1H, *J* = 11.5Hz and 2.0Hz, NCH$_A$*H$_B$*),

3.21 (dd, 1H, *J* = 21.0Hz and 1.9Hz, 2'-CH_AH$_B$), 2.82 (dd, 1H, *J* = 21.0Hz and 6.4Hz, 2'-CH$_A$$H_B$), 2.36 (ddd, 1H, *J* = 17.3Hz, 13.2Hz and 4.1Hz, 1 of 3-CH_2), 2.26-2.04 (m, 3H, 1 of 3-CH_2, 2-CH_2), 1.82 (m, 1H, 1-CH), 1.46 (s, 9H, C(CH_3)$_3$), 1.19 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, d-DMSO, 363K) δ_C 193.8 (C=O), 183.6 (1'-C), 151.5 (NC=O), 146.7 (4'-C), 111.7 (5'-C), 99.0 (3'-C), 80.1 (C(CH$_3$)$_3$), 53.3 (NCH$_2$), 52.2 (1-C), 44.4, 40.9, 38.4, 38.3, 38.1, 36.1, 34.4, 31.6, 30.4, 27.9, 27.2, 25.5; **Keto form observed: ^{1}H NMR** (400 MHz, d-DMSO, 363K) δ_H 5.75 (t, 1H, *J* = 7.3Hz and 3.8Hz, 3'-CH), 3.80 (dd, 1H, *J* = 11.1Hz and 5.5Hz, NCH_AH$_B$), 3.40 (s, 1H, 5-CH), 3.37 (dd, 1H, 11.2Hz and 5.9Hz, NCH$_A$$H_B$), 2.91 (dd, 1H, *J* = 22.4Hz and 4.4Hz, 2'-CH_AH$_B$), 2.76 (dd, 1H, 22.5Hz and 3.1Hz, 2'-CH$_A$$H_B$) 2.55 (dd, 1H, *J* = 13.5Hz and 4.8Hz, 1 of 3-CH_2), 2.47 (m, 1H, 1 of 3-CH_2); **^{13}C NMR** (100 MHz, d-DMSO, 363K) δ_C 205.9 (C=O), 205.1 (C=O), 152.0 (NC=O), 140.5 (4'-C), 94.7 (3'-C), 66.6 (5'-C), 53.1 (NCH$_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
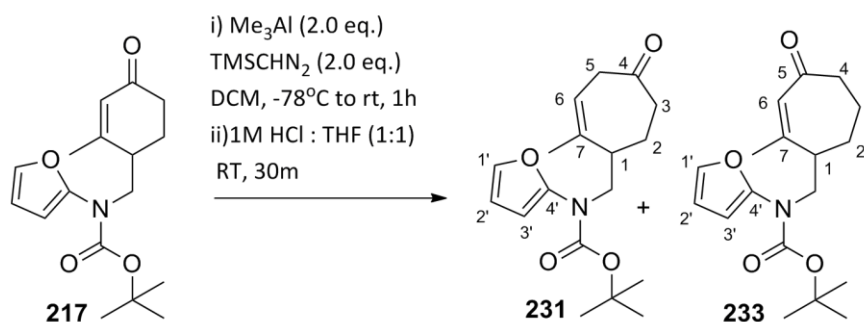
To a solution of enone **217** (100 mg, 0.33 mmol) in dichloromethane (12 mL) at -78 ^{o}C was added a 2.0 M solution of trimethylaluminium in toluene (0.33 mL, 0.66 mmol) drop-wise, followed by a 2.0 M solution of trimethylsilyldiazomethane in hexanes (0.33 mL, 0.66 mmol) drop-wise. The reaction mixture was stirred at -78 ^{o}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 (Na$_2$SO$_4$), 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 (Na$_2$SO$_4$), 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)methyl)carbamate; 231

IR ν_{max}(oil) 2967 (CH), 1751 (C=O), 1649 (C=O); **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 6.96 (s, 1H, 1'-C*H*), 6.13 (s, 1H, 3'-C*H*), 5.79 (bs, 1H, 2'-C*H*), 5.13 (t, 1H, *J* = 6.1Hz, 6-C*H*), 3.64-3.41 (m, 2H, NC*H*$_2$), 2.89 (ddd, 2H, *J* = 20.0Hz, 14.3Hz and 5.0Hz, 5-C*H*$_2$), 2.38-2.28 (m, 2H, 3-C*H*$_2$), 2.21 (ddd, 1H, *J* = 17.0Hz, 8.7Hz and 3.4Hz, 1-C*H*), 1.82 (ddd, 1H, *J* = 13.0Hz, 8.3Hz and 4.1Hz, 1 of 2-C*H*$_2$), 1.77-1.68 (m, 1H, 1 of 2-C*H*$_2$), 1.50 (s, 3H, C*H*$_3$), 1.23 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 209.8 (*C*=O), 148.3 (*C*O$_2$C), 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 (O*C*(CH$_3$)$_3$), 50.1 (N*C*H$_2$), 43.9 (5-*C*), 41.9 (3-*C*), 40.0 (1-*C*), 28.1 (3 x OC(*C*H$_3$)$_3$), 24.6 (2-*C*), 24.1 (*C*H$_3$); **MS *m/z*** (ES+): 342 ([M+Na]$^+$); **HRMS** Found [M+NH$_4$]$^+$ 337.2115 (C$_{18}$H$_{29}$O$_4$N$_2$) requires (M) 337.2122.

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

IR ν_{max}(oil) 2967 (CH), 1705 (C=O), 1599 (C=O); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.13 (dd, 1H, *J* = 2.0Hz and 0.8Hz, 1'-C*H*), 6.34-6.25 (m, 1H, 3'-C*H*), 5.96 (bs, 1H, 2'-C*H*), 5.82 (s, 1H, 6-C*H*), 3.68 (ddd, 2H, *J* = 18.3Hz, 14.1Hz and 7.2Hz, NC*H*$_2$), 2.61-2.50 (m, 2H, 1-C*H* and 1 of 4-C*H*$_2$), 2.45-2.08 (m, 3H, 1 of 4-C*H*$_2$ and 3-C*H*$_2$), 1.95 (td, 2H, *J* = 6.7Hz and 4.36Hz, 2-C*H*$_2$), 1.53 (s, 3H, C*H*$_3$), 1.40 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 196.5 (*C*=O), 160.6 (7-*C*), 154.9 (*C*O$_2$C), 148.0 (1'-*C*), 137.9 (4'-*C*), 128.7 (6-*C*), 111.0 (2'-*C*), 101.3 (3'-*C*), 80.8 (O*C*(CH$_3$)$_3$), 48.1 (N*C*H$_2$), 40.0 (4-*C*), 35.7 (1-*C*), 28.3 (3 x OC(*C*H$_3$)$_3$),

25.2 ($\underline{C}H_3$), 23.4 (3-$\underline{C}$) 22.7 (2-$\underline{C}$); ; **MS** *m/z* (ES+): 342 ([M+Na]$^+$); **HRMS** Found [M+H]$^+$ 320.1859 ($C_{18}H_{26}O_4N$) 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
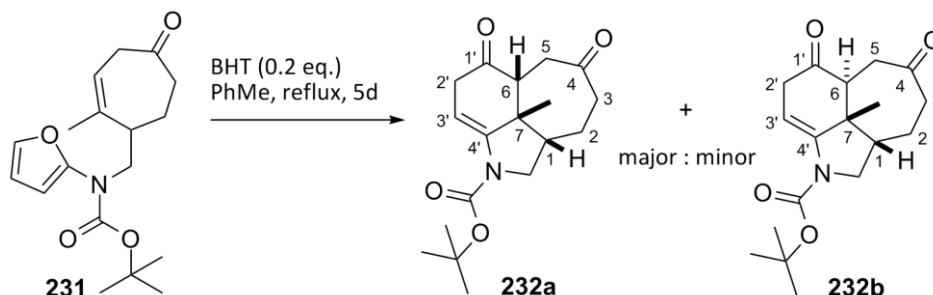
To a stirred solution of **231** (100 mg, 0.31 mmol) in toluene (5 mL) was added butylated hydroxyl toluene (14 mg, 0.06 mmol) in one portion at room temperature and then refluxed for 5 days and until TLC confirmed complete consumption of starting material. The reaction mixture was concentrated *in vacuo* 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 ^{1}H NMR and ^{13}C NMR were performed at 343K in deuterated benzene.

IR ν_{max}(oil) 2955 (CH), 1767 (C=O), 1711 (C=O), 1647 (C=O); **Major 232a:** ^{1}**H NMR** (400 MHz, C_6D_6, 343K) δ_H 5.97 (bs, 1H, 3'-C$\underline{H}$), 3.28 (dd, 1H, *J* = 10.0Hz and 7.7Hz, NC$\underline{H}_A$H$_B$), 2.81 (t, 1H, *J* = 10.7Hz, NCH$_A\underline{H}_B$), 2.71 (dd, 1H, *J* = 17.3Hz and 2.5Hz, 2'-C$\underline{H}_A$H$_B$), 2.65 (ddd, 1H, *J* = 13.7Hz, 3.0Hz and 0.8Hz, 6-C$\underline{H}$), 2.59 (dd, 1H, *J* = 17.3Hz and 7.0Hz, 2'-CH$_A\underline{H}_B$), 2.20 (td, 2H, *J* = 16.3Hz and 13.1Hz, 5-C$\underline{H}_2$), 2.06-1.96 (m, 1H, 1 of 3-C$\underline{H}_2$), 1.84 (td, 1H, *J* = 11.6Hz, 8.0Hz, 1 of 3-C$\underline{H}_2$), 1.62-1.52 (m, 1H, 1-C$\underline{H}$), 1.41 (s, 9H, C(C$\underline{H}_3$)$_3$), 0.94-0.86 (m, 2H, 2-C$\underline{H}_2$), 0.67 (s, 3H, C$\underline{H}_3$); ^{13}**C NMR** (100 MHz, C_6D_6, 343K) δ_C 208.7 ($\underline{C}$=O), 204.8 ($\underline{C}$=O), 152.6 (N$\underline{C}$=O), 144.8 (4'-$\underline{C}$), 97.4 (3'-$\underline{C}$), 80.3 (O$\underline{C}$(CH$_3$)$_3$), 52.5 (6-$\underline{C}$), 51.7 (N$\underline{C}$H$_2$), 48.7 (7-$\underline{C}$), 41.8 (2'-$\underline{C}$), 41.1 (3-$\underline{C}$), 40.6 (5-$\underline{C}$), 38.6 (1-$\underline{C}$), 28.3 (3 x OC($\underline{C}$H$_3$)$_3$), 21.8 ($\underline{C}$H$_3$), 21.6 ($\underline{C}$H$_3$), 20.0 (2-$\underline{C}$); **Minor 232b observed:** ^{1}**H NMR** (400

MHz, C_6D_6, 343K) δ_H 6.06 (bs, 1H, 3'-C$\underline{H}$), 3.44 (dd, 1H, J = 5.8Hz and 11.4Hz, NC$\underline{H}_A$H$_B$), 3.09 (d, 1H, J = 11.4Hz, NCH$_A$$\underline{H}_B$), 2.78-2.75 (m, 1H, 2'-C$\underline{H}_A$H$_B$), 2.56-2.53 (m, 1H, 2'-CH$_A$$\underline{H}_B$), 0.73 (s, 3H, C$\underline{H}_3$); **¹³C NMR** (100 MHz, C_6D_6, 343K) δ_C 207.0 ($\underline{C}$=O), 206.5 ($\underline{C}$=O), 152.1 (N$\underline{C}$=O), 145.1 (4'-$\underline{C}$), 98.2 (3'-$\underline{C}$), 80.5 (O$\underline{C}$(CH$_3$)$_3$), 54.6 (6-$\underline{C}$), 51.4 (N$\underline{C}$H$_2$), 47.5 (7-$\underline{C}$), 41.7 (2'-$\underline{C}$), 41.2 (3-$\underline{C}$), 40.3 (5-$\underline{C}$), 35.2 (1-$\underline{C}$), 27.8 (3 x OC($\underline{C}$H$_3$)$_3$), 20.2 (2-$\underline{C}$); **MS m/z** (ES+): 342 ([M+Na]$^+$); **HRMS** Found [M+H]$^+$ 320.1852 ($C_{18}H_{26}O_4N$) requires (M) 320.1856.

(±)-*tert*-Butyl 1'-hydroxy-7-methyl-5-oxo-1,2,3,4,6,2'-hexahydro-1H-cyclohepta[cd]indole-4'(7H)-carboxylate; 236
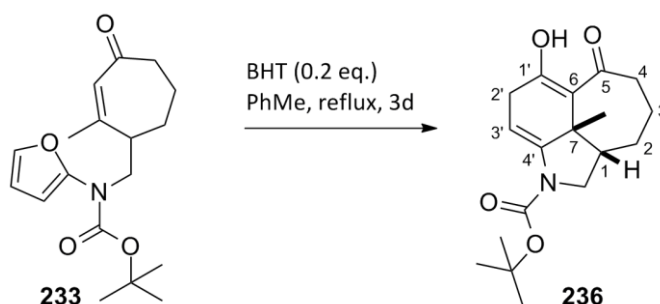

To a stirred solution of **233** (100 mg, 0.32 mmol) in toluene (5 mL) was added butylated hydroxyl toluene (14 mg, 0.71 mmol) in one portion at room temperature and then refluxed for 3 days and until TLC confirmed complete consumption of starting material. The reaction mixture was concentrated *in vacuo* 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** v_{max}(oil) 3352 (OH), 2842 (CH), 1724 (C=O), 1677 (C=O); **¹H NMR** (400 MHz, C_6D_6) δ_H 14.12 (bs, 1H, O$\underline{H}$), 5.66 (bs, 1H, 3'-C$\underline{H}$), 3.74 (dd, 1H, J = 11.3Hz and 7.6Hz, NC$\underline{H}_A$H$_B$), 3.25 (dd, 1H, J = 14.0Hz and 7.6Hz, NCH$_A$$\underline{H}_B$), 2.97 (m, 1H, 1 of 2'-C$\underline{H}_A$H$_B$), 2.73 (m, 1H, 2'-CH$_A$$\underline{H}_B$), 2.45 (m, 1H, 1 of 4-C$\underline{H}_2$), 2.08 (m, 1H, 1 of 4-C$\underline{H}_2$), 1.98 (m, 1H, 1 of 2-C$\underline{H}_2$), 1.84 (m, 1H, 1 of 2-C$\underline{H}_2$), 1.59 (m, 2H, 3-C$\underline{H}_2$), 1.48 (m, 1H, 1-

C$\underline{H}$), 1.35 (s, 3H), 1.29 (s, 9H); **MS** **m/z** (ES+): 342 ([M+Na]$^+$); **HRMS** Found [M+H]$^+$ 320.1860 (C$_{18}$H$_{26}$NO$_4$) requires (M) 320.1857.

5-(*tert*-Butyldiphenylsiloxy)-pent-2-yn-1-ol; 238[108]
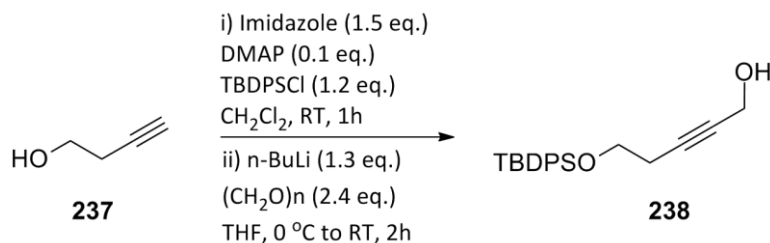
To a solution of 3-butyne-1-ol **237** (3.54 g, 50.0 mmol) in dichloromethane (80 mL) was added imidazole (5.11 g, 75.0 mmol), 4-dimethylaminopyridine (0.06 g, 0.50 mmol) and *tert*-butyldiphenylchlorosilane (16.5 g, 60.0 mmol) at room temperature. The reaction mixture was stirred for 1 hour and until 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$_3$) δ_H 7.72 (m, 4H, Ar-$\underline{H}$), 7.42 (m, 6H, Ar-$\underline{H}$), 4.33 (t, 2H, J = 2.1Hz, C$\underline{H}_2$OH), 3.61 (q, 2H, J = 6.2Hz, C$\underline{H}_2$OSi), 2.40 (tt, 2H, J = 6.1Hz and 2.1Hz,

C$\underline{H}_2$CH$_2$OSi), 1.05 (s, 9H, C(C$\underline{H}_3$)$_3$) ^{1}*H NMR in agreement with the literature*; **MS *m/z*** (ES+): 361 ([M+Na]$^+$)

(5-Bromo-pent-2-ynyloxy)-*tert*-butyl-diphenylsilane; 239[109]
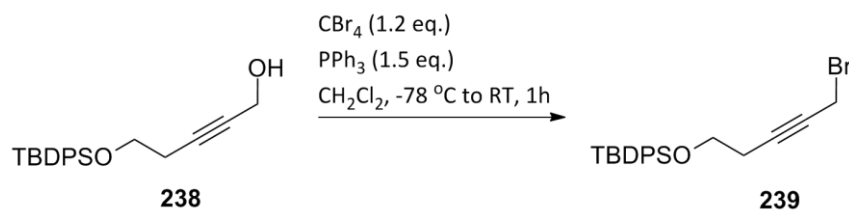
To a stirred solution of alcohol **238** (13.5 g, 39.9 mmol) and tetrabromomethane (15.9 g, 47.9 mmol) in dichloromethane (1 L) at -78 ^{o}C was added a solution of triphenylphosphine (15.7 g, 59.9 mmol) in dichloromethane (1 L) drop-wise. The reaction mixture was warmed to room temperature and stirred 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.

^{1}H NMR (500 MHz, CDCl$_3$) δ_H 7.71 (m, 4H, Ar-$\underline{H}$), 7.41 (m, 6H, Ar-$\underline{H}$), 4.31 (t, 2H, *J* = 2.1Hz, C$\underline{H}_2$Br), 3.33 (t, 2H, *J* = 7.4Hz, C$\underline{H}_2$OSi), 2.71 (tt, 2H, *J* = 7.4Hz and 2.1Hz, C$\underline{H}_2$CH$_2$OSi), 1.05 (s, 9H, C(C$\underline{H}_3$)$_3$) ^{1}*H 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
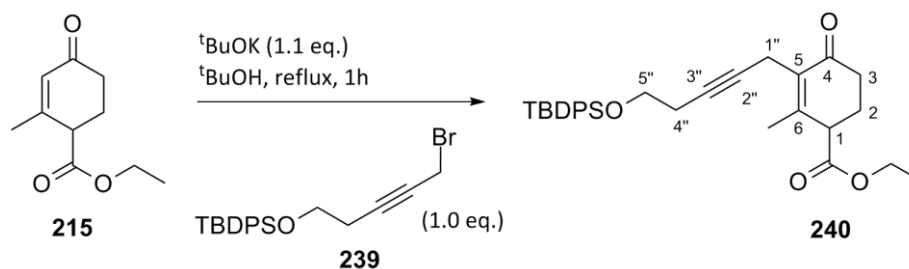
To a stirred solution of potassium *tert*-butoxide (4.62 g, 41.3 mmol) in *tert*-butanol (200 mL) was added a solution of Hagemann's ester **215** (7.50 g, 41.3 mmol) in *tert*-butanol (100 mL) at room temperature. The reaction mixture was stirred for 1 hour until a solution of **239** (15.0 g, 37.5 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 (MgSO$_4$), 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 ν_{max}(oil) 2981 (CH), 1705 (C=O), 1666 (C=O); **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.59 (td, 4H, *J* = 7.8Hz and 1.4Hz, Ar-*H*), 7.38-7.27 (m, 6H, Ar-*H*), 4.10 (q, 2H, *J* = 7.1Hz, CO$_2$C*H$_2$*CH$_3$), 3.64 (t, 2H, *J* = 7.1Hz, 5''-C*H$_2$*), 3.28 (td, 1H, *J* = 16.8Hz and 2.2Hz, 1 of 1''-C*H$_A$*H$_B$), 3.21 (t, 1H, *J* = 4.9Hz, 1-C*H*), 2.97 (td, 1H, *J* = 16.8Hz and 2.2Hz, 1 of 1''-CH$_A$*H$_B$*), 2.50 (ddd, 2H, *J* = 13.6Hz, 11.2Hz and 5.2Hz, 3-C*H$_2$*), 2.36-2.27 (m, 2H, 4''-C*H$_2$*), 2.22-2.05 (m, 2H, 2-C*H$_2$*), 1.98 (s, 3H, C*H$_3$*), 1.18 (t, 3H, *J* = 7.1Hz, CO$_2$CH$_2$C*H$_3$*), 0.96 (s, 9H, C(C*H$_3$*)$_3$); **^{13}C NMR** (125 MHz, CDCl$_3$) δ_C 195.9 (*C*=O), 171.9 (*C*O$_2$C), 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 (O*C*H$_2$CH$_3$), 61.3 (5''-*C*), 47.7 (1-*C*), 34.3 (3-*C*), 26.7 (3 x C(*C*H$_3$)$_3$), 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 (C$_{31}$H$_{38}$NaO$_4$Si) requires (M) 525.2432

(5-(5''-(*tert*-Butyldiphenylsilyloxy)pent-2-ynyl)-4,4-dimethoxy-6-methylcyclohex-1-enyl)methanol; 241
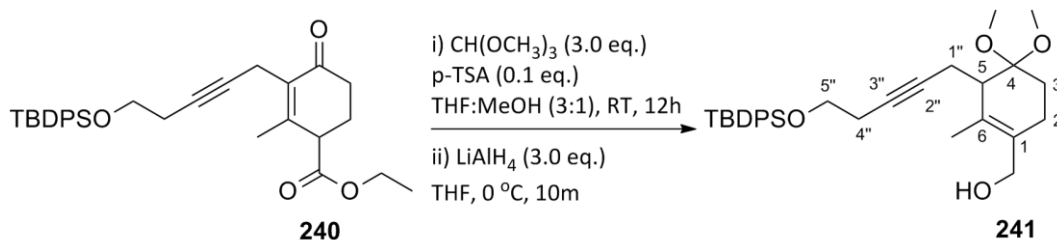
To a stirred solution of **240** (6.00 g, 11.9 mmol) in tetrahydrofuran (150 mL) and methanol (50 mL) was added trimethylorthoformate (3.93 mL, 35.9 mmol) followed by para-toluene sulfonic acid (0.23 g, 1.19 mmol) in one portion. The reaction mixture was stirred for 12 hours at room temperature and until 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 ($MgSO_4$) 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 ^{o}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*. Purification by flash column chromatography (diethyl ether : light petroleum ether, 4 : 1) afforded **241** (2.4 g, 40%) as a colourless oil.

IR ν_{max}(oil) 3425 (OH), 2931 (CH); **^{1}H NMR** (300 MHz, CD_2Cl_2) δ_H 7.61-7.55 (m, 4H, Ar-*H*), 7.38-7.24 (m, 6H, Ar-*H*), 3.92 (s, 2H, C*H$_2$*OH), 3.62 (t, 2H, *J* = 7.1Hz, 5''-C*H$_2$*), 3.06 (s, 3H, OC*H$_3$*), 3.04 (s, 3H, OC*H$_3$*), 2.46-2.35 (m, 1H, 5-C*H*), 2.30 (tt, 1H, *J* = 7.3Hz and 2.3Hz, 1''-

C$\underline{H}_A$H$_B$), 2.20-2.13 (m, 2H, 4''-C$\underline{H}_2$), 2.09-1.95 (m, 1H, 1''-CH$_A$$\underline{H}_B$), 1.82-1.72 (m, 3H, 2-C$\underline{H}_2$ and 1 of 3-C$\underline{H}_2$), 1.69 (s, 3H, C$\underline{H}_3$), 1.65-1.54 (m, 1H, 1 of 3-C$\underline{H}_2$), 0.95 (s, 9H, C(C$\underline{H}_3$)$_3$); ^{13}**C NMR** (75 MHz, CD$_2$Cl$_2$) δ_C 135.9 (6 x Ar-$\underline{C}$), 134.1 (1-$\underline{C}$), 130.9 (6-$\underline{C}$), 130.1 (2 x Ar-$\underline{C}$), 128.0 (4 x Ar-$\underline{C}$), 101.7 (4-$\underline{C}$), 80.6 (3''-$\underline{C}$), 78.8 (2''-$\underline{C}$), 63.4 (O$\underline{C}$H$_2$), 62.7 (5''-$\underline{C}$), 48.1 (O$\underline{C}$H$_3$), 48.0 (O$\underline{C}$H$_3$), 46.3 (5-$\underline{C}$), 27.0 (2-$\underline{C}$), 26.3 (3 x C($\underline{C}$H$_3$)$_3$), 25.0 (4''-$\underline{C}$), 23.3 ($\underline{C}$(CH$_3$)$_3$), 21.0, 19.4, 18.7; **MS** *m/z* (ES+): 529 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 529.2743 (C$_{31}$H$_{42}$NaO$_4$Si) 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
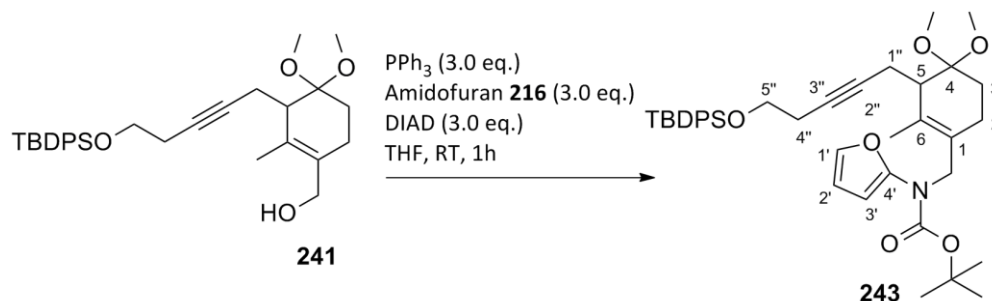
To a stirred solution of alcohol **241** (2.40 g, 4.74 mmol) in dry tetrahydrofuran (12.5 mL) was added triphenylphosphine (3.73 g, 14.2 mmol), amidofuran **216** (2.61 g, 14.2 mmol) and di*iso*propyl azodicarboxylate (2.88 g, 14.2 mmol) successively at room temperature. The reaction mixture was stirred 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 ν_{max}(oil) 2957 (CH), 1582 (C=O); ^{1}**H NMR** (400 MHz, CD$_2$Cl$_2$) δ_H 7.60-7.56 (m, 4H, Ar-$\underline{H}$), 7.36-7.27 (m, 6H, Ar-$\underline{H}$), 7.06 (dd, 1H, *J* = 2.0Hz and 0.9Hz, 1'-C$\underline{H}$), 6.19 (dd, 1H, *J* = 3.2Hz and 2.1Hz, 3'-C$\underline{H}$), 5.86 (bs, 1H, 2'-C$\underline{H}$), 4.06 (s, 2H, NC$\underline{H}_2$), 3.62 (t, 2H, *J* = 7.0Hz, 5''-C$\underline{H}_2$), 3.05 (s, 3H, OC$\underline{H}_3$), 3.02 (s, 3H, OC$\underline{H}_3$), 2.38-2.26 (m, 3H, 5-C$\underline{H}$ and 4''-C$\underline{H}_2$), 2.14-2.08 (m, 1H, 1 of 2-C$\underline{H}_2$), 1.91 (d, 2H, *J* = 7.8Hz, 1''-C$\underline{H}_2$), 1.87-1.79 (m, 1H, 1 of 2-C$\underline{H}_2$), 1.78-1.70 (m, 2H, 3-C$\underline{H}_2$), 1.50 (s, 3H, C$\underline{H}_3$), 1.32 (s, 9H, OC(C$\underline{H}_3$)$_3$), 0.95 (s, 9H,

SiC(C$\underline{H}_3$)$_3$); ^{13}C NMR (75 MHz, CD$_2$Cl$_2$) δ_C 154.6 (C$\underline{O}_2$C), 148.4 (1'-$\underline{C}$), 138.8 (4'-$\underline{C}$), 135.9 (4 x Ar-$\underline{C}$), 134.1 (5-$\underline{C}$), 130.0 (2 x Ar-$\underline{C}$), 128.0 (6 x Ar-$\underline{C}$), 125.8 (1-$\underline{C}$), 111.1 (2'-$\underline{C}$), 102.8 (3'-$\underline{C}$), 101.5 (4-$\underline{C}$), 81.1 (3''-$\underline{C}$), 81.0 ($\underline{C}$(CH$_3$)$_3$), 78.4 (2''-$\underline{C}$), 63.3 (5''-$\underline{C}$), 49.5 (N$\underline{C}$H$_2$), 48.1 (O$\underline{C}$H$_3$), 48.0 (O$\underline{C}$H$_3$), 46.8 (5-$\underline{C}$), 28.3 (3 x OC($\underline{C}$H$_3$)$_3$), 26.9 (3 x SiC($\underline{C}$H$_3$)$_3$), 26.1, 24.8, 23.3, 21.4, 19.4, 18.8; **MS *m/z*** (ES+): 694 ([M+Na]$^+$); **HRMS** Found [M+NH$_4$]$^+$ 689.3981 (C$_{40}$H$_{57}$N$_2$O$_6$Si) 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
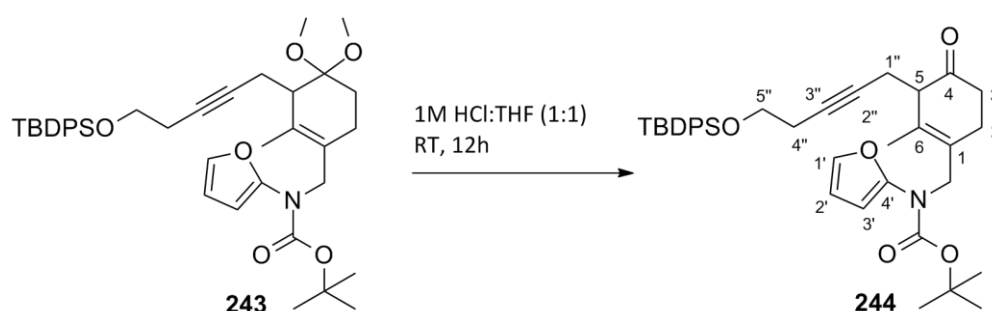

To a stirred solution of **243** (1.20 g, 1.79 mmol) in tetrahydrofuran (5 mL) was added 1.0 M hydrochloric acid (5 mL) at room temperature. The reaction mixture was stirred at this temperature until TLC confirmed complete consumption of starting material. The reaction mixture was quenched with saturated 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 (MgSO$_4$), 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 ν_{max}(oil) 2995 (CH), 1750 (C=O), 1660 (C=O); ^{1}**H NMR** (400 MHz, CD$_2$Cl$_2$) δ_H 7.60-7.55 (m, 4H, Ar-$\underline{H}$), 7.38-7.28 (m, 6H, Ar-$\underline{H}$), 7.08 (dd, 1H, J = 2.0Hz and 0.9Hz, 1'-C$\underline{H}$), 6.21 (dd, 1H, J = 3.2Hz and 2.1Hz, 3'-C$\underline{H}$), 5.88 (d, 1H, J = 2.7Hz, 2'-C$\underline{H}$), 4.19 (q, 2H, J = 14.5Hz, NC$\underline{H}_2$), 3.59 (t, 2H, J = 7.1Hz, 5''-C$\underline{H}_2$), 2.56-2.46 (m, 1H, 5-C$\underline{H}$), 2.44-2.15 (m, 8H, 4''-C$\underline{H}_2$, 1''-C$\underline{H}_2$, 2-C$\underline{H}_2$ and 3-C$\underline{H}_2$), 1.48 (s, 3H, C$\underline{H}_3$), 1.34 (s, 9H, OC(C$\underline{H}_3$)$_3$), 0.95 (s, 9H, SiC(C$\underline{H}_3$)$_3$); ^{13}**C NMR** (125 MHz, CD$_2$Cl$_2$) δ_C 209.9 ($\underline{C}$=O), 153.3 (N$\underline{C}$=O), 147.2 (1'-$\underline{C}$),

137.7 (4'-$\underline{C}$), 134.7 (4 x Ar-$\underline{C}$), 132.8 (6-$\underline{C}$), 128.8 (2 x Ar-$\underline{C}$), 128.4 (1-$\underline{C}$), 126.9 (6 x Ar-$\underline{C}$), 110.0 (2'-$\underline{C}$), 101.5 (3'-$\underline{C}$), 80.2 (2''-$\underline{C}$), 78.1 (O$\underline{C}$(CH$_3$)$_3$), 77.0 (3''-$\underline{C}$), 62.0 (5''-$\underline{C}$), 48.3 (N$\underline{C}$H$_2$), 37.0 (5-$\underline{C}$), 28.9 (3 x OC($\underline{C}$H$_3$)$_3$), 27.1 (3 x SiC($\underline{C}$H$_3$)$_3$), 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 (C$_{38}$H$_{47}$NNaO$_5$Si) 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
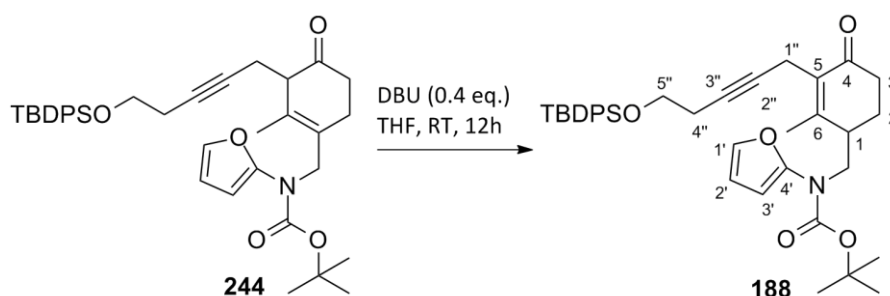

To a stirred solution of **244** (1.10 g, 1.78 mmol) in tetrahydrofuran (10 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.11 g, 0.72 mmol) and stirred for 12 hours and until TLC confirmed complete consumption of starting material. The reaction mixture was concentrated *in vacuo* and the crude residue 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 ν_{max}(oil) 2981 (CH), 1705 (C=O), 1666 (C=O); **^{1}H NMR** (400 MHz, CD$_2$Cl$_2$) δ_H 7.60-7.54 (m, 4H, Ar-$\underline{H}$), 7.35-7.24 (m, 6H, Ar-$\underline{H}$), 7.10 (dd, 1H, *J* = 1.9Hz and 0.7Hz, 1'-C$\underline{H}$), 6.27 (dd, 1H, *J* = 3.0Hz and 2.1Hz, 3'-C$\underline{H}$), 5.94 (bs, 1H, 2'-C$\underline{H}$), 3.68 (dd, 1H, *J* = 14.0Hz and 10.6Hz, 1 of NC$\underline{H}_2$), 3.61 (t, 2H, *J* = 6.9Hz, 5''-C$\underline{H}_2$), 3.58-3.50 (m, 1H, 1 of NC$\underline{H}_2$), 3.02 (dd, 2H, *J* = 51.6Hz and 16.7Hz, 1''-C$\underline{H}_2$), 2.51-2.36 (m, 2H, 3-C$\underline{H}_2$), 2.29 (tt, 2H, *J* = 6.8Hz and 2.1Hz, 4''-C$\underline{H}_2$), 2.18 (td, 1H, *J* = 17.5Hz and 4.0Hz, 1-C$\underline{H}$), 1.89 (s, 3H, C$\underline{H}_3$), 1.89-1.75 (m, 2H, 2-C$\underline{H}_2$), 1.35 (s, 9H, OC(C$\underline{H}_3$)$_3$), 0.94 (s, 9H, SiC(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100 MHz, CD$_2$Cl$_2$) δ_C 196.4 ($\underline{C}$=O), 157.4 (N$\underline{C}$=O), 148.8 (1'-$\underline{C}$), 138.5 (4'-$\underline{C}$) 135.9 (2 x Ar-$\underline{C}$), 134.1 (6-$\underline{C}$), 133.5 (5-$\underline{C}$), 130.0 (6 x Ar-$\underline{C}$), 128.0 (4 x Ar-$\underline{C}$), 111.4 (2'-$\underline{C}$), 101.4 (3'-$\underline{C}$), 81.9

(O$\underline{C}$(CH$_3$)$_3$), 78.7 (3''-$\underline{C}$), 76.4 (2''-$\underline{C}$), 63.2 (5''-$\underline{C}$), 48.4 (N$\underline{C}$H$_2$), 41.3 (3-$\underline{C}$), 33.2 (1-$\underline{C}$), 28.3 (3 x OC($\underline{C}$H$_3$)$_3$), 26.9 (3 x SiC($\underline{C}$H$_3$)$_3$), 23.8, 23.2, 20.3, 19.4, 14.8; **MS *m/z*** (ES+): 648 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 648.3117 (C$_{38}$H$_{47}$NNaO$_5$Si) 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
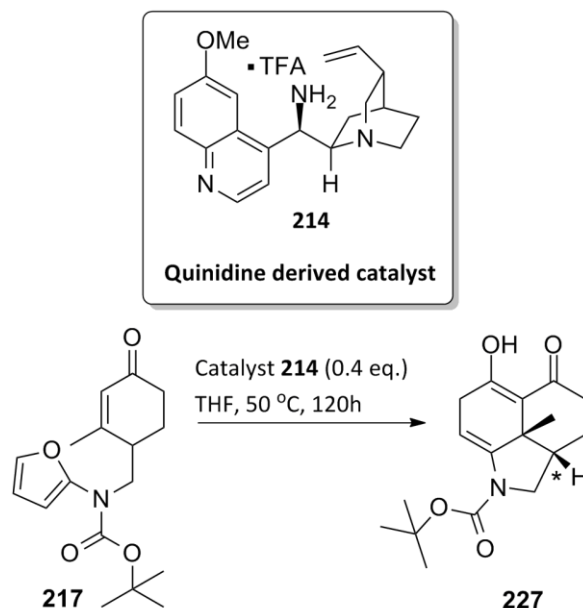
To a stirred solution of organocatalyst **214** (20 mg, 0.03 mmol) in dry tetrahydrofuran (2 mL) was added a solution of enone **217** (50 mg, 0.16 mmol) in dry tetrahydrofuran (1 mL) and warmed to 50 ^{o}C. The reaction mixture was stirred at this temperature until TLC confirmed complete consumption 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 ^{1}H NMR was identical to **227** which was previous prepared from **217** using a catalytic amount of butylated hydroxy toluene in boiling toluene. **[α]$_D$^{23}:** +15 (c 0.26, CHCl$_3$).

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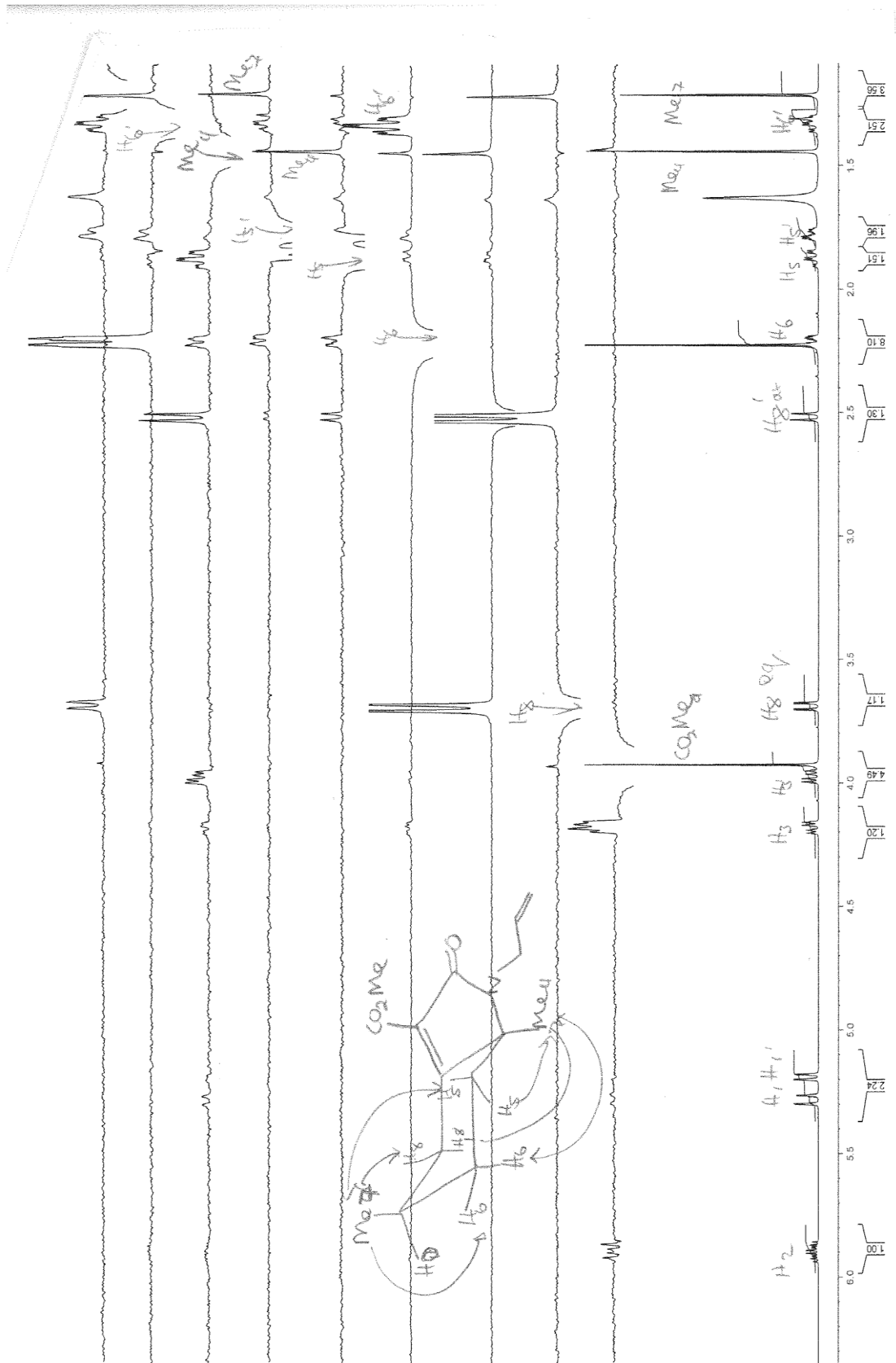
CHAPTER EIGHT: APPENDIX

8.1 NOE DATA FOR 93a
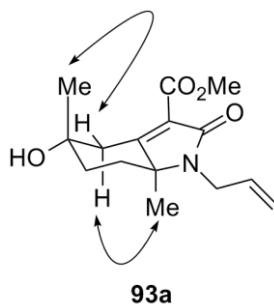
93a

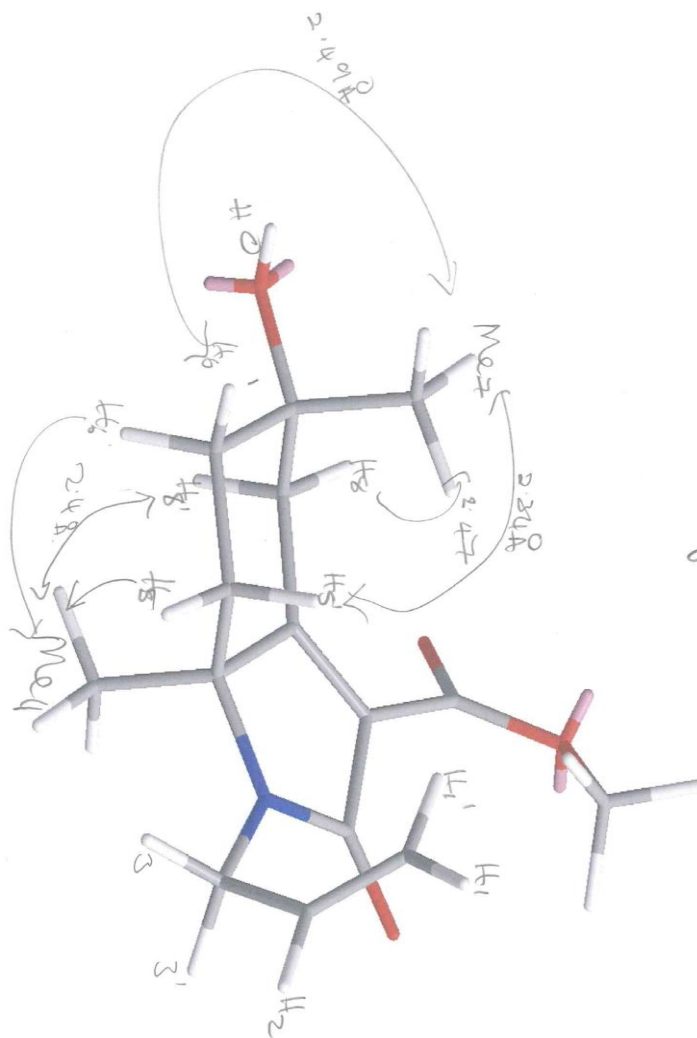Data obtained at The University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK
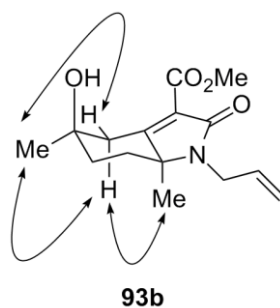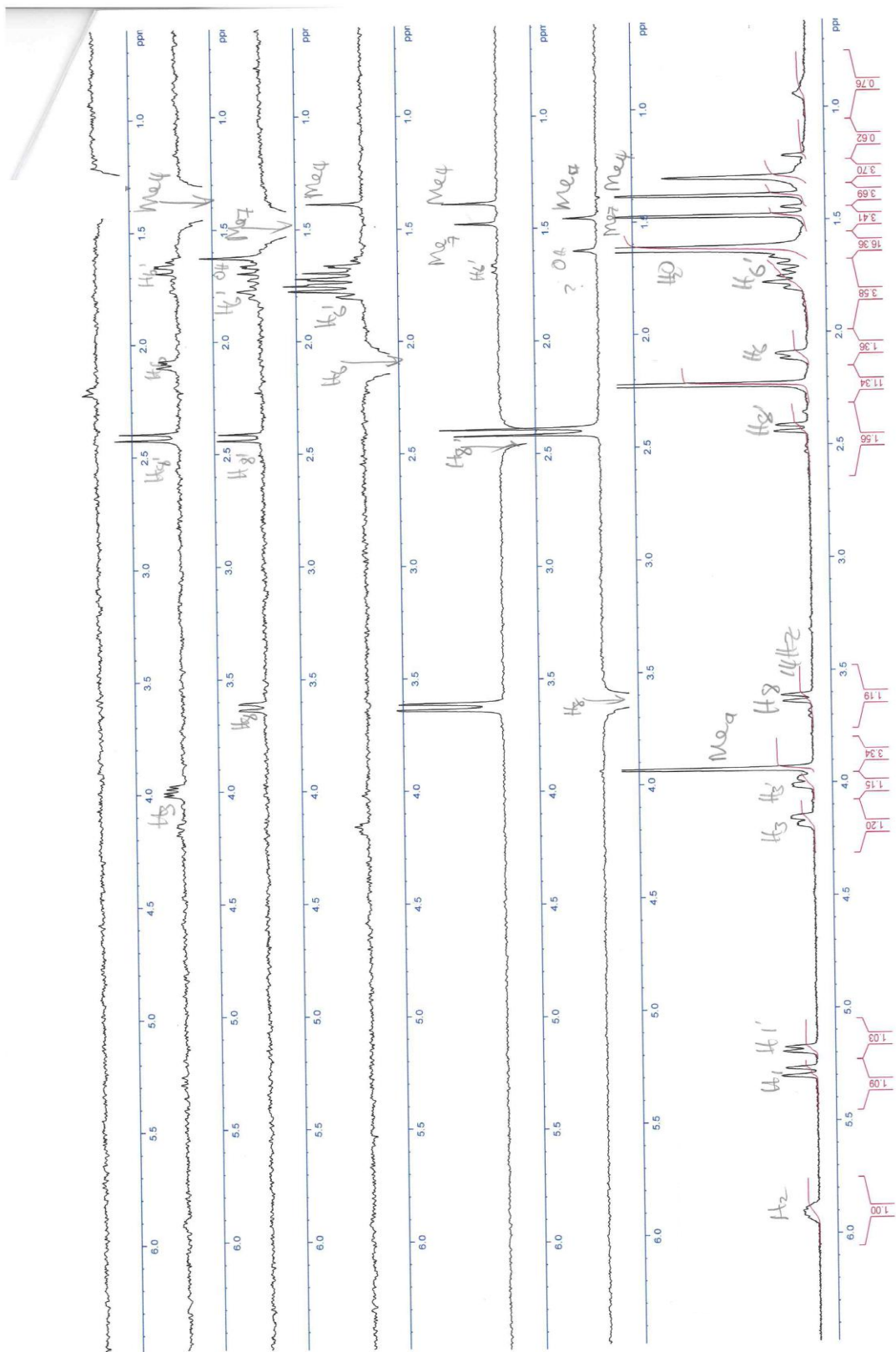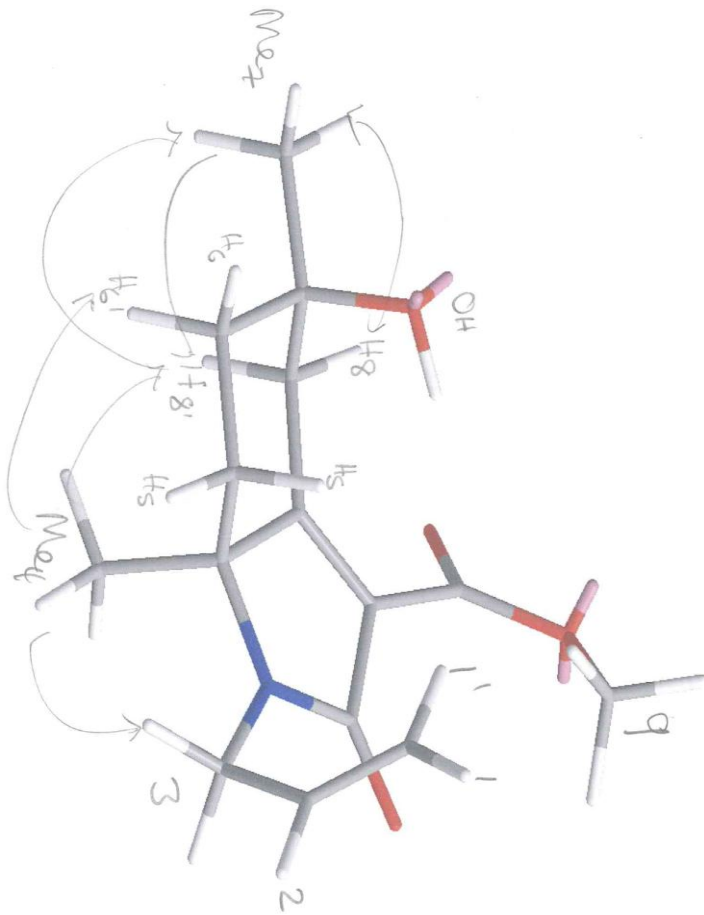
Data includes:

1) Irradiation at 1.22 pm

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

NUBSDO gradientNOE

8.2 NOE DATA FOR 93b

93b

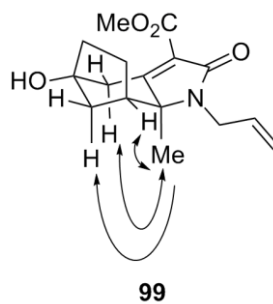Data obtained at The University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK

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

99

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

Data includes: 1) Irradiation at 1.42 ppm

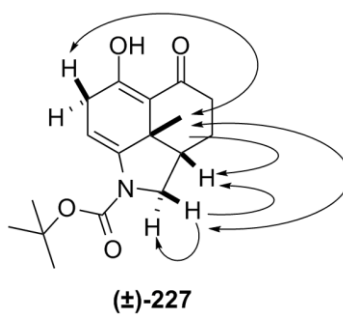2) Irradiation at 2.41 to 2.46 ppm

3) Irradiation at 2.73 ppm

AstraZeneca R&D Charnwood/Avlon

400 MHz NMR Service

SN1016334908 Ward, John W kxcj971 EN02318-22-01
Control at 8.00 ppm
Irradiation No.1: singlet at 1.42 ppm
Irradiation No.2: multiplet 2.46 to 2.41 ppm
Irradiation No.3: multiplet 2.
Acq Date: Jan 21 2009
Solvent: CDCL3
Temp.: 25.0 C / 298.1 K
Sample #80
File: Jan218001
unity-INOVA-400   "harpo"

PULSE SEQUENCE: noeph_auto
Relax. delay 5.000 sec
Pulse 90.0 degrees
Acq. time 1.905 sec
Width 8398.1 Hz
128 repetitions
OBSERVE H1, 399.8203310 MHz
DECOUPLE H1, 399.8223453 MHz
Power -2 dB
off during acquisition
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 41 minutes

8.4 NOE DATA FOR 227

(±)-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

AstraZeneca R&D Charnwood/Avlon
400 MHz NMR Service

SN101 6335677 Ward, John W kxcj971 EN02318-48-01
Control at 5.00 ppm
Irradiation No.1: multiplet 1.16 to 1.16 ppm
Irradiation No.2: multiplet 3.28 to 3.19 ppm
Irradiation No.3: multiplet 4.02 to 3.93 ppm
Acq Date: Jan 30 2009
Solvent: DMSO
Temp. 25.0 C / 298.1 K
Sample #15
File: Jan301501
unity INOVA-400 "harpo"

PULSE SEQUENCE: noesph_auto
Relax. delay 5.000 sec
Pulse 90.0 degrees
Acq. time 1.905 sec
Width 8398.1 Hz
128 repetitions
OBSERVE   H1, 399.8222371 MHz
DECOUPLE H1, 399.8242445 MHz
Power -2 dB
off during acquisition
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 41 minutes