
**Exploiting Ring-Fused
gem-Dibromocyclopropanes in Novel C-C Bond
Forming Reactions: Applications to the
Synthesis of Natural Product Frameworks**

*A thesis submitted for the degree of
Doctor of Philosophy of the Australian National University*

Rebecca M. Taylor MSc (Hons.)

Research School of Chemistry



Canberra, Australia

March, 2005

Declaration

I declare that, to the best of my knowledge, the material presented within this thesis represents the result of original work carried out by the author and has not been submitted for examination for any other degree. This thesis is less than 100,000 words in length. Wherever possible, established methodologies have been acknowledged by citation of the original publications from which they derive.

A handwritten signature in black ink, appearing to read 'Rebecca M. Taylor', with a stylized, cursive script.

Rebecca M. Taylor

30th March, 2005

Acknowledgements

Although a thesis is an incredibly individual endeavour; it is never the product of only one person. Therefore, it is with great appreciation that I thank the following people:

Firstly, I would like to thank my supervisor, Martin Banwell, for providing me with the opportunity to work in his research group and for always allowing me the freedom to explore my own ideas. Your constant dedication and enthusiasm for chemistry have been greatly appreciated. Perhaps even more importantly, however, throughout the course of my PhD you have taught me many valuable skills which I will take far beyond the chemistry bench.

I am indebted to various members of the technical staff at the RSC for their assistance throughout the course of my studies. Most notable Tony Herlt (HPLC), Chris Blake (NMR), Gordon Lockhart and John Allen (mass spectrometry). Thank you also to Drs Jens Renner and David Loong for proofreading parts of this manuscript.

I am grateful to the members of the Banwell group and, more broadly, the many people that I have met throughout the course of my PhD. You have all contributed, in your own way, to make this time of my life one which I will never forget.

To my brother Brendan, thank you for your many words of wisdom. Your support, encouragement and interest in a field completely removed from your own have been greatly appreciated.

Last, but definitely not least, a very special thank you to my mum and dad. I would never be who I am or where I am today if it wasn't for your constant love, support and encouragement and for that I am eternally grateful. You are, without a doubt, the best parents that anyone could ever wish for.

Abstract

Since the discovery of an efficient method for the preparation of *gem*-dihalocyclopropanes emerged in the 1950's, these motifs have played a vital role in organic chemistry and, as such, have been exploited in a fascinating array of chemical transformations. Their ready availability and novel reactivity make them potentially intriguing starting materials in synthetic studies. However, a lack of definition of the basic scope and limitations of the chemistry of *gem*-dihalocyclopropanes means that, at present, they remain under-utilised in total synthesis. A major objective, therefore, of the work described within this thesis was to exploit their well-recognised ability to undergo electrocyclic ring-opening (Figure i) with nucleophilic trapping of the resulting π -allyl cation **126** so as to form novel polycyclic systems of synthetic interest. However, only a limited amount of work has been directed towards exploiting carbon-centred nucleophiles in such processes and, thus, it was deemed pertinent to explore both inter- and intra-molecular variants of such reactions.

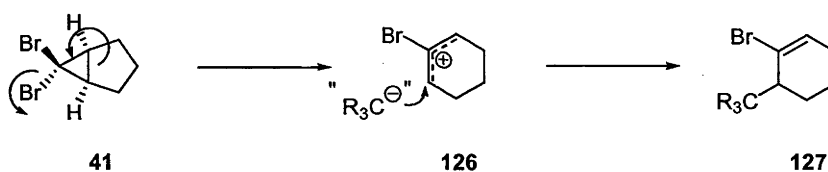
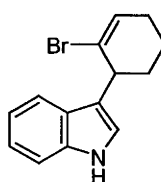


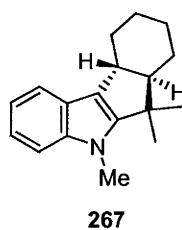
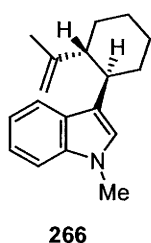
Figure i

New methods for the regioselective functionalisation of aromatic systems, particularly those involving carbon-carbon bond formation, remains a continuing challenge in organic chemistry. Consequently, Chapter Two attempts to highlight the potential for *gem*-dihalocyclopropanes to participate in synthetically valuable processes that achieve such ends. As highlighted in this Chapter, the “parent” *gem*-dihalocyclopropane **41** is observed to react with a range of heteroaromatic carbon-centred nucleophiles to deliver the anticipated products, e.g. compound **129**, arising from reaction of the aforementioned cyclopropane **41** with indole (**128**) in the presence of a silver(I)-salt.

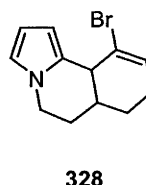
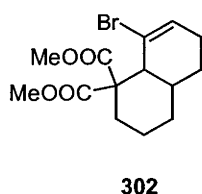


129

Chapter Three describes the work carried out to expand on some of the successful results reported in Chapter Two. In particular, Chapter Three focuses on studies involving the diastereoselective trapping of π -allyl cations with the C-3 of indole. A range of chiral auxiliaries were incorporated into the starting ring-fused *gem*-dihalocyclopropane and the desired trapping process occurred with varying degrees of diastereoselectivity. A discussion on the application of such methodology to the synthesis of compounds **266** and **267**, embodying the hapalindole and fischerindole alkaloid frameworks, respectively, is then described.



Chapter Four details attempts to employ a range of carbon-centred nucleophiles including oximes, malonates, indoles and pyrroles in analogous intramolecular trapping processes. Successful cyclisation was observed in a number of cases including those leading to the potentially useful polycyclic frameworks shown below. It is hoped that future endeavours will exploit skeleta of this type in total synthesis studies.



In Chapter Five a description of attempts to apply the methodology discussed in Chapter Four, *via* a cascade of cationic cyclisation reactions, to the synthesis of 13-azasteroids is presented. An overview of possible future directions in this area are described in Chapter Six.

Glossary

The following abbreviations have been used throughout this thesis:

Ac	acetyl
AcOH	acetic acid
Ac ₂ O	acetic anhydride
AgTFA	silver trifluoroacetate
AIBN	2,2'-azobisisobutyronitrile
APT	attached proton test (¹³ C NMR spectroscopy)
aq.	aqueous
atm	atmosphere
BF ₃ ·Et ₂ O	boron trifluoride diethyl etherate
Bn	benzyl
Boc	<i>tertiary</i> -butoxycarbonyl
Bu	butyl
<i>t</i> -Bu	<i>tertiary</i> -butyl
<i>t</i> -BuOH	<i>tertiary</i> -butanol (2-methyl-2-propanol)
<i>c</i>	concentration (g/100 mL)
<i>ca.</i>	<i>circa</i> (approximately)
cat.	catalyst
CSA	10-camphorsulfonic acid
CuBr·Me ₂ S	copper(I) bromide-dimethyl sulfide complex
δ	chemical shift (parts per million)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide

DMI	1,3-dimethyl-2-imidazolidinone
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphorylazide
d.r.	diastereomeric ratio
<i>E</i>	<i>entgegen</i> (opposite)
ee	enantiomeric excess
e.g.	<i>exempli gratia</i> (for example)
EI	electron impact
equiv. or eq.	equivalents
ESI	electrospray ionisation
Et	ethyl
<i>et al.</i>	<i>et alia</i> (and others)
EtOH	ethanol
eV	electron volt
g	gram
GC-MS	gas chromatography-mass spectrometry
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum (spectroscopy)
Hz	Hertz
int	interface
<i>inter alia</i>	among other things
IR	infrared
<i>i</i> -Pr	<i>iso</i> -propyl
<i>J</i>	coupling constant (Hz)
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide

lit.	literature
M	molar
M ⁺	molecular ion (mass spectra)
Me	methyl
MeOH	methanol
MHz	megahertz
min(s)	minute(s)
mmol	millimole
mol	mole
MM2	molecular mechanics, Version 2 (Allinger modification)
Mol. Sieves	molecular sieves
m.p.	melting point (°C)
MS	mass spectrum (spectroscopy)
<i>m/z</i>	mass-to-charge ratio
NaHMDS	sodium hexamethyldisilazide
NaOMe	sodium methoxide
NBS	<i>N</i> -bromosuccinimide
NMO	4-methylmorpholine- <i>N</i> -oxide
NMP	<i>N</i> -methylpyrrolidinone
NMR	nuclear magnetic resonance
ν_{\max}	infrared absorption maxima (cm ⁻¹)
OCM	olefin cross-metathesis
org	organic phase
PCC	pyridinium chlorochromate
Ph	phenyl
PivCl	pivaloyl chloride
PPA	polyphosphoric acid
PTC	phase transfer catalyst
py	pyridine
RCM	ring-closing metathesis
<i>R_f</i>	retardation factor

R_t	retention time
rt	room temperature (assumed to be ~18 °C)
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TEBAC	benzyltriethylammonium chloride
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
tetraglyme	tetraethylene glycol
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
Ts	<i>p</i> -toluenesulfonyl or tosyl
THF	tetrahydrofuran
TLC	thin layer chromatography
™	trade mark
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
UV	ultraviolet
V	Volts
v	volume
<i>viz.</i>	<i>videlicet</i> (namely)
w	weight
Z	<i>zusammen</i> (together)
<	less than
>	greater than
°C	degrees Celsius
Δ	heat
<	less than
>	greater than

Table of Contents

CHAPTER ONE

Introduction

1.1	Overview	1
1.2	Preparation of <i>gem</i> -Dihalocyclopropanes	2
1.2.1	Generation of the Dihalocarbene Species	2
1.2.2	Regio- and Stereo-chemical Issues Associated with Dihalocarbene Additions to Alkenes	4
1.2.3	Competitive Reactions Observed with Dihalocarbene Addition	5
1.3	Cyclopropane Ring-Cleavage Reactions	5
1.3.1	Mechanistic Aspects	6
1.3.2	Methods for Promoting the Electrocyclic Ring-Opening of <i>gem</i> -Dihalocyclopropanes	8
1.4	Applications of <i>gem</i> -Dihalocyclopropanes in Synthesis	9
1.4.1	Intermolecular π -Allyl Cation Trapping Reactions	9
1.4.1.1	Recapture of the π -Allyl Cation by the Departed Halide	9
1.4.1.2	Intermolecular π -Allyl Cation Trapping Reactions Involving Nitrogen Nucleophiles	10
1.4.1.3	Intermolecular π -Allyl Cation Trapping Reactions Involving Carbon Nucleophiles	12
1.4.1.4	Solvolysis	12
1.4.2	Intramolecular π -Allyl Cation Trapping Reactions	14
1.4.2.1	Intramolecular Trapping of the π -Allyl Cation by Nitrogen Nucleophiles	16
1.4.2.2	Intramolecular Trapping of the π -Allyl Cation by Carbon Nucleophiles	17
1.4.3	Applications of <i>gem</i> -Dihalocyclopropanes in Total Synthesis	19
1.5	Objectives of Research Work Described in this Thesis and Overview of Thesis Organisation	25
1.6	References	27

CHAPTER TWO

Intermolecular Trapping of π -Allyl Cations Produced by the Electrocyclic Ring-Opening of *gem*-Dibromocyclopropanes

2.1	Introduction	31
2.2	Intermolecular π -Allyl Cation Trapping by C-Centred Nucleophiles	33
2.2.1	Initial Studies with Indole (128)	33
2.2.1.1	Extension of Methodology to Tryptamine (136)	38
2.2.2	π -Allyl Cation Trapping Utilising Other Electron-Rich Aromatic Heterocycles	40
2.2.2.1	Employing Pyrrole (141) as the Nucleophile	40
2.2.2.2	Employing Furan (145) as the Nucleophile	42
2.2.3	Extension to Non-Aromatic Systems	43
2.3	Introduction of a Heteroatom into the Ring System Adjacent to the Cyclopropane Moiety	44
2.4	Conclusions	49
2.5	References	50

CHAPTER THREE

Enantioselective Preparation of the Polycyclic Ring Systems Associated with Certain Hapalindole and Fischerindole Alkaloids

3.1	Introduction	53
3.2	The Hapalindole and Fischerindole Alkaloids	54
3.2.1	Isolation and Structure of the Hapalindole Alkaloids	54
3.2.2	Biological Activity and Proposed Biogenesis of the Hapalindoles	55
3.2.3	The Fischerindole Alkaloids	57
3.3	Previous Total Syntheses of the Hapalindole Alkaloids	57
3.3.1	Overview	57

3.3.2	Total Syntheses	58
3.4	Retrosynthetic Analysis Associated with the Present Studies	67
3.5	Synthetic Studies	69
3.5.1	Using the (+)-Menthyl Moiety as an Alcohol Protecting Group and Chiral Auxiliary	69
3.5.2	Using the (2 <i>R</i> ,3 <i>R</i>)-Dimethylethylene Ketal-based Moiety as a Ketone Protecting Group and Chiral Auxiliary	75
3.5.3	Examining (<i>R,R</i>)-1,4-Diphenyl-butane-2,3-diol as an Auxiliary	83
3.5.4	Model Studies Directed Towards the Hapalindole and Fischerindole Frameworks	89
3.5.4.1	Overview	89
3.5.4.2	Initial Attempts at Installing the Acyl Moiety	90
3.5.4.3	Revised Strategy	95
3.5.4.4	Elaboration of Compound 262 to the Tricyclic Hapalindole Framework	98
3.5.4.5	Extension of Methodology to Fischerindole Framework	101
3.6	Conclusions	102
3.7	References	103

CHAPTER FOUR

Intramolecular Nucleophilic Trapping of π -Allyl Cations Derived from the Electrocyclic Ring-Opening of *gem*-Dibromocyclopropanes

4.1	Introduction	107
4.2	Oximes as Trapping Nucleophiles	107
4.2.1	Overview	107
4.2.2	Synthesis of the Requisite Cyclopropanes 268 and 269	108
4.2.2.1	Synthesis of the Required 6,6-Dibromobicyclo[3.1.0]hexan-2-one (273) System	109
4.2.2.2	Initial Approach to the Synthesis of Key Intermediate 284	111
4.2.2.3	Revised Synthetic Strategy	112

4.2.3	Attempts to Effect Cyclisation of Oximes 268 and 269	118
4.3	Malonates as Trapping Nucleophiles	119
4.3.1	Overview	119
4.3.2	Synthesis of the Required Cyclopropanes 298 and 299	120
4.3.3	Cyclisation Studies	121
4.4	Trapping Studies Involving the C-2 Position of Indole	123
4.4.1	Overview	123
4.4.2	Synthesis of the Required Cyclisation Precursors	124
4.4.3	Cyclisation Studies	126
4.5	Intramolecular π -Allyl Cation Trapping Studies with Pyrrole (141)	131
4.5.1	Overview	131
4.5.2	Synthesis of Cyclisation Precursor 319	132
4.5.3	Cyclisation Studies	135
4.5.4	Extension of Trapping Studies to Incorporate Indole (128)	136
4.6	Conclusions	137
4.7	References	139

CHAPTER FIVE

Studies Directed Towards the Synthesis of 13-Azasteroids

5.1	Introduction	141
5.1.1	The Steroid Class of Natural Products	141
5.1.2	Common Strategies Employed in Steroid Total Synthesis	142
5.1.2.1	Intramolecular Diels-Alder Approach	142
5.1.2.2	Transannular Diels-Alder Approach	143
5.1.2.3	Biomimetic-Type Syntheses	145
5.1.3	Possible Structural Variations and Their Effect on Biological Activity	151
5.1.4	Azasteroids and Their Synthesis	152
5.2	Retrosynthetic Analysis Associated with the Present Studies	153

5.3	Initial Approach to Cyclisation Precursors 393 and 394	154
5.4	Second Approach to Cyclisation Precursors 393 and 394	156
5.4.1	Synthesis of Phosphonium Salts 401 and 402	157
5.4.2	Synthesis of Cationic Cyclisation Precursor 393	158
5.4.3	Cationic Cyclisation	160
5.5	Conclusions	160
5.6	References	161

CHAPTER SIX

Future Directions

6.1	Possibilities for Future Work Arising from the Research Described in Chapter Two	165
6.1.1	Attempts at Trapping the π -Allyl Cation at the C-2 Position of Indole (128)	165
6.1.2	Synthetic Potential of the 3-(2-Piperidyl)indole Moiety	168
6.2	Possibilities for Future Work Arising from the Research Described in Chapter Three	170
6.2.1	Incorporation of the Isonitrile Functionality	170
6.2.2	Proposed Strategy for Installation of the Geminally-Related Vinyl and Methyl Groups of 170	171
6.2.3	Towards the Tetracyclic Hapalindole Framework	173
6.3	Possibilities for Future Work Arising from the Research Described in Chapter Four	174
6.3.1	Extension on Trapping the π -Allyl Cation at the C-2 of Indole (128)	174
6.4	Possibilities for Future Work Arising from the Research Described in Chapter Five	177
6.5	Conclusions	178
6.6	References	179

CHAPTER SEVEN

Experimental Procedures Associated with Work Described in Chapters Two to Five

7.1	General Procedures	181
7.2	Experimental Section for Chapter Two	185
7.3	Experimental Section for Chapter Three	203
7.4	Experimental Section for Chapter Four	241
7.5	Experimental Section for Chapter Five	291
7.6	References	298

Introduction

1.1 Overview

gem-Dihalocyclopropanes play a vital role in organic synthesis and, as such, have been exploited in a fascinating array of chemical transformations.¹ The two major features which have contributed to the widespread use of these compounds as building blocks in synthesis are their ready availability and novel patterns of reactivity. Amongst the broad range of reactions *gem*-dihalocyclopropanes are observed to engage in (Figure 1.1) two distinct sub-groups can be identified. The first involves reactions which proceed with retention of the cyclopropane moiety as seen, for example, in halogen substitution reactions. The second and more interesting group consists of reactions involving departure of one of the associated halides (as a halide ion) and accompanying ring cleavage. It is this type of reaction which is the central focus of this thesis. Accordingly, a brief commentary on the preparation of *gem*-dihalocyclopropanes is provided in the next section and this is followed by a discussion of the electrocyclic ring-opening reactions of *gem*-dihalocyclopropanes and their exploitation, through such processes, in synthesis.

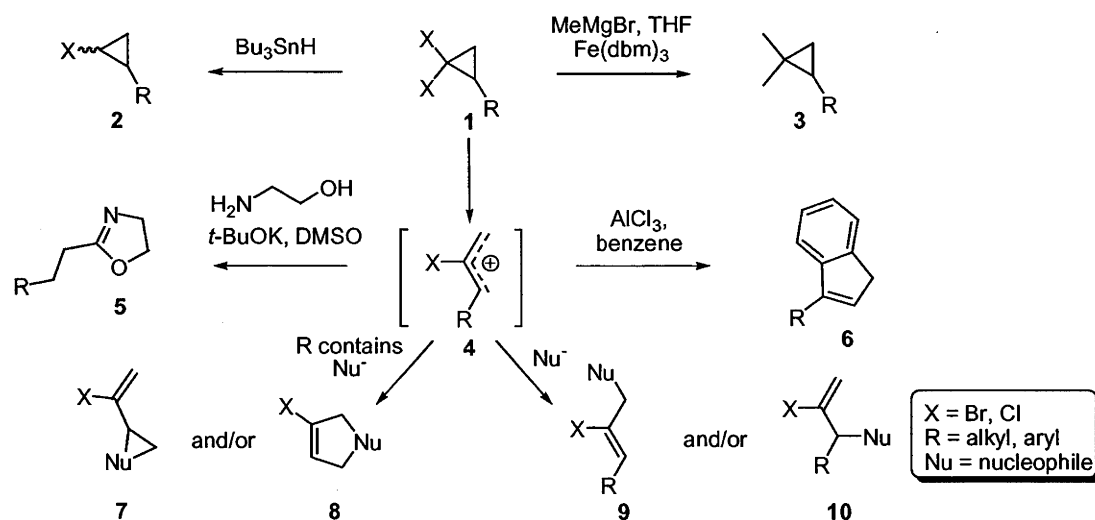


Figure 1.1: Selected Examples of Possible Reaction Modes of *gem*-Dihalocyclopropanes

1.2 Preparation of *gem*-Dihalocyclopropanes

1.2.1 Generation of the Dihalocarbene Species

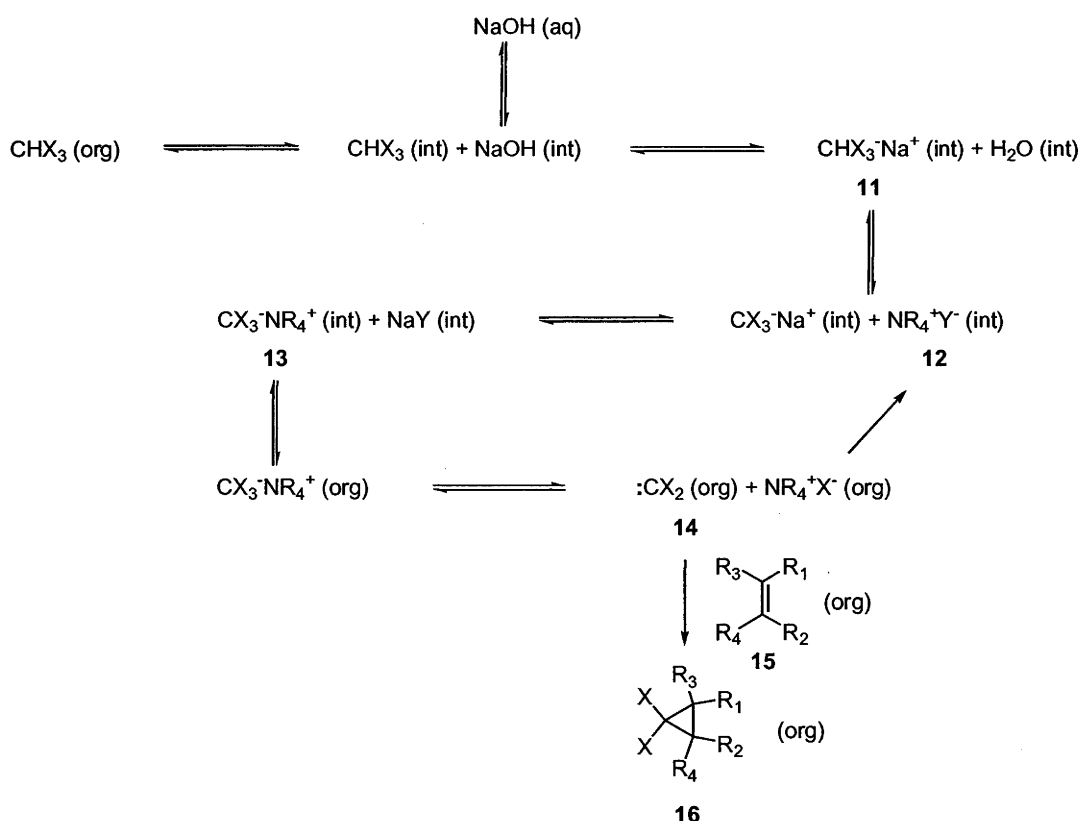
The existence of *gem*-dihalocyclopropanes was first proposed over a hundred years ago,² although it wasn't until the 1950's that an efficient method for the preparation of these compounds emerged. An initial proposal by Geuther, in 1862, suggested that dichlorocarbene might be an intermediate in the basic hydrolysis of chloroform.³ Further kinetic analysis of this process by Hine in 1950 also supported this idea, although at this stage it was thought that the basic hydrolysis of chloroform could, in fact, be accommodated by a variety of mechanisms.⁴ Finally, in 1954, Doering and Hoffmann provided unequivocal evidence for the existence of dihalocarbenes.⁵ During the course of this work, these workers not only provided experimental evidence for the formation of dichlorocarbene from mixtures of chloroform and potassium *tert*-butoxide but they also reported that this electron-deficient species readily reacts, under strictly anhydrous conditions, with a range of olefins to produce the corresponding *gem*-dichlorocyclopropanes. Whilst a variety of methods have since been developed for the generation of dihalocarbenes, the addition of such species to alkenes remains the only truly synthetically useful route to *gem*-dihalocyclopropanes.

Currently the most popular method for the generation of dihalocarbenes is the phase-transfer catalysis approach introduced by Makosza.⁶ This involves the vigorous mixing of a biphasic system consisting of the appropriate haloform and a 50% w/v aqueous sodium hydroxide solution in the presence of a phase transfer catalyst (PTC). The PTC most often employed is a quaternary ammonium salt such as benzyltriethylammonium chloride (TEBAC). This procedure represents a vast improvement on previous methods which require the use of strictly anhydrous conditions due to the rapid rate at which carbenes react with water and hydroxide ions. Despite the fact that the Makosza method requires the reaction to be performed in the presence of a large excess of aqueous sodium hydroxide, it is still extremely effective in delivering high yields of *gem*-dihalocyclopropanes, even from alkenes of low nucleophilicity. These observations suggest that very little contact is made, during the reaction process, between the dihalocarbene and the aqueous base. As a result even base-

sensitive substrates such as allylic acetates can be successfully subjected to reaction with dihalocarbenes under these conditions.⁷

A considerable amount of effort has been expended in identifying a plausible mechanism for the Makosza-type conversion of alkenes into the title compounds.⁸ As depicted in Figure 1.2, the initial step most likely involves a sodium hydroxide-promoted deprotonation of the haloform at the interface (int) between the two immiscible phases. This results in the formation of trimethyl anion sodium salt **11** which subsequently undergoes ion exchange with the quaternary ammonium salt, **12**, of the PTC to deliver the unstable ammonium methylide **13**. This ion pair then enters the organic phase (org) where it dissociates to form dihalocarbene **14**, with accompanying regeneration of the ammonium salt. Finally, irreversible addition of the carbene to the organic-soluble alkene **15** furnishes the observed *gem*-dihalocyclopropane **16** which is lipophilic and remains in the organic phase.

Figure 1.2: Proposed Mechanism for the Formation of *gem*-Dihalocyclopropanes Under Phase-Transfer Catalysed (PTC) Conditions



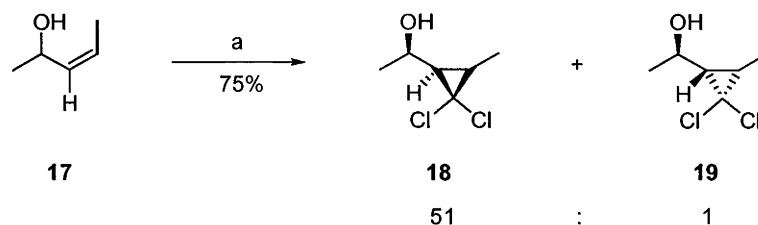
Whilst the pre-eminent method for the synthesis of *gem*-dihalocyclopropanes is undoubtedly the one just described, in some cases long reaction times are required and side products can be observed, especially when bromoform is employed.⁹ This situation has, therefore, prompted the search for improvements. The first report of the use of sonication techniques for this purpose was published in 1982.¹⁰ During this work, Regan and Singh discovered that simultaneous (vigorous) stirring and sonication of powdered sodium hydroxide and chloroform affords the dihalocarbene without the necessity of a phase-transfer catalyst. Subsequently, a series of reports detailing the combined use of sonication and phase-transfer conditions emerged and it was ultimately found that addition of a phase-transfer catalyst to a solid-liquid reaction system (which is then sonicated) is highly effective in dramatically shortening reaction times and, simultaneously, increasing the yields of the product(s) so-obtained.^{11,12,13}

1.2.2 Regio- and Stereo-chemical Issues Associated with Dihalocarbene Additions to Alkenes

Regardless of the technique employed, all of the aforementioned methods for the synthesis of *gem*-dihalocyclopropanes involve the generation of a singlet (ground state) dihalocarbene species which adds, in a concerted fashion and often with some level of diastereoselection, to a suitably nucleophilic alkene. Due to the manner in which this addition reaction proceeds, the geometry observed in the newly formed cyclopropane generally reflects that of the starting alkene. There are a small number of cases, however, where the opposite stereochemistry is observed, particularly upon dibromocarbene addition to *trans*-cycloalkenes.^{14,15}

The electrophilic nature of dihalocarbenes often causes addition to occur preferentially at the more electron-rich double bond. This, therefore, allows for regioselective addition to polyunsaturated substrates.¹⁶ A final note-worthy feature is that useful levels of diastereoselectivity can be observed during the addition process. While dihalocarbenes generally add to the less-hindered face of the alkene, when certain allylic alcohols are employed the OH group can exert a strong directing effect such that the carbene adds to the same face of the adjacent alkene as depicted in the examples shown below (Scheme 1.1).¹⁷

Scheme 1.1: Oxygen Directing Effect Observed Upon Dichlorocarbene Addition to Allylic Alcohol **17**



Reagents and conditions: (a) CHCl_3 , TEBAC, NaOH, 18 °C, 4 h.

1.2.3 Competitive Reactions Observed with Dihalocarbene Addition

The formation of *gem*-dihalocyclopropanes through addition of dihalocarbenes to olefins is generally a straightforward and efficient process. However, some side-reactions have been observed. Firstly, the trihalomethyl anion (CX_3^-), the immediate precursor to the dihalocarbene, can act as a nucleophile and add to electron-deficient double bonds or displace allylic leaving groups.¹⁸ Alternatively, if the dihalocarbene addition process is performed on unsaturated cyclic ethers or unsaturated carboxylic acids then competitive C-H and O-H insertion reactions can be observed.^{19,20,21,22} However, these unwanted side-reactions are generally easily avoided through careful design of the reaction conditions or by employing suitably protected forms of the “offending” functional groups.

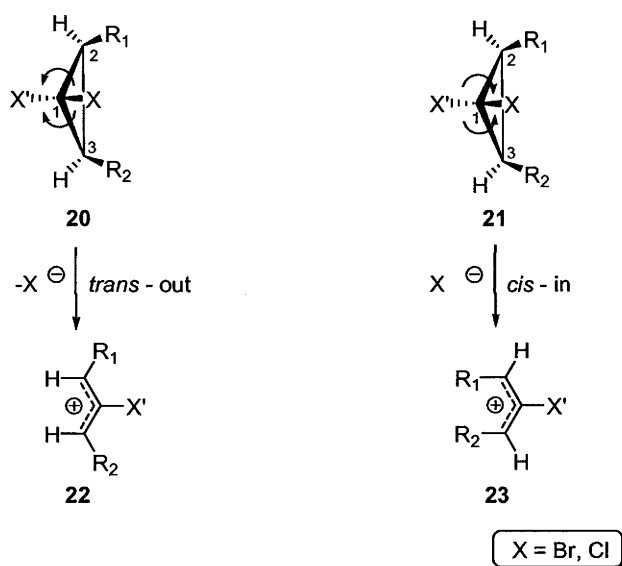
1.3 Cyclopropane Ring-Cleavage Reactions

As mentioned in the introductory section, the reactions of *gem*-dihalocyclopropanes fall into two distinct groups, those proceeding with retention of the cyclopropyl ring and those involving ring-cleavage. Due to the focus of this thesis, this section will only deal with the mechanistic and synthetic aspects of the second of these processes. In doing so it is hoped to highlight the synthetic utility of *gem*-dihalocyclopropanes.

1.3.1 Mechanistic Aspects

In 1965 Woodward and Hoffmann proposed, based on the requirements for the conservation of orbital symmetry, that the concerted ring-opening of cyclopropyl cations, generated by C-X cleavage in the precursor *gem*-dihalocyclopropyl unit, to π -allyl cations would proceed stereospecifically and in a disrotatory fashion.²³ As depicted in Figure 1.3, two such modes of ring-opening, wherein the cyclopropyl cation rearranges to the isomeric π -allyl cations, are possible.

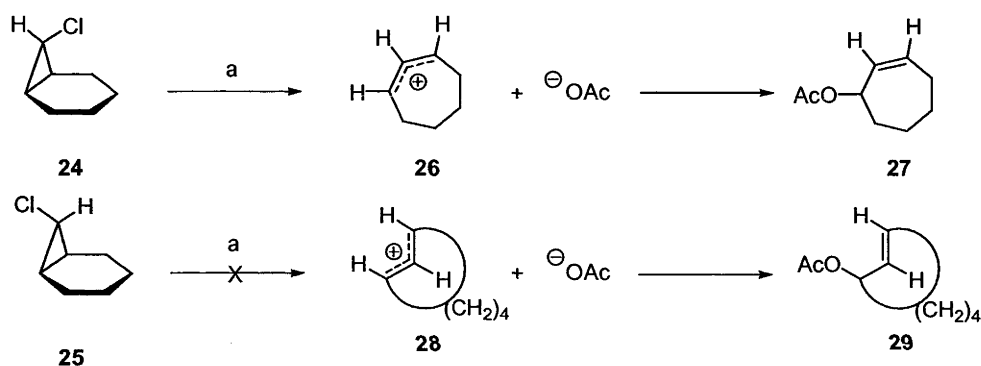
Figure 1.3: Possible Disrotatory Modes for Ring-Opening of Cyclopropyl Cations



Further work by de Puy later the same year led to the hypothesis that, in fact, only one of these disrotatory modes is actually operational when *gem*-dihalocarbene adducts of small-ring cycloalkenes are involved.²⁴ Thus, during this work, the reactivities of *endo*- and *exo*-7-chlorobicyclo[4.1.0]heptanes, (**24**) and (**25**) (Scheme 1.2), were examined and it was found that whilst the former substrate readily engaged in acetolysis to afford allylic acetate **27**, isomer **25** was completely unreactive under the same conditions. As a result of such observations the so-called Woodward-Hoffmann-de Puy rule was formulated. This states that,

as shown in Figure 1.3, cyclopropanes undergo ring-opening to the corresponding π -allyl cation *via* a *trans*-out, *cis*-in disrotatory process. Therefore, cleavage of the C-2 and C-3 bond is concerted with loss of leaving group (X^-) at C-1. Substituents which are *trans*-related to the leaving group then move outwards whilst those which are *cis*-related move inwards. Applying such rules to the examples discussed in Scheme 1.2, the lack of conversion of compound **25** into *trans*-alkene **29** arises from the fact that the required outward rotation would lead to the formation of the inordinately highly strained *trans* π -allyl cation **28**.

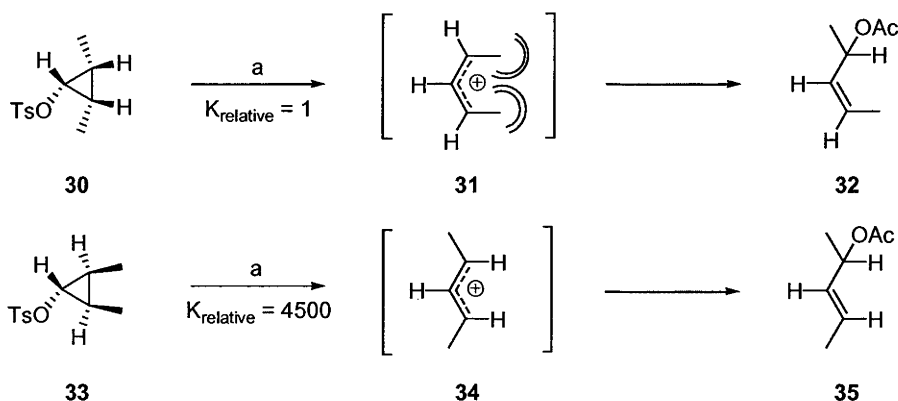
Scheme 1.2: Differing Reactivities of the Epimeric 7-Chlorobicyclo[4.1.0]heptanes **24** and **25** in the Presence of NaOAc/AcOH



Reagents and conditions: (a) NaOAc, AcOH, 125 °C.

For *gem*-dihalocyclopropanes which do not bear large substituents or for systems which are not fused to small- or medium-sized rings the difference in possible outcomes is not as dramatic as that seen in Scheme 1.2 and, often, ring-cleavage products arising from both possible modes of reaction are observed. However, as depicted in Scheme 1.3, the steric bulk of the methyl substituents in substrate **30** inhibits formation of the requisite π -allyl cation **31** and, as such, the reaction of isomer **33** proceeds at a significantly accelerated rate and through cation **34** to give product **35**.²⁵

Scheme 1.3: *Electrocyclic Ring-Opening/Acetyloysis of Diastereoisomeric p-Tosyloxycyclopropanes 30 and 33*



Reagents and conditions: (a) NaOAc, AcOH, 150 °C.

1.3.2 Methods for Promoting the Electrocyclic Ring-Opening of *gem*-Dihalocyclopropanes

The electrocyclic ring-opening of *gem*-dihalocyclopropanes can be effected either thermally or chemically. The thermal reaction almost certainly proceeds *via* simultaneous cleavage of the C2-C3 bond and ionisation of the carbon-halogen bond as seen in Figure 1.3. The thermal stability of *gem*-dihalocyclopropanes is often highly dependent on stereochemical and electronic factors as well as, in the cases where the three-membered ring is annulated to another ring, the nature of the carbon framework within which it is embedded. The rate at which any thermally-induced reaction proceeds has been shown to depend, to a large extent, on the nature of the departing halide and the stability of the resulting π -allyl cation. For these reasons, therefore, *gem*-dibromocyclopropanes have been found to engage in ring-opening more readily than their dichloro- or, especially, difluoro-counterparts. This is, therefore, one of the main reasons why *gem*-dibromocyclopropanes have enjoyed relatively widespread use in chemical synthesis. Nevertheless, successful applications of *gem*-dichlorocyclopropanes in this process have also been reported.^{26,27,28,29} A few examples exist where *gem*-diiodocyclopropanes have been synthesised; however, in general, they are not readily prepared and are frequently far too sensitive for most synthetic applications.

Whilst various chemical methods exist for the initiation of the electrocyclic ring-opening reaction of *gem*-dihalocyclopropanes the most noteworthy one, which has been widely utilised throughout the course of the work described in this thesis, involves the use of silver(I)-salts. Not only does the application of such halophiles generally accelerate the rate at which the ring-opening reaction occurs but it also frequently means that mild and indeed rather specific reaction conditions can be employed. The observed increase in reaction rate is undoubtedly due to the silver-ion facilitating ionisation of the relevant carbon-halogen bond. Furthermore, the halide ion is completely removed due to the low solubility of the ensuing silver halides in most solvent systems and thereby preventing it from participating in nucleophilic interception of the π -allyl cation so-generated. This π -allyl cation can then be trapped by the counter-ion to silver(I). The synthetic ramifications of such possibilities are discussed in the Section 1.4.3.

1.4 Applications of *gem*-Dihalocyclopropanes in Synthesis

As noted in the introductory section of this chapter, the electrocyclic ring-opening of *gem*-dihalocyclopropanes and trapping of the resulting π -allyl cation is a process that has been employed in a range of synthetic contexts. As is also apparent in Figure 1.1, this can proceed in either an inter- or intra-molecular fashion. A brief survey of some methodological applications of the title compounds in both an inter- and intra-molecular reaction with a range of nucleophiles is provided on the following pages. Subsequent to this, various examples of the application of these methodologies in natural product synthesis are discussed.

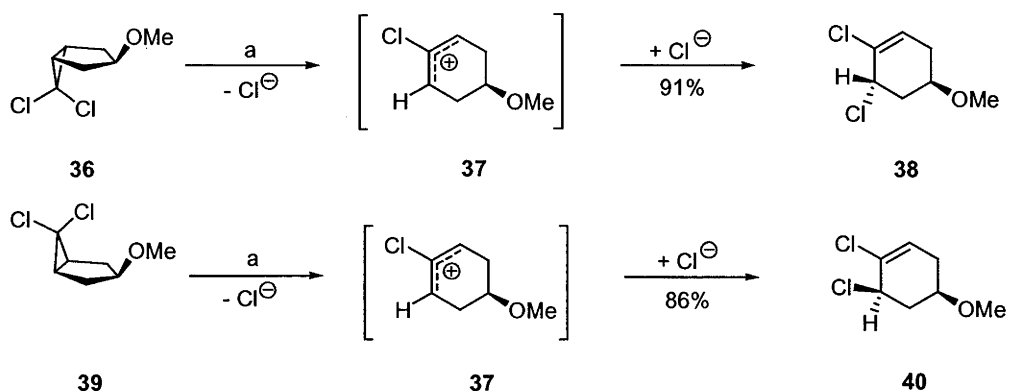
1.4.1 Intermolecular π -Allyl Cation Trapping Reactions

1.4.1.1 Recapture of the π -Allyl Cation by the Departed Halide Ion

As discussed above, the electrocyclic ring-opening of a *gem*-dihalocyclopropane moiety occurs with concomitant departure of one of the halogens as a halide ion to generate the corresponding π -allyl cation. In various instances it has also been shown that, in the absence of an alternative nucleophile, the newly departed halide ion recaptures the derived π -allyl cation. Work by Fleming and Thomas has established that this process occurs in a

stereospecific manner.^{30,31} Thus, as shown in Scheme 1.4, it appears that attack of the halide ion on the π -allyl cation so-formed occurs preferentially at the same face of the molecule from which it departed. Such outcomes are undoubtedly a consequence of the operation of the principle of least motion.

Scheme 1.4: Stereospecific Trapping of the Departed Halide Ion

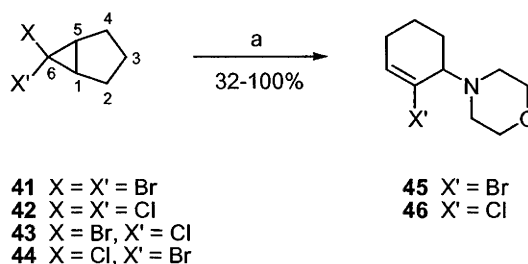


Reagents and conditions: (a) Sealed tube, 160 °C, 4 h.

1.4.1.2 Intermolecular π -Allyl Cation Trapping Reactions Involving Nitrogen Nucleophiles

In 1970 Sandler reported the first example of the use of amines in the trapping of π -allyl cations derived from the electrocyclic ring-opening of *gem*-dihalobicyclo[3.1.0]hexanes.³² In this work, cyclopropanes **41-44** were reacted, under thermal conditions, with morpholine to generate compounds of the general type **45** or **46** (Scheme 1.5). As shown, *gem*-dibromo- and *gem*-dichloro-cyclopropanes, along with the mixed halide analogues, were all investigated. The results obtained provided further support for the notion that the electrocyclic ring-opening and trapping of the resulting π -allyl cation occurs in a stereospecific fashion, with the halide *trans* to the C-1 and C-5 protons being lost preferentially.

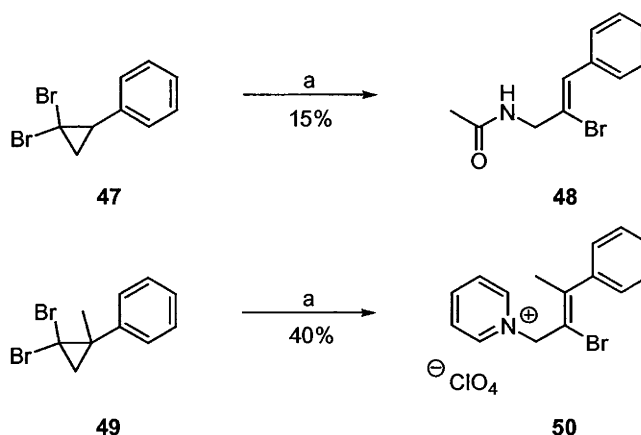
Scheme 1.5: π -Allyl Cation Trapping with Morpholine



Reagents and conditions: (a) morpholine, 128 °C, 0.25-24 h.

Work carried out by Arct and co-workers,³³ utilising silver perchlorate in a buffered pyridine solution, has revealed (Scheme 1.6) that the π -allyl cation derived from ring-opening of *gem*-dibromocyclopropane **47** can be trapped by nitriles in a Ritter-type reaction to give products such as amide **48**. However, this type of process is sensitive to steric effects. It was proposed that the presence of methyl substituents adjacent to the halogens on the cyclopropyl moiety, as seen in substrate **49**, would sufficiently stabilise the π -allyl cation such that it has a long enough life time to break through the nitrile solvation shell and then undergo reaction with the stronger nucleophile, namely pyridine. However, in the absence of these methyl substituents the unstable and short-lived cation was unable to leave the nitrile solvation shell and, hence, engaged primarily in a Ritter-type reaction.

Scheme 1.6: π -Allyl Cation Trapping with Acetonitrile and Pyridine

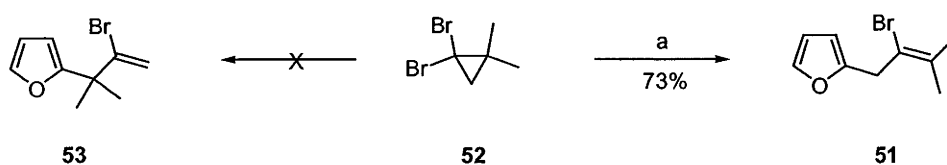


Reagents and conditions: (a) AgClO₄, pyridine, CH₃CN, 95 °C, 15 h, then H₂O.

1.4.1.3 Intermolecular π -Allyl Cation Trapping Reactions Involving Carbon Nucleophiles

Treatment of several *gem*-dihalocyclopropanes with silver perchlorate in the presence of furan and a calcium carbonate buffer resulted in a regioselective allylation reaction (of the furan) to give product **51**.³⁴ Unsymmetrical *gem*-dibromocyclopropanes such as compound **52** were expected to furnish products of the type **53**. Interestingly, however, it was observed, in all cases, that furan reacted preferentially, and through C-2, with the less-substituted terminus of the intermediate π -allyl cation to afford the regioisomeric compound **51**.

Scheme 1.7: Regioselective Intermolecular π -Allyl Cation Trapping with Furan



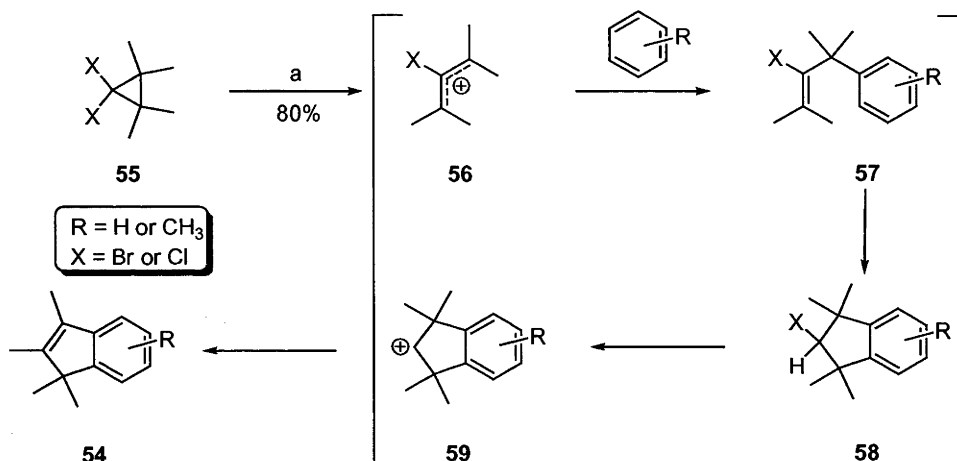
Reagents and conditions: (a) AgClO_4 , CaCO_3 , furan, THF/ether (1:3 v/v mixture), reflux, 6 h.

1.4.1.4 Solvolysis

There has been a number of studies concerned with the formation of novel “solvolysis” products observed when various simple *gem*-dihalocyclopropanes are treated with aluminium trichloride in the presence of a suitable aromatic solvent.^{35,36,37} Thus, by utilising solvents such as benzene, toluene and xylene under Friedel-Crafts-type reaction conditions indenyl derivatives of the general structure **54** were isolated. These are presumably formed *via* the pathway shown in Scheme 1.8. Thus, the π -allyl cation, **56**, derived from substrate **55** is trapped in an intermolecular fashion by the aromatic solvent to generate, following proton loss, intermediate **57**. A Friedel-Crafts-type reaction of alkenyl halide **57** would then afford indene **58**. Reaction of compound **58** with aluminium trichloride would be expected to generate cation **59** which is anticipated to engage in a Wagner-Meerwein rearrangement. Following proton loss from the newly formed (benzylic) cation the observed indene **54** would be obtained. Work by

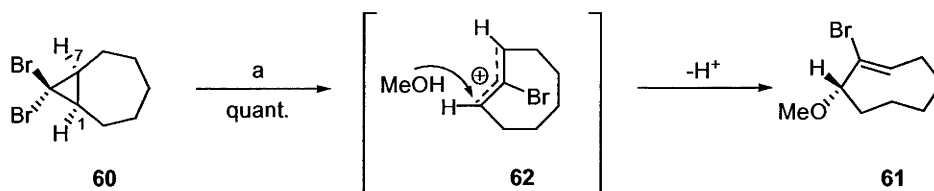
Weyerstahl and co-workers also established that simple modifications of such a process can yield the corresponding benzofurans.³⁸

Scheme 1.8: Proposed Mechanism for the Formation of Indenes via Solvolysis



Reagents and conditions: (a) AlCl_3 , benzene, 18-80 °C, 16 h.

Solvolysis products arising from reaction of nucleophilic solvents, such as methanol, with the π -allyl cation derived from the silver(I)-promoted electrocyclic ring-opening of *gem*-dihalocyclopropanes have also been reported.^{39,40,41} Reese and Shaw found during the course of their work (Scheme 1.9) that this reaction proceeded in a stereoselective fashion with only one of the possible diastereomeric ethers being observed. Hence, in the presence of anhydrous methanol and silver perchlorate, cyclopropane **60** underwent electrocyclic ring-opening and trapping to deliver the allyl ether **61** as the sole isolable product. This observation is in full accord with earlier suggestions that ring-opening proceeds in a disrotatory fashion with accompanying loss of the *exo*-bromine. Solvolysis then occurred at the same side of the *trans, trans*-allylic system **62** as the leaving group departed with resulting inversion of configuration at C-1 or C-7 to afford the observed product **61**.

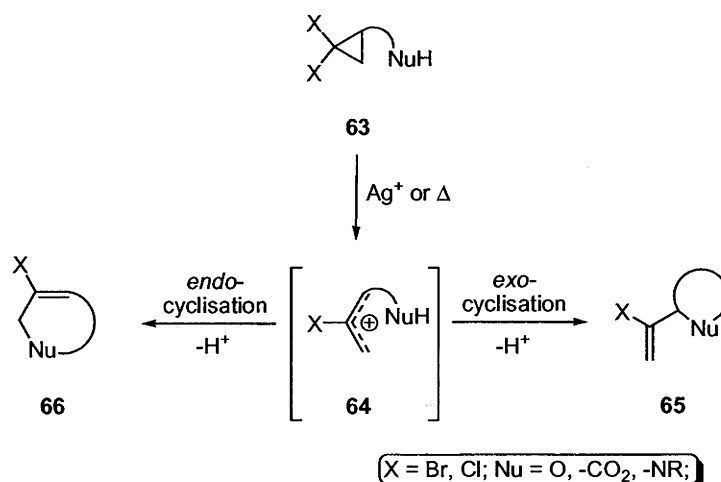
Scheme 1.9: Methanolysis of 8,8-Dibromobicyclo[5.1.0]octane (**60**)

Reagents and conditions: (a) AgClO_4 , MeOH , $20\text{ }^\circ\text{C}$, 5 min.

1.4.2 Intramolecular π -Allyl Cation Trapping Reactions

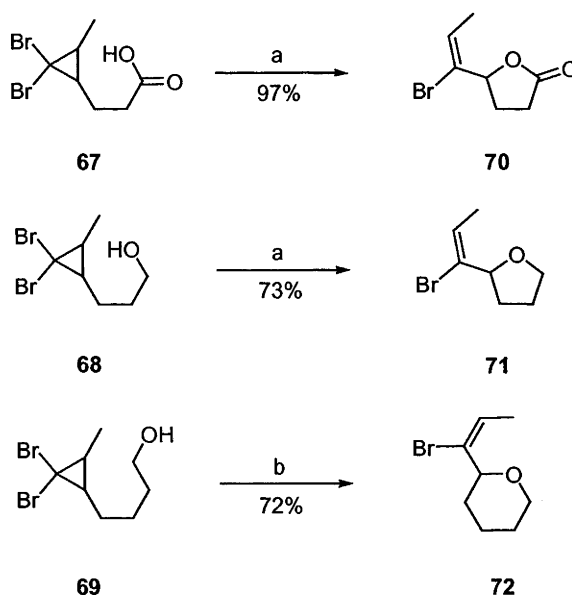
Akin to the intermolecular examples discussed above, intramolecular trapping of the π -allyl cation derived from the electrocyclic ring-opening of a *gem*-dihalocyclopropane can be achieved by the tethering of an internal nucleophile. *Exo*- and *endo*-cyclisation modes are often possible as illustrated in general terms in Figure 1.4. Whilst both of these processes have been observed, it is generally found, as a result of the operation of kinetic effects, that the *exo*-cyclisation mode is favoured. Specific examples involving each such mode of cyclisation are presented below.

Figure 1.4: Possible Modes of Cyclisation Associated with the Intramolecular Trapping of the π -Allyl Cations Generated by Electrocyclic Ring-Opening of *gem*-Dihalocyclopropanes



Danheiser and co-workers utilised tethered *gem*-dibromocyclopropyl systems in the synthesis of various oxygen heterocycles (Scheme 1.10).⁴² Thus, upon subjection to silver(I)-promoted electrocyclic ring-opening conditions, compounds **67**, **68** and **69** reacted *via* the *exo*-cyclisation pathway to afford lactone **70**, tetrahydrofuran **71** and tetrahydropyran **72**, respectively. Hence, the electrocyclic cleavage of the cyclopropane generated a cation which underwent trapping by the pendant carboxylic acid or alcohol functionality. Many cyclisation reactions of these sorts have been found to proceed in a diastereoselective manner. This methodology must be regarded as rather significant because it provides new routes to a range of compounds likely to be of value as intermediates in a variety of synthesis programs.

Scheme 1.10: *Intramolecular π -Allyl Cation Trapping Reactions Involving an *exo*-Cyclisation Process*

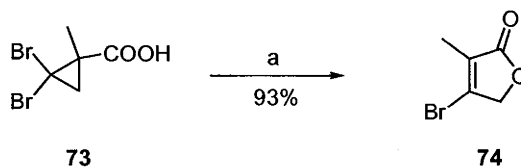


Reagents and conditions: (a) AgTFA, TFE, 25 °C, 8.5 h; (b) AgNO₃, CH₃NO₂, 25 °C, 8 d.

The corresponding but less-favoured *endo*-process has also been observed. For example, Sydnes and co-workers discovered that by utilising a solvent such as 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoro-2-propanol the products of such a reaction can be obtained, usually as the sole isolable reaction products.^{43,44,45} Therefore, as shown in Scheme 1.11, treatment of

compound **73** in 2,2,2-trifluoroethanol with silver trifluoroacetate furnished furanone **74** in excellent yield.

Scheme 1.11: *Intramolecular π -Allyl Cation Trapping Reaction Involving an endo-Cyclisation Process*

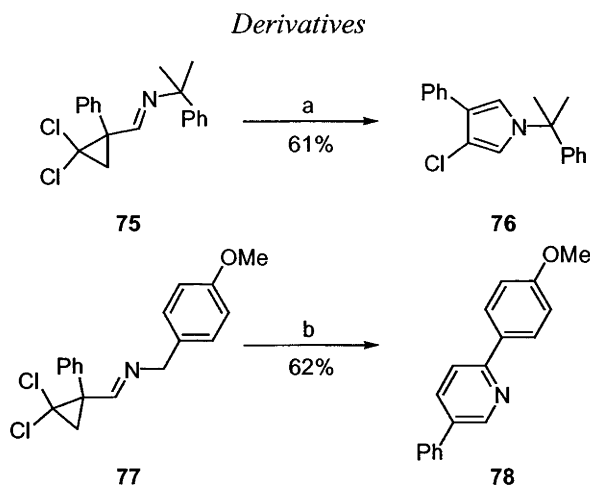


Reagents and conditions: (a) AgTFA, TFE, reflux, 19 h.

As is apparent from the aforementioned examples, the π -allyl cation generated from the electrocyclic ring-opening of a *gem*-dihalocyclopropane derivative can be successfully trapped in an intramolecular fashion by an oxygen nucleophile. Synthetically useful products have also been obtained when either nitrogen- or carbon-centred nucleophiles were employed. Examples of these are discussed in the following sections.

1.4.2.1 Intramolecular Trapping of the π -Allyl Cation by Nitrogen Nucleophiles

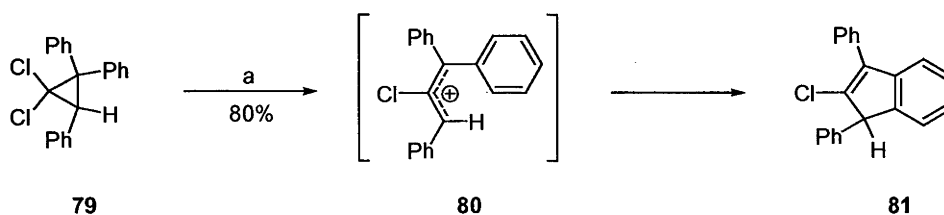
A range of examples of the use of nitrogen-centred nucleophiles in intramolecular trapping processes have been reported.⁴⁶ For example, the thermolysis of *N*-*tert*-alkyl- and *N*-aryl-2,2-dihalocyclopropanecarboxaldehydes has been shown to give, *via* an ionic mechanism, *tert*-alkyl- or aryl-substituted 3-halopyrroles, respectively (Scheme 1.12). Alternatively, if a hydrogen substituent is present on the carbon atom adjacent to the imino nitrogen then 2-phenylpyridine derivatives, such as **78**, are obtained. The key step associated with this unique transformation is a prototropic shift from the benzylic site. This process has been successfully exploited in the synthesis of *ter*-, *quater*- and *quinque*-aryls possessing a pyridine ring.⁴⁷

Scheme 1.12: Synthesis of Aryl-Substituted 3-Halopyrrole 76 and 2-Phenylpyridine 78


Reagents and conditions: (a) benzene, 220 °C, 12 h; (b) imidazole, DMI, 220 °C, 12 h.

1.4.2.2 Intramolecular Trapping of the π -Allyl Cation by Carbon Nucleophiles

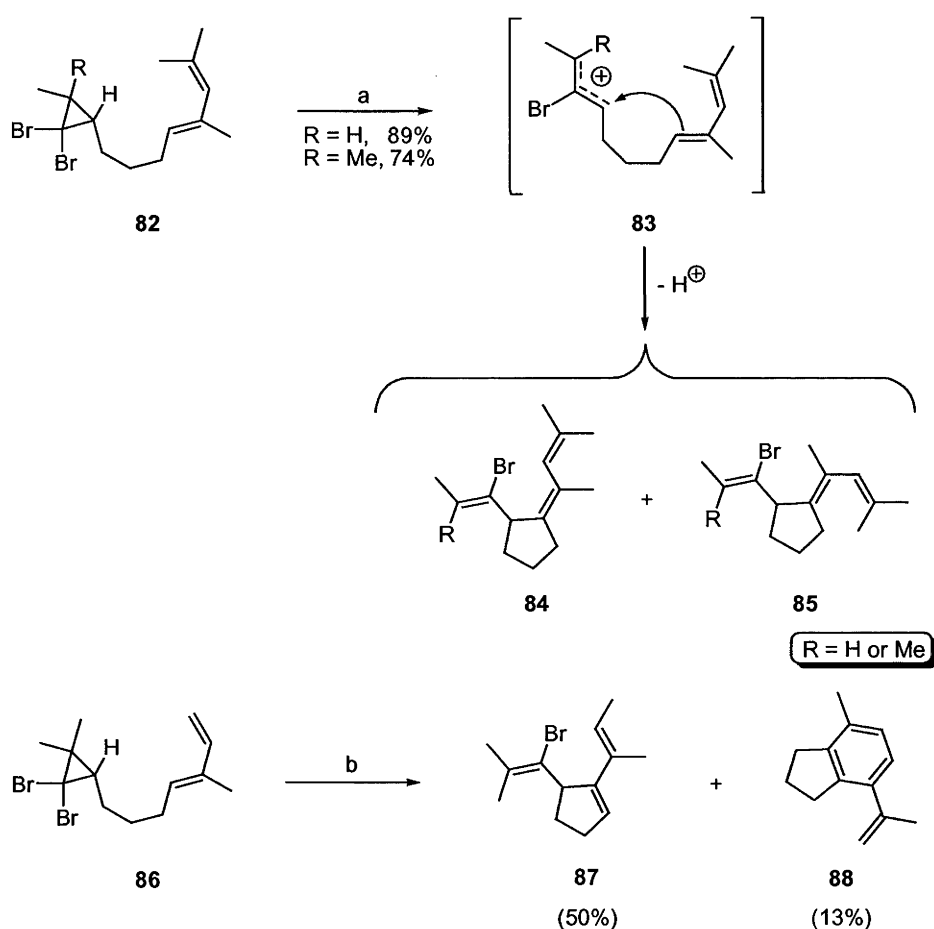
There are only a few reports of the π -allyl cation derived from the electrocyclic ring-opening of *gem*-dihalocyclopropanes being trapped by C-centred nucleophiles in an intramolecular fashion. For example, indene **81** was obtained by Dehmlow and Schönefeld when *gem*-dichlorocyclopropane **79** was heated under vacuum (Scheme 1.13).⁴⁸ Presumably the initial step in this conversion involves formation of π -allyl cation **80** under thermally-promoted ring-opening conditions and this is subsequently trapped, in an *endo*-cyclic fashion, by the aromatic π -system to furnish, after proton loss and accompanying aromatisation, the observed indene **81**.

Scheme 1.13: Intramolecular Trapping of the π -Allyl Cation with an Aromatic π -System


Reagents and conditions: (a) 170 °C, 10^{-3} Torr.

In 1996 Gassman and co-workers reported the formation of trienic cyclopentane derivatives *via* a cationic cyclisation process initiated by a cyclopropane ring-cleave reaction.⁴⁹ Thus, upon treatment of substrate **82** with silver perchlorate an initial electrocyclic ring-opening reaction occurred to generate intermediate **83** which then lost a proton to afford either a 1.4:1 (R = H) or 1:1 (R = Me) mixture of the trienic cyclopentane derivatives **84** and **85**. Interestingly, the analogous cyclopropane **86** lacking geminally-related and terminal methyl groups on the diene tether afforded, amongst other products similar to compounds **84** and **85**, adduct **88**. This latter outcome was thought to be due to the instability of the intermediate triene system so-formed and hence *in situ* oxidation delivered the more stable aromatic indane **88**.

Scheme 1.14: Trapping of the π -Allyl Cation with an Unsaturated Carbon



Reagents and conditions: (a) AgClO₄, Et₂O, 18 °C, 14 h; (b) AgClO₄, Et₂O, 18 °C, 24 h.

1.4.3 Applications of *gem*-Dihalocyclopropanes in Total Synthesis

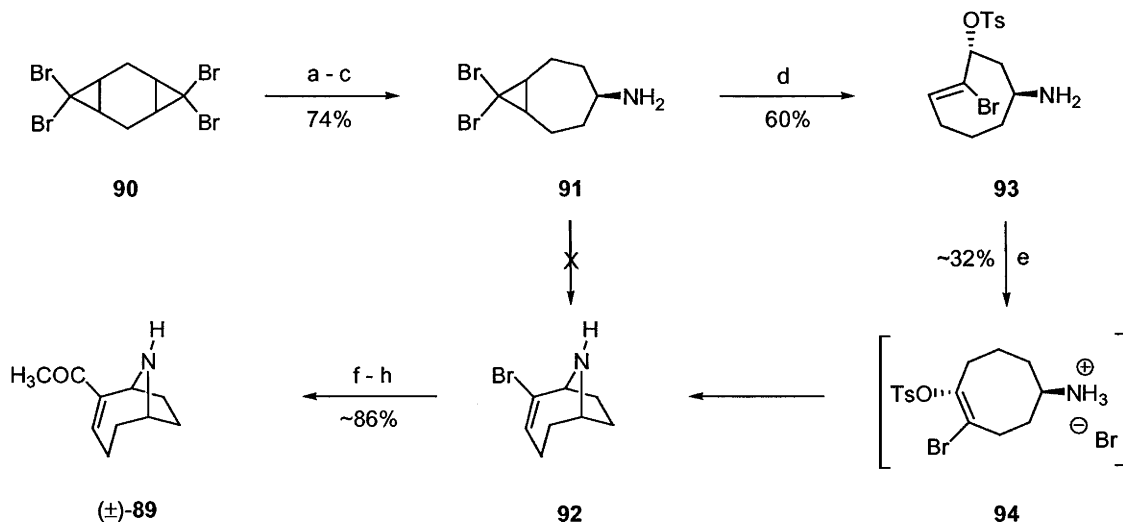
As mentioned previously, using silver(I)-salts is a common and convenient method for the promotion of the electrocyclic ring-opening of *gem*-dihalocyclopropanes. In this case, the halogen is removed by the silver(I)-salt hence preventing it from participating in nucleophilic interception of the π -allyl cation so-generated. Furthermore, when the original silver(I)-salt involves a nucleophilic counter-ion then this species can trap the π -allyl cation. This feature has been exploited in the synthesis of a variety of natural products. Perhaps the most notable example of the application of this technique is seen in the synthesis of anatoxin-a (**89**), as developed by Danheiser and refined by Trost.

Originally isolated in 1977 from the blue-green alga *Anabaena flos-aquae*,⁵⁰ anatoxin-a (**89**) has been a popular synthetic target⁵¹ because of its potent neuro-toxic properties and novel structure.⁵² Danheiser and co-workers reported an elegant synthesis of anatoxin-a (**89**) in 1985 which used two consecutive electrocyclic ring-opening reactions of *gem*-dibromocyclopropyl moieties (Scheme 1.15).⁵³ In their initial approach a thermally-induced electrocyclic ring-opening of cyclopropane **91** and subsequent trapping of the pendant free amine was pursued in an effort to prepare bromide **92**. However, under such conditions only trace amounts of the desired product were observed. The major compound obtained appeared to be a *trans*-cyclooctene, an observation in full accord with previous reports which established that 8,8-dibromobicyclo[5.1.0]octane systems preferentially undergo a *trans*-out, *cis*-in electrocyclic ring-opening process with accompanying loss of the *exo*-bromide to furnish *trans*-cyclooctene derivatives.

To circumvent these difficulties, a modified approach was pursued and employed silver(I) *p*-toluenesulfonate to initiate the electrocyclic cleavage and thus generate the *trans*-cyclooctene **93** which possessed a tosyl group in the allylic position. With compound **93** in hand, a subsequent one-pot photoisomerisation and transannular cyclisation sequence proved successful in generating the pivotal and originally targeted amine **92**. To complete the synthesis, Boc-protection followed by acylation, using a lithium-for-halogen exchange

reaction to generate an intermediate cycloalkenyl lithium, and subsequent deprotection then afforded anatoxin-a (**89**) in seven steps and 17% overall yield.

Scheme 1.15: Danheiser's Synthesis of (\pm)-Anatoxin-a (**89**)

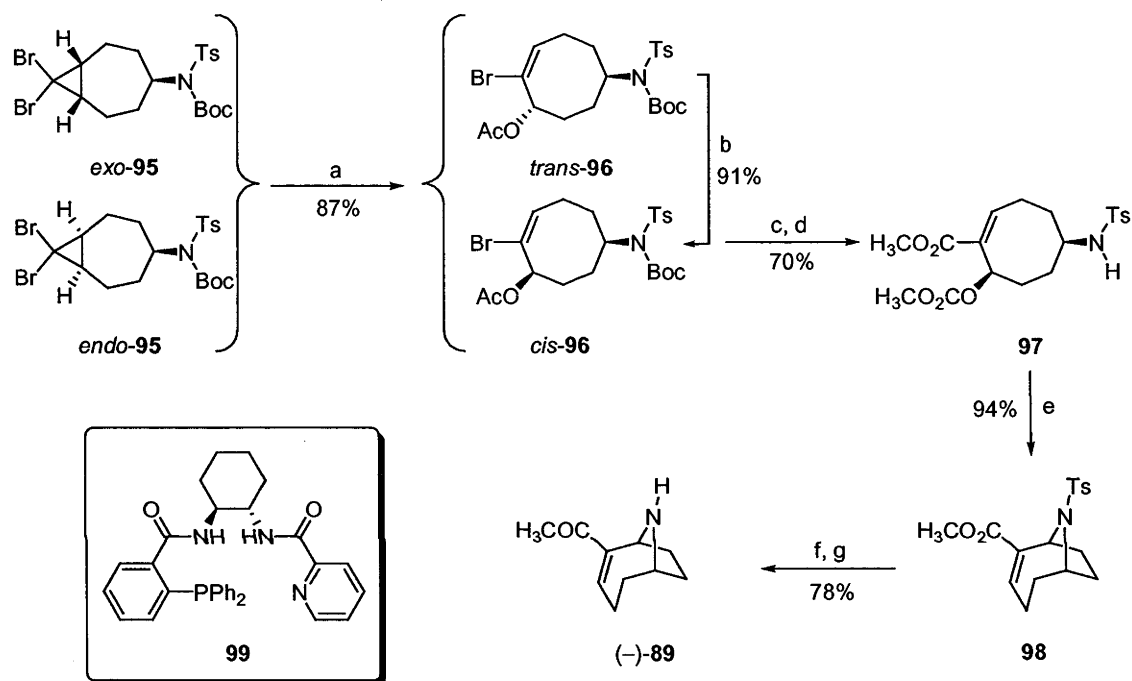


Reagents and conditions: (a) AgTFA, H₂SO₄, CH₂Cl₂, 40 °C, 6 h then 18 °C, 20 h; (b) H₂, (Ph₃P)₃RhCl, benzene, 25 °C, 6 h; (c) NaB₃CN, NH₄OAc, 2-propanol, 3 Å mol. sieves, 18 °C, 72 h; (d) AgOTs, CH₃CN, 80 °C, 45 h; (e) HBr (g), benzene then *hν*, benzene, CH₃CN, 12-14 min then Et₃N, CH₃CN, 70 °C, 18 h; (f) (Boc)₂O, CH₂Cl₂, 18 °C, 16 h; (g) *t*-BuLi, CH₃CON(Me)OMe, THF, -78 °C, 45 min then 18 °C, 15 min; (h) TFA, CH₂Cl₂, 0 °C, 5 min.

Trost and Oslob have also published a stereoselective synthesis of (-)-anatoxin-a (**89**)⁵⁴ utilising a combination of *gem*-dibromocyclopropane and π -allyl palladium chemistry (Scheme 1.16). In this work, a mixture of the *exo*- and *endo*-isomers of cyclopropane **95** was subjected to reaction with silver acetate in refluxing acetic acid, thus simultaneously effecting ring-opening and trapping of the resultant π -allyl cation with the acetate counter-ion of the silver(I)-salt. Although it was anticipated that, under such conditions, the resulting *trans*-cyclooctenyl species would undergo spontaneous isomerisation to afford the desired *cis*-isomer, a 1:4.8 mixture of *cis*- and *trans*-isomers of compound **96** was, in fact, obtained. Nevertheless, isomerisation, under Mitsunobu conditions, of the *trans*-isomer to its *cis*-

counterpart could be readily accomplished in high yield. The latter compound was then converted, over two steps, into acetate **97** which subsequently underwent a Pd[0]-catalysed and enantioselective cyclisation reaction. Azabicycle **98** so-obtained was then efficiently converted into (-)-anatoxin-a (**89**) by the straightforward sequence depicted.

Scheme 1.16: Trost's Synthesis of (-)-Anatoxin-a (89**)**

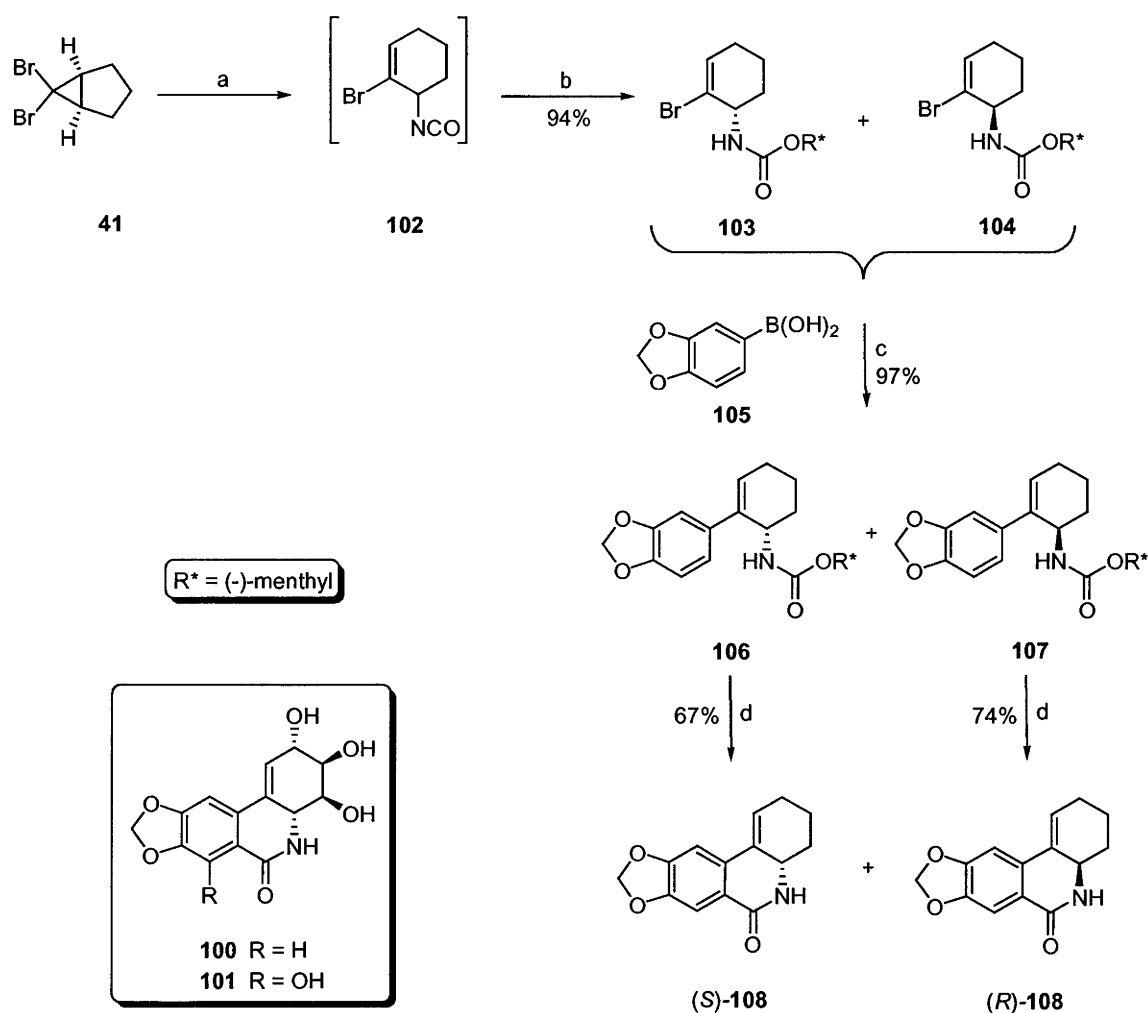


Reagents and conditions: (a) AgOAc, AcOH, reflux, overnight then (Boc)₂O, DMAP, Et₃N, CH₂Cl₂, 18 °C, 4 h; (b) K₂CO₃, MeOH, 18 °C, 1 h then PPh₃, AcOH, DIAD, benzene, 18 °C, 3 h; (c) CO (600 psi), Pd(PPh₃)₄, Et₃N, MeOH, DMPU, 100 °C, 14 h; (d) K₂CO₃, MeOH, 18 °C, 20 min then *n*-BuLi, THF, ClCO₂CH₃, -78 to 18 °C then TFA, CH₂Cl₂, 18 °C, 1 h; (e) Pd₂(dba)₃.CHCl₃, chiral ligand **99**, CH₂Cl₂, 0 °C, 14 h; (f) LiOH, water, MeOH, 18 °C, 4 h then NaH, (COCl)₂, CH₂Cl₂, 0 to 18 °C, 1.5 h then AlCl₃, CH₂Cl₂, -50 °C, 1 h then (CH₃)₃Al, -30 °C, 2 h; (g) Na(Hg), Na₂HPO₄, -40 °C, 15 min.

Work within the Banwell group has also utilised this type of methodology in the synthesis of the tetracyclic skeleta associated with the therapeutically important alkaloids lycoricidine (**100**) and narciclasine (**101**).^{55,56} The pivotal step involved trapping of the relevant π -allylation with the isocyanate anion derived from the appropriate silver(I)-salt so as to afford isocyanate **102** (Scheme 1.17). This latter species was not isolated but, rather, reacted *in situ*

with (-)-menthol to furnish an inseparable and 1:1 mixture of the diastereomeric menthyl carbamates **103** and **104**. Suzuki-Miyaura cross-coupling of these products with boronic acid **105** then afforded the diastereoisomeric and now chromatographically separable products **106** and **107**. Independent subsection of each of these compounds to Bischler-Napieralski cyclisation conditions then delivered the targeted and monochiral lactams (*S*)-**108** and (*R*)-**108**.

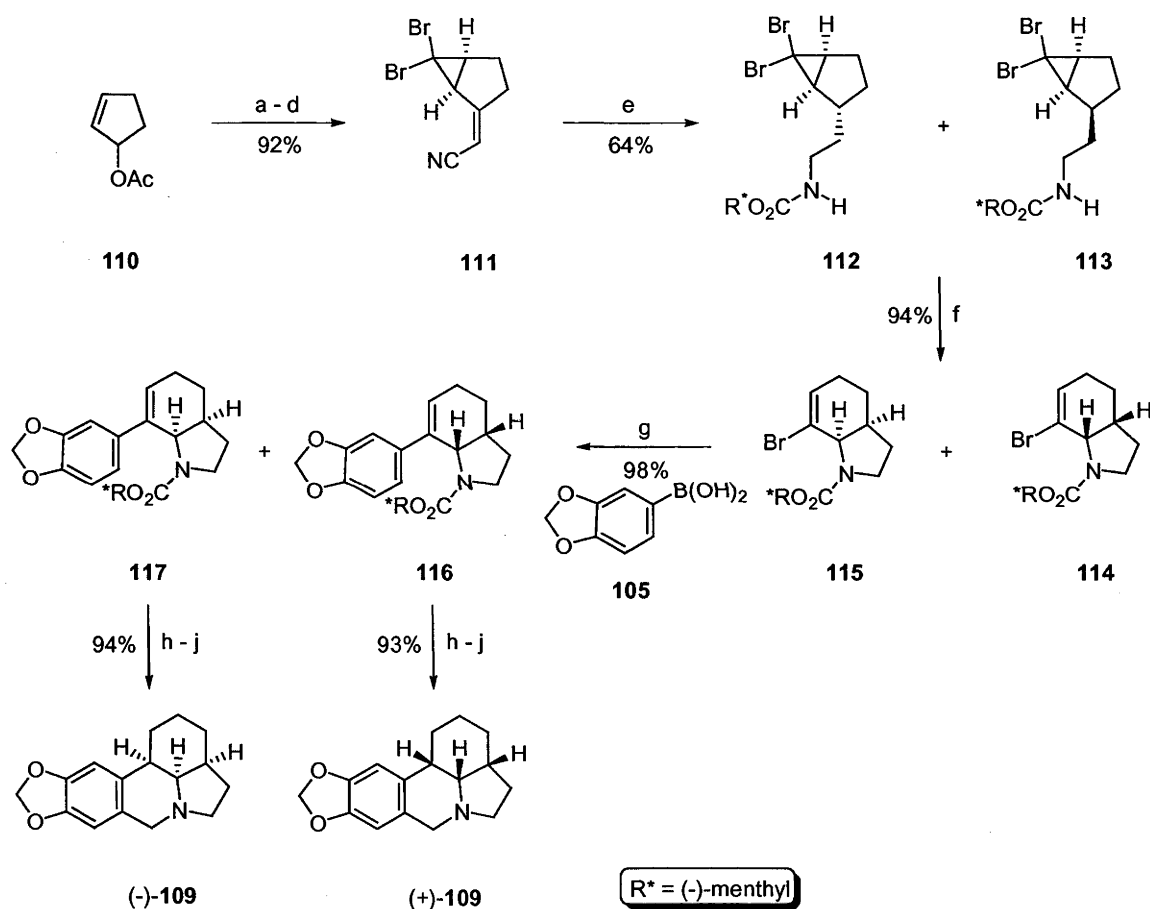
Scheme 1.17: Banwell's Synthesis of the Tetracyclic Framework Associated with Lycoricidine (**100**) and Narciclasine (**101**)



Reagents and conditions: (a) AgOCN, 1,4-dioxane, 100 °C, 4 h; (b) (-)-menthol, 1,4-dioxane, 100 °C, 24 h; (c) Pd(PPh₃)₄, EtOH, benzene, Na₂CO₃ (2 M aqueous solution), 80 °C, 12 h; (d) POCl₃, 80 °C, sealed tube, 7 h then HCl (0.2 M aqueous solution), THF/water (10:1 v/v mixture), 18 °C, 0.5 h.

The ability to establish new heterocyclic ring systems using such methodology was also exploited in the development of one of the most concise syntheses of the (+)- and (-)-forms of γ -lycorane (**109**) reported thus far. This work, carried out by Banwell and co-workers,⁵⁷ involved, as the key step, the silver(I)-promoted electrocyclic ring-opening of cyclopropanes **112** and **113** which were readily prepared in the manner indicated (Scheme 1.18).

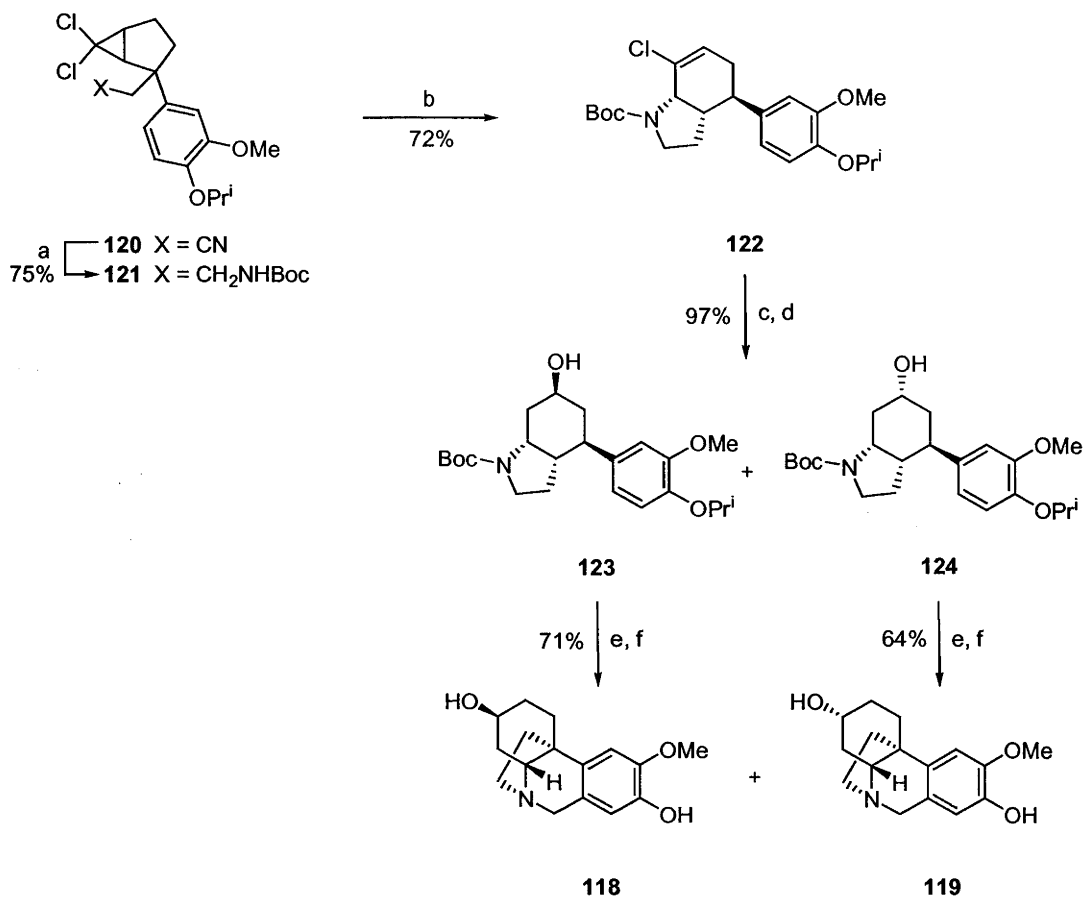
Scheme 1.18: Banwell's Synthesis of the (+)- and (-)- Forms of γ -Lycorane (**109**)



Reagents and conditions: (a) CHBr_3 , TEBAc, NaOH, benzene, 0-18 °C, 16 h; (b) KOH, MeOH, 0-18 °C, 16 h; (c) PCC, CH_2Cl_2 , 0 °C, 8 h; (d) NaH, diethyl (cyanomethyl)phosphonate, DME, 0 °C, 1.5 h; (e) H_2 (3 atm), PtO_2 , CHCl_3 , EtOH, 18 °C, 3 h then (-)-menthyl chloroformate, pyridine, CH_2Cl_2 , 18 °C, 16 h; (f) AgOAc, TFE, 18 °C, 10 h; (g) $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , benzene, EtOH, reflux, 16 h; (h) H_2 (1 atm), 10% Pd/C, EtOAc, 18 °C, 16 h; (i) POCl_3 , sealed tube, 80 °C, 30 h; (j) LiAlH_4 , THF, reflux, 3 h.

In both cases cyclisation occurred to furnish the hexahydroindoles **114** and **115** in approximately equal yields. This observation provided further confirmation of the irrelevance of the stereochemical relationship between the nucleophilic tether and the cyclopropane, whilst also suggesting the involvement of a common and discrete cationic intermediate. As is apparent in Scheme 1.18, this cyclisation reaction was performed in the presence of a chiral auxiliary so as to allow both the (+)- and (-)-forms of γ -lycorane (**109**) to be targeted. As enunciated in the previously described natural product synthesis studies, ring-opening and trapping of the incipient π -allyl cation provides a cycloalkenyl bromide moiety which is capable of undergoing further reaction. Thus, the newly formed hexahydroindoles were reacted with arylboronic acid **105** in a traditional Suzuki-Miyaura cross-coupling reaction to provide the 7-arylated derivatives **116** and **117**. These could be separated chromatographically. Hydrogenation of the styrene-type double bond within the latter compounds, then a Bischler-Napieralski cyclisation reaction followed by reduction of the ensuing lactam carbonyl subsequently afforded the (+)- and (-)-forms of γ -lycorane (**109**).

An analogous approach was employed by the same group in the synthesis of the crinine alkaloids (\pm)-maritinamine (**118**) and (\pm)-*epi*-maritinamine (**119**).⁵⁸ As shown in Scheme 1.19, the nitrile moiety present within the *ca.* 2:1 mixture of epimeric adducts of cyclopropane **120** was hydrogenolysed and subsequently treated with *tert*-butoxycarbonyl anhydride to afford the corresponding carbamate **121**. The electrocyclic ring-opening of cyclopropane **121** and concomitant trapping of the resulting π -allyl cation by the tethered carbamate nitrogen then proceeded in the presence of silver tetrafluoroborate at 40 °C to provide, after reinstatement of the Boc-group partially lost during the cyclisation reaction, the C3a-arylated hexahydroindole **122**. This alkene was then subjected to reductive dechlorination and oxymercuration with Hg(OAc)₂ to afford a chromatographically separable mixture of epimeric alcohols **123** and **124**. Independent subjection of these compounds to a Pictet-Spengler reaction and ensuing de-isopropylation was ultimately successful in furnishing target natural products **118** and **119**.

Scheme 1.19: Banwell's Synthesis of (±)-Maritinimine (**118**) and (±)-*epi*-Maritinimine (**119**)

Reagents and conditions: (a) H_2 (3 atm), PtO_2 , EtOH, CHCl_3 , 25 °C, 12 h then $(\text{Boc})_2\text{O}$, Et_3N , THF, 25 °C, 15 h; (b) AgBF_4 , THF, 40 °C, 21 h then $(\text{Boc})_2\text{O}$, Et_3N , THF, 25 °C, 15 h; (c) Na, *t*-BuOH, THF, 66 °C, 3 h; (d) $\text{Hg}(\text{OAc})_2$, THF/water, 25 °C, 24 h then NaBH_4 , 3 M NaOH (aq.), 25 °C, 0.5 h; (e) $(\text{CH}_2\text{O})_n$, HCO_2H , 80 °C, 18 h then K_2CO_3 , MeOH, 25 °C, 1 h; (f) BCl_3 , CH_2Cl_2 , 0 °C, 0.25 h.

1.5 Objectives of Research Work Described in this Thesis and Overview of Thesis Organisation

As emphasised throughout the introductory section, *gem*-dihalocyclopropyl-containing compounds can clearly serve as useful synthetic building blocks in the preparation of a wide variety of target molecules. A lack of definition, however, of the basic scope and limitations of the chemical behaviour of such systems means that they remain under-utilised in total

synthesis at the present time. A major objective, therefore, of the work detailed in the following Chapters was to exploit the well-recognised ability of *gem*-dihalocyclopropanes to undergo electrocyclic ring-opening and, using carbon-centred nucleophiles, to then trap, in either an inter- or intra-molecular manner, the resultant π -allyl cation so as to provide a useful new method for carbon-carbon bond formation. The exploitation of the products of such processes in the synthesis of natural product frameworks was another major objective of these studies.

Chapter Two describes initial studies carried out so as to determine if the π -allyl cation derived from ring-opening of the “parent” cyclopropane **41** could be captured by a range of heteroaromatic-based and C-centred nucleophiles. Non-aromatic systems and π -allyl cation species incorporating ring-nitrogens were also investigated.

The work detailed in Chapter Three expands on some of the successful results reported in Chapter Two. Thus, this Chapter focuses on studies involving π -allyl cation trapping, in a diastereoselective manner, with the C-3 of indole. A range of chiral auxiliaries were incorporated into the starting ring-fused *gem*-dihalocyclopropane and the desired trapping process was observed to occur with varying extents. A discussion on the application of such methodology to the synthesis of the hapalindole and fischerindole alkaloid frameworks is then described.

Chapter Four details attempts to employ a range of carbon-centred nucleophiles including oximes, malonates, indoles and pyrroles in analogous intramolecular trapping processes.

In Chapter Five a description of attempts to apply the methodology discussed in Chapter Four, *via* a cascade of cationic cyclisation reactions, to the synthesis of 13-azasteroids is presented. Chapter Six details an overview of the possibilities for future work in the area and, finally, Chapter Seven presents the relevant experimental data relating to the work described in the preceding Chapters.

1.6 References

- ¹ For reviews in this area see: (a) Fedoryński, M.; *Chem. Rev.*, **2003**, *103*, 1099-1132. (b) Banwell, M.G., Reum, M.E.; in *Advances in Strain in Organic Chemistry*, Halton, B. (Ed.), JAI Press Ltd: London, **1991**, Vol. 1, pp. 19-64. (c) Kostikov, R.R., Molchanov, A.P., Hopf, H.; in *Topics in Current Chemistry*, De Meijere, A. (Ed.), Springer Verlag: Berlin, **1990**, Vol. 155, pp. 41-80. (d) Weyerstahl, P.; in *The Chemistry of Functional Groups, Supp. D*, Patai, S., Rappoport, Z. (Ed.), John Wiley & Sons Ltd: New York, **1983**, Chapter 27, pp. 1451-1495.
- ² Gustavson, G.; *J. Prakt. Chem.*, **1890**, *42*, 495.
- ³ Geuther, A.; *Justus Liebig's Ann. Chem.*, **1862**, *123*, 121.
- ⁴ Hine, J.; *J. Am. Chem. Soc.*, **1950**, *72*, 2438-2445.
- ⁵ Doering, W.E., Hoffmann, A.K.; *J. Am. Chem. Soc.*, **1954**, *76*, 6162-6165.
- ⁶ Makosza, M., Wawrzyniewicz, M.; *Tetrahedron Lett.*, **1969**, *53*, 4659-4662.
- ⁷ Banwell, M.G.; *J. Chem. Soc., Chem. Commun.*, **1983**, *23*, 1453-1454.
- ⁸ Makosza, M.; *Pure Appl. Chem.*, **1975**, *43*, 439-462.
- ⁹ Dehmlow, E.V., Lissel, M.; *Chem. Ber.*, **1978**, *111*, 3873-3878.
- ¹⁰ Regen, S.L., Singh, A.; *J. Org. Chem.*, **1982**, *47*, 1587-1588.
- ¹¹ Xu, L., Tao, F.; *Synth. Commun.*, **1988**, *18*, 2117-2121.
- ¹² Xu, L., Smith, W.B., Brinker, U.H.; *J. Am. Chem. Soc.*, **1992**, *114*, 783-784.
- ¹³ Xu, L., Brinker, U.H.; in *Synthetic Organic Sonochemistry*, Luche, J.L. (Ed.), Plenum Press: New York, **1998**, pp. 344-345.
- ¹⁴ Dehmlow, E.V., Kramer, R.; *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 706-707.
- ¹⁵ Hartwig, J.F., Jones Jr., M., Moss, R.A., Ławrynowicz, W.; *Tetrahedron Lett.*, **1986**, *27*, 5907-5910.
- ¹⁶ Nitta, N., Okada, S., Kato, M.; *Bull. Chem. Soc. Jpn*, **1984**, *57*, 2463-2467.
- ¹⁷ Mohamdi, F., Still, W.C.; *Tetrahedron Lett.*, **1986**, *27*, 893-896.
- ¹⁸ Dehmlow, E.V.; *Liebigs Ann. Chem.*, **1972**, *758*, 148-154.
- ¹⁹ Dehmlow, E.V.; in *Methoden der Organische Chemie (Houben-Weyl)*, Regitz, M. (Ed.), Georg Thieme Verlag: Stuttgart, Vol. E19b, **1989**.

- ²⁰ Dehmlow, E.V., Franke, K.; *Liebigs Ann. Chem.*, **1979**, *10*, 1456-1464.
- ²¹ Kraakman, P.A., de Wolf, W.H., Bickelhaupt, F.; *J. Am. Chem. Soc.*, **1989**, *111*, 8534-8535.
- ²² Le, N.A., Jones, M., Bickelhaupt, F., de Wolf, W.H.; *J. Am. Chem. Soc.*, **1989**, *111*, 8491-8493.
- ²³ Woodward, R.B., Hoffmann, R.; *J. Am. Chem. Soc.*, **1965**, *87*, 395-397.
- ²⁴ Cristol, S.J., Sequeira, R.H., de Puy, C.H.; *J. Am. Chem. Soc.*, **1965**, *87*, 4007-4008.
- ²⁵ de Puy, C.H., Schnack, L.G., Hausser, J.W., Wiedemann, W.; *J. Am. Chem. Soc.*, **1965**, *87*, 4006.
- ²⁶ Castro, J.L., Castedo, L., Riguera, R.; *Tetrahedron Lett.*, **1985**, *26*, 1561-1564.
- ²⁷ Castro, J.L., Castedo, L., Riguera, R.; *J. Org. Chem.*, **1987**, *52*, 3579-3584.
- ²⁸ Corbett, R.M., Lee, C-S., Sulikowski, M.M., Reibenspies, J., Sulikowski, G.A.; *Tetrahedron*, **1997**, *53*, 11099-11108.
- ²⁹ Banwell, M.G., Harvey, J.E., Jolliffe, K.A.; *J. Chem. Soc., Perkin Trans. 1*, **2001**, *17*, 2002-2005.
- ³⁰ Fleming, I., Thomas, E.J.; *Tetrahedron Letters*, **1971**, *27*, 2485-2488.
- ³¹ Fleming, I., Thomas, E.J.; *Tetrahedron*, **1972**, *28*, 4989-5001.
- ³² Sandler, S.R.; *J. Org. Chem.*, **1970**, *35*, 2023-2025.
- ³³ Arct, J., Prawda, A., Kozyriew, W.; *Bull. Soc. Chim. Belg.*, **1979**, *88*, 67-69.
- ³⁴ Shimizu, N., Watanabe, K., Tsuno, Y.; *Bull. Chem. Soc. Jpn*, **1984**, *57*, 1165-1166.
- ³⁵ Nerdel, F., Buddrus, J.; *Tetrahedron Lett.*, **1965**, *36*, 3197-3198.
- ³⁶ Skattebøll, L., Boulette, B.; *J. Org. Chem.*, **1966**, *31*, 81-85.
- ³⁷ Müller, C.H., Weyerstahl, P.; *Tetrahedron*, **1975**, *31*, 1787-1789.
- ³⁸ Reinhard, D., Weyerstahl, P.; *Chem. Ber.*, **1977**, *110*, 138-145.
- ³⁹ Reese, C.B., Shaw, A.; *J. Am. Chem. Soc.*, **1970**, *92*, 2566-2568.
- ⁴⁰ Reese, C.B., Shaw, A.; *J. Chem. Soc., Chem. Commun.*, **1970**, *20*, 1365-1366.
- ⁴¹ Sydnes, L.K., Hemmingsen, T.H.; *Acta Chem. Scand.*, **1985**, *B39*, 93-102.
- ⁴² Danheiser, R.L., Morin Jr., J.M., Yu, M., Basak, A.; *Tetrahedron Lett.*, **1981**, *22*, 4205-4208.
- ⁴³ Sydnes, L.K., Hemmingsen, T.H.; *Acta Chem. Scand.*, **1988**, *B42*, 651-673.

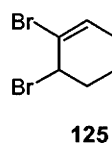
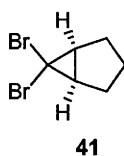
- ⁴⁴ Svendsen, J.S., Sydnese, L.K.; *Acta Chem. Scand.*, **1990**, *44*, 202-204.
- ⁴⁵ Sydnese, L.K., Mungaroo, R., Aanesen, B.A.; *Acta Chem. Scand.*, **1998**, *52*, 1386-1391.
- ⁴⁶ Kagabu, S., Tsuji, H., Kawai, I., Ozeki, H.; *Bull. Chem. Soc. Jpn.*, **1995**, *68*, 341-349.
- ⁴⁷ Kagabu, S., Mizoguchi, S.; *Synthesis*, **1996**, *3*, 372-376.
- ⁴⁸ Dehmlow, E.V., Schönefeld, J.; *Liebigs Ann. Chem.*, **1971**, *744*, 42-50.
- ⁴⁹ Gassman, P.G., Tan, L., Hoye, T.R.; *Tetrahedron Lett.*, **1996**, *37*, 439-442.
- ⁵⁰ Devlin, J.P., Edwards, O.E., Gorham, P.R., Hunter, N.R., Pike, R.K., Stavric, B.; *Can. J. Chem.*, **1977**, *55*, 1367-1371.
- ⁵¹ (a) Aggarwal, V.K., Humphries, P.S., Fenwick, A.; *Angew. Chem. Int. Ed.*, **1999**, *38*, 1985-1986. (b) Mansell, H.L.; *Tetrahedron*, **1996**, *52*, 6025-6061. (c) Parsons, P.J., Camp, N.P., Underwood, J.M., Harvey, D.M.; *Tetrahedron*, **1996**, *52*, 11637-11642. (d) Oh, C-Y., Kim, K-S., Ham, W-H.; *Tetrahedron Lett.*, **1998**, *39*, 2133-2136. (e) Parsons, P.J., Camp, N.P., Edwards, N., Sumoreeah, L.R.; *Tetrahedron*, **2000**, *56*, 309-315. (f) Wegge, T., Schwarz, S., Seitz, G.; *Tetrahedron: Assym.*, **2000**, *11*, 1405-1410. (g) Brenneman, J.B., Martin, S.F.; *Org. Lett.*, **2004**, *6*, 1329-1331.
- ⁵² Devlin, J.P., Edwards, O.E., Gorham, P.R., Hunter, N.R., Pike, R.K., Stavric, B.; *Can. J. Chem.*, **1977**, *55*, 1367-1371.
- ⁵³ Danheiser, R.L., Morin Jr., J.M., Salaski, E.J.; *J. Am. Chem. Soc.*, **1985**, *107*, 8066-8073.
- ⁵⁴ Trost, B.M., Oslob, J.D.; *J. Am. Chem. Soc.*, **1999**, *121*, 3057-3064.
- ⁵⁵ Banwell, M.G., Cowden, C.J., MacKay, M.F.; *J. Chem. Soc., Chem. Commun.*, **1994**, *1*, 61-62.
- ⁵⁶ Banwell, M.G., Cowden, C. J.; *Aust. J. Chem.*, **1994**, *47*, 2235-2254.
- ⁵⁷ Banwell, M.G., Harvey, J.E., Hockless, D.C.R., Wu, A.W.; *J. Org. Chem.*, **2000**, *65*, 4241-4250.
- ⁵⁸ Banwell, M.G., Harvey, J.E., Jolliffe, K.A.; *J. Chem. Soc., Perkin Trans. 1*, **2001**, *17*, 2002-2005.

Intermolecular Trapping of π -Allyl Cations Produced by the Electrocyclic Ring-Opening of *gem*-Dibromocyclopropanes

2.1 Introduction

A continuing challenge in organic chemistry, and especially in certain types of natural product synthesis, is the development of new methods for the regioselective functionalisation of aromatic systems,¹ particularly those involving carbon-carbon bond formation. In seeking such methods, along with pursuing our desire to exploit the synthetic potential of *gem*-dihalocyclopropanes, the work described below was undertaken.

As detailed in the introductory section of this thesis, various nucleophiles have been successfully utilised to trap the π -allyl cations resulting from the electrocyclic ring-opening of *gem*-dihalocyclopropanes. However, a very limited amount of work has been focused on exploiting carbon-centred nucleophiles in the trapping process. Cyclopropane **41** represented the substrate of choice for all of the methodological studies discussed herein. This was specifically chosen because annulation of a three-membered ring to a five-membered one provides a system that embodies sufficient strain to allow its ready engagement, under mild conditions, in the required electrocyclic ring-opening reactions. Another important attribute of cyclopropane **41** is that it can be rapidly prepared, in multigram quantities, from inexpensive and commercially available starting materials.

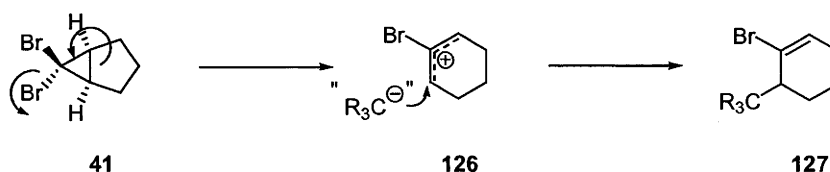


The required cyclopropane, **41**, was synthesised by addition of dibromocarbene to cyclopentene and, initially, utilising a method reported by Banwell and co-workers² which involved classical Makosza phase-transfer conditions for generating the reactive intermediate.³ A slightly superior approach was found when the dibromocarbene addition reaction was performed under sonication conditions. This protocol, which was pioneered by Xu and Brinker,⁴ led to a significant reduction in reaction time as well as minor improvements in yield. As previously noted, purification of compound **41** could be achieved by distillation, although it was imperative that the temperature be maintained below 100 °C to prevent isomerisation to the corresponding ring-opened isomer, *viz.* 2,3-dibromocyclohexene (**125**). It was also found during the course of these studies that any bromoform contaminating this product could be readily removed by flash column chromatography. As expected, the spectroscopic data derived from compound **41** were in full accord with the assigned structure. Thus, only four resonances were observed in the ¹³C NMR spectrum of dibromide **41** indicating that this compound possesses a C₂-plane of symmetry. The fact that no absorption band due to C=C stretching was visible in the infrared spectrum, along with the lack of any olefinic signals in the ¹H NMR spectrum, also confirmed that the purification of compound **41** had been achieved without any accompanying ring-opening. The 70 eV EI mass spectrum displayed the expected cluster of molecular ions at *m/z* 242, 240 and 238 and in the 1:2:1 ratio anticipated for compounds which contain two bromines. An accurate mass measurement on the ions at *m/z* 242 and 238 established their compositions were C₆H₈⁸¹Br₂ and C₆H₈⁷⁹Br₂, respectively.

The electrocyclic ring-opening/ π -allyl cation trapping reaction sequence which it was envisaged that cyclopropane **41** would engage in is shown in Figure 2.1. The initial step is a concerted disrotatory ring-opening of dibromide **41** involving cleavage of the C1-C5 bond.⁵ Simultaneously, ionisation of the carbon to *endo*-bromine bond occurs to deliver π -allyl cation **126**. Any added and sufficiently potent carbon nucleophile would be expected to intercept this cation, thus affording a compound of the general structure **127** and incorporating a new carbon-carbon bond.

Generally speaking, the electrocyclic ring-opening reaction of *gem*-dihalocyclopropanes to π -allyl cations can be effected either using silver(I)-salts or thermally, although application of the former conditions tends to result in slightly higher yields of product.

Figure 2.1: *General Pathway for the Electrocyclic Ring-Opening of gem-Dibromocyclopropane 41 and Trapping of the Resultant Cation, 126, by C-Centred Nucleophiles*



With ready access to cyclopropane 41, the foreshadowed trapping studies, involving *C*-centred nucleophiles, could be pursued. Heteroaromatic compounds such as indole, pyrrole and furan are known to be potent *C*-centred nucleophiles and are, therefore, activated to electrophile attack. As such, these compounds were employed as potential *C*-centred nucleophiles in the initial studies reported below.

2.2 Intermolecular π -Allyl Cation Trapping by *C*-Centred Nucleophiles

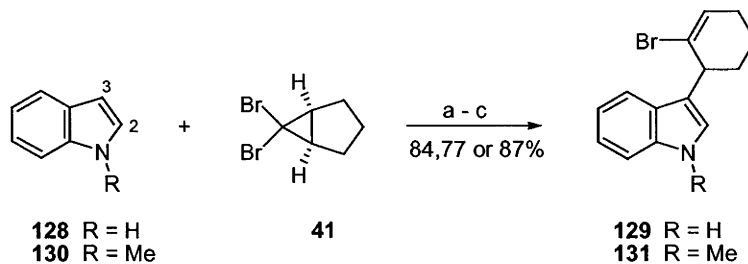
2.2.1 Initial Studies with Indole (128)

For many decades the synthesis and reactivity of indole derivatives has been of great interest to chemists. This is not only due to the wide range of biological activities attributable to indole-containing compounds, but also because this heterocyclic ring system is embodied in a large number of natural products. Therefore, new methodologies for the functionalisation of the indole ring system remains a topic of considerable interest and this was, hence, where the author's studies commenced.

Upon reaction of indole (**128**) with the “parent” 6,6-dibromobicyclo[3.1.0]hexane (**41**), in the presence of silver tetrafluoroborate, the anticipated product **129** was obtained in excellent yield (Scheme 2.1). Thus, the π -allyl cation derived from compound **41** was trapped by the nucleophilic C-3 of indole with the resultant formation of a new carbon-carbon bond as embodied in product **129**. It should be noted, at this point, that the reaction just described was carried out in the dark due to the light-sensitive nature of silver tetrafluoroborate. This precaution of protecting the silver(I)-promoted reaction from light was observed in all of the studies reported herein. The conversion of substrates **128** and **41** into product **129** could also be effected thermally but purification of the product so-obtained was somewhat problematic with the result that lower yields (77% vs 84%) were observed.

The spectral data derived from compound **129** clearly established that the cyclohexyl ring was attached at the C-3 position of indole (Figure 2.2). In particular, in the ^1H NMR spectrum the absence of a resonance, normally appearing at δ 6.45, due to the proton associated with the C-3 of indole as well as the presence of a signal due to H-2 of an indole (at δ 7.14) supports this argument. The appearance of a triplet at δ 6.32 ($J = 3.9$ Hz), which is attributed to the alkenyl proton in the bromocyclohexenyl system, as well as the fact that signals due to the cyclohexyl protons integrated in a 7:6 ratio with those due to the indolic resonances is also consistent with the assigned structure. Proof that reaction had not occurred at N-1 was also apparent in the ^1H NMR spectrum by virtue of the presence of a broad singlet at δ 8.02, which was attributable to the NH of the indole ring system. In complete accord with structure **129**, the ^{13}C NMR spectrum displayed fourteen resonances. As anticipated, the EI mass spectrum revealed the expected pair of molecular ions (m/z 277 and 275) in the 1:1 ratio characteristic of a monobrominated compound. An accurate mass measurement on each of these established that they possessed the expected composition, *viz.* $\text{C}_{14}\text{H}_{14}\text{BrN}$.

A product arising from attack of the π -allyl cation derived from cyclopropane **41** on the indole nitrogen might have been expected under the conditions described above. However, such processes are usually only observed at $\text{pH} > 7$.⁶ It is on these grounds, therefore, that the absence of any *N*-substituted products is explained.

Scheme 2.1: Reaction of Indole (128) and N-Methylindole (130) with Cyclopropane 41


Reagents and conditions: (a) AgBF₄, THF, 18 °C, 7 h (R = H); (b) 100 °C, 6 h (R = H); (c) AgBF₄, THF, 18 °C, 4 h (R = Me).

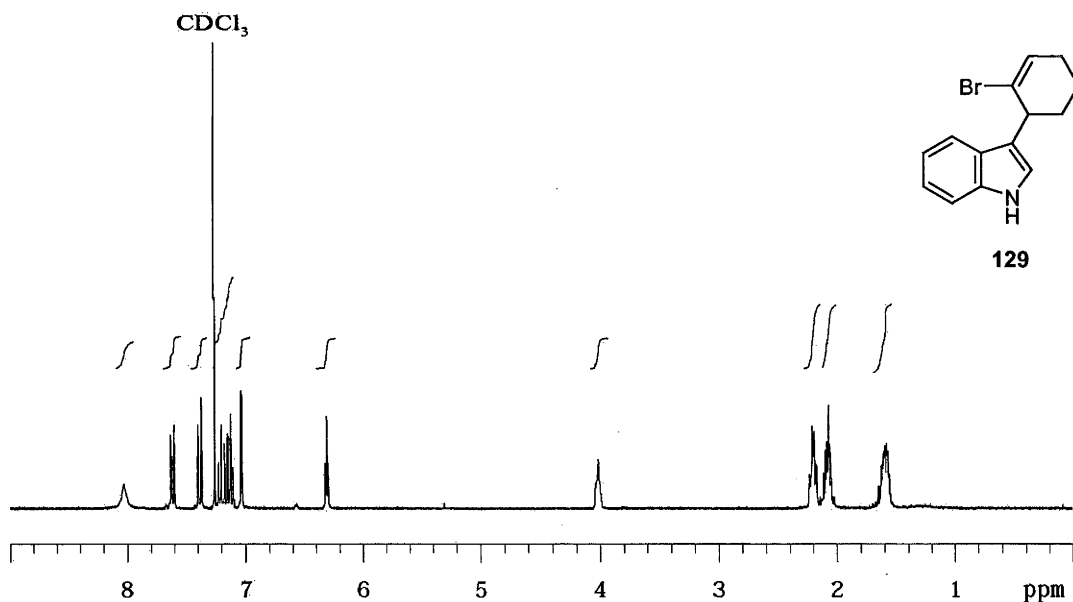


Figure 2.2: 300 MHz ¹H NMR Spectrum of Compound 129 in CDCl₃

The reaction of commercially available *N*-methylindole (130) and 6,6-dibromobicyclo[3.1.0]hexane (41) in the presence of silver tetrafluoroborate proceeded in an analogous manner to that associated with the conversion of substrate 128 to product 129 and afforded the *N*-methylated analogue, 131, of compound 129 in 87% yield (Scheme 2.1).

Once again, the spectral data derived from compound 131 revealed, unequivocally, that the desired “coupling” reaction had occurred. Thus, a proton resonance traditionally attributable

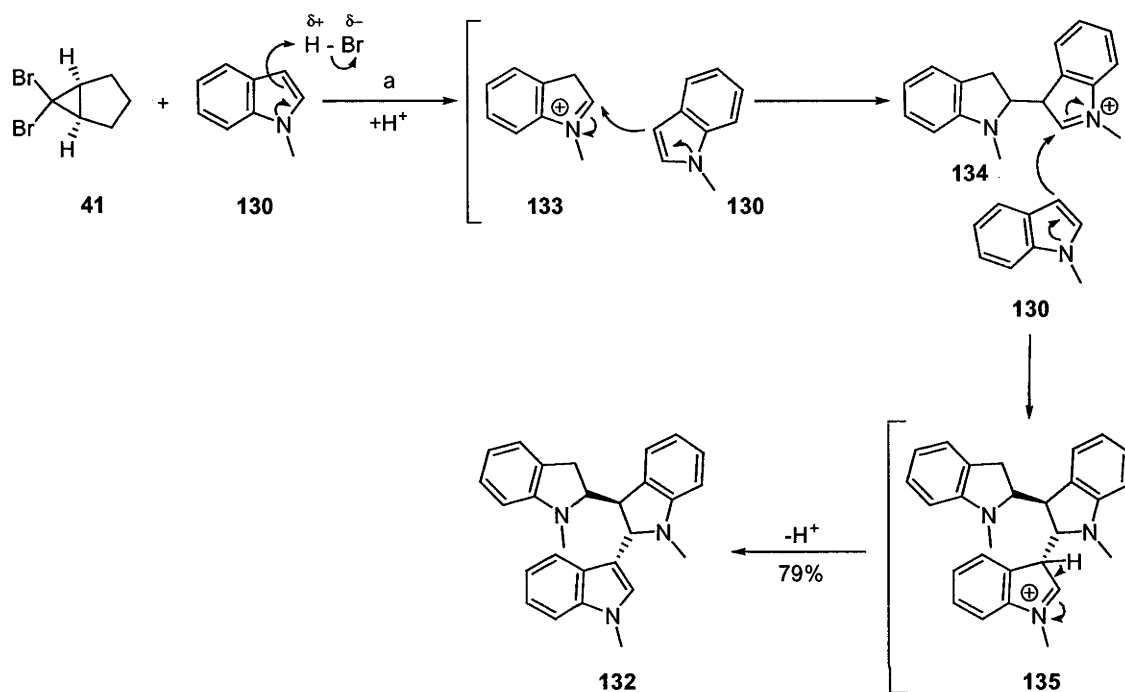
to H-3 of the indolic ring system was no longer apparent and the signal due to the olefinic proton of the newly formed cycloalkenyl bromide was observed as a doublet of triplets at δ 6.32 ($J = 3.9$ and 0.9 Hz). The first of these couplings is due to interaction between the alkenic proton and the adjacent methylene hydrogens on the cyclohexyl ring. The smaller coupling is the result of a long-range or W-coupling between the aforementioned proton and the methine proton attached to the cyclohexyl ring. The ^{13}C NMR spectrum of compound **131** displayed the expected fifteen resonances and the 70 eV EI mass spectrum again showed the anticipated 1:1 ratio of molecular ions, this time appearing at m/z 291 and 289. Confirmation of the assigned composition $\text{C}_{15}\text{H}_{16}\text{BrN}$ was established through an accurate mass measurement.

An interesting and unexpected result was obtained when efforts were made to effect the conversion of compounds **130** and **41** into adduct **131** under thermal conditions. Spectroscopic studies revealed that formation of a *tris-N*-methylated indole trimer had occurred and only very minor quantities ($< 10\%$) of the expected product, **131**, had been formed. The ^1H and ^{13}C NMR spectra of trimer **132** each clearly indicated the presence of three distinct *N*-methyl groups in the compound. EI mass spectrometry revealed a molecular ion at m/z 393 and an accurate mass measurement on this species established that it was of the expected composition, *viz.* $\text{C}_{27}\text{H}_{27}\text{N}_3$.

A reasonable mechanism can be postulated to account for the formation of this unexpected product (Scheme 2.2). Thus, HBr, which is likely to be present in the reaction mixture,⁷ protonates *N*-methylindole (**130**) at C-3. The resulting iminium ion **133** can then be attacked by a second molecule of *N*-methylindole (**130**). As a result, a new iminium ion is formed which also participates in a reaction with another equivalent of *N*-methylindole (**130**). In principle, this process could continue *ad infinitum* and thus lead to polyindoles. However, it is proposed that in the present case the process slows after the addition of three indole units due to developing steric congestion. As a result, intermediate **135** undergoes competitive proton loss to furnish the observed trimer **132**. This compound was obtained as a single diastereomer and it is suggested that the outer indole-type units would most likely be attached

to the central one in a *trans*-relationship as a result of the operation of steric effects in the second of the two Mannich-type processes shown.

Scheme 2.2: Possible Mechanism for the Formation of Compound **132**



Reagents and conditions: (a) 100 °C, 18 h.

Varying the stoichiometry of the reactants **41** and **130** was examined in an attempt to suppress the unwanted formation of trimer **132**. However, at best a maximum of *ca.* 10% of the desired product **131** was obtained utilising the conditions described in the Experimental Section of this thesis. Based on these observations it is clearly apparent that, in this instance, use of a silver(I)-salt provides a more favourable outcome in terms of promoting the desired ring-opening/nucleophilic trapping sequence.

2.2.1.1 Extension of Methodology to Tryptamine (136)

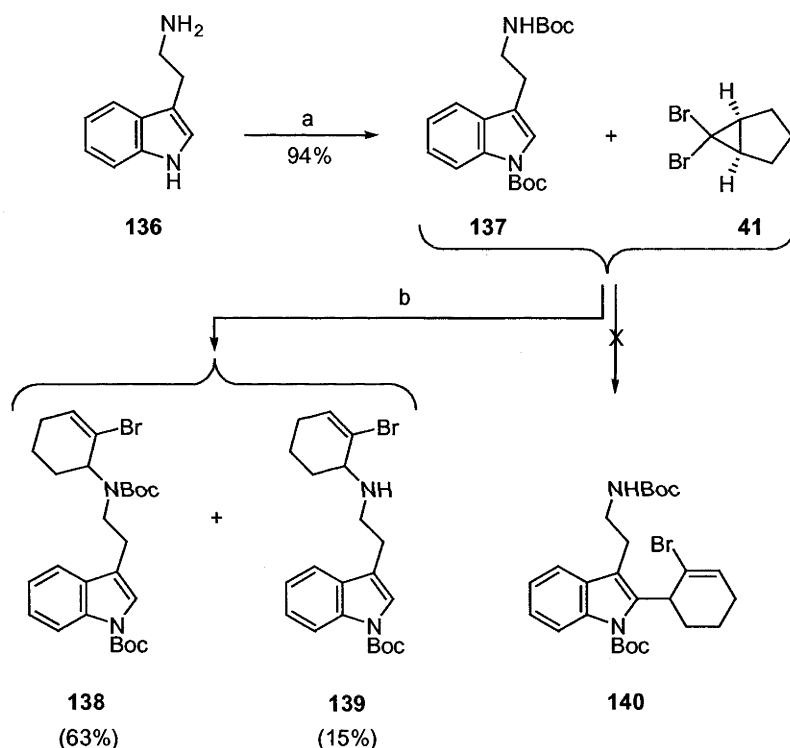
Following the successful trapping of the π -allyl cation generated from the electrocyclic ring-opening of *gem*-dibromocyclopropane **41** by the C-3 position of indole, investigations were undertaken to ascertain whether the next most nucleophilic position, namely C-2, within this heterocyclic system would participate in a similar reaction if the former one was blocked to possible attack. To such ends, tryptamine (**136**) was chosen as the nucleophile, due to its commercial availability and the potential that exists to exploit the anticipated reaction product in total synthesis (Scheme 2.3).

To avoid competitive side-reactions between the π -allyl cation derived from ring-opening of **41** and the two free nitrogens of tryptamine, compound **136** was doubly protected as the *bis*-Boc derivative **137** under standard conditions, utilising two equivalents of di-*tert*-butyl dicarbonate. In the ^1H NMR spectrum of compound **137**, the most distinctive feature was the presence of two singlets, at δ 1.67 and 1.44, due to the *tert*-butyl group protons associated with the Boc-units. Not surprisingly, the remainder of the spectrum was otherwise comparable to that of precursor **136**. Similarly, in the ^{13}C NMR spectrum signals due to the two carbamate protecting groups were clearly visible at δ 155.8/149.6, 83.4/79.1 and 28.3/28.1. These were assigned to the carbonyl groups, the quaternary centres of the *t*-butyl groups and the two sets of three methyl groups of the *t*-butyl moieties, respectively. EI mass spectrometric analysis revealed a molecular ion and an accurate mass measurement on this ion then established that this possessed the expected molecular formula, namely $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_2$.

When compound **137** was reacted with 6,6-dibromobicyclo[3.1.0]hexane (**41**) and silver tetrafluoroborate under anhydrous conditions the desired compound **140**, arising from trapping of the π -allyl cation by the C-2 of the indole ring system, was not observed. Rather, the two depicted and chromatographically separable products **138** and **139** were obtained in 63% and 15% yields, respectively. Characteristic features in the ^1H NMR spectrum of **138** such as a triplet at δ 6.20 ($J = 3.9$ Hz) due to the newly introduced olefinic proton, a broad singlet at δ 4.67 due to the cyclohexyl methine proton at the site of trapping and, of course, the six extra proton resonances present upfield in the cyclohexyl region all confirmed that the π -

allyl cation had been involved in a trapping process with starting material **137**. However, as all of the indolic protons associated with the starting material were still present in the product, the desired coupling, at C-2 and leading to the desired 2,3-disubstituted indole **140**, had obviously not occurred. The ^{13}C NMR spectrum, as well as low and high resolution MS data, were in full accord with the depicted structure **138**, of composition $\text{C}_{26}\text{H}_{35}\text{BrN}_2\text{O}_4$.

Scheme 2.3: Reaction of Tryptamine (136) with Cyclopropane 41



Reagents and conditions: (a) $(\text{Boc})_2\text{O}$, DMAP, Et_3N , CH_2Cl_2 , 18°C , 3 h; (b) AgBF_4 , THF, 18°C , 8 h.

A similar spectral data set was acquired for compound **139**. The salient features observed in both the ^1H and ^{13}C NMR spectra of this compound were the absence of signals due to a second Boc-protecting group. Hence cleavage of one such group associated with the starting material **137** must have occurred. That this “monodeprotection” reaction had indeed occurred was confirmed by high resolution mass spectrometry which established that compound **138** possessed the molecular formula $\text{C}_{21}\text{H}_{27}\text{BrN}_2\text{O}_2$.

Unfortunately, it appears that the Boc-protecting group on the exocyclic nitrogen of tryptamine does not prevent this heteroatom from acting as a nucleophile in trapping cation **126**. Furthermore, given the nature of the second product, amine **139**, the Boc-protecting group is clearly not completely stable to the reaction conditions employed. The anticipated coupling was obviously not observed in this instance and further studies directed towards achieving such ends are discussed in Chapter Six.

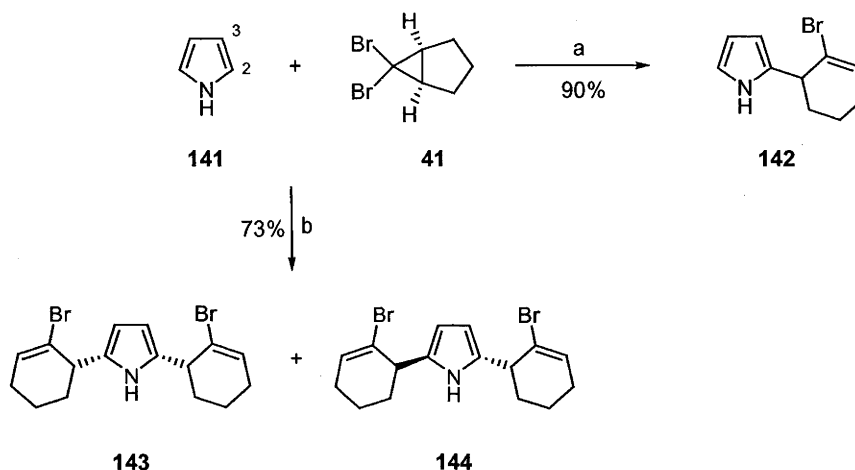
2.2.2 π -Allyl Cation Trapping Utilising Other Electron-Rich Aromatic Heterocycles

2.2.2.1 Employing Pyrrole (**141**) as the Nucleophile

Having established that the π -allyl cation generated from the electrocyclic ring-opening of cyclopropane **41** can be successfully trapped by the C-3 of indole (**128**), a study of the capacity of other electron-rich aromatic heterocycles to act as trapping agents was undertaken. It has long been acknowledged that pyrrole (**141**) undergoes kinetic electrophilic substitution predominantly, if not exclusively, at C-2 and for the same sorts of reasons that electrophilic attack occurs preferentially at C-3 in indole (**128**).⁸ Thus, a product of the structure **142** might be anticipated upon subjection of a mixture of pyrrole (**141**) and cyclopropane **41** to reaction with a silver(I)-salt (Scheme 2.4). In the event, a solution of equimolar amounts of pyrrole (**141**) and cyclopropane **41** in THF was treated with silver tetrafluoroborate and after four hours compound **142** was indeed isolated as a clear, colourless oil and in 90% yield. Conclusive evidence to substantiate this structural assignment derives from spectral data obtained. Most notably, the ¹H NMR spectrum displayed four signals in the olefinic region, which were attributed to the three pyrrolic protons and the alkenic proton of the newly established bromocyclohexene unit. In both the ¹H and ¹³C NMR spectra resonances attributable to H-3 and H-4 as well as C-3 and C-4 were present (δ_{H} 6.27 and 6.03, δ_{C} 108.4 and 106.0). Similarly, signals due to C-2 and C-5 were observed (at δ_{C} 131.6 and 116.6) but only one signal due to a proton attached to such a carbon was apparent (δ_{H} 6.72). This result implied that the π -allyl cation **126** had attached at the expected position, namely C-2 of pyrrole (**141**). Verification that the reaction had not occurred at the pyrrole nitrogen was

evident by virtue of the appearance of a broad NH singlet at δ 8.10 in the ^1H NMR spectrum. The appearance of an absorption band at 3418 cm^{-1} in the infrared spectrum also established the presence of a free NH moiety. The 70 eV EI mass spectrum of compound **142** displayed molecular ions at m/z 227 and 225 in the expected 1:1 ratio. High resolution measurements on both ions confirmed that the composition of compound **142** was $\text{C}_{10}\text{H}_{12}\text{BrN}$.

Scheme 2.4: Reaction of Pyrrole (**141**) with Cyclopropane **41** in the Presence of AgBF_4



Reagents and conditions: (a) 1 eq. **141**, 1 eq. **41**, AgBF_4 , THF, $18\text{ }^\circ\text{C}$, 4 h; (b) 1 eq. **141**, 2 eq. **41**, AgBF_4 , THF, $18\text{ }^\circ\text{C}$, 4 h.

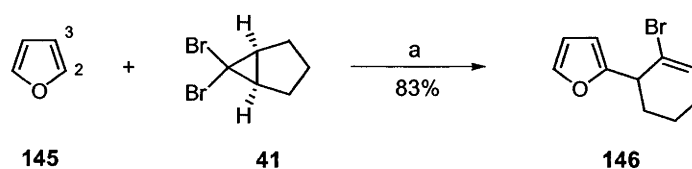
Interestingly, disubstitution of the pyrrole ring could also be achieved. Thus, upon treating a 2:1 mixture of 6,6-dibromobicyclo[3.1.0]hexane (**41**) and pyrrole (**141**) with silver tetrafluoroborate in THF at $18\text{ }^\circ\text{C}$ for four hours a *ca.* 1:1 and inseparable mixture of the diastereoisomeric 2,5-disubstituted pyrroles, **143** and **144**, was obtained along with traces of the mono-adduct **142**. The ^{13}C NMR spectrum of this mixture clearly displayed sixteen resonances, as would be expected for a mixture of *d,l*- and *meso*-diastereoisomers. The ^1H NMR spectrum of this mixture showed a broad singlet at δ 7.94 corresponding to the two NH protons and two multiplets at δ 6.25 and 6.22-6.19, attributable to the H-3 and H-4 protons. EI mass spectrometry revealed molecular ions at m/z 387, 385 and 383 and in the 1:2:1 ratio

expected for a dibrominated material. An accurate mass measurement established that the composition of *bis*-adducts **143** and **144** was as expected, namely $C_{16}H_{19}Br_2N$.

2.2.2.2 Employing Furan (145) as the Nucleophile

Another electron-rich aromatic heterocycle that readily undergoes electrophilic substitution reactions with a wide range of electrophiles is furan (**145**). It is also known that the C-2 position of this compound is generally more susceptible to electrophilic attack than the C-3 position and presumably, like the pyrrole system, this is due to the more extended conjugation of the intermediate cation generated by electrophilic attack at the C-2 position.⁹ Therefore, due to the similarities in reactivity exhibited by pyrrole and furan, it is conceivable that furan (**145**) will react with the π -allyl cation derived from 6,6-dibromobicyclo[3.1.0]hexane (**41**) in a manner analogous to that observed earlier. In the event, subjection of a 1:1 mixture of **41** and **145** in anhydrous THF to reaction with silver tetrafluoroborate gave compound **146** as a clear, colourless oil and in 83% yield (Scheme 2.5).

Scheme 2.5: Reaction of Furan (**145**) with Cyclopropane **41** in the Presence of $AgBF_4$



Reagents and conditions: (a) $AgBF_4$, THF, 18 °C, 7 h.

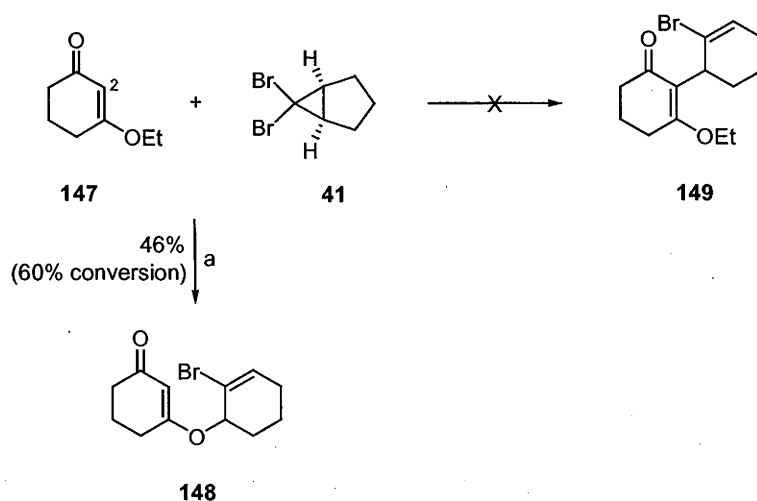
Four olefinic resonances were observed in the 1H NMR spectrum of compound **146**, three attributable to the protons on the furan ring system and one, at δ 6.28 (dt, $J = 3.9$ and 1.2 Hz), being assigned to the newly established cycloalkenyl bromide moiety. In both the 1H and ^{13}C NMR spectra resonances attributable to H-3 and H-4 as well as C-3 and C-4 were present (δ_H 6.33 and 6.15, δ_C 110.1 and 106.9). Similarly, signals due to C-2 and C-5 were observed at δ_C 155.7 (C) and 141.4 (CH) but only one signal due to a proton attached to such a carbon was

apparent (δ_{H} 7.34). This result implied that the π -allyl cation **126** had attacked at the expected position, namely C-2 of furan (**145**). A characteristic isotope pattern was observed for the molecular ions (m/z 228 and 226) and accurate mass measurements on these confirmed the molecular formula of adduct **146** as $\text{C}_{10}\text{H}_{11}\text{BrO}$.

2.2.3 Extension to Non-Aromatic Systems

The results obtained, as detailed above, for the electrocyclic ring-opening and subsequent nucleophilic trapping of cyclopropane **41** with various heteroaromatic compounds prompted investigations into the use of non-aromatic systems as C-centred nucleophiles. As shown in Scheme 2.6, commercially available 2-ethoxy-2-cyclohexen-1-one (**147**) was the first substrate employed in such studies. Not only was compound **147** chosen for its ready availability but it was also thought that the presence of the ethoxy-moiety would sufficiently activate C-2 so as to render it capable of attack by the π -allyl cation generated from ring-opening of compound **41**.

Scheme 2.6: Outcome of Reaction of β -ketoester **147** and Cyclopropane **41** with AgBF_4



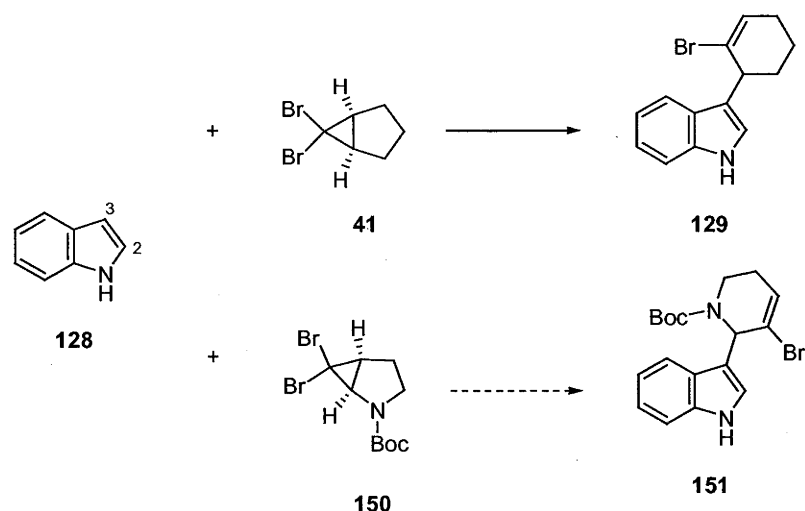
Reagents and conditions: (a) AgBF_4 , THF, 18 °C, 12 h.

In the event, when a 1:1 mixture of 2-ethoxy-2-cyclohexen-1-one (**147**) and cyclopropane **41** in anhydrous THF was treated with silver tetrafluoroborate (Scheme 2.6), a large amount of starting enone was recovered from the reaction mixture. However, a new product was also observed and this has tentatively been assigned as adduct **148** based on the spectroscopic data obtained. Thus, key features that led to the assignment of this structure were the presence of signals at δ 6.40 and 5.38 in the ^1H NMR spectrum which are attributed to the olefinic signal associated with a bromocyclohexenyl unit and the olefinic signal associated with the enone, respectively. In the ^{13}C NMR spectrum all of the twelve resonances expected for ether **148** were observed while mass spectral analysis, in both low and high resolution modes, revealed the $[\text{M}-\text{Br}]^+$ fragment ion as the predominant species. No molecular ion could be detected in this instance.

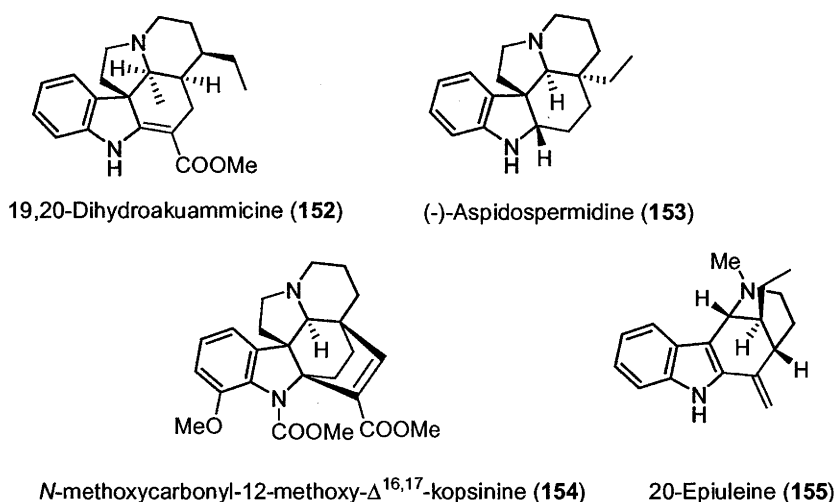
Formation of this compound is mechanistically reasonable given that HBr is a side product of the electrocyclic ring-opening of cyclopropane **41** and, hence, should facilitate cleavage of the enol ether moiety within substrate **147** to give the corresponding β -hydroxycyclohexenone. Although this enolic product is, in principle, an ambident nucleophile, attack of the π -allyl cation **126** appears to occur preferentially at oxygen and not, unfortunately, at carbon. While the desired coupling was not observed in this instance useful information on the limitations of the reaction of π -allyl cations derived from ring-fused *gem*-dibromocyclopropanes had been obtained and this should prove beneficial for further synthetic design.

2.3 Introduction of a Heteroatom into the Ring System Adjacent to the Cyclopropane Moiety

In the previous sections of this Chapter electrocyclic ring-opening reactions of “all carbon” cyclopropanes, such as **41**, and intermolecular trapping of the resulting π -allyl cations by a variety of carbon-centred nucleophiles have been described. This section focuses on extending this methodology so as to generate π -allyl cation species that incorporate nitrogen within the ring. So, for example, if compound **150** could be induced to undergo electrocyclic ring-opening and the resulting π -allyl cation trapped by carbon-centred nucleophiles such as indole (**128**), then adduct **151** might be expected to be formed (Figure 2.3).

Figure 2.3: Possible Extension of Methodology to Involve 2-Azabicyclo[3.1.0]hexane Systems

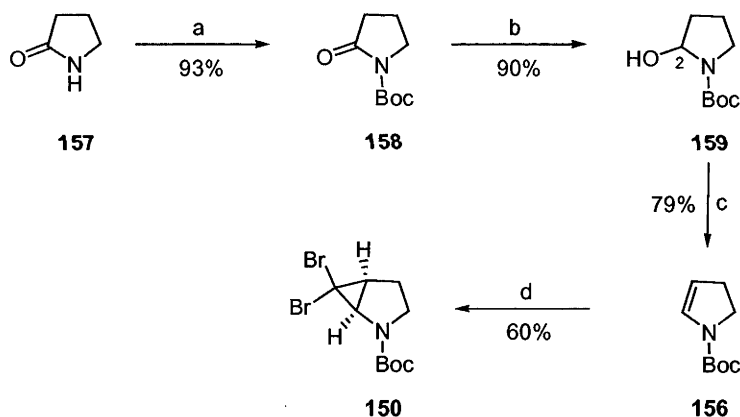
If realised such a conversion would be of considerable interest from a synthetic point-of-view because adduct **151** structurally resembles the 3-(2-piperidyl)indole moiety which is present in the Strychnan-, Aspidospermatan-, Plumeran- and Uleine-type indole alkaloids.¹⁰ Representative examples of such alkaloids include compounds **152**, **153**, **154** and **155**.



The obvious precursor to the required cyclopropane **150** would be cyclic enecarbamate **156** (Scheme 2.7). Such enamines are common synthetic intermediates and therefore various methods for their assembly have been reported.¹¹ A rapid and convenient procedure for the

conversion of Boc-protected lactams into enecarbamates, as reported by Dieter and Sharma in 1996, was followed in the preparation of compound **156**.¹² Thus, commercially available 2-pyrrolidinone (**157**) was converted into the corresponding Boc-protected lactam **158** under standard conditions, utilising di-*tert*-butyl dicarbonate, DMAP and triethylamine. After purification the desired product was obtained in excellent yield (93%) and as a pale-yellow oil. As expected, a strong spectroscopic resemblance was observed between the starting lactam and product **158** with the only noticeable differences in both the ¹H and ¹³C NMR spectra being the obvious inclusion of the carbamate moiety. EI mass spectrometry and an accurate mass measurement on the molecular ion so-observed established the molecular formula of compound **158** as C₉H₁₅NO₃.

Scheme 2.7: Synthetic Route Used in the Preparation of Cyclopropane **150**



Reagents and conditions: (a) (Boc)₂O, DMAP, Et₃N, CH₂Cl₂, 18 °C, 2 h; (b) DIBAL-H, THF, -78 °C, 2 h; (c) HMPA, 170 °C, 4 h; (d) CHBr₃, TEBAAC, NaOH, CH₂Cl₂, 2 h.

With compound **158** in hand, the reported procedure¹² could then be followed to complete the synthesis of enecarbamate **156**. Thus, reduction of the lactam was effected using DIBAL-H. The desired cyclic aminol **159** was thus obtained, after purification, in 90% yield and as a clear, colourless oil. In full accord with the previously reported spectroscopic data,¹² this compound existed as a mixture of rotamers. The distinctive feature in the ¹H NMR spectrum

of compound **159**, which confirmed that the desired reduction of precursor **158** had occurred, was the appearance of a resonance, in the form of a complex multiplet, at δ 5.50-5.36. This is assigned to the proton (H-2) adjacent to both the alcohol and nitrogen moieties. The salient features in the ^{13}C NMR spectrum were the disappearance of the previously observed carbonyl resonance at δ 173.9 for precursor **158** and replacement of this with signals at δ 81.1 and 81.0, attributable to a carbon (C-2) carrying alcohol and amine functionalities and split due to the presence of the two rotameric forms of the Boc-protecting group within compound **159**. An accurate mass measurement also confirmed the composition to be that depicted, namely $\text{C}_9\text{H}_{17}\text{NO}_3$.

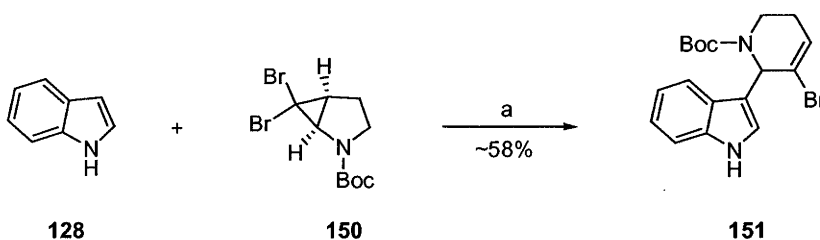
The final step in the synthesis of enecarbamate **156** involved dehydration of compound **159** and this was readily accomplished in boiling HMPA. In this way cyclic enamine **156** was obtained in 79% yield. The proton and carbon resonances arising from the newly formed olefin were clearly visible at δ_{H} 6.45 (1H) and 4.99 (1H) and at δ_{C} 129.4 (CH) and 107.0 (CH). The 70 eV EI mass spectrum was in full agreement with the structure and an accurate mass measurement on the protonated molecular ion appearing at m/z 170 confirmed the composition of the product as $\text{C}_9\text{H}_{15}\text{NO}_2$.

Subjection of compound **156** to a Brinker-type dibromocarbene addition reaction¹³ afforded the requisite cyclopropane **150** in 60% yield. The ^1H NMR spectrum of this compound no longer displayed any resonances in the olefinic region but, rather, two new proton signals were observed upfield at $\sim \delta$ 2 ppm. Similarly, in the ^{13}C NMR spectrum no signals due to olefinic carbons were seen. However, resonances characteristic of cyclopropane functionality were evident at δ 48.8 (48.5) (CH), 36.1 (35.7) (CH) and 34.8 (34.1) (C). In correspondence with these observations, no enamine C=C stretching band was observed in the infrared spectrum. The 70 eV EI mass spectrum of compound **150** displayed molecular ions at m/z 343, 341 and 339 and these were present in a 1:2:1 ratio, as is expected for a dibrominated compound. Informative fragmentation ions were also observed at m/z 260 and 240/238, corresponding to loss of a bromine radical and loss of the *tert*-butoxycarbonyl moiety, respectively. A third fragmentation ion was present at m/z 160 and this corresponds to the consecutive loss of the two aforementioned groups. The molecular ion proved too weak for

accurate mass measurement but it was possible to obtain this measurement on all of the fragmentation ions discussed above and such studies implied, therefore, the composition of compound **150** was $C_{10}H_{15}Br_2NO_2$.

With adduct **150** successfully prepared efforts could then be directed towards replicating the “coupling” which was earlier observed between indole (**128**) and 6,6-dibromobicyclo[3.1.0]hexane (**41**). To this end, a suspension of cyclopropane **150**, indole (**128**) and silver tetrafluoroborate in anhydrous THF was stirred magnetically at ambient temperature for 16 hours (Scheme 2.8). Subsequent filtration and purification by flash column chromatography delivered a product, which has been tentatively assigned as the expected compound **151**. This reaction has only been conducted on a small scale to date and has hence precluded the collection of a full range of spectroscopic data at this time. However, the 1H NMR and EI mass spectra are in accord with this provisional assignment.

Scheme 2.8: Towards the 3-(2-piperidyl)indole Type Moiety **151**



Reagents and conditions: (a) $AgBF_4$, THF, 18 °C, 16 h.

In particular, pertinent features observed in the 1H NMR spectrum were the resonance attributable to the cycloalkenyl bromide proton (at δ 6.49) and the 1:1 ratio of signals due to protons associated with the cyclohexyl and indolic ring moieties. A 70 eV EI mass spectrum displayed the molecular ions to be m/z 364 and 362, as is expected for a mono-bromo-containing compound. An accurate mass measurement was obtained on the most dominant fragmentation ion, namely that corresponding to loss of a bromine atom from the molecular ion, $[M-Br]^+$, and based on this the molecular formula is presumed to be that of the depicted

structure (C₁₈H₂₁BrN₂O₂). One of the major problems associated with obtaining a workable quantity of product **151** for full characterisation appears to arise from loss of the carbamate protecting group during the reaction. Therefore, it appears logical that this work should be repeated with a more stable protecting group such as an *N*-methyl moiety. The use of such a group also has the added advantage that it is present in the natural products of the Uleine group (see, for example, structure **155**) and, therefore, would ultimately reduce the number of steps required if a total synthesis of such systems was to be pursued. Work in this area is ongoing and further applications are discussed in Chapter Six. Most importantly, however, it should be noted that the desired “coupling” reaction does in fact appear to have been successful and, therefore, this type of conversion could prove widely applicable in the synthesis of a vast range of natural products.

2.4 Conclusions

A diverse range of heteroaromatic systems capable of functioning as *C*-centred nucleophiles have been successfully utilised to trap the π -allyl cations arising from the electrocyclic ring-opening of *gem*-dibromocyclopropanes, hence highlighting the potential of these three-membered carbocycles to participate in a synthetically valuable method for carbon-carbon bond formation. Key *C*-centred nucleophiles effectively exploited in this manner include indoles, pyrrole and furan. Furthermore, it was also observed that *bis*-substitution could be accomplished by addition of an extra equivalent of cyclopropane **41** into the reaction mixture as highlighted by the efficient formation of compounds **143** and **144** as shown in Scheme 2.4.

During the course of the abovementioned methodological studies some of the limitations of such reactions were also uncovered. Based on the reported findings it would appear, as is possibly expected, that attack of the derived π -allyl cation may preferentially occur at nitrogen or oxygen as opposed to carbon. Hence this suggests that protection of these functionalities would have to be carried out before the desired carbon-carbon bond forming reaction is attempted. Such information is obviously highly beneficial for further synthetic design and in ultimately determining the scope of the title process and their potential in the total synthesis of alkaloidal natural products.

Despite the limitations noted above it was also established, as demonstrated through the work reported in the latter part of this Chapter, that extension of this methodology from bicyclo[3.1.0]hexane systems to their 2-azabicyclo[3.1.0]hexane counterparts can be achieved. This last outcome serves to further highlight the immense synthetic potential of this type of conversion.

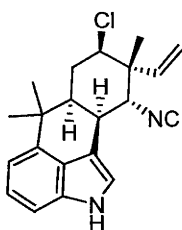
2.5 References

- ¹ Caine, D.; in *Comprehensive Organic Synthesis*, Trost, B.M., Fleming, I. (Eds.), Pergamon Press: Oxford, **1991**, Vol. 3, pp. 34-35.
- ² Banwell, M.G., Cowden, C.J., Mackay, M.F.; *J. Chem. Soc., Chem. Commun.*, **1994**, *1*, 61-62.
- ³ Makosza, M., Wawrzyniewicz, M.; *Tetrahedron Lett.*, **1969**, *10*, 4659-4662.
- ⁴ Xu, L., Brinker, U.H.; in *Synthetic Organic Sonochemistry*, Luche, J.L. (Ed.), Plenum Press: New York, **1998**, pp. 344-345.
- ⁵ Banwell, M.G., Reum, M.E.; in *Advances in Strain in Organic Chemistry*, Halton B. (Ed.), JAI Press Ltd: London, **1991**, Vol. 1, pp. 19-64.
- ⁶ Sundberg, R.J.; *Indoles*, Academic Press: London, **1996**.
- ⁷ Banwell, M.G., Reum, M.E.; in *Advances in Strain in Organic Chemistry*, Halton, B. (Ed.), JAI Press Ltd: London, **1991**, Vol. 1, pp. 19-64.
- ⁸ Jones, R.A., Bean, G.P.; *The Chemistry of Pyrroles*, Academic Press: London, **1977**.
- ⁹ Koreeda, M., Yang, W.; in *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.A. (Ed.), John Wiley and Sons: Chichester, **1995**, Vol. 4, pp. 2600-2604.
- ¹⁰ Kiskürek, M.V., Leeuwenberg, A.J.M., Heese, M.; in *Alkaloids: Chemical and Biological Perspectives*, Pelletier, S.W. (Ed.), John Wiley & Sons: New York, **1983**, Chapter 5.
- ¹¹ Oliveira, D.F., Miranda, P.C.M.L., Correia, C.R.D.; *J. Org. Chem.*, **1999**, *64*, 6646-6652 and references therein.
- ¹² Deiter, R.K., Sharma, R.R.; *J. Org. Chem.*, **1996**, *61*, 4180-4184.
- ¹³ Xu, L., Brinker, U.H.; in *Synthetic Organic Sonochemistry*, Luche, J.L. (Ed.), Plenum Press: New York, **1998**, pp. 344-345.

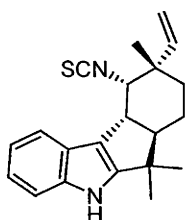
Enantioselective Preparation of the Polycyclic Ring Systems Associated with Certain Hapalindole and Fischerindole Alkaloids

3.1 Introduction

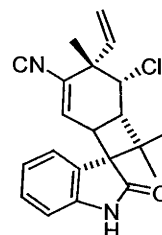
For many decades it has been recognised that blue-green algae are a source of an enormous array of both structurally and biologically interesting secondary metabolites. For example, a range of intriguing isonitrile-containing indole alkaloids have been observed amongst branched, filamentous blue-green algae (cyanobacteria) belonging to the *Stigonemataceae*. To date a number of related classes of such compounds have been identified and these encompass the hapalindoles,¹ fischerindoles,^{2,3} wetwitindolinones,^{3,4} ambiguine isonitriles,^{5,6} hapalonamides^{7,8} and hapalindolinones.⁹ Representative members of these groups of compounds are shown immediately below.



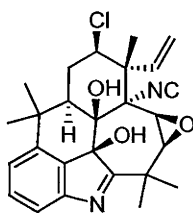
Hapalindole A (160)



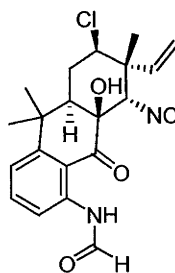
Fischerindole U isothiocyanate (161)



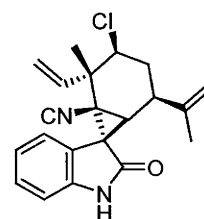
Wetwitindolinone A (162)



Ambiguine D Isonitrile (163)



Hapalonamide V (164)



Hapalindolone A (165)

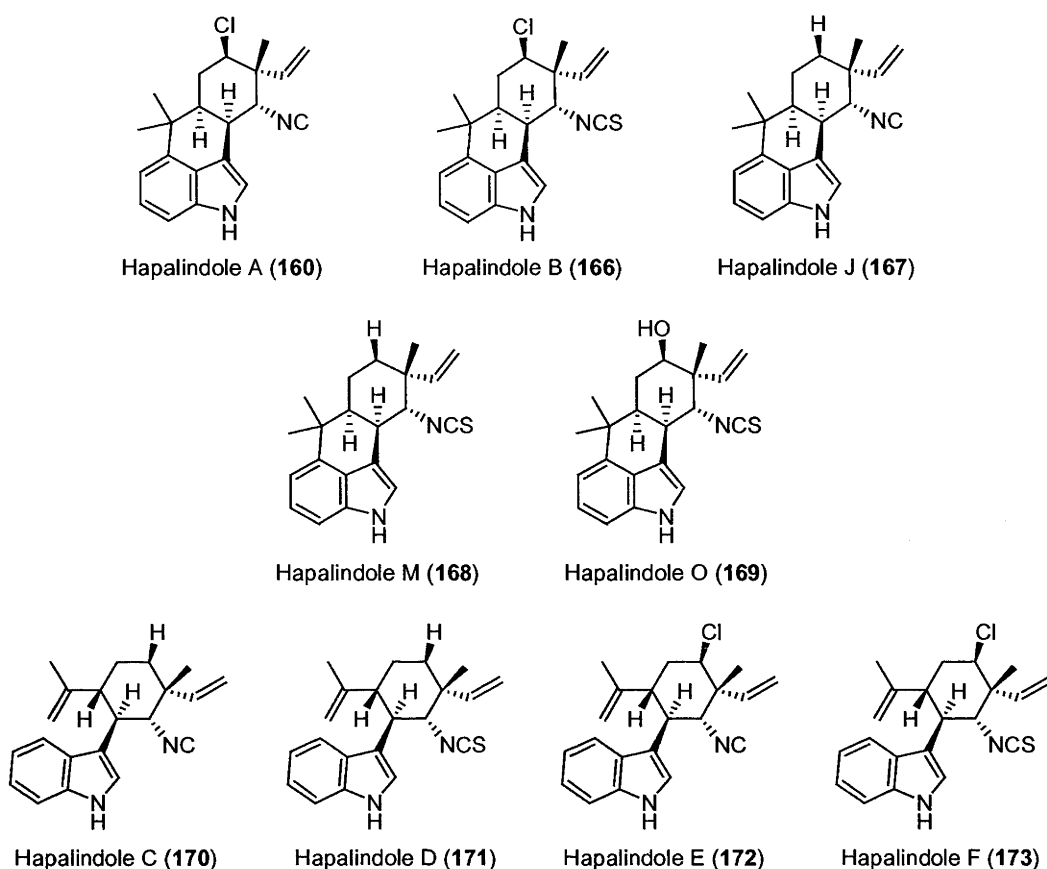
Whilst all of these alkaloids exhibit a strong structural relationship and all are significant natural products, for the purposes of providing background material relevant to the work described in this Chapter, only the hapalindole and fischerindole classes will be discussed in detail in the following sections.

3.2 The Hapalindole and Fischerindole Alkaloids

3.2.1 Isolation and Structure of the Hapalindole Alkaloids

The initial isolation and structural elucidation of the hapalindole alkaloids was carried out in 1982 by Moore and co-workers and using, as the source organism, the terrestrial blue-green algae *Hapalosiphon fontinalis* – a soil cyanobacterium indigenous to the Marshall Islands (located in the central Pacific Ocean north of New Zealand).¹⁰ The hapalindoles are not exclusive to *H. fontinalis*, however, having been isolated from a range of other organisms.¹¹ To date approximately twenty hapalindole alkaloids have been isolated and characterised. They can be further divided into two broad classes on the basis of chemical structure. Approximately fifteen such alkaloids possess a previously unknown tetracyclic indoloterpene framework, whilst the remainder embody a highly substituted 3-cyclohexylindole structure. As discussed in more detail below, these latter compounds are thought likely to be the biogenetic precursors to the tetracyclic members of the class.

The majority of hapalindole alkaloids possess either isonitrile or isothiocyanate functionality attached to the cyclohexanyl subunit. Both chlorinated and non-chlorinated examples of these natural products are known. The most abundant (and first isolated) member of the class is hapalindole A (**160**). The absolute stereochemistry of this compound was initially established through extensive spectroscopic studies and the assignments made on this basis were later confirmed by single-crystal X-ray crystallography.¹² The structures of the remainder of the hapalindole alkaloids were determined either by X-ray crystallography or through comparisons between the derived NMR data and those previously obtained for hapalindole A (**160**). In many cases the proposed structures have since been confirmed by total synthesis.

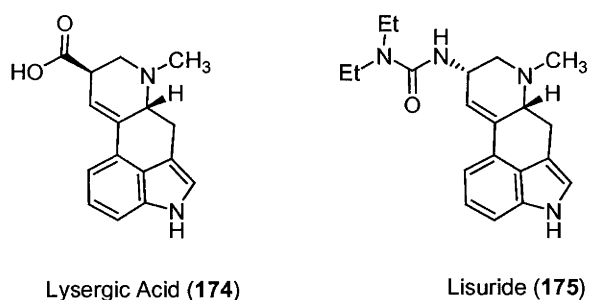
Figure 3.1: Selected Tri- and Tetra-cyclic Hapalindoles

3.2.2 Biological Activity and Proposed Biogenesis of the Hapalindoles

The hapalindole alkaloids are known to possess antibacterial, antimycotic¹² and antialgal activity.¹³ Indeed these alkaloids are responsible, at least in part, for the fungicidal activity of the lipophilic extract of several species of *Hapalosiphon*, *Fischerella*, *Westiellopsis prolifica* and *Westiella intricata*.¹⁴ Whilst the ability of these compounds to kill bacteria and fungi is well documented their precise modes of action remained unknown until recently. However, it is now thought that the biological activity observed can be attributed to the ability of these alkaloids to inhibit DNA-directed RNA synthesis and, therefore, *in vivo* protein production.^{15,16}

Hapalosiphon fontinalis has not yet been shown to produce related formamides and amines which often accompany natural products incorporating isonitrile and/or isothiocyanate

moieties. However, an obvious structural resemblance observed between the ergot alkaloids, examples of which include lysergic acid (**174**) and lisuride (**175**), and the hapalindole alkaloids prompted the preparation, by semi-synthetic means, of the corresponding formamides and amines for pharmacological evaluation. Disappointingly, this structural variation markedly reduced both antibacterial and antifungal activity.¹⁷



Biogenetically speaking, it appears that the tricyclic hapalindole alkaloids are formed through a condensation of intermediates, **176** and **177**, derived from geraniol pyrophosphate and tryptophan,¹⁸ respectively as is depicted in Figure 3.2 for the previously isolated¹⁹ hapalindole **178**. As mentioned earlier, it is also postulated that the tricyclic hapalindole alkaloids may in fact be the biogenetic precursors of their tetracyclic congeners [e.g. hapalindole L (**179**)], presumably as a result of the operation of a cationic cyclisation process.²⁰

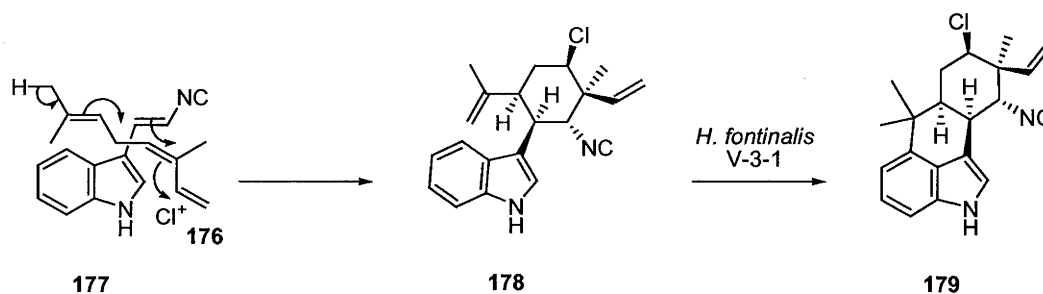


Figure 3.2: Proposed Biogenesis of Hapalindole L (**179**).

3.2.3 The Fischerindole Alkaloids

As noted earlier, the fischerindoles are a class of compounds structurally related to the hapalindoles. They possess a novel octahydroindeno[2,1-*b*]indole isonitrile structure and were first isolated from a terrestrial cyanophyte *Fischerella muscicola* in the early 1990's. Like the hapalindoles, various fischerindoles exhibit antifungal activity and, in general, tend to possess the same relative stereochemistry as seen in the corresponding hapalindole. Indeed they are thought to arise *via* an enzyme-mediated and/or acid-catalysed condensation of the isopropenyl moiety of the tricyclic hapalindoles onto the C-2 position of the indole substructure.²¹ This process has since been shown to occur (non-enzymatically) in the presence of acid.²² Interestingly, whilst the hapalindole alkaloids have been isolated from the *Fischerella* cyanophyte, no fischerindole alkaloids have, thus far, been isolated from *Hapalosiphon fontinalis*.

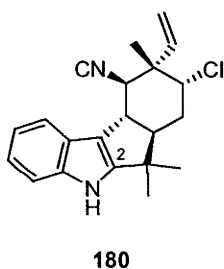


Figure 3.3: *Fischerindole L (180): A Representative Member of the Fischerindole Class of Alkaloid*

3.3 Previous Total Syntheses of the Hapalindole Alkaloids

3.3.1 Overview

Since the initial isolation of the hapalindoles in 1982 their complex structures and biological activity have prompted a number of groups to undertake total synthesis studies. One obvious challenge associated with such endeavours arises from the fact that the hapalindoles possess multiple rings and stereocentres. The latter feature, when considered together with the lack of heteroatoms to aid in the C-C bond formation process, serves to highlight the demands placed

upon the synthetic chemist in attempting to assemble such systems. Despite this, several elegant approaches have been implemented. The following section provides an overview of the completed total syntheses of various hapalindole alkaloids and attempts to highlight the strategies and tactics that have been employed in the construction of both the tri- and tetra-cyclic frameworks associated with these natural products.

3.3.2 Total Syntheses

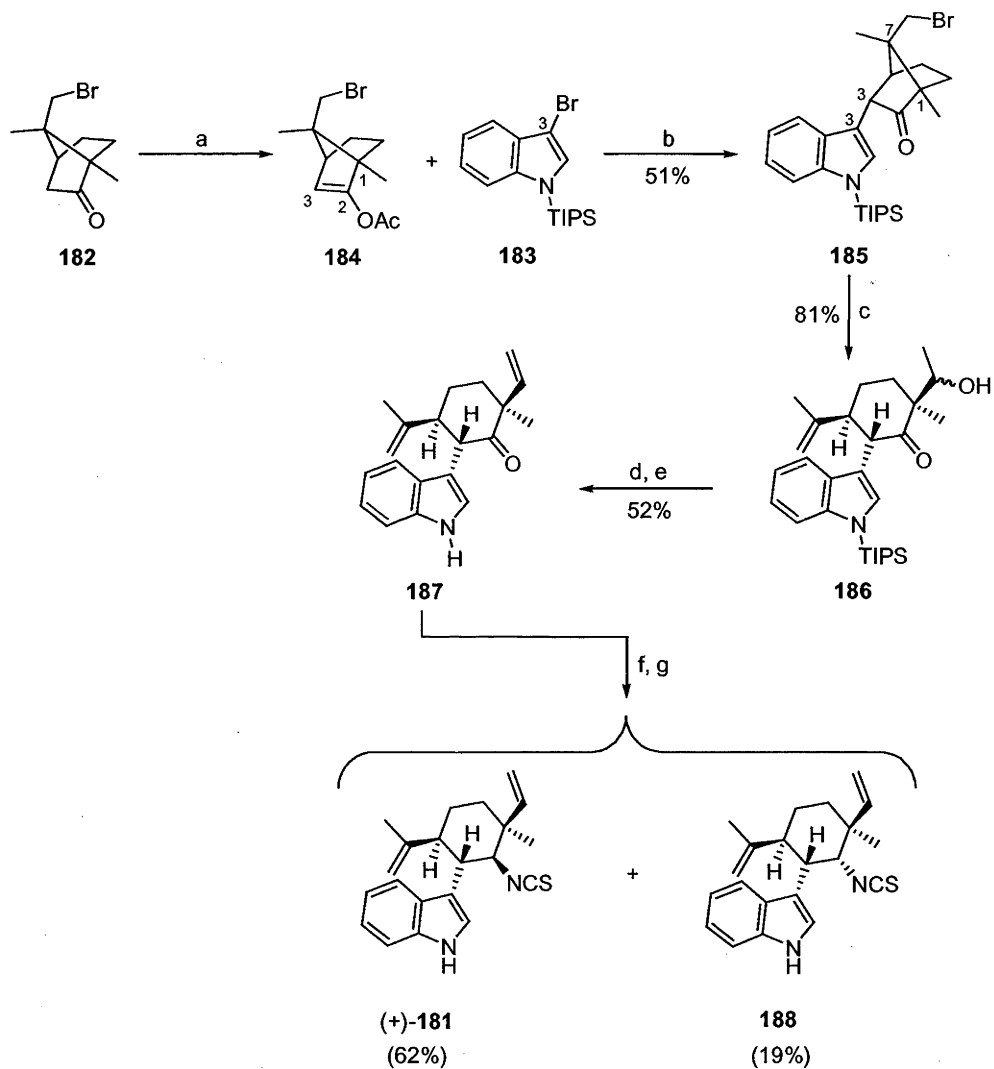
Albizati's Synthesis – 1993

In 1993 Albizati and Vaillancourt reported an enantioselective synthesis of (+)-hapalindole Q (**181**) from (+)-(1*R*)-9-bromocamphor (**182**) which proceeded in eight steps and 8% overall yield (Scheme 3.1).²³ Undoubtedly the highlight of this approach was the stereoselective fragmentation of an intermediate bicyclo[2.2.1]heptane into a cyclohexanone possessing the relevant chiral and quaternary carbon centre adjacent (α -) to the carbonyl moiety. This synthesis also served to highlight the versatility of camphor derivatives as chiral building blocks.

The synthetic strategy required the creation of a linkage between the C-3 position of indole and the C-3 position of 9-bromocamphor (**182**), with an *endo*-configuration being established at the latter centre. The desired transformation was achieved through a $\text{Cl}_2\text{Pd}[(o\text{-tol})_3\text{P}]_2$ -catalysed reaction of the protected 3-bromoindole **183** with the tin enolate of 9-bromocamphor (**182**), itself generated *in situ* from enol acetate **184**. This resulted in the acquisition of the desired *endo*-camphor derivative **185** in 51% yield. Adduct **185** then underwent fragmentation of the C1-C7 bond upon treatment with sodium naphthalenide at -78°C . The enolate so-formed was alkylated directly with acetaldehyde to yield products **186**, which were isomeric only at the carbinol centre which would subsequently be removed. These compounds were converted into an isomeric mixture of the corresponding mesylates which, upon subjection to an iodine-promoted thermal elimination, gave the α -vinylated ketone **187** as a single stereoisomer in 52% yield over two steps. Reductive amination with ammonium acetate and sodium cyanoborohydride, followed by treatment with 1,1'-

thiocarbonyldiimidazole consequently provided (+)-hapalindole Q [(+)-**181**] in 62% yield. This was accompanied by 19% of the chromatographically separable epimer **188**.

Scheme 3.1: Albizati's Total Synthesis of (+)-Hapalindole Q (**181**)

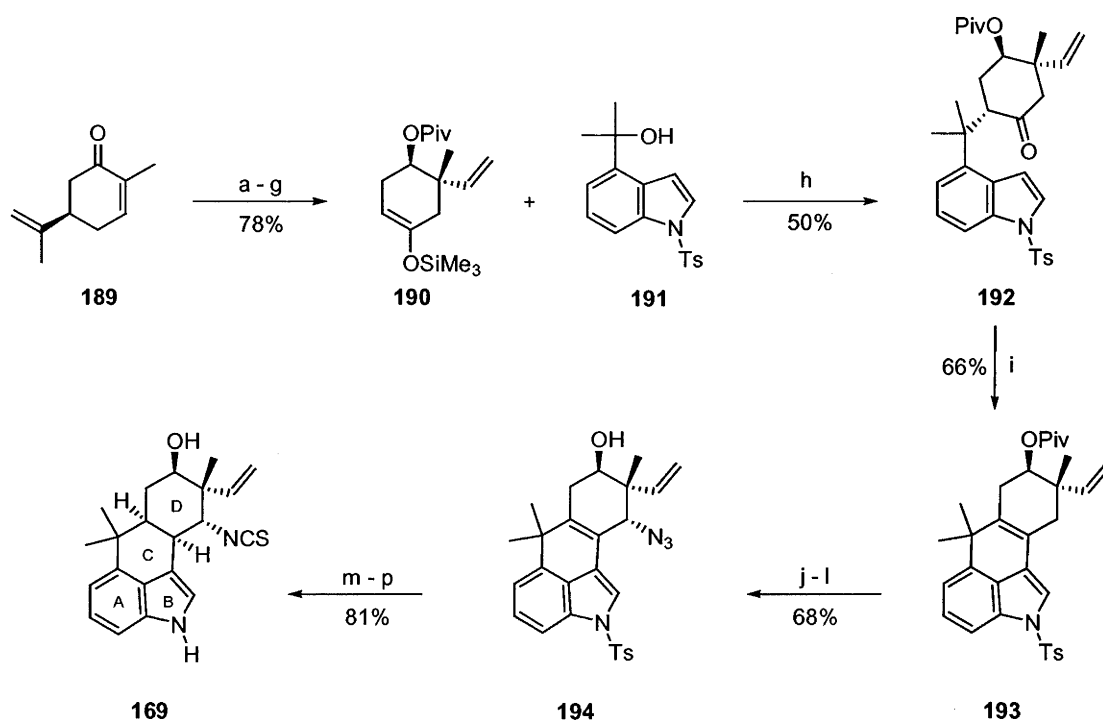


Reagents and conditions: (a) LDA, THF, -78 °C, 1.5 h then Ac₂O, -78 to 0 °C; (b) Bu₃SnOMe, Cl₂Pd[(*o*-tol)₃P]₂, toluene, 100 °C, 5 h; (c) Na-naphthalenide, THF, tetraglyme, -78 °C, 15 min then CH₃CHO, -78 °C, 1.5 h; (d) MsCl, Et₃N, DMAP, CH₂Cl₂, 0 to 18 °C, 4 h; (e) NaI, HMPA, 130 °C, 36 h; (f) NaBH₃CN, NH₄OAc, MeOH, THF, 25 °C, 7 d; (g) CS(imid)₂, CH₂Cl₂, 0 °C, 3 h.

Natsume's Synthesis – 1994

Throughout the early 1990's Natsume and co-workers reported total syntheses of the racemic modifications of hapalindoles J, M, H and U.^{24,25,26,27} Utilising the same methodology, and selecting appropriate chiral pool compounds as starting materials, they were also able to achieve, in 1994, an enantioselective total synthesis of tetracyclic (-)-hapalindole O (**169**) (Scheme 3.2).²⁸

Scheme 3.2: Natsume's Total Synthesis of (-)-Hapalindole O (169**)**



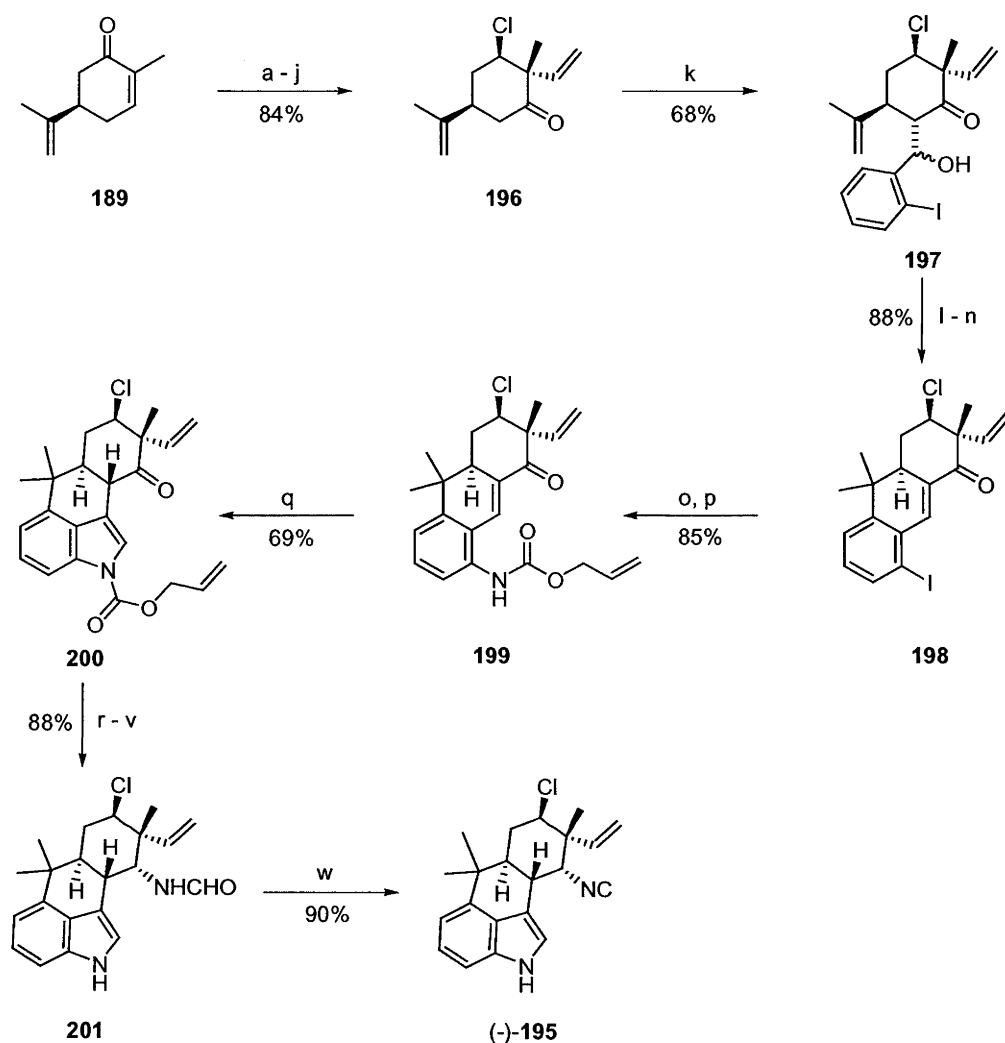
Reagents and conditions: (a) LiAlH_4 , Et_2O , $-10\text{ }^\circ\text{C}$, 5 h; (b) PivCl , pyridine, Et_2O , 0 to $18\text{ }^\circ\text{C}$, 36 h; (c) CrO_3 , dimethylpyrazole, CH_2Cl_2 , -20 to $0\text{ }^\circ\text{C}$, 15 h; (d) NaOMe , MeOH , $0\text{ }^\circ\text{C}$, 1.5 h; (e) vinyl magnesium bromide, $\text{CuBr}\cdot\text{Me}_2\text{S}$, THF , -40 to $-30\text{ }^\circ\text{C}$, 30 min; (f) HCl , dioxane, $90\text{ }^\circ\text{C}$, 4.3 h; (g) LDA , Me_3SiCl , THF , $-73\text{ }^\circ\text{C}$, 10 min then Et_3N , $-73\text{ }^\circ\text{C}$, 3 min; (h) SnCl_4 , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 15 min; (i) $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 24 h; (j) NBS , $(\text{PhCOO})_2$, CCl_4 , reflux, 15 min; (k) NaN_3 , DMF , $18\text{ }^\circ\text{C}$, 3.5 h; (l) DIBAL-H , toluene, $-78\text{ }^\circ\text{C}$, 10 min then MeOH , -78 to $18\text{ }^\circ\text{C}$, then 1M HCl (aq.) , THF , $18\text{ }^\circ\text{C}$, 5 min; (m) ethyl vinyl ether, pyridinium *p*-toluenesulfonate, CH_2Cl_2 , $18\text{ }^\circ\text{C}$, 10 h; (n) LiAlH_4 , THF , $0\text{ }^\circ\text{C}$, 8 h; (o) CS(imid)_2 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 12 h; (p) AcOH , MeOH , H_2O , $18\text{ }^\circ\text{C}$, 6 h.

The distinctive feature of this last synthesis was that the A-, B- and D-rings were established initially and then cyclisation onto the C-3 position of indole allowed for C-ring construction and, thereby, completion of the required tetracyclic framework. Thus, beginning with (*R*)-(-)-carvone (**189**), the silyl enol ether **190** was synthesised in seven steps and this subsequently underwent a coupling reaction with indole **191** in the presence of tin (IV) chloride. Treatment of product **192** with boron trifluoride etherate then afforded intermediate **193** in 66% yield. At this point the required nitrogen functionality was introduced in a previously reported fashion.²⁹ Thus, allylic bromination, conversion of the resulting bromide into the corresponding azide and reductive cleavage of the pivaloyl group afforded compound **194**. The hydroxy group so-revealed was then reprotected as the ethoxyethyl derivative. An unusual and stereo-controlled reduction of this last compound with lithium aluminium hydride, treatment of the crude products with 1,1'-thiocarbonyldiimidazole and removal of the ethoxyethyl moiety with acetic acid in methanol/water finally yielded hapalindole O (**169**).

Fukuyama's Synthesis – 1994

Whilst various total syntheses of the hapalindole alkaloids had been reported by 1994, the synthetically more challenging hapalindoles containing chlorine adjacent to a quaternary centre still remained elusive at this time. However, in this year, Fukuyama and Chen addressed such issues through their enantioselective synthesis of (-)-hapalindole G (**195**).³⁰ Their initial approach involved the cationic cyclisation of a tricyclic precursor onto the C-4 position of indole as had been previously reported.³¹ However, under acidic conditions, exclusive formation of the undesired 2-substituted indole was observed. Subsequently an alternative approach (Scheme 3.3) was developed to circumvent such problems. This new strategy involved assembly of the A-, C-, D-ring systems in the first instance leaving the formation of the B-ring until much later in the sequence and hence distinguishing this synthesis from any others that had been reported to this point. Thus, aldol reaction of ketone **196**, obtained in ten steps from (-)-carvone (**189**), followed by addition of titanium tetraisopropoxide and *o*-iodobenzaldehyde gave the aldol product **197** as a mixture of epimers.

Scheme 3.3: Fukuyama's Total Synthesis of (-)-Hapalindole G (195)



Reagents and conditions: (a) 30% H₂O₂, MeOH, 6 M NaOH (aq.), -15 °C; (b) H₂NNH₂·H₂O, MeOH, 0.1 M acetic acid, 18 °C; (c) MeO₂CCH₂COCl, Et₃N, CH₂Cl₂, -30 °C; (d) *p*-AcNHC₆H₄SO₂N₃, DBU, CH₃CN, 23 °C; (e) Cu(II)bis(salicylidene-*tert*-butylamine), CH₂Cl₂, 70 °C; (f) LiCl, CSA, DMF, 140 °C; (g) LDA, THF, -78 °C then CBr₄, -78 to 23 °C, (h) DIBAL-H, CH₂Cl₂, -78 °C then EtOH, NaBH₄, 23 °C; (i) Zn-Cu couple, EtOH, reflux; (j) Jones' reagent, acetone, 23 °C; (k) LDA, THF, (*i*-PrO)₄Ti, -78 °C then *o*-IC₆H₄CHO; (l) Ac₂O, pyridine, 60 °C; (m) DBU, benzene, reflux; (n) TFA, CH₃SO₃H, 23 °C; (o) Pd(OAc)₂, PPh₃, Et₃N, CO (1 atm), CH₃CN, H₂O, 80 °C; (p) DPPA, Et₃N, allyl alcohol, toluene, 110 °C; (q) LiCHSMes(SOMe), THF, -78 °C then H₂O, HgCl₂, HClO₄, 80 °C; (r) NaBH₄, MeOH, 23 °C; (s) Ms₂O, pyridine, 65 °C; (t) LiN₃, 2% H₂O-DMF, 100 °C; (u) Na/Hg, EtOH, reflux; (v) HCO₂H, Ac₂O, pyridine, CH₂Cl₂, 23 °C; (w) COCl₂, Et₃N, CH₂Cl₂, 0 °C.

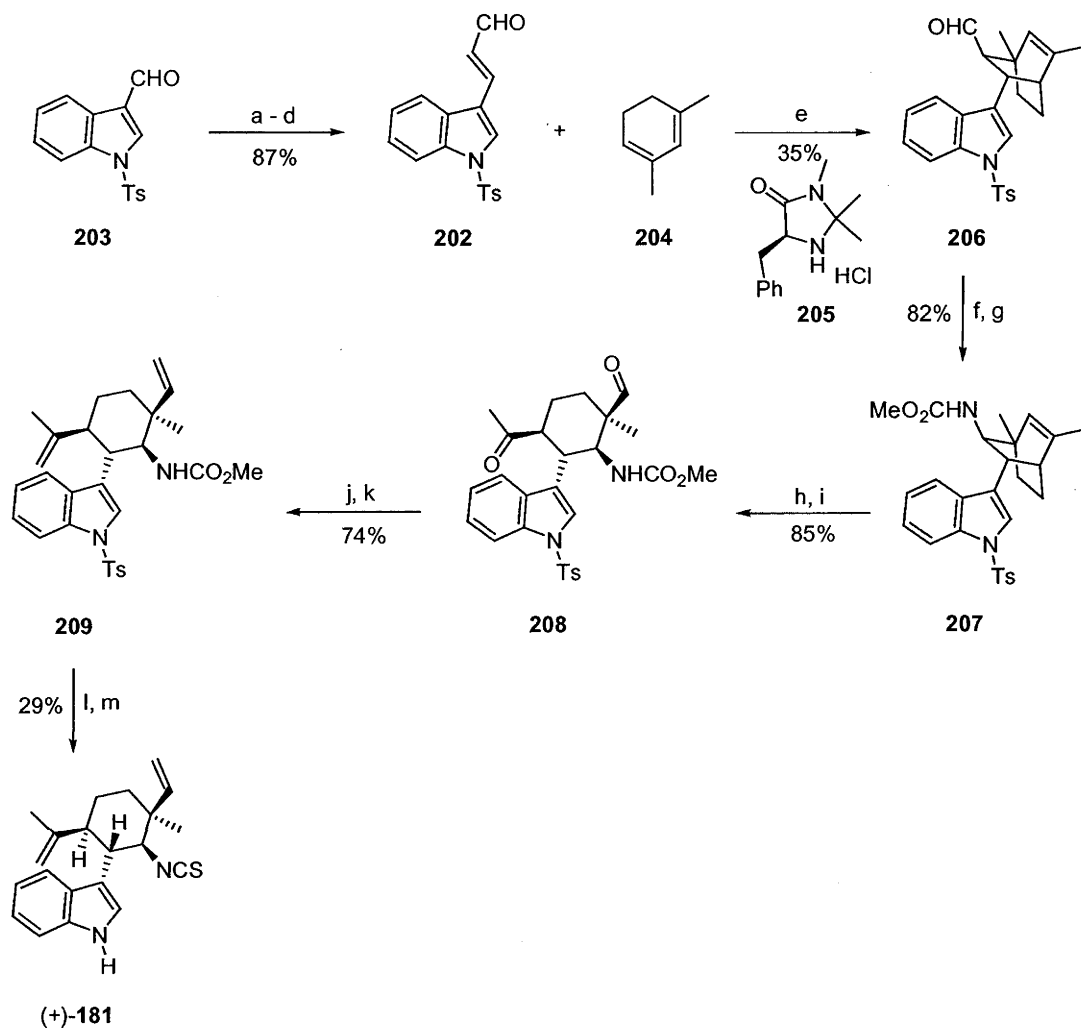
Subsequent acetylation, elimination of the resultant acetate and treatment of the ensuing enone with trifluoroacetic acid and methanesulfonic acid afforded the desired tricyclic enone **198** in 88% overall yield. Carbamate **199** was then obtained *via* a palladium-mediated carbonylation of the aryl iodide followed by a transformation of the resulting carboxylic acid into the allyl urethane according to the Shioiri-Yamada procedure, which involves the application of diphenylphosphorylazide (DPPA) in a modified Curtius rearrangement.³²

Conjugate addition of lithiated methyl(methylthio)methyl sulfoxide to enone **199** followed by acid treatment in the presence of mercuric chloride then furnished indole **200** as a single stereoisomer in 69% yield. Through a series of standard functional group interconversions this last compound was converted, stereoselectively, into the corresponding formamide **201** and finally, through dehydration with triethylamine and phosgene, into (-)-hapalindole G (**195**).

Kerr's Synthesis – 2003

Following on from their reports of various relevant methodological studies^{33,34} and application of these in a synthesis of (±)-hapalindole Q (**181**),³⁵ Kerr and Kinsman reported an enantioselective total synthesis of (+)-hapalindole Q (**181**) in 2003 (Scheme 3.4).³⁶ The key feature of this synthesis involved the use of a Diels-Alder reaction to construct the carbon skeleton and thereby establishing the required relative stereochemistry at all four contiguous stereogenic carbon centres on the cyclohexane ring. On consideration of various methods available to achieve enantiofacial differentiation in the key Diels-Alder reaction the most appropriate was thought to involve the use of organocatalysts. This choice was inspired by the work of MacMillan^{37,38} and examination of the possible transition states available in this sort of case suggested that diene attack would be restricted to the appropriate face of the alkene and so lead, ultimately, to an enantioselective synthesis of (+)-hapalindole Q (**181**). In the event, the required enal dienophile **202** was prepared in four steps from known indole **203** *via* a Knoevenagel reaction, esterification of the ensuing acid and a subsequent reduction-oxidation sequence.

Scheme 3.4: Kerr's Total Synthesis of (+)-Hapalindole Q (181)



Reagents and conditions: (a) malonic acid, pyridine, 20 mol% pyrrolidine, reflux, 2 h; (b) EtOH, cat. H₂SO₄, reflux, 24 h; (c) DIBAL-H, CH₂Cl₂, -10 to 0 °C, 2 h; (d) DMP, CH₂Cl₂, 0 °C, 1 h; (e) DMF, MeOH, H₂O, **205**, 18 °C, 20 min then **204**, 18 °C, 36 h; (f) NaClO₂, NaH₂PO₄(aq.), 2-methyl-2-butene, *t*-BuOH, 18 °C, 1 h; (g) DPPA, Et₃N, toluene, reflux then MeOH, sealed tube, 150 °C, 17 h; (h) 5 mol% K₂OsO₂(OH)₄, 15 mol% DABCO, MeSO₂NH₂, K₂CO₃, K₃Fe(CN)₆, THF, H₂O, 18 °C, 2 d; (i) NaIO₄/SiO₂, CH₂Cl₂, 18 °C, 2 h; (j) KO^{*t*}Bu, Ph₃PCH₃I, THF, 18 °C, 1.5 h; (k) KO^{*t*}Bu, Ph₃PCH₃I, toluene, 60 °C, 2 h; (l) TBAF, THF, reflux, 12 h; (m) CS(imid)₂, CH₂Cl₂, 0 °C, 20 h.

With compound **202** in hand, Diels-Alder reaction with diene **204**, mediated by MacMillian's organocatalyst **205** in a 1:1 mixture of DMF/MeOH containing 5% water, afforded cycloadduct **206** in 35% yield and 70% de (93% ee for the desired *endo*-**206**). Although this

reaction only delivered the desired cycloadduct in modest yield, the fact that a complex intermediate *en route* to target **181** could be achieved in such an expedient and enantioselective fashion from readily available and achiral starting materials makes this a very attractive approach.

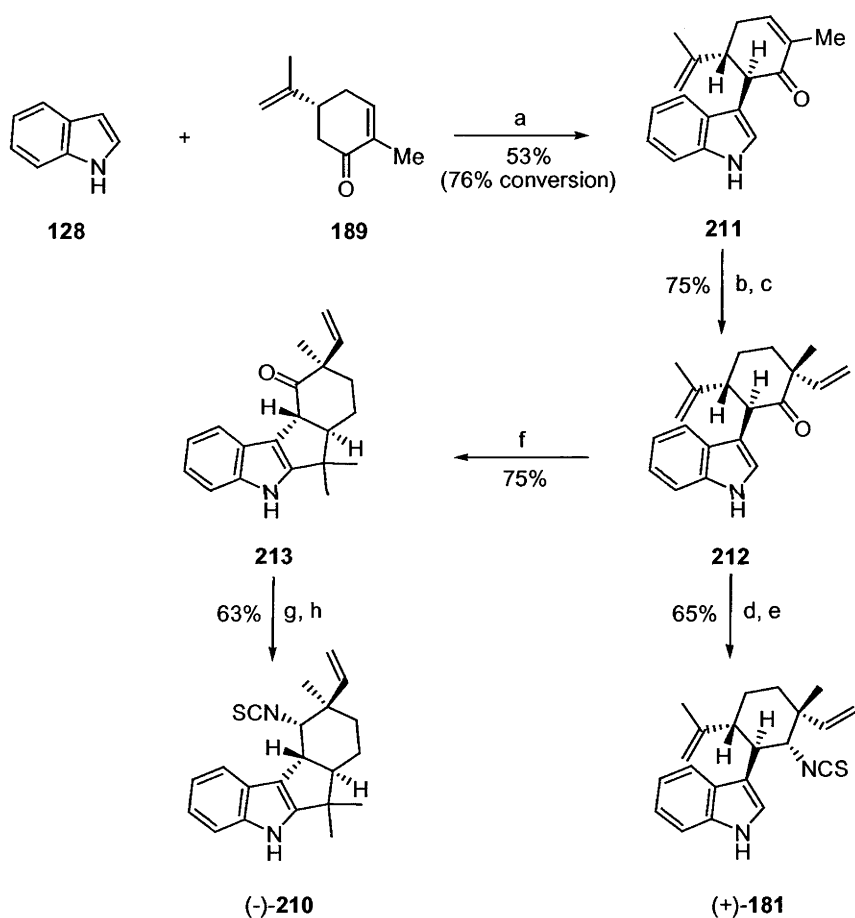
With the key compound, adduct **206**, in hand all that remained for completion of the synthesis was a number of functional group interconversions. To these ends, compound **206** was oxidised with sodium chlorite to afford a 85:15 mixture of the *endo*- and *exo*-isomers of the corresponding acid, each of which underwent a Curtius rearrangement to deliver carbamate **207**. This last compound was then subjected to standard *cis*-1,2-dihydroxylation conditions to afford a *ca.* 3:1 mixture of the diastereoisomeric diols. A kinetic separation of the diastereomers was achieved and the diol mixture cleaved on silica-supported NaIO₄ to give keto-aldehyde **208**. Two-fold Wittig-type methylenation of this last compound was then carried out to afford diene **209** in 74% over two steps. Deprotection of both the indole and amine nitrogens was achieved in one pot with TBAF and the product then converted into (+)-hapalindole Q (**181**) utilising the procedure described previously for the completion of Albizati and Vaillancourt's synthesis, namely treatment with 1,1'-thiocarbonyldiimidazole.³⁹ As a result, Kerr's synthesis was completed in twelve steps and 1.7% overall yield.

Baran's Synthesis – 2004

Undoubtedly the most impressive hapalindole synthesis reported thus far is that due to Baran and Richter (Scheme 3.5).⁴⁰ Employing an approach analogous to the phenolate radical coupling process utilised in Barton's classic synthesis of usnic acid,⁴¹ short, enantioselective and protecting group-free total syntheses of both (+)-hapalindole Q (**181**) and (-)-12-*epi*-fischerindole U isothiocyanate (**210**) were achieved in an overall yield of 22% and 15%, respectively, from (*R*)-carvone (**189**). Not only does this work provide the highest yielding and most concise syntheses of these compounds reported to date but also, throughout the course of this study, new methodology for the direct coupling of indoles with carbonyl compounds was developed. Thus, compound **211** was synthesised in one step by a coupling of the corresponding radicals derived *via* oxidation of the anions of indole (**128**) and carvone

(189). The optimal conditions employed for this reaction were found to involve deprotonation of the two starting materials with LHMDS followed by addition of copper(II) 2-ethylhexanoate and, in this manner, the desired coupling reaction proceeded in a 53% yield at 76% conversion.

Scheme 3.5: Baran's Total Syntheses of (+)-Hapalindole Q (181) and (-)-12-epi-Fischerindole U (210)

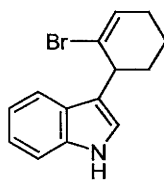


Reagents and conditions: (a) LiHMDS, THF, -78 °C, 30 min then Cu(II) 2-ethylhexanoate, THF, -78 °C, 12 h; (b) LiHMDS, THF, -78 °C, 20 min then L-Selectride, -78 °C, 1 h then CH₃CHO, H₂O₂, NaOH, -78 to 23 °C, 12 h; (c) Martin sulfurane, CHCl₃, 23 °C, 10 min; (d) NH₄OAc, NaBH₃CN, MeOH, THF, 150 °C, 2 min; (e) CS(imid)₂, CH₂Cl₂, 23 °C; (f) TMSOTf, MeOH, CH₂Cl₂, 0 °C, 1 h; (g) NH₄OAc, NaBH₃CN, MeOH, THF, 18 °C, 48 h; (h) CS(imid)₂, CH₂Cl₂, 18 °C, 4 h.

With compound **211** in hand, the total synthesis of target (+)-**181** could then be completed in a few short steps, namely: (i) deprotonation of the indole, conjugate reduction and stereoselective quenching of the resulting enolate with acetaldehyde; (ii) dehydration of the aldol product, (iii) microwave-enhanced reductive amination and, finally, (iv) isothiocyanate formation. The total synthesis of target (-)-**210** could be accomplished through a similarly brief sequence. Thus, an acid-catalysed and biomimetic ring-closure afforded ketone **213** which underwent a standard reductive amination reaction to furnish the expected amine. Conversion of the latter moiety into the corresponding isothiocyanate under standard conditions then completed the synthesis of compound (-)-**210**.

3.4 Retrosynthetic Analysis Associated with the Present Studies

The obvious structural relationship between compound **129**, obtained in one step upon reaction of 6,6-dibromobicyclo[3.1.0]hexane (**41**) with indole (**128**), and certain of the hapalindole alkaloids provided the motivation for the work detailed in the remaining parts of this Chapter. An especially attractive feature of this reaction product is that it could be prepared in gram quantities from readily available starting materials.



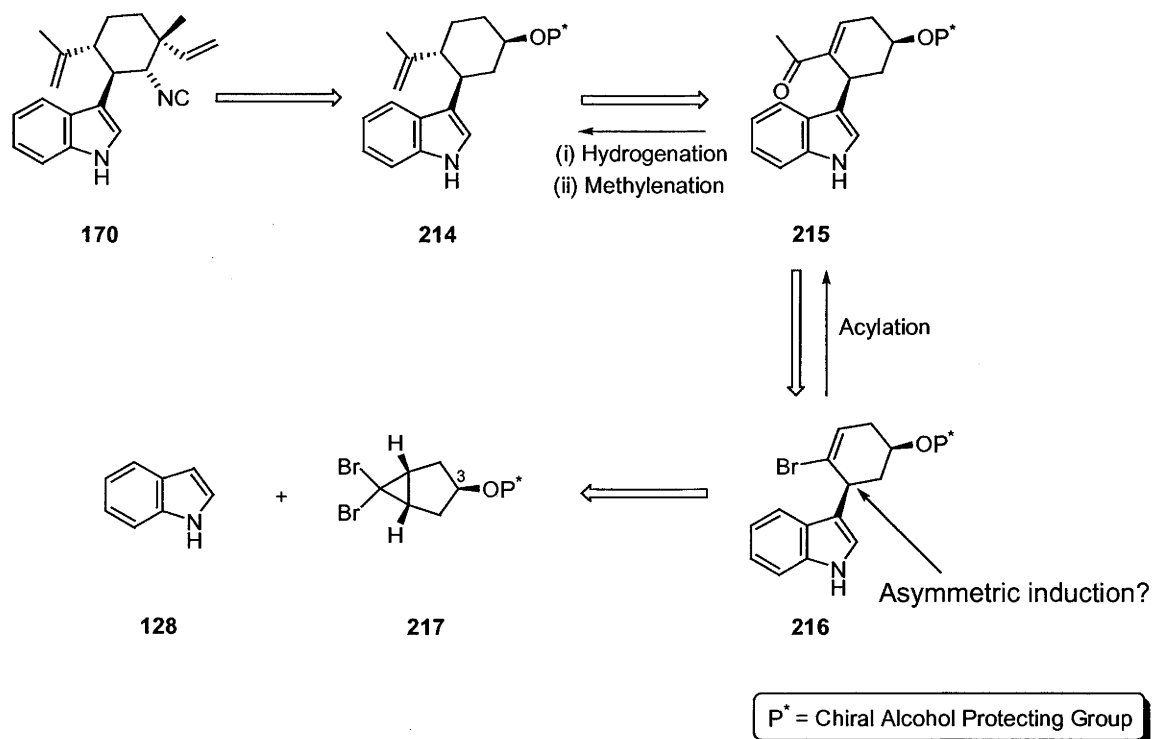
129

A retrosynthetic analysis for hapalindole C (**170**), that might exploit the ready availability of compound **129** and the sorts of processes leading to it, is depicted in Figure 3.4. Thus, once the tricyclic core structure **214** has been obtained, in the manner indicated, conversion of the protected secondary alcohol into the corresponding ketone would provide, *via* enolisation and functionalisation at the α -carbon, a means for incorporating the isonitrile group. The ketone carbonyl would also serve as a platform for installation of the geminally-related methyl and vinyl groups seen in the target **170**. The precursor to compound **214** would be enone **215**. Thus, hydrogenation of the double bond within **215** would provide an epimerisable centre and molecular modelling studies suggested that the vicinally-related acyl and indole moieties on

the cyclohexane ring would adopt the thermodynamically more stable *trans*-relationship through epimerisation at the centre bearing the acyl group. Following this, a methylenation reaction would complete the installation of the requisite isopropenyl unit, as shown in structure **214**.

The pivotal acyl group within compound **215** could be incorporated using the cycloalkenyl bromide precursor **216**, while formation of the later compound could conceivably be achieved under conditions analogous to those employed in the construction of compound **129**. Of course, it would be advantageous to perform the relevant electrocyclic ring-opening/ π -allyl cation trapping step in a manner that allows for the enantiopure natural product to be targeted. To such ends, installation of a chiral alcohol protecting group at C-3 on the 6,6-dibromobicyclo[3.1.0]hexane framework was considered worth examining in an attempt to influence which terminus of the derived and pseudo-symmetrical π -allyl cation is attacked by indole (**128**). To construct the requisite cyclopropane, **217**, dibromocarbene addition to a suitably protected form of cyclopenten-3-ol was pursued as is detailed in the following section.

Figure 3.4: Retrosynthetic Analysis of Hapalindole C (**170**)

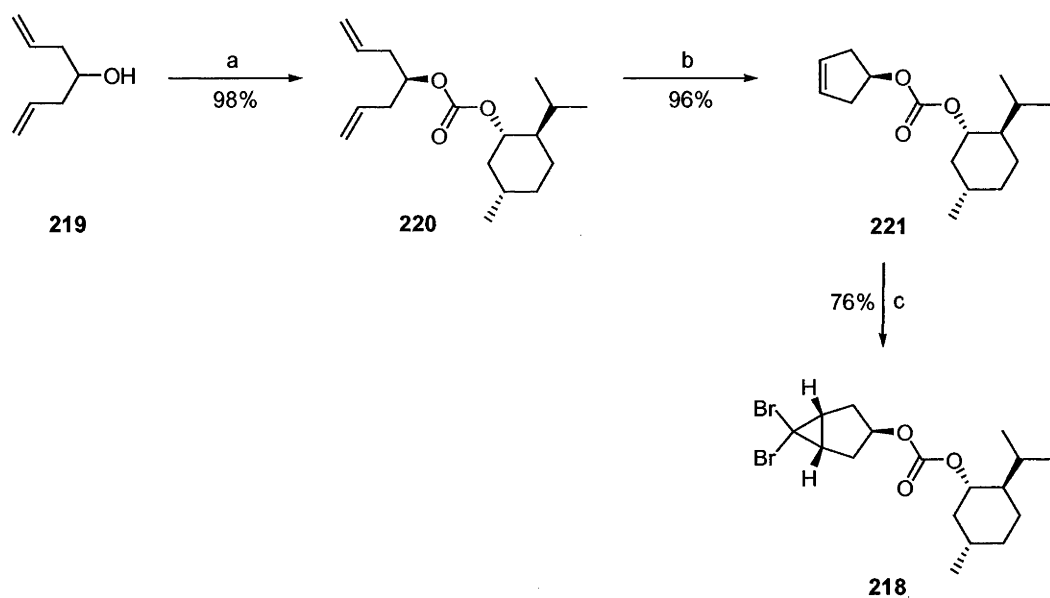


3.5 Synthetic Studies

3.5.1 Using the (+)-Menthyl Moiety as an Alcohol Protecting Group and Chiral Auxiliary

The synthesis of the target cyclopropane **218**, incorporating the (+)-menthyl residue, was achieved by the route specified in Scheme 3.6.

Scheme 3.6: Synthesis of Target Cyclopropane **218**



Reagents and conditions: (a) (+)-menthyl chloroformate, pyridine, DMAP, 0 to 18 °C, 18 h; (b) Grubbs' II catalyst 5 mol%, CH_2Cl_2 , reflux, 2.5 h; (c) CHBr_3 , TEBAC, NaOH, CH_2Cl_2 , 2 h.

Thus, commercially available 1,6-heptadiene-4-ol (**219**) was reacted with (+)-menthyl chloroformate under standard conditions to provide carbonate **220** in 98% yield. The ^1H NMR spectrum of compound **220** (Figure 3.5) featured multiplets centred at δ 5.72 and 5.05 that integrated to two and four protons, respectively. These were attributed to the protons of the terminal olefins. Due to the complex splitting patterns observed for these olefinic protons, and the fact that they appeared not to be part of a simple AB-spin system, a computer

simulation of the expected splitting pattern for the signal observed at δ 5.72 (and due to H-1) in compound **220** was undertaken. As is apparent in Figure 3.6, a strong correlation exists between the observed and calculated splitting patterns. From these calculations it was also possible to ascertain that the actual coupling constants (J) for this resonance were 17.1, 10.2, 7.3, 6.7 and 2.2 Hz. As shown in Table 3.1 these have been assigned as the *trans*-coupling, the *cis*-coupling, the two allylic-couplings and the long-range coupling with H₆, respectively.

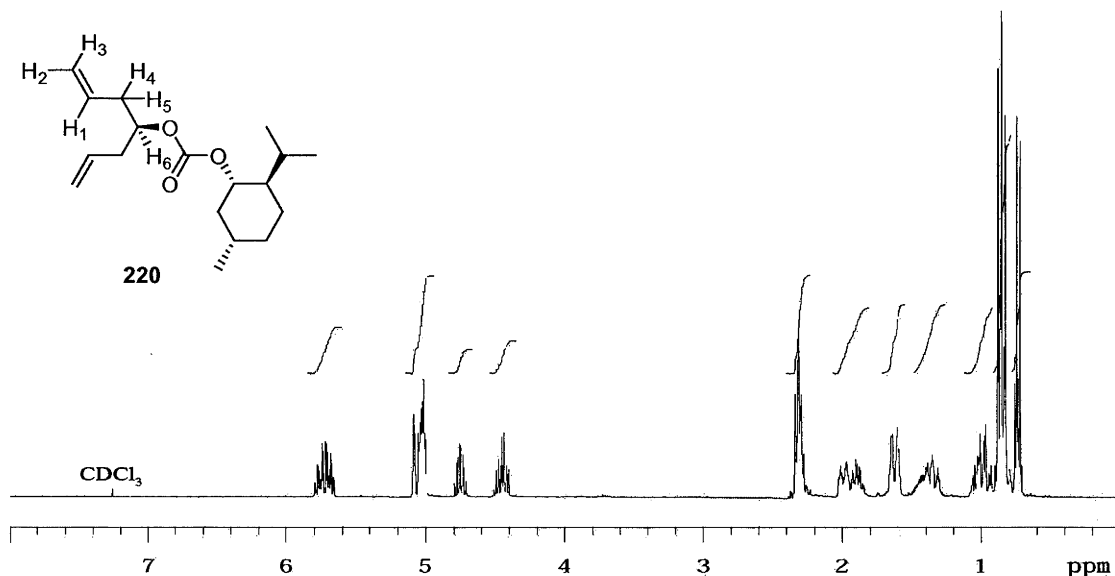


Figure 3.5: 300 MHz ^1H NMR Spectrum of Compound **220** in CDCl_3

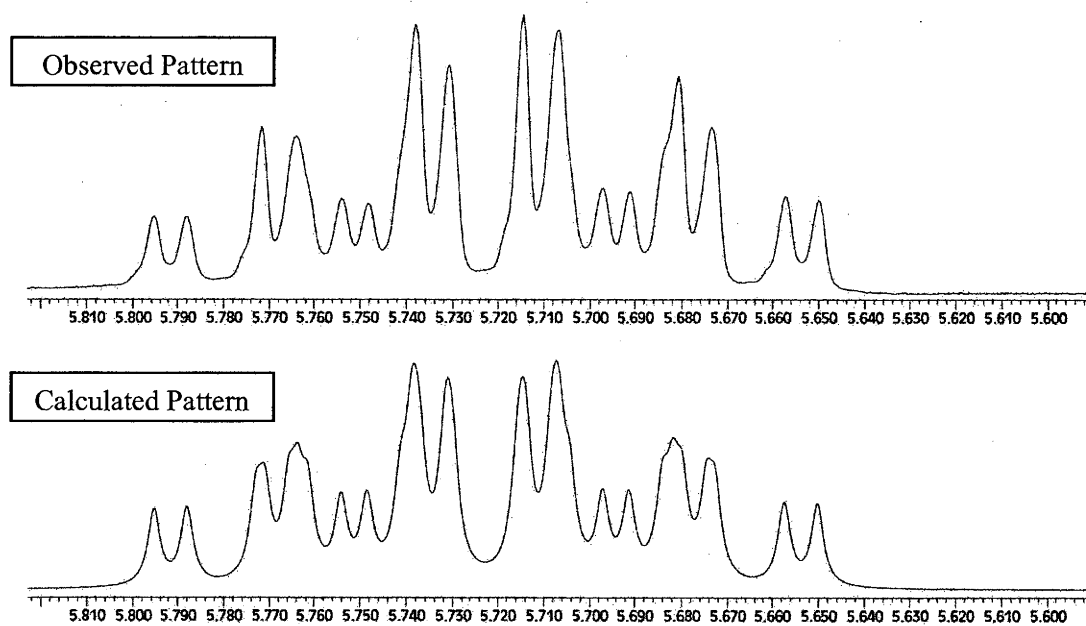
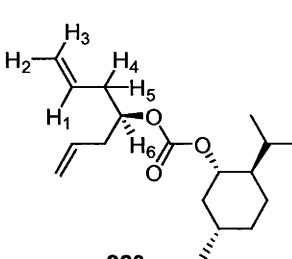


Figure 3.6: Observed and Calculated Splitting Patterns for the Signal Appearing at δ 5.72 in the 300 MHz ^1H NMR Spectrum of Compound **220**

Table 3.1: Assignment of Coupling Constants for the Signal Observed at δ 5.72 in the 300 MHz ^1H NMR Spectrum of Carbonate **220**



Protons Involved in Coupling	Relationship	Coupling Constant J (Hz)
$\text{H}_1 - \text{H}_2$	<i>cis</i>	10.2
$\text{H}_1 - \text{H}_3$	<i>trans</i>	17.1
$\text{H}_1 - \text{H}_4$	allylic	6.7 or 7.3
$\text{H}_1 - \text{H}_5$	allylic	6.7 or 7.3
$\text{H}_1 - \text{H}_6$	long-range	2.2

In the experimentally-derived proton spectrum, three prominent signals were also present at δ 0.91, 0.88 and 0.77, each of which integrate to three protons and are believed to correspond to the methyl groups present on the menthyl moiety, therefore, implying that the protected product has, indeed, been formed. A resonance due to a quaternary carbon appearing at δ 154.5 in the ^{13}C NMR spectrum as well as the presence of a strong absorption band at 1738 cm^{-1} in the infrared spectrum, indicative of a carbonate residue, provided further evidence of the successful attachment of a menthyl group onto the dienol subunit. Although the EI mass spectrum did not show a clear molecular ion, it did display prominent fragment ions at m/z 156, 139, 112 and 95. These appear to correspond to the loss of a $\text{C}_{10}\text{H}_{18}$ fragment, a $\text{C}_{10}\text{H}_{19}\text{O}$ fragment, a $\text{C}_{11}\text{H}_{18}\text{O}_2$ fragment and a $\text{C}_{11}\text{H}_{19}\text{O}_3$ fragment, respectively, from the molecular ion associated with diene **220** and can be taken as the “typical” fragment ions expected for this type of substrate. An accurate mass measurement on the fragment at m/z 156 established that it possessed the expected composition, namely $\text{C}_8\text{H}_{12}\text{O}_3$. An electrospray mass spectrum in the positive ion mode was also run and the use of this softer ionisation technique allowed the protonated form of the molecular ion (m/z 295) and the molecular ion/sodium ion conjugate (m/z 317) to be observed.

The requisite cyclopentene **221** was thought likely to be accessible *via* ring-closing metathesis of the two proximate double bonds associated with the menthyl-protected diene **220**. The

Grubbs' II catalyst proved to be the one of choice for promoting this reaction and provided the target cyclopentene **221** in 96% yield. Conspicuous features in the ^1H NMR spectrum of product **221**, and which confirmed unequivocally that the desired metathesis reaction had occurred, were the disappearance of the olefinic resonances, previously observed at δ 5.72 and 5.10-5.00 in substrate **220**. Furthermore, and as expected for a symmetrical compound, a singlet due to the cyclopentenyl olefinic protons appeared at δ 5.70 in the spectrum of product **221**. In the ^{13}C NMR spectrum the previously observed signals due to the carbons of the terminal olefins and appearing at δ 133.2 (2 x CH), 118.1 (CH_2) and 118.0 (CH_2) were no longer present and a new signal, characteristic of a cyclopentene-type olefin, was visible at δ 128.0. The 70 eV EI mass spectrum, whilst not displaying a visible molecular ion, did, however, provide an informative fragmentation pattern and an accurate mass measurement on the ion associated with one of these known fragmentations, $[\text{M}-(\text{C}_{10}\text{H}_{18})]^+$, strongly suggested that the molecular formula for compound **221** is $\text{C}_{16}\text{H}_{26}\text{O}_3$.

With compound **221** in hand the required cyclopropane **218** could be targeted. Due to a significant reduction in reaction time, the Brinker conditions⁴² were employed to effect dibromocarbene addition to alkene **221** and adduct **218** was thereby obtained as a yellow oil in 76% yield after only two hours. As depicted in Figure 3.7, the singlet, which had previously been attributed to the olefinic protons in the ^1H NMR spectrum of precursor alkene **221**, was no longer visible. This observation, coupled with an increase in the number of upfield signals, integrating to two additional protons, is consistent with the expected conversion of cyclopentene **221** into the dibromocarbene adduct **218**. Further evidence for this transformation derived from the ^{13}C NMR spectrum. Here the previously observed alkene resonances associated with the substrate were no longer apparent and new signals, corresponding to the three carbons of the cyclopropyl ring, were visible at δ 35.8 (2 x CH) and 31.4 (C). The derived EI mass spectral data and particularly the isotope patterns associated with the molecular ion cluster indicated that two bromines had been successfully incorporated into the product and a high-resolution EI mass spectrum on the dominant fragment ions $\{m/z$ 302, 300 and 298 – $[\text{M}-(\text{C}_{10}\text{H}_{18})]^+$, which were present in a 1:2:1 ratio, as expected for a dibrominated compound} confirmed the assigned structure. Although the stereochemistry of this compound has not been rigorously proven, cyclopropane **218** was obtained as a single

diastereomer and it is believed that a *anti*-relationship has been established between the cyclopropyl and menthyl groups in this product. This assumption is based on the notion that dibromocarbene will preferentially attack from the less-hindered face of the π -system within alkene **221**.

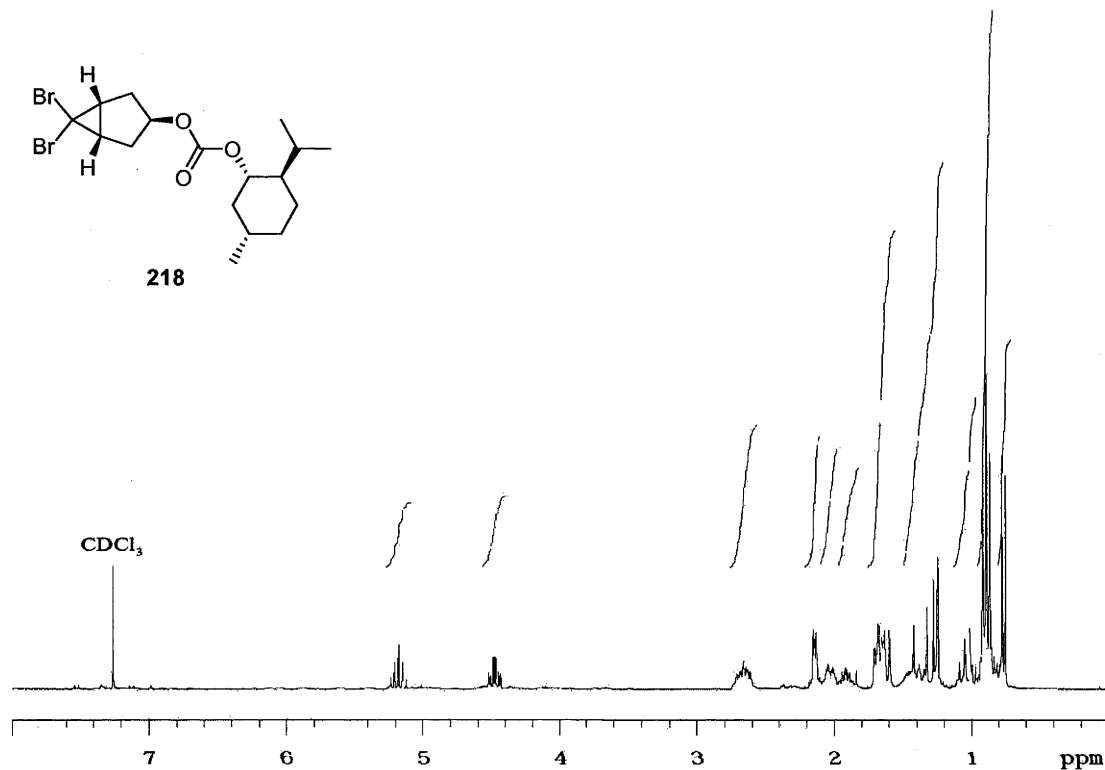
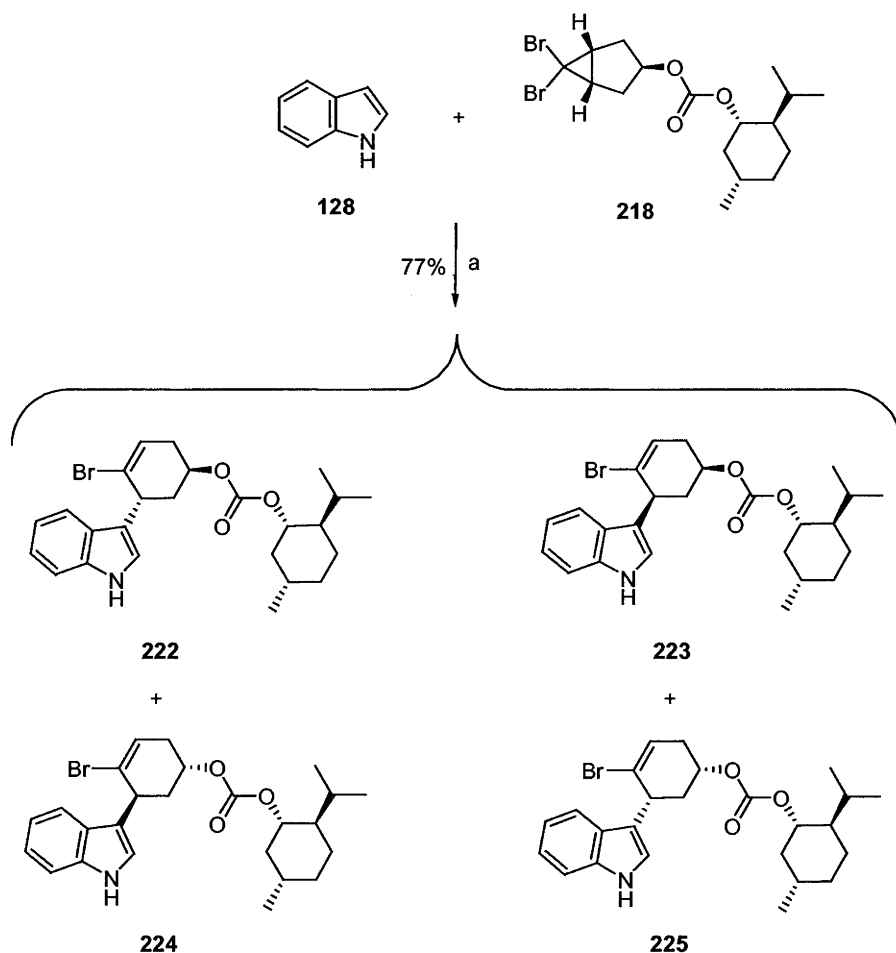


Figure 3.7: 300 MHz ^1H NMR Spectrum of Cyclopropane **218** in CDCl_3

With compound **218** in hand, efforts could be directed towards effecting a coupling such as that observed in the model study involving the 6,6-dibromobicyclo[3.1.0]hexane (**41**) system and indole (**128**). To such ends, a solution of cyclopropane **218** and indole (**128**) in THF was protected from light and treated, at ambient temperature, with silver tetrafluoroborate. As observed earlier with the simpler system the required intermolecular trapping of the π -allyl cation through the C-3 position of indole was observed. This was confirmed by ^1H NMR spectral analysis of the product mixture which showed that resonances due to indolic protons and to those associated with the menthyl moiety were present in the anticipated ratio. Further evidence that cyclopropane **218** had undergone ring-opening and subsequent trapping by the C-3 of indole was the absence of a resonance due to an indolic C-3 proton (normally appearing as a doublet at *ca.* δ 6.45) and the characteristic presence of protons associated with a cycloalkenyl bromide moiety observed, in this case, as a triplet at δ 6.19. The ^{13}C NMR

spectral data were also in full agreement with the assigned structure and high-resolution EI mass measurements on the molecular ions observed at m/z 475 and 473 confirmed the expected compositions, *viz.* $C_{25}H_{32}^{81}BrNO_3$ and $C_{25}H_{32}^{79}BrNO_3$, respectively. Unfortunately, however, the NMR data suggested that at least two products were present in a 1:1 ratio, implying that the coupling had occurred with little, if any, diastereoselectivity. In fact, once the major products had been separated and then subjected to HPLC analysis it became apparent that the four possible diastereomers **222-225**, shown in Scheme 3.7, were present in a *ca.* 1:1:1:1 ratio.

Scheme 3.7: Reaction of Cyclopropane **218** with Indole (**128**)

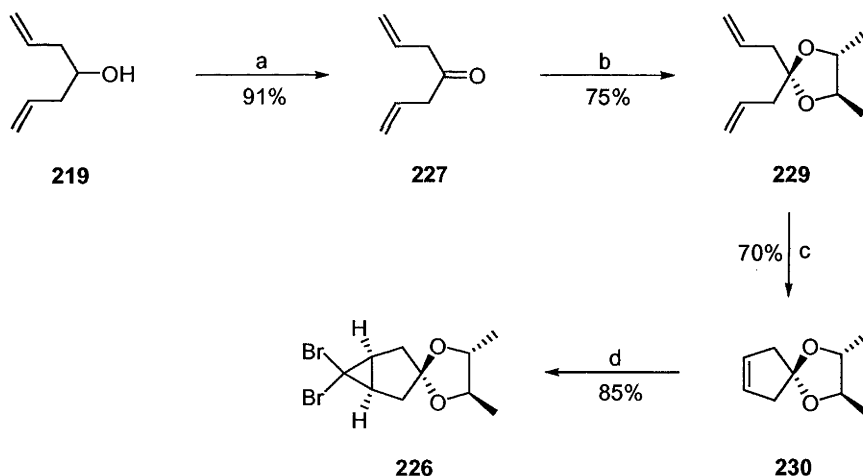


Reagents and conditions: (a) $AgBF_4$, THF, 18 °C, 16 h.

3.5.2 Using the (2*R*,3*R*)-Dimethylethylene Ketal-based Moiety as a Ketone Protecting Group and Chiral Auxiliary

Despite the rather discouraging but perhaps unsurprising results obtained during efforts to effect the diastereoselective trapping of the π -allyl cation generated by silver(I)-promoted electrocyclic ring-opening of cyclopropane **218** with indole (**128**), it was decided there could be some merit in investigating the use of alternative chiral auxiliaries. In particular, it was anticipated that due to the added steric bulk of a chiral ketal, in comparison to the menthylcarbonate-based auxiliary discussed in the preceding section, a greater degree of stereocontrol might be observed in the pivotal ring-opening and trapping step. Hence, cyclopropane **226** was targeted by the sequence shown in Scheme 3.8.

Scheme 3.8: *Synthesis of Target Cyclopropane 226*



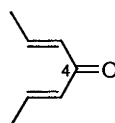
Reagents and conditions: (a) PCC, CH_2Cl_2 , 0 to 18 °C, 16 h; (b) 2*R*,3*R*-butanediol, *p*-TsOH, benzene, reflux, 2 h; (c) Grubbs' II catalyst 5 mol%, CH_2Cl_2 , reflux, 3 h; (d) CHBr_3 , TEBAC, NaOH, CH_2Cl_2 , 2 h.

The initial oxidation of commercially available diallyl alcohol **219** to the corresponding and previously reported ketone⁴³ proved somewhat problematic. Various reagents were examined in an attempt to effect this transformation and these are summarised in Table 3.2.

Table 3.2: Reaction Conditions Trialled for the Oxidation of Alcohol **219** to Ketone **227**

Entry	Reagents and Conditions	Outcome
1	Dess-Martin Periodinane, CH ₂ Cl ₂ , 0 to 18 °C, 3 h.	60% conversion to Product 227
2	Dess-Martin Periodinane, pyridine, CH ₂ Cl ₂ , 0 to 18 °C, 3 h.	No improvement on % conversion
3	Oxalyl chloride, CH ₂ Cl ₂ , Et ₃ N, DMSO, -78 to 0 °C, 18 h.	Product 228 (86% yield)
4	TPAP, NMO, CH ₂ Cl ₂ , 4 Å mol. Sieves, 0 to 18 °C, 66 h.	Starting material only recovered
5	Pyridinium Chlorochromate, CH ₂ Cl ₂ , 0 to 18 °C, 16 h.	Product 227 (91% yield)

Initial efforts employed the mild oxidant DMP.⁴⁴ Whilst an encouraging 60% conversion was obtained under these conditions no improvement could be accomplished, even by buffering the reaction mixture. Unexpectedly, application of the Swern oxidation conditions⁴⁵ failed to afford any of the desired ketone **227**, but rather exclusive formation of the isomeric compound **228** was observed and wherein the C=C double bonds had become conjugated with the C4-ketone.

**228**

In contrast, use of the TPAP oxidant⁴⁶ failed to give any reaction whatsoever, even after sixty six hours. The fact that chromium oxidants have been found to be highly effective in the oxidation of homoallylic alcohols⁴⁷ prompted an examination of the use of pyridinium chlorochromate for the present purpose. Gratifyingly, this proved to be extremely successful, delivering the desired product **227** in 91% yield.

In accordance with the assigned structure, a doublet of doublet of triplets ($J = 17.2, 10.2$ and 7.2 Hz), (see inset, Figure 3.8), integrating to two protons, was observed at δ 5.92 in the ^1H NMR spectrum of compound **227**. This splitting pattern is characteristic of the internal protons associated with terminal olefins, which tend to display *cis*-, *trans*- and allylic-couplings. Also apparent was a series of multiplets at δ 5.21, 5.18 and 5.12, integrating for four protons, and attributed to the terminal olefinic protons. This information provided the required evidence that the assigned structure for product **227** was correct and that the terminal double bonds had not moved into conjugation with the central carbonyl moiety as is observed in isomer **228**. An accurate mass measurement confirmed that the desired oxidation had occurred and that the product obtained was of the expected composition, *viz.* $\text{C}_7\text{H}_{10}\text{O}$.

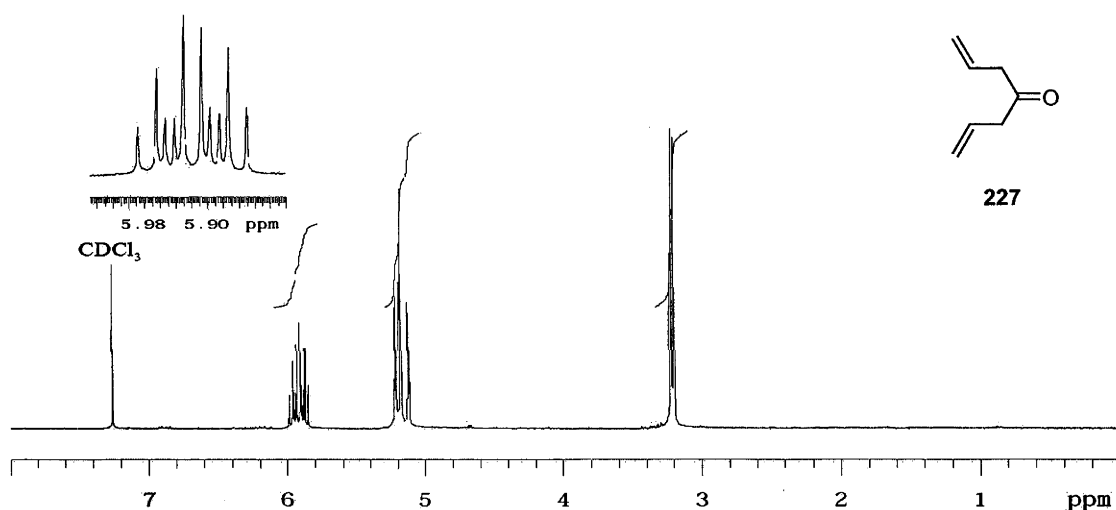


Figure 3.8: 300 MHz ^1H NMR Spectrum of Ketone **227** in CDCl_3

With this compound in hand, protection of the ketone carbonyl with the aforementioned chiral auxiliary was undertaken. Using a procedure analogous to that described by Dolbier and Garza for the protection of hepta-1,6-dien-4-one (**227**) as the corresponding ethylene acetal,⁴⁸ the former compound was heated at reflux with *2R,3R*-butanediol and *p*-toluenesulfonic acid in benzene and under Dean-Stark conditions to effect azeotropic removal of water. In the ^1H NMR spectrum of the derived ketal, a doublet of doublet of triplets ($J = 15.6, 9.3$ and 7.2 Hz) integrating as two protons, and a series of multiplets, totalling four protons, were seen at δ 5.85, 5.12 and 5.08, respectively. It is apparent from these data that the ketone carbonyl protection had occurred without any adverse effect on the terminal alkenes. The ^{13}C NMR

spectrum of ketal **229** confirmed that the desired protection reaction had taken place by virtue of the appearance of resonances at δ 78.8 and 16.5 which correspond to the carbons on the ketal backbone and the two associated methyl groups, respectively. In addition, the EI mass spectrum of compound **229** displayed a molecular ion at m/z 182 but due to the volatility of the compound, an accurate mass measurement could not be made on this species. Rather, this was performed on the base peak appearing at m/z 141, which arises from loss of a propyl radical from the molecular ion. This established the expected formula for this fragment ion, *viz.* $C_8H_{13}O_2$. With the desired ketal **229** now clearly in hand, the proposed ring-closing metathesis and carbene addition steps could be investigated.

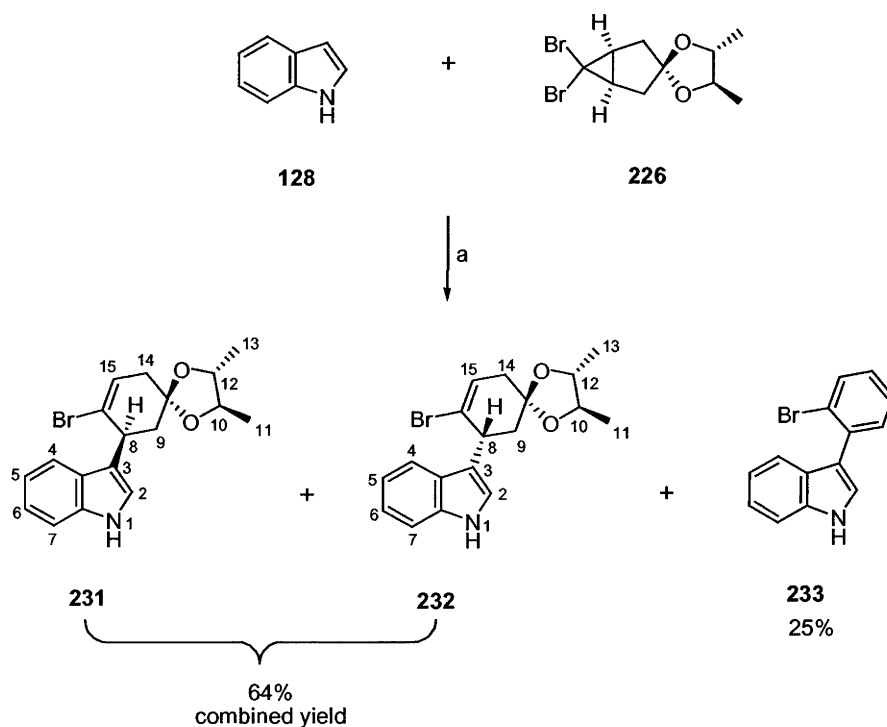
Once again, the Grubbs' II catalyst was utilised to effect the ring-closing metathesis⁴⁹ of diene **229** and the targeted cyclopenten-3-one ketal **230** obtained in 70% yield. Unsurprisingly, the conditions and time-frame required to effect this transformation were almost identical to those utilised previously in the preparation of the menthyl-protected congener **221**. The most diagnostic feature observed in the 1H NMR spectrum of compound **230** was the absence of signals previously attributable to vinylic protons and the appearance of a two-proton triplet ($J = 0.9$ Hz) at δ 5.68 due to the cyclopentenyl protons. Similarly in the ^{13}C NMR spectrum, the two signals previously observed at δ 133.2 and 118.2 and assignable to the olefinic carbons in precursor **229**, had been replaced by a signal at δ 128.1 and this is attributed to the chemically-equivalent carbons of the newly installed cyclopentenyl double-bond.

To construct the requisite cyclopropane, **226**, dibromocarbene addition to the protected cyclopenten-3-one structure **230** was now pursued. As discussed in Section 3.5.1, Brinker conditions, utilising TEBAC as the phase transfer catalyst, were employed due to the significant reduction in reaction time that follows from employing these conditions over the more conventional ones developed by Makosza.⁵⁰ The reaction proceeded cleanly to deliver a single isolable product in 85% yield and this was assigned as compound **226**. Distinctive features in the 1H NMR spectrum, which indicated that the carbene addition had occurred, were the absence of any signals attributable to olefinic protons and the appearance of a new and complex multiplet in the region δ 1.86-1.70. This is assigned to the protons associated with the newly introduced cyclopropyl moiety. Similarly, in the ^{13}C NMR spectrum the

signals associated with the sp^2 -hybridised carbons in the precursor appearing at δ 128.1 were no longer present but those typical of a *gem*-dihalo-substituted cyclopropyl group were evident at δ 44.9 (C), 41.0 (CH) and 40.9 (CH). It should be noted that both of the methine carbons on the cyclopropyl moiety are magnetically non-equivalent, hence confirming, as expected, the lack of symmetry within adduct **226** due to the presence of the diastereotopic methyl groups. Further confirmation of this structure followed from the EI mass spectrum in which molecular ions were observed at m/z 328, 326 and 324 in the 1:2:1 ratio expected for a dibrominated compound. An accurate mass measurement on the central molecular ion confirmed this was of the expected composition, *viz.* $C_{10}H_{14}^{79}Br^{81}BrO_2$.

With compound **226** in hand, efforts could now be directed towards conducting an analogous reaction to that of the model study involving the 6,6-dibromobicyclo[3.1.0]hexane (**41**) system and indole (**128**). In the event (Scheme 3.9), on stirring a mixture of indole (**128**) and cyclopropane **226** in the presence of silver tetrafluoroborate the required ring-opening and intermolecular trapping of the π -allyl cation by indole (**128**) was accomplished. Based on NMR spectral analysis of the diastereomeric mixture so-obtained, the ratio of products was ascertained to be 4:1 (**231:232**). These desired products were accompanied by varying quantities of the chromatographically separable 3-arylated indole **233**. The mixture of compounds **231** and **232** was subjected to preparative HPLC and the now pure diastereomers separated and characterised independently.

As expected, the data sets acquired for each of diastereomers **231** and **232** were almost identical, the only major difference being the optical rotations which were of similar magnitude but opposite sign, *viz.* $\{[\alpha]_D -21 (c\ 0.4, CH_3Cl)\}$ and $\{[\alpha]_D +30 (c\ 0.1, CH_3Cl)\}$ for **231** and **232** respectively. The 1H NMR spectral data (Table 3.3) derived from these materials, confirmed that the desired “coupling” has indeed occurred at the C-3 of the indole moiety, the absence of a signal due to H-3 on the indolic framework being a particularly diagnostic feature. The presence of distinctive proton signals at δ 6.15 (6.13) (dt, $J = 6.0$ and 2.4 Hz, 1H) in each case and which are attributed to the cycloalkenyl bromide protons provided further support for the assigned structures.

Scheme 3.9: Reaction of Cyclopropane **226** with Indole (**128**) in the Presence of AgBF_4 

Reagents and conditions: (a) AgBF_4 , THF, 18 °C, 16 h.

The derived ^{13}C NMR spectra were also in full accord with the illustrated structures. In addition, in both cases the EI mass spectrum showed equal intensity molecular ions at m/z 363 and 361 as is expected for a mono-brominated compound. An accurate mass measurement on these ions established, for both compounds **231** and **232**, that the composition was as expected, namely $\text{C}_{18}\text{H}_{20}\text{BrNO}_2$.

Table 3.3: 300 MHz ^1H NMR Spectral Data for Compounds **231** and **232***

^1H	Compound 231	Compound 232
	δ (multiplicity)	δ (multiplicity)
1	10.09 (broad s, 1H)	10.10 (broad s, 1H)
4	7.57 (dd, $J = 7.8$ and 1.2 Hz, 1H)	7.56 (dd, $J = 7.2$ and 1.2 Hz, 1H)
7	7.38 (dd, $J = 7.8$ and 1.2 Hz, 1H)	7.38 (dd, $J = 7.2$ and 1.2 Hz, 1H)
2	7.23 (d, $J = 2.4$ Hz, 1H)	7.23 (d, $J = 2.4$ Hz, 1H)
5	7.07 (dt, $J = 7.8$ and 1.2 Hz, 1H)	7.07 (dt, $J = 7.2$ and 1.2 Hz, 1H)
6	6.99 (dt, $J = 7.8$ and 1.2 Hz, 1H)	6.99 (dt, $J = 7.2$ and 1.2 Hz, 1H)
15	6.15 (dt, $J = 6.0$ and 2.4 Hz, 1H)	6.13 (dt, $J = 6.0$ and 2.4 Hz, 1H)
8	4.12 (m, 1H)	4.13 (m, 1H)
10 & 12	3.72 (m, 2H)	3.65 (m, 2H)
9a	2.63 (ddd, $J = 6.0, 3.6$ and 2.4 Hz, 1H)	2.57 (ddd, $J = 6.0, 3.6$ and 2.4 Hz, 1H)
14a	2.37 (m, 1H)	2.32 (m, 1H)
14b	2.35 (m, 1H)	2.29 (m, 1H)
9b	2.14 (ddd, $J = 8.4, 6.0$ and 2.4 Hz, 1H)	2.06 (m, 1H)
13	1.26 (d, $J = 6.0$ Hz, 3H, CH_3)	1.26 (d, $J = 6.0$ Hz, 3H, CH_3)
12	1.16 (d, $J = 6.0$ Hz, 3H, CH_3)	1.20 (d, $J = 6.0$ Hz, 3H, CH_3)

* Spectra recorded in CD_3COCD_3

To date the assignment of compounds **231** and **232** as representing the major and minor products of reaction, respectively, has not been rigorously confirmed but reasonable mechanistic arguments can be advanced to support the illustrated stereochemistries. Thus, if one considers the π -allyl cation generated from the silver(I)-promoted electrocyclic ring-opening of cyclopropane **226**, it is clear that there are four ways in which the indole can attack such a species as depicted by the four quadrants in Figure 3.9. Nucleophilic attack of indole through diagonally related quadrants will deliver the same product and it would be reasonably expected that the preferred reaction trajectory will involve ones which are distal from the methyl groups of the auxiliary. Based on this argument, then, structure **231** is assigned as representing the major diastereomer.

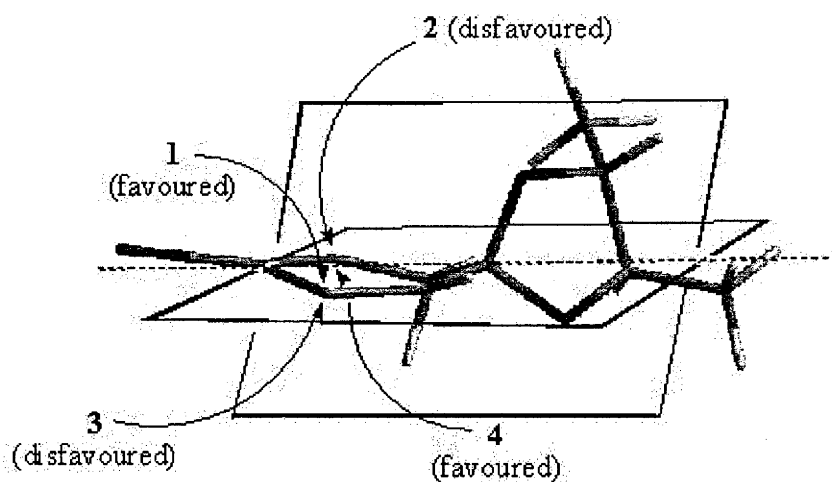
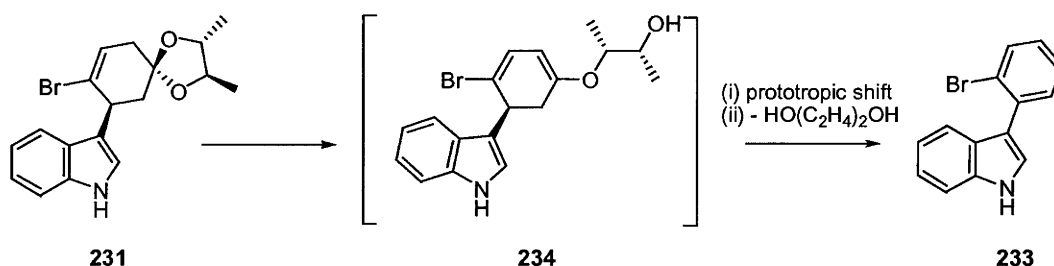


Figure 3.9: Four Possible Sites of Attack on the Pseudo-Symmetrical π -Allyl Cation Derived from the Electrocyclic Ring-Opening of Cyclopropane **226**

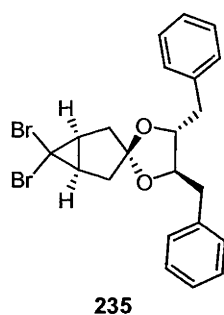
As noted earlier, a by-product **233**, possessing a 3-arylated indole structure, was also obtained from the reaction between the chiral auxiliary-containing 6,6-dibromobicyclo[3.1.0]hexane **226** and indole (**128**). This compound is thought to arise through the process depicted in Figure 3.10. Thus, cracking of the ketal moiety within compound **231** or its diastereomer would deliver diene **234** (or its epimer) which could undergo a prototropic shift and subsequent loss of the elements of butane-2,3-diol with accompanying aromatisation to afford the observed product **233**. Interestingly, when the electrocyclic ring-opening/nucleophilic trapping reaction sequence was performed in the presence of six equivalents of silver tetrafluoroborate then arene **233** was the exclusive product of reaction.

Figure 3.10: Proposed Mechanism for the Formation of the Undesired Side-product **233** Derived from **231**



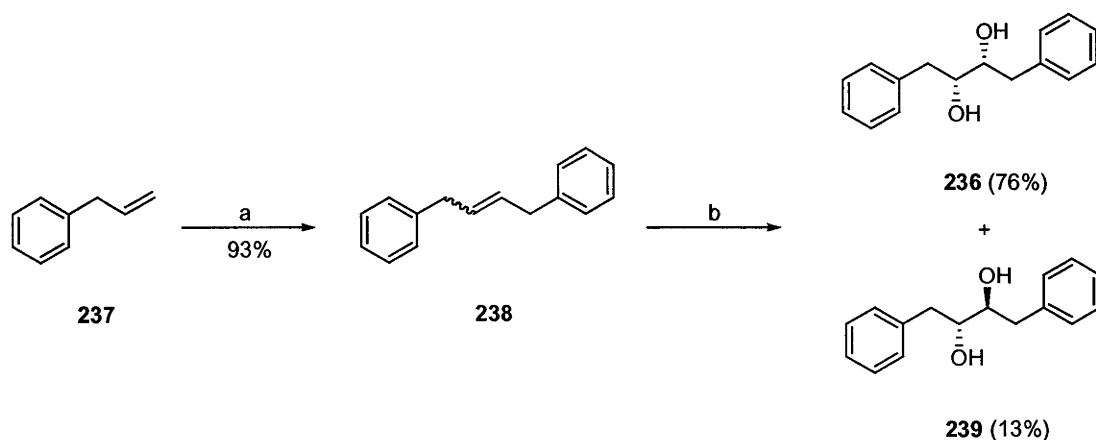
3.5.3 Examining (*R,R*)-1,4-Diphenyl-butane-2,3-diol as an Auxiliary

In light of the results detailed in the foregoing section, it was considered that there could be some merit in increasing the steric bulk of the ketal-based auxiliary so as to exert a greater amount of stereocontrol in the electrocyclic ring-opening and nucleophilic trapping sequence. Therefore cyclopropane **235**, containing the (*R,R*)-1,4-diphenyl-butane-2,3-diol-derived ethylene ketal as the chiral auxiliary, was targeted for synthesis with a view to examining its capacity to participate, stereoselectively, in an electrocyclic ring-opening/nucleophilic trapping sequence with indole (**128**).



The previously reported⁵¹ and requisite (*R,R*)-1,4-diphenyl-butane-2,3-diol (**236**) was readily synthesised in good yield *via* the route depicted in Scheme 3.10.

Scheme 3.10: Synthesis of (*R,R*)-1,4-Diphenyl-butane-2,3-diol (**236**)



Reagents and conditions: (a) Grubbs' I catalyst 5 mol%, CH₂Cl₂, reflux, 18 h, (b) AD mix-β, OsO₄, K₃Fe(CN)₆, K₂CO₃, MeSO₂NH₂, *t*-BuOH, H₂O, 0 °C, 48 h.

Thus, commercially available allyl benzene (**237**) underwent self-metathesis⁵² in the presence of Grubbs' I catalyst to deliver 1,4-diphenyl-2-butene (**238**) in excellent yield (93%). Based on the integration of the relevant signals in the ¹H NMR spectrum of the crude reaction mixture (Figure 3.11), and also on the two distinctive signals observed at δ 38.8 and 33.3 in the ¹³C NMR spectrum, the ratio of *E*- and *Z*-isomers was calculated to be 5.6:1. The *E*-isomer was identified as the major product from comparisons with literature data.⁵³

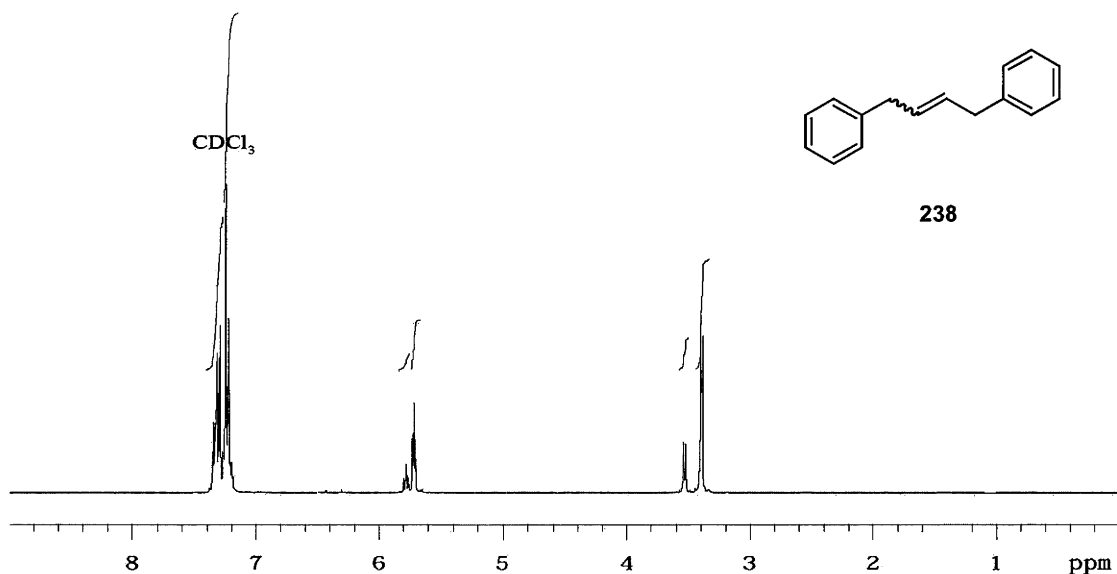
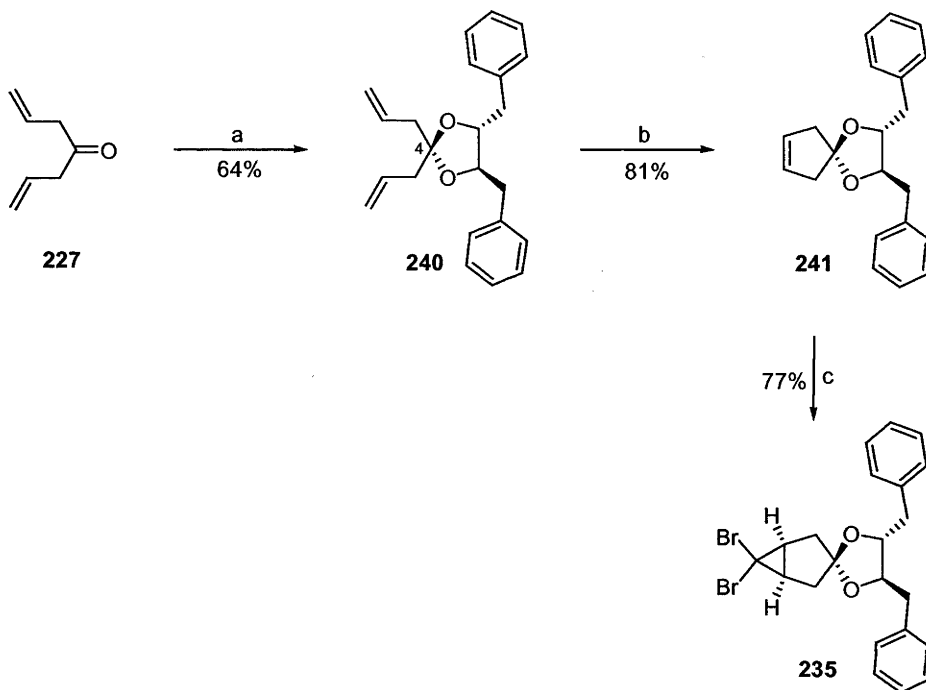


Figure 3.11: 300 MHz ¹H NMR Spectrum of a 5.6:1 Mixture of *E*- and *Z*-Isomers of Alkene **238** (Spectrum recorded in CDCl₃)

With compound **238** in hand, this was subjected to a Sharpless asymmetric dihydroxylation reaction⁵⁴ utilising AD mix- β and the desired diol **236** was thus obtained in 76% yield. Potassium ferricyanide was employed as a stoichiometric reoxidant in this reaction to ensure that a product of high *ee* was obtained.⁵⁵ The chromatographically purified material was then subjected to several fractional recrystallisations (hexane/acetone) to afford the *R,R*-enantiomer in > 99% *ee*. In full accord with previously reported data,⁵⁶ (*R,R*)-1,4-diphenyl-butane-2,3-diol (**236**) was obtained in good yield and the composition (C₁₆H₁₈O₂) confirmed by an accurate mass measurement. Good comparisons could also be made between the recorded (126-130 °C) and literature (126-128 °C) melting points.

Now that the requisite precursor, **236**, to the chiral auxiliary had been synthesised, implementation of the reaction sequence depicted in Scheme 3.11 could be pursued.

Scheme 3.11: Synthesis of Cyclopropane **235**



Reagents and conditions: (a) (*R,R*)-1,4-diphenyl-butane-2,3-diol, *p*-TsOH, benzene, reflux, 18 h; (b) Grubbs' II catalyst, 5 mol%, CH₂Cl₂, reflux, 5 h; (c) CHBr₃, TEBAAC, NaOH, CH₂Cl₂, 2 h.

Following the same procedures as used earlier, cyclopropane **235** was obtained in three steps from ketone **227** (Scheme 3.11). Thus, the latter compound was reacted, under Dean-Stark conditions, with (*R,R*)-1,4-diphenyl-butane-2,3-diol (**236**). Presumably due to the steric bulk imposed by the benzyl groups, this reaction proceeded at a much slower rate than that observed for the equivalent dimethylated system. Analysis of the ¹H NMR spectrum, however, indicated that the desired protection reaction had occurred, with signals attributable to the protons associated with the terminal olefins and chiral auxiliary integrating in the expected manner. The chemical shifts and splitting of the signals due to the olefinic protons also indicated that the diene subunit had remained unchanged during the protection protocol.

In accord with the ^1H NMR data, the ^{13}C NMR spectrum of diene **240** (Figure 3.12) confirmed the presence of signals associated with both the diallyl unit and the chiral auxiliary within this product. EI mass spectrometry provided further evidence for the desired structure **240** by displaying the expected molecular ion at m/z 334 and an accurate mass measurement on this species established that it had the anticipated composition, *viz.* $\text{C}_{23}\text{H}_{26}\text{O}_2$. With the successful inclusion of the chiral auxiliary onto the diene system, the ring-closing metathesis and subsequent carbene addition steps could be carried out.

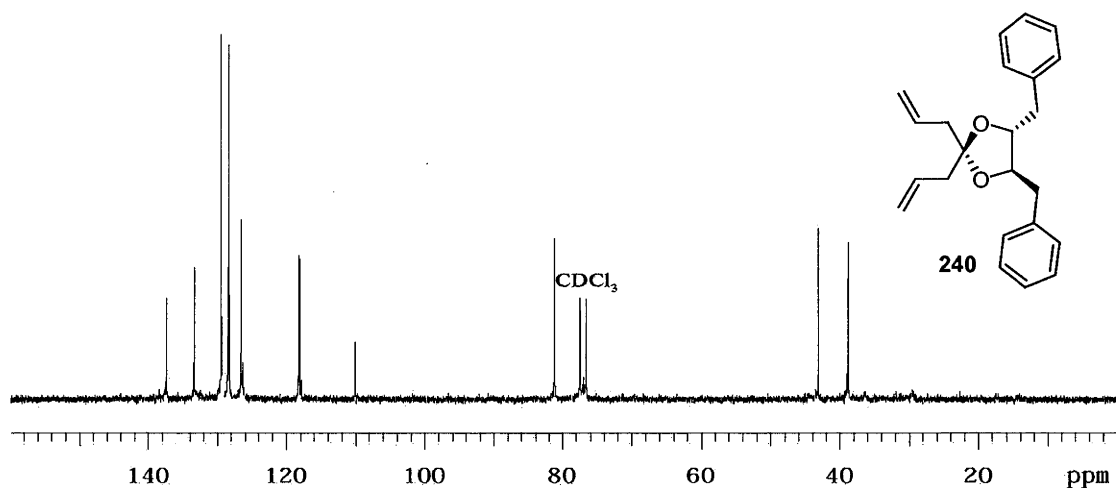


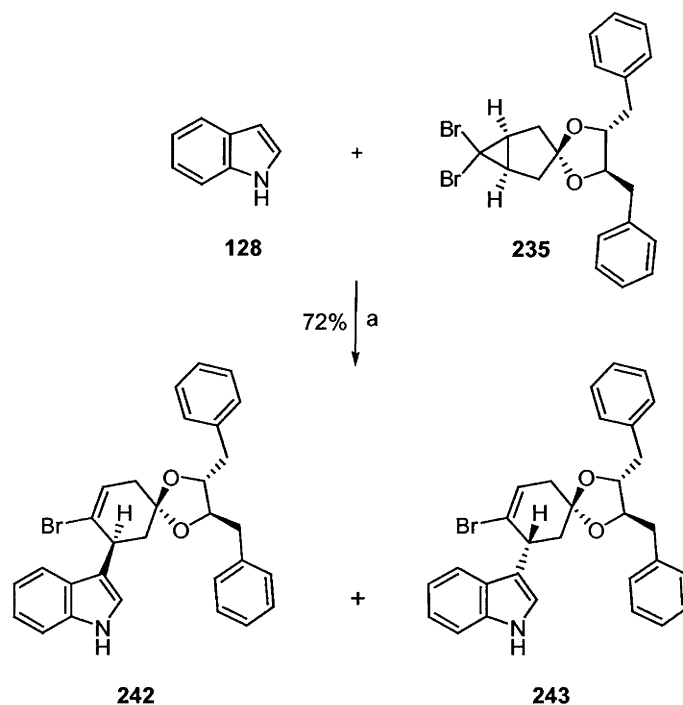
Figure 3.12: 75 MHz ^{13}C NMR Spectrum of Diene **240** in CDCl_3

Thus, a degassed solution of diene **240** in dichloromethane was heated at reflux in the presence of 5 mol% of Grubbs' II catalyst for five hours to ultimately deliver the protected cyclopenten-3-one **241**. Confirmation that the desired ring-closing metathesis had been accomplished was evident from examination of the ^1H NMR spectrum. The three signals (δ 5.87-5.74, 5.10 and 5.06) attributed to the protons on the terminal double bonds associated with diene **240** had been replaced by a two-proton singlet at δ 5.67. Similarly, in the ^{13}C NMR spectrum previously observed resonances due to the methylene carbons were no longer apparent and, instead, a new signal had appeared at δ 128.0, akin to that observed for the dimethylated congener. Compound **241** also exhibited a molecular ion at m/z 306 under EI conditions and an accurate mass measurement on this species established that it possessed the expected composition, namely $\text{C}_{21}\text{H}_{22}\text{O}_2$.

Compound **241** was subjected to the Brinker cyclopropanation conditions to afford a single isolable product which was assigned the structure **235**. As was seen in both the previously discussed menthyl and dimethylated ethylene ketal examples, evidence for the successful carbene addition to alkene **241** could be easily obtained by analysis of the derived spectroscopic data. Thus, the ^1H NMR spectrum no longer displayed any signals in the olefinic region but rather an additional two-proton multiplet was visible considerably further upfield. Similarly, the ^{13}C NMR spectrum showed the absence of resonances previously attributed to the alkene functionality in compound **241**. Instead new signals, appearing at δ 44.7 (C), 35.5 (CH) and 35.1 (CH) and typical of those due to carbons associated with a cyclopropane ring, were apparent. An EI mass spectrum showed the central molecular ion as m/z 478 whilst also displaying prominent isotopic ions at m/z 480 and 476 in an overall 1:2:1 ratio. This implied that two bromine atoms had been incorporated into the product. The predicted composition was verified by an accurate mass measurement, which established that the molecular formula was $\text{C}_{22}\text{H}_{23}\text{Br}_2\text{O}_2$.

With the requisite cyclopropane **235** in hand, studies concerned with the ring-opening of this compound and trapping of the resulting π -allyl cation with indole (**128**) were undertaken (Scheme 3.12). Thus, under identical conditions to those discussed earlier for the trapping of both the menthyl and dimethylated ethylene ketal systems, cyclopropane **235** underwent a silver(I)-promoted electrocyclic ring-opening reaction in the presence of indole (**128**). As with both of the aforementioned cases, the desired ring-opening and trapping sequence was successful, affording a mixture of products **242** and **243** in 72% combined yield. The ^1H NMR spectrum of this mixture revealed that the indolic protons and the protons associated with the chiral auxiliary were present in the anticipated ratio. The absence of the proton attributed to H-3 of the indole moiety and the presence of characteristic cycloalkenyl bromide signals for each diastereomer, visible at δ 6.13 and 6.09, provided further evidence that the desired coupling product had been obtained. The ^{13}C NMR spectrum of the same mixture was also in full accord with the assigned structure. As is expected for a mono-brominated compound, an EI mass spectrum showed a pair of molecular ions at m/z 515 and 513 and in a 1:1 ratio. An accurate mass measurement on these species then established their compositions to be $\text{C}_{30}\text{H}_{28}\text{BrNO}_2$.

Scheme 3.12: Reaction of Cyclopropane 235 with Indole (128)



Reagents and conditions: (a) AgBF₄, THF, 18 °C, 16 h.

At present conflicting results have been obtained from both the HPLC chromatograms and the NMR spectra of the semi-purified material in regard to the amount of diastereomeric control that the dibenzylated auxiliary has exerted in the discussed electrocyclic ring-opening and trapping sequence. NMR analysis of the purified material suggests the presence of a 2:1 mixture of diastereoisomeric products but this is not consistent with HPLC analysis of the crude reaction mixture which suggests the diastereoselectivity of the reaction may be significantly higher. It is believed that enrichment of the minor isomer may be occurring during the HPLC purification process, which is causing an alteration in the observed diastereomeric ratio. It is for this reason, therefore, that a conclusive comment cannot be made regarding the effectiveness of the dibenzylated auxiliary in this reaction. It should be noted, however, that the diastereomeric mixture obtained can be readily separated by HPLC techniques and therefore, regardless of the amount of control the auxiliary is exerting, this methodology still provides a simple and effective entry point for the assembly of enantiopure

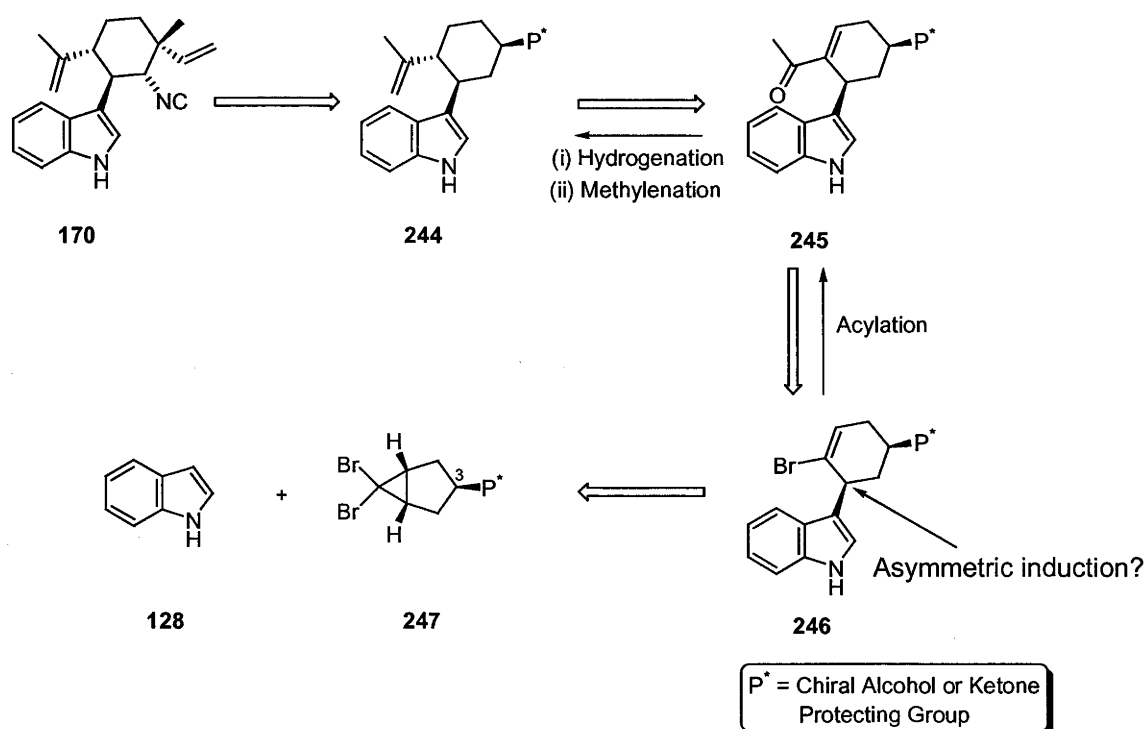
forms of the tricyclic hapalindole frameworks. Work in this area is ongoing and in the future other auxiliaries will be investigated in an attempt to improve on the diastereomeric ratios observed to date.

3.5.4 Model Studies Directed Towards the Hapalindole and Fischerindole Frameworks

3.5.4.1 Overview

With methodology in place for the rapid and efficient assembly of the hapalindole framework in enantiomerically pure form, studies were undertaken to elaborate the relevant compounds and thereby incorporate some of the additional functionality required for the synthesis of the natural product. As enunciated earlier, the initial plan involved exploiting the cycloalkenyl bromide resulting from the electrocyclic ring-opening of the corresponding *gem*-dibromocyclopropane as a platform to install the pivotal acyl moiety (Figure 3.13). Efforts directed towards such ends are discussed in the following sections.

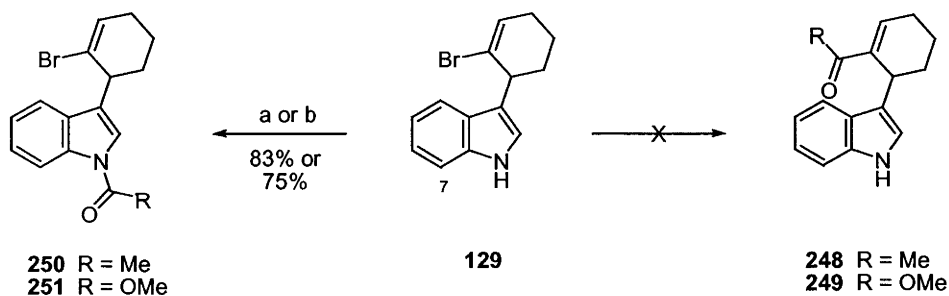
Figure 3.13: Retrosynthetic Analysis of Hapalindole C (170)



3.5.4.2 Initial Attempts at Installing the Acyl Moiety

Initial studies in this area commenced with attempts to lithiate the cycloalkenyl bromide within compound **129** (Scheme 3.13), which is readily formed, as discussed previously, in one step from reaction between 6,6-dibromobicyclo[3.1.0]hexane (**41**) and indole (**128**). It was anticipated that by using three equivalents of *tert*-butyllithium the nitrogen on the indole moiety would be deprotonated and a lithium-for-bromine exchange would then take place to deliver the corresponding cycloalkenyl lithium. This dianion would then be expected to react selectively, at carbon, with an appropriate electrophile to deliver the required acylated product.

Scheme 3.13: Attempts at Installation of an Acyl/Methyl Ester Moiety into Compound **129**



Reagents and conditions: (a) *t*-BuLi (3eq), THF, -78 °C, 0.5 h then AcCl, THF, -78 °C, 2 h; (b) *t*-BuLi (3eq), THF, -78 °C, 0.5 h then MeOCOCl, THF, -78 °C, 2 h.

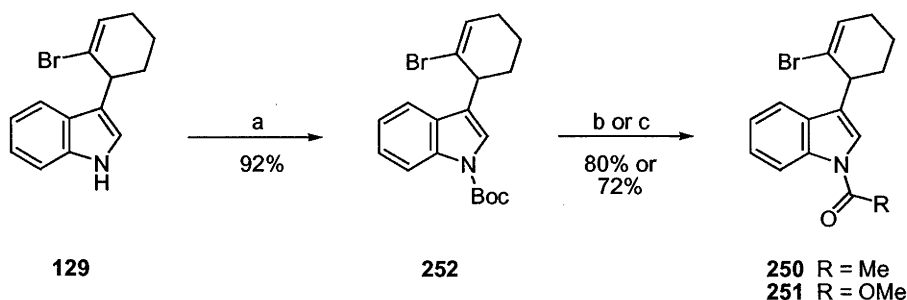
In the event, however, this was not the case and despite trialling various conditions the sole product that could be obtained was compound **250**, wherein the acyl group arising from the added electrophile has been incorporated at nitrogen. Key features in the ^1H NMR spectrum which led to this assignment were the shift of H-7 from δ 8.02 (in substrate **129**) to 8.45 (in the product and inferring that protection had occurred at nitrogen) and the appearance of a three-proton singlet at δ 2.65 (indicating the inclusion of acyl functionality into the molecule in the form of an acetamide). The ^{13}C NMR spectrum indicated that the product had arisen through incorporation of both methyl (δ 24.2) and carbonyl (δ 151.7) functionalities. The presence of a carbonyl moiety was also confirmed by infrared spectroscopy (ν_{max} 1680 cm^{-1})

and accurate mass measurements on the molecular ions observed in the 70 eV EI mass spectrum established that the composition of this product was $C_{16}H_{16}BrNO$.

To account for this outcome, it was proposed that the desired lithium-for-halogen exchange reaction was a slow process. Consequently, an even greater excess of *t*-butyllithium was subsequently added but this still did not change matters. At this stage the acetyl chloride was replaced with methyl chloroformate in an attempt to generate the corresponding methyl carbamate. However, akin to the previously discussed example, the sole product obtained was compound **251**. Similar features to those discussed for compound **250** were seen in both the 1H and ^{13}C NMR spectra of product **251**, hence leading to this structural assignment. EI mass spectrometry studies established that the product still contained a bromine whilst also indicating that a carbomethoxy moiety had been incorporated. Verification of the expected composition, namely $C_{16}H_{16}BrNO_2$, was obtained through an accurate mass measurement.

The next logical step, therefore, was to protect the nitrogen of compound **129** in an attempt to prevent reaction from occurring at this centre (Scheme 3.14). Hence, compound **129** was converted into the corresponding carbamate **252** under standard conditions. As expected, the derived spectral data were in full accord with the assigned structure.

Scheme 3.14: Boc Protection and Subsequent Lithiation



Reagents and conditions: (a) $(Boc)_2O$, DMAP, Et_3N , CH_2Cl_2 , 18 °C, 2 h; (b) *t*-BuLi (2eq), THF, -78 °C, 0.5 h then AcCl, THF, -78 °C, 2 h; (c) *t*-BuLi (2eq), THF, -78 °C, 0.5 h then MeOCOCli, THF, -78 °C, 2 h.

On subjection of compound **252** to the lithium-for-halogen exchange conditions shown in Scheme 3.14 and in the presence of both acetyl chloride and methyl chloroformate, the desired products were not observed but, rather, the previously observed compounds **250** and **251**, respectively, were obtained once again. As expected, these products were spectroscopically indistinguishable from those samples obtained earlier.

A range of other conditions were then trialled in an attempt to effect the desired lithium-for-halogen exchange reaction and trapping of the derived cyclohexenyl lithium with acetyl chloride, methyl chloroformate, methyl cyanoformate and *N*-methoxy-*N*-methylacetamide (**253**). During the course of these studies attempts were also made to lithiate using *n*-butyllithium but these proved to be equally unsuccessful. Despite using identical conditions to those reported by Danheiser and co-workers,⁵⁷ whereby a successful lithiation of a related cycloalkenyl bromide moiety in the presence of a Boc-protected primary amine was performed, this transformation could not be achieved with substrate **252**. Presumably this is because the carbamate protecting group on the indole nitrogen is far more labile than a Boc-protected amine, such as that used by Danheiser and, therefore, the Boc-derivative **252** is not robust enough to withstand the conditions required for the pivotal lithium-for-halogen exchange.

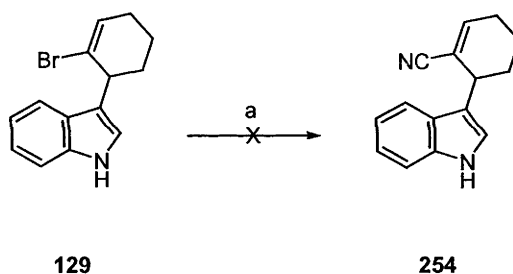
In view of the foregoing results, it was considered that there could be some merit in attempting to install the required functionality by alternate means. Therefore, efforts were directed towards examining palladium-catalysed cross-coupling reactions. Thus, a Stille cross-coupling process, utilising (α -ethoxyvinyl)trimethylstannane as the nucleophile⁵⁸ followed by an acidic work-up, was attempted under a range of different conditions. However, no reaction was observed. A similar result was obtained when attempts were made to effect a palladium-catalysed carbonylation reaction in the presence of methanol.⁵⁹

It would appear from these results detailed above that the cycloalkenyl bromide moiety within compound **129** will not readily participate in the desired coupling reactions and so efforts were directed towards converting the cycloalkenyl bromide into another organometallic species before the anticipated electrophilic trapping reaction was again attempted.

Organomagnesium reagents have been found to be highly reactive and are widely used in organic chemistry today. Hence, by employing chemistry developed by Knochel⁶⁰ attempts were made to form the corresponding organomagnesium derivative before quenching this with an electrophile such as methyl chloroformate. However, the substrate **129** appeared to be inert to these reaction conditions.

Efforts were also directed towards performing a palladium-catalysed cyano-debromination of the bromoolefin,⁶¹ utilizing potassium cyanide, 18-crown-6 and tetrakis(triphenylphosphine)palladium (Scheme 3.15). Once again, however, only starting material was recovered.

Scheme 3.15: Attempted Palladium-Catalysed Cyano-Debromination of Cycloalkenyl Bromide **129**



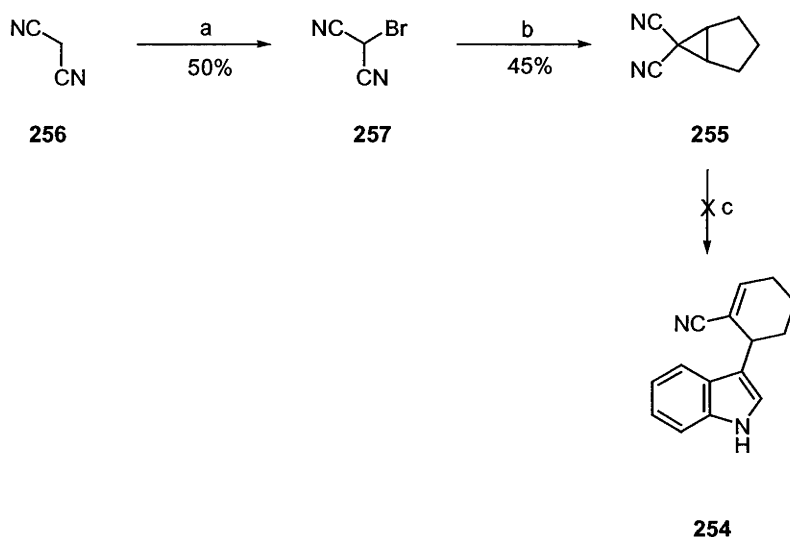
Reagents and conditions: (a) Pd(PPh₃)₄, KCN, 18-crown-6, benzene, 18 to 75 °C, 26 h.

An alternate approach would be to incorporate the desired functionality onto the cyclopropane ring system before the electrocyclic ring-opening and subsequent trapping with indole (**128**) was carried out. As a result the dicyanocyclopropane **255** was targeted (Scheme 3.16).

Following literature procedures^{62,63} 6,6-dicyanobicyclo[3.1.0]hexane (**255**) was readily synthesised in two steps from malononitrile (**256**) (Scheme 3.16). Thus, bromination of malononitrile (**256**) afforded bromodicyanomethane (**257**) as a colourless crystalline solid in 50% yield. This then underwent a free radical addition reaction to cyclopentene to afford the

desired cyclopropane **255** (45%) and the spectral data obtained for this compound were in full accord with those reported in the literature. With compound **255** in hand, replication of the model studies with indole (**128**) were carried out. Unfortunately however, despite heating a neat and 1:1 mixture of cyclopropane **255** and indole (**128**) at elevated temperatures (200 °C), no product of the desired type, *viz.* **254**, was observed.

Scheme 3.16: Synthesis of Dicyanocyclopropane 255 and Attempted Trapping Reaction

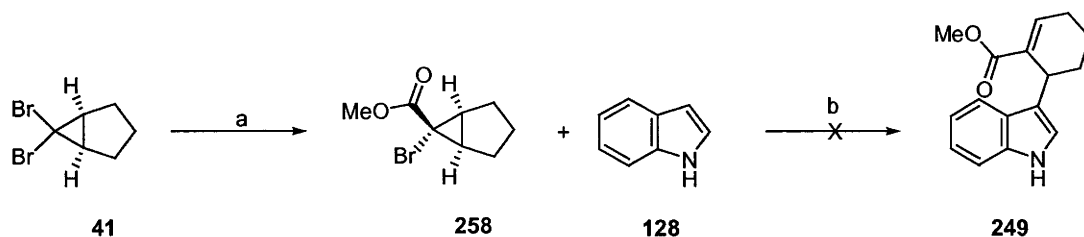


Reagents and conditions: (a) Br₂, H₂O, 0 °C, 4 h; (b) cyclopentene, CH₂Cl₂, *hν*, 7 h then Et₃N, CH₂Cl₂, 0.5 h; (c) indole, 200 °C, 48 h.

Utilising an analogous approach, it was believed that reaction of cyclopropane **258** with indole (**128**) could deliver compound **249** which already has the desired functionality incorporated, hence avoiding the apparent problems associated with manipulating the unreactive cycloalkenyl bromide moiety within compound **129**. Of course it is acknowledged that this approach will only be successful if incorporation of the methyl ester moiety proceeds with retention of the *endo*-bromine. Precedence, however, suggested that the required stereocontrol could be accomplished at low temperatures.⁶⁴ Therefore, cyclopropane **258** was targeted (Scheme 3.17). Synthesis and purification of this compound proved to be somewhat problematic. Nevertheless by reducing the reaction temperature to -100 °C in the lithiation

step the desired product **258** appeared to be formed (as judged by ^1H NMR spectral analysis). However, when the crude product was reacted with indole (**128**) under the standard silver(I)-promoted ring-opening conditions none of the desired product **249** was observed.

Scheme 3.17: *Synthesis of Cyclopropane 258 and Attempted Trapping Reaction*



Reagents and conditions: (a) *t*-BuLi, THF, $-100\text{ }^\circ\text{C}$, 5 h then MeOCOC(OMe), THF, $-100\text{ }^\circ\text{C}$, 3 h; (b) AgBF₄, THF, $18\text{ }^\circ\text{C}$, 16 h.

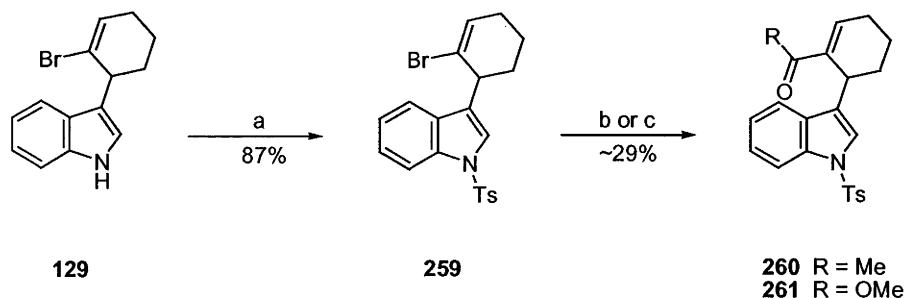
3.5.4.3 Revised Strategy

Despite the rather discouraging results detailed in the foregoing section, it was considered that there could be some merit in revisiting the initial strategy, whereby the acyl or methyl ester moiety would be incorporated using organolithium chemistry, but this time employing a highly stable indole nitrogen protecting group in a substrate related to compound **129**. Ample literature precedence for sulfonyl-based protecting groups surviving lithiation conditions when incorporated on the indole nitrogen prompted an examination of the feasibility of utilising this protecting group during the lithium-for-halogen exchange reaction.

To these ends, the tosyl-protected derivative of compound **129** was produced under standard conditions⁶⁵ and in good yield (87%) (Scheme 3.18). Typical features expected in both the ^1H and ^{13}C NMR spectra for the introduction of a tosyl group onto the indole nitrogen were observed and the composition, namely C₂₁H₂₀BrNO₂S, of this compound confirmed through an accurate mass measurement. Subsequent reaction of compound **259** with *t*-butyllithium and acetyl chloride or methyl chloroformate provided some very interesting results. Whilst a mixture of products was obtained, NMR data indicated that, for the first time, compounds

resembling those previously sought, namely the acylated systems **260** and **261**, had been formed albeit in modest yields.

Scheme 3.18: Revised Strategy – Examining the Tosyl Protecting Group

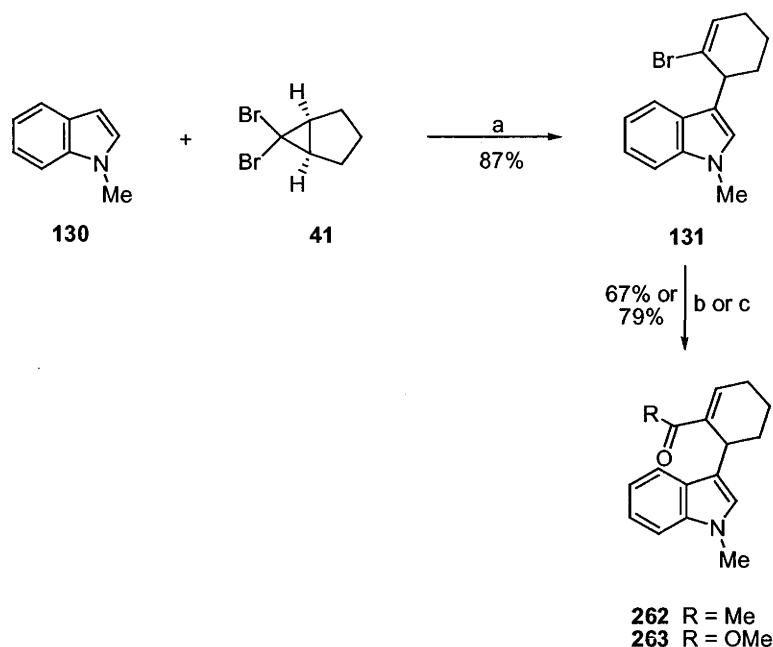


Reagents and conditions: (a) *n*-BuLi, THF, -78 to 0 °C, 1 h then *p*-TsCl, -78 to 18 °C, 16 h; (b) *t*-BuLi, THF, -78 °C, 0.5 h then AcCl, -78 to 18 °C, 16 h; (c) *t*-BuLi, THF, -78 °C, 0.5 h then MeOCOCl, -78 to 18 °C, 16 h.

Tantalised by these results, it was decided to investigate the highly stable methyl-protected system **131** as a substrate for the lithium-for-halogen exchange reaction and in the hope that products of the type **262** and **263** could be obtained (Scheme 3.19).

Compound **131** was readily synthesised in one step from *N*-methylindole (**130**) and 6,6-dibromobicyclo[3.1.0]hexane (**41**), as previously described in Chapter Two. The organolithium derivative of this compound, obtained *via* halogen-metal exchange of **131** with *t*-butyllithium, was then subjected to reaction with *N*-methoxy-*N*-methylacetamide (**253**),^{66,67} a reagent shown by Danheiser *et al.* to be uniquely effective in achieving the desired acylation reaction on a related cycloalkenyl bromide.⁶⁸ After considerable optimisation of the reaction conditions, compound **262** could be obtained as the sole isolable product and in 67% yield. During the course of these optimisation studies it was found that decomposition and undesired side-products were observed if the reaction temperature was allowed to rise significantly above -78 °C.

Scheme 3.19: Investigating Methyl as a Protecting Group



Reagents and conditions: (a) AgBF_4 , THF, 18 °C, 4 h; (b) *t*-BuLi, THF, -78 °C, 0.5 h then $\text{CH}_3\text{CON}(\text{Me})\text{OMe}$ (**253**), -78 °C, 3h; (c) *t*-BuLi, THF, -78 °C, 0.5 h then MeOCOCCl , -78 °C, 3h.

Evidence that the desired reaction had occurred was initially derived from examination of the ^1H NMR spectrum of the major and chromatographically purified reaction product. In particular, the appearance of a new three-proton singlet at δ 2.23 suggested the inclusion of the acyl group whilst the observation of a signal attributable to an indole *N*-methyl moiety suggested that the acyl moiety had been included elsewhere in the molecule, most likely at the desired position. All of the indolic protons were also present further indicating that the reaction had taken place at the desired position. The ^{13}C NMR spectrum (Figure 3.14) was in full accord with the depicted structure **262**, whilst the infrared spectrum also confirmed the introduction of a conjugated acyl substituent. A single molecular ion peak was observed in the mass spectrum, hence confirming that bromine was no longer present in the molecule. As expected, an accurate mass measurement established the composition of this material to be $\text{C}_{17}\text{H}_{19}\text{NO}$.

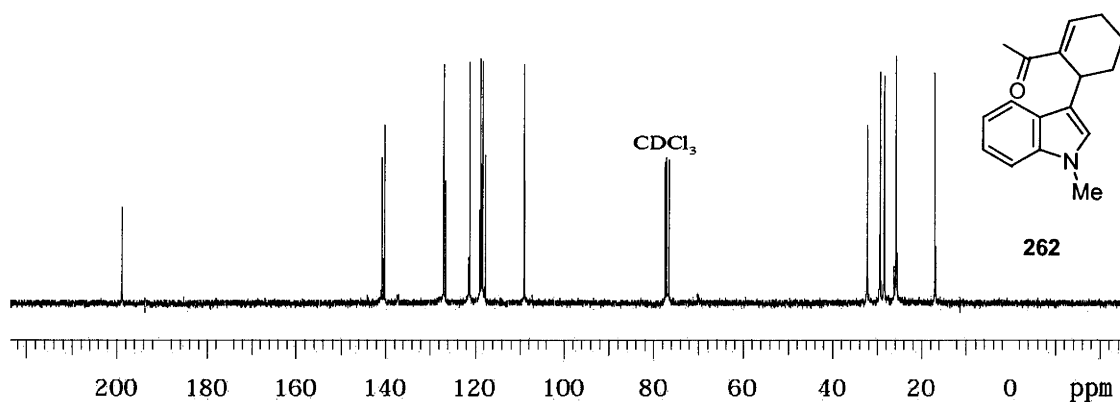


Figure 3.14: 75 MHz ^{13}C NMR Spectrum of Compound **262** in CDCl_3

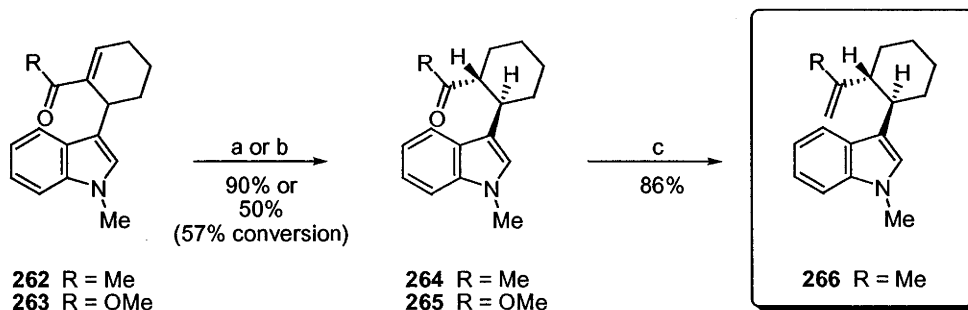
Analogous reaction between compound **131** and methyl chloroformate was also carried out, this time providing product **263** as a pale-orange oil in 79% yield. The ^1H NMR spectrum of this material displayed a three-proton singlet at δ 3.61 and this was attributed to the protons of the newly introduced methoxy functionality. Resonances due to all of the indolic protons were observed, eliminating the possibility that carbomethoxylation may have occurred somewhere on the indole ring. Furthermore, there was a significant downfield shift in the cycloalkenyl proton, strongly suggesting that the adjacent bromine in the starting material had been replaced by a methyl ester moiety. The ^{13}C NMR spectrum showed the expected seventeen resonances and these could all be clearly assigned to the depicted structure **263**.

3.5.4.4 Elaboration of Compound **262** to the Tricyclic Hapalindole Framework

With compound **262** now in hand, the synthesis of the framework associated with the tricyclic hapalindole alkaloids could be targeted (Scheme 3.20). A palladium-catalysed hydrogenation of the cycloalkenyl bond, using 10% palladium on charcoal, delivered compound **264** as a single isomer. Whilst various solvent mixtures were investigated for the discussed hydrogenation, optimal results were obtained when a 1:1 mixture of methanol and ethyl acetate was employed. It would appear that solubility issues are mainly responsible for the particular effectiveness of this solvent combination. The main spectral features, which led to the assignment of the illustrated structure, were the obvious disappearance of the resonance attributed to the cycloalkenyl proton and, analogously, in the ^{13}C NMR spectrum the replacement of C and CH resonances with the corresponding CH and CH_2 signals expected for

the hydrogenated product. Finally an accurate mass measurement confirmed the composition to be $C_{17}H_{21}NO$.

Scheme 3.20: Synthesis of the Tricyclic Hapalindole Framework 266



Reagents and conditions: (a) H_2 (1 atm), 10% Pd/C, MeOH/EtOAc, 18 °C, 16 h (R = Me); (b) H_2 (1 atm), 10% Pd/C, MeOH/EtOAc, 18 °C, 48 h (R = OMe); (c) Cp_2TiMe_2 , toluene, 65 °C, 14 h.

Based on MM2 molecular modelling calculations and on comparisons made with previously reported data derived from related compounds it appears most likely that, as depicted, a *trans*-relationship has been established between the acyl and indole moieties attached to the cyclohexane ring. Presumably, this reduction step leads to a mixture of *cis*- and *trans*-products in the first instance but under the acidic conditions involved equilibration occurs and the latter and thermodynamically more stable product predominates.

Efforts were also directed towards removing the cyclohexenyl double bond in compound **263** and whilst this transformation was ultimately accomplished utilising the indicated conditions numerous unsuccessful attempts were made to drive this reaction to completion. Despite experimenting with various solvents and solvent mixtures, including performing the reaction under four atmospheres of hydrogen in a Fischer-Porter apparatus and trying alternate catalysts such as rhodium on alumina, the maximum yield of compound **265** that could be obtained was 50% at 57% conversion. Work in this area is ongoing and it is hoped that in due course an improved set of hydrogenation conditions will be established.

The only remaining transformation required to obtain the tricyclic hapalindole framework **266** was the methylenation of the acyl moiety within compound **264**. Whilst this conversion could, in principle at least, be achieved using a variety of methods, including those employing Wittig-type reagents, geminal dimetallic derivatives or nucleophilic metallocarbenes, in this instance readily synthesisable dimethyltitanocene was the reagent of choice. The ease of use, minimisation of unwanted side-reactions and high yielding conversions reported for methylenation reactions using this reagent were all factors that contributed towards the decision to use this species. In the event, reaction of methyl ketone **264** with dimethyltitanocene⁶⁹ under an argon atmosphere afforded olefin **266** in 86% yield. Full characterisation of this compound, including an accurate mass measurement on the molecular ion, supported the assigned structure. Thus, the ¹H NMR spectrum displayed a doublet at δ 4.68 ($J = 7.8$ Hz), attributable to the protons associated with the newly formed terminal olefin, whilst the previously observed singlet of the acyl methyl was now seen as a triplet ($J = 0.6$ Hz) due to small couplings with the adjacent olefinic protons. The expected eighteen resonances were observed in the ¹³C NMR spectrum (Figure 3.15), the most informative appearing at δ 109.8 which, based on APT spectral analysis, was assigned as the CH₂ signal associated with the newly introduced olefin. Further evidence that the desired methylenation had occurred was also provided by the lack of signals, in both the ¹³C NMR and infrared spectra, due to a C=O moiety. The infrared spectrum did, however, display a weak absorption maxima at 1641 cm⁻¹, typical for terminal double bond C=C stretching band. As previously alluded to, low and high resolution EI mass spectrometry confirmed the expected molecular formula for compound **266**, viz. C₁₈H₂₃N.

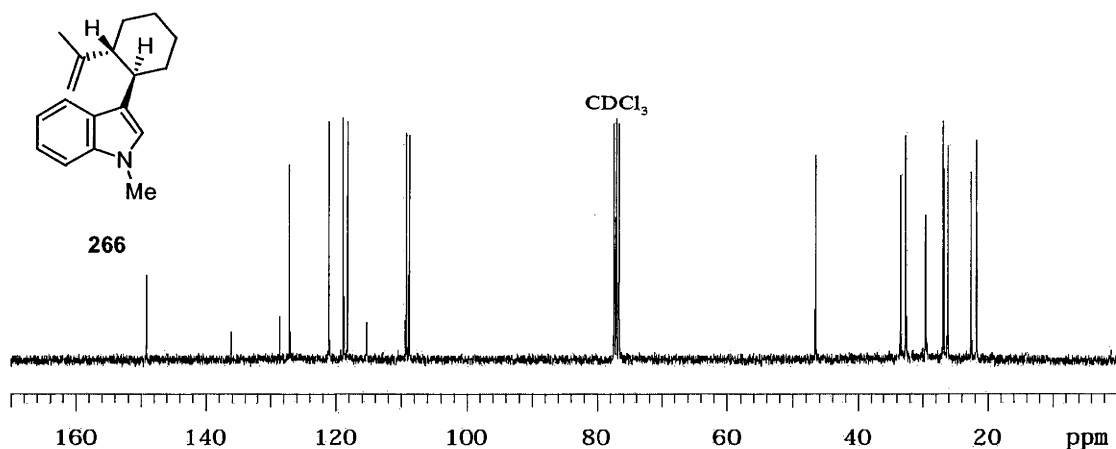
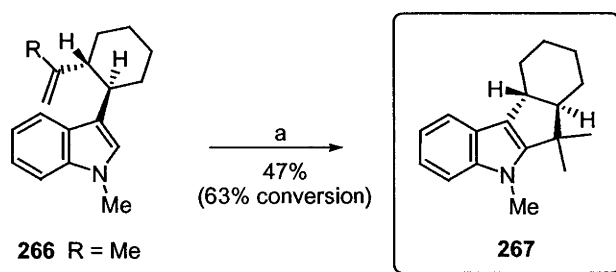


Figure 3.15: 75 MHz ¹³C NMR Spectrum of Olefin **266** in CDCl₃

3.5.4.5 Extension of Methodology to Fischerindole Framework

As previously reported,⁷⁰ the tricyclic hapalindole alkaloids undergo an acid-catalysed and biomimetic ring-closure on to the C-2 position of indole to afford the fischerindole alkaloid skeleton (Scheme 3.21). Therefore, compound **266** was subjected to identical conditions to those described by Baran and Richter in their synthesis of (-)-12-*epi*-fischerindole U isothiocyanate (**210**).⁷¹ As expected, compound **267** was delivered in good yield. The spectral data obtained for compound **267** were in general agreement with the data previously reported for (-)-12-*epi*-fischerindole U isothiocyanate (**210**). Distinctive features in both the ¹H and ¹³C NMR spectra, confirming that the desired cyclisation had occurred, were the absence of resonances due to a C-2 indolic proton (δ_{H} 6.99) and the equivalent carbon (δ_{C} 109.8) as well as the appearance of two new quaternary carbon resonances. Further evidence for this conversion arose from the observation that the terminal olefin resonances of the substrate had been replaced with two distinct new methyl group resonances appearing at δ 1.35 and 1.26 in the ¹H NMR spectrum and two coincident signals at δ 24.1 in the ¹³C NMR spectrum. The composition depicted was confirmed by low and high resolution mass spectrometry.

Scheme 3.21: Synthesis of the Fischerindole Alkaloid Skeleton **267**



Reagents and conditions: (a) TMSOTf, MeOH, CH₂Cl₂, 0 °C, 1 h.

Whilst it is acknowledged that the above-mentioned syntheses of both the tricyclic hapalindole framework and the analogous fischerindole skeleton has provided *N*-methyl-protected derivatives, literature precedence suggests that removal of this methyl group can

readily be achieved by oxidation with benzoyl peroxide and subsequent hydrolysis of the resulting benzoyloxymethyl derivative.⁷²

3.6 Conclusions

The work detailed above has served to showcase, in a wider context, the utility of the methodology developed in Chapter Two. By exploiting the adducts derived from the silver(I)-promoted ring-opening reaction between a 6,6-dibromobicyclo[3.1.0]hexane system (**41**) and indole (**128**), the rapid assembly of the polycyclic frameworks associated with the biologically and structurally interesting hapalindole and fischerindole classes of alkaloids has been achieved. During the course of these studies an effective protecting group, required for the successful installation of the acyl or methyl ester moieties, was also identified. The knowledge gained in these model studies is likely to be highly useful in future studies directed towards the total syntheses of various members of the hapalindole and fischerindole class of compounds.

Not only have the aforementioned frameworks been successfully obtained, but simple and effective methodology was also developed for exerting diastereocontrol in the pivotal reaction between 3-substituted derivatives of 6,6-dibromobicyclo[3.1.0]hexane (**41**) and indole (**128**). This sequence, which provides additional functionality around the ajoined cyclohexyl ring capable of undergoing further (and relevant) elaboration, should ultimately allow for the natural products to be targeted in both an efficient and enantioselective fashion.

In more general terms, however, and perhaps more importantly, the work described within this Chapter has been successful in further demonstrating the effectiveness of employing *gem*-dihalocyclopropanes as starting materials for the synthesis of complex organic compounds.

3.7 References

- ¹ Moore, R.E., Cheuk, C., Yang, X-Q.G., Patterson, G.M.L., Bonjouklian, R., Smitka, T.A., Mynderse, J.S., Foster, R.S., Jones, N.D., Swartzendruber, J.K., Deeter, J.B.; *J. Org. Chem.*, **1987**, *52*, 1036-1043.
- ² Park, A., Moore, R.E., Patterson, G.M.L.; *Tetrahedron Lett.*, **1992**, *33*, 3257-3260.
- ³ Stratmann, K., Moore, R.E., Bonjouklian, R., Deeter, J.B., Patterson, G.M.L., Shaffer, S., Smith, C.D., Smitka, T.A.; *J. Am. Chem. Soc.*, **1994**, *116*, 9935-9942.
- ⁴ Jimenez, J.I., Huber, U., Moore, R.E., Patterson, G.M.L.; *J. Nat. Prod.*, **1999**, *62*, 569-572.
- ⁵ Smitka, T.A., Bonjouklian, R., Doolin, L., Jones, N.D., Deeter, J.B., Yoshida, W.Y., Prinsep, M.R., Moore, R.E., Patterson, G.M.L.; *J. Org. Chem.*, **1992**, *57*, 857-861.
- ⁶ Huber, U., Moore, R.E., Patterson, G.M.L.; *J. Nat. Prod.*, **1998**, *61*, 1304-1306.
- ⁷ Moore, R.E., Yang, X-Q.G., Patterson, G.M.L.; *J. Org. Chem.*, **1987**, *52*, 3773-3777.
- ⁸ Moore, R.E., Yang, X-Q.G., Patterson, G.M.L., Bonjouklian, R., Smitka, T.A.; *Phytochemistry*, **1989**, *28*, 1565-1567.
- ⁹ Schwartz, R.E., Hirsch, C.F., Springer, J.P., Pettibone, D.J., Zink, D.L.; *J. Org. Chem.*, **1987**, *52*, 3706-3708.
- ¹⁰ Moore, R.E., Cheuk, C., Patterson, G.M.L.; *J. Am. Chem. Soc.*, **1984**, *106*, 6456-6457.
- ¹¹ Daloze, D.K.D., Braekman, J.C.; *J. Nat. Prod.*, **1995**, *58*, 1781-1785.
- ¹² Moore, R.E., Cheuk, C., Yang, X-Q.G., Patterson, G.M.L., Bonjouklian, R., Smitka, T.A., Mynderse, J.S., Foster, R.S., Jones, N.D., Swartzendruber, J.K., Deeter, J.B.; *J. Org. Chem.*, **1987**, *52*, 1036-1043.
- ¹³ Moore, R.E., Cheuk, C., Patterson, G.M.L.; *J. Am. Chem. Soc.*, **1984**, *106*, 6456-6457.
- ¹⁴ Daloze, D.K.D., Braekman, J.C.; *J. Nat. Prod.*, **1995**, *58*, 1781-1785.
- ¹⁵ Doan, N.T., Rickards, R.W., Rothschild, J.M., Smith, G.D.; *J. App. Phycol.*, **2000**, *12*, 409-416.
- ¹⁶ Doan, N.T., Stewart, P.R., Smith, G.D.; *FEMS Microbiology Letters*, **2001**, *196*, 135-139.
- ¹⁷ Bonjouklian, R., Moore, R.E., Patterson, G.M.L.; *J. Org. Chem.*, **1988**, *53*, 5866-5870.
- ¹⁸ Park, A., Moore, R.E., Patterson, G.M.L.; *Tetrahedron Lett.*, **1992**, *33*, 3257-3260.
- ¹⁹ Schwartz, R.E., Hirsch, C.F., Sesin, D.F., Flor, J.E.; *J. Ind. Microbiol.*, **1990**, *5*, 113-123.

- ²⁰ Bonjouklian, R., Moore, R.E., Patterson, G.M.L.; *J. Org. Chem.*, **1988**, *53*, 5866-5870.
- ²¹ Park, A., Moore, R.E., Patterson, G.M.L.; *Tetrahedron Lett.*, **1992**, *33*, 3257-3260.
- ²² Fukuyama, T., Chen, X.; *J. Am. Chem. Soc.*, **1994**, *116*, 3125-3126.
- ²³ Vaillancourt, V., Albizati, K.F.; *J. Am. Chem. Soc.*, **1993**, *115*, 3499-3502.
- ²⁴ Muratake, H., Natsume, M.; *Tetrahedron Lett.*, **1989**, *30*, 1815-1818.
- ²⁵ Muratake, H., Natsume, M.; *Tetrahedron*, **1990**, *46*, 6331-6342.
- ²⁶ Muratake, H., Natsume, M.; *Tetrahedron*, **1990**, *46*, 6343-6350.
- ²⁷ Muratake, H., Natsume, M.; *Tetrahedron*, **1990**, *46*, 6351-6360.
- ²⁸ Sakagami, M., Muratake, H., Natsume, M.; *Chem. Pharm. Bull.*, **1994**, *42*, 1393-1398.
- ²⁹ Muratake, H., Natsume, M.; *Tetrahedron Lett.*, **1989**, *30*, 1815-1818.
- ³⁰ Fukuyama, T., Chen, X.; *J. Am. Chem. Soc.*, **1994**, *116*, 3125-3126.
- ³¹ Bonjouklian, R., Moore, R.E., Patterson, G.M.L.; *J. Org. Chem.*, **1988**, *53*, 5866-5870.
- ³² Shioiri, T., Ninomiya, K., Yamada, S-I.; *J. Am. Chem. Soc.*, **1972**, *94*, 6203-6205.
- ³³ Kinsman, A.C., Kerr, M.A.; *Org. Lett.*, **2000**, *2*, 3517-3520.
- ³⁴ Brown, M.A., Kerr, M.A.; *Tetrahedron Lett.*, **2001**, *42*, 983-985.
- ³⁵ Kinsman, A.C., Kerr, M.A.; *Org. Lett.*, **2001**, *3*, 3189-3191.
- ³⁶ Kinsman, A.C., Kerr, M.A.; *J. Am. Chem. Soc.*, **2003**, *125*, 14120-14125.
- ³⁷ Ahrendt, K.A., Borths, C.J., MacMillan, D.W.C.; *J. Am. Chem. Soc.*, **2000**, *122*, 4243-4244.
- ³⁸ Northrup, A.B., MacMillan, D.W.C.; *J. Am. Chem. Soc.*, **2002**, *124*, 2458-2460.
- ³⁹ Vaillancourt, V., Albizati, K.F.; *J. Am. Chem. Soc.*, **1993**, *115*, 3499-3502.
- ⁴⁰ Baran, P.S., Richter, J.M.; *J. Am. Chem. Soc.*, **2004**, *126*, 7450-7451.
- ⁴¹ Barton, D.H.R., Deflorin, A.M., Edwards, O.E.; *J. Chem. Soc.*, **1956**, *1*, 530-534.
- ⁴² Xu, L., Brinker, U.H.; in *Synthetic Organic Sonochemistry*, Luche, J.L. (Ed.), Plenum Press: New York, **1998**, pp. 344-345.
- ⁴³ Dreyfuss, M.P.; *J. Org. Chem.*, **1963**, *28*, 3269-3272.
- ⁴⁴ Meyer, S.D., Schreiber, S.L.; *J. Org. Chem.*, **1994**, *59*, 7549-7552.
- ⁴⁵ Swern, D., Huang, S.L.; *J. Org. Chem.*, **1978**, *43*, 4537-4538.
- ⁴⁶ Ley, S.V., Norman, J., Griffith, W.P., Marsden, S.P.; *Synthesis*, **1994**, *7*, 639-666.
- ⁴⁷ Korshevets, I.A., Mistryukov, E.A.; *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1986**, *3*, 614-616.
- ⁴⁸ Dolbier, W.R., Garza, O.T.; *J. Org. Chem.*, **1978**, *43*, 3848-3851.

- ⁴⁹ Grubbs, R.H., Bielawski, C.W., Louie, J.; *J. Am. Chem. Soc.*, **2001**, *123*, 11312-11313.
- ⁵⁰ Makosza, M., Wawrzyniewicz, W.; *Tetrahedron Lett.*, **1969**, *10*, 4659-4662.
- ⁵¹ Wallace, T.W., Wardell, I., Li, K-D., Leeming, P., Redhouse, A.D., Challand, S.R.; *J. Chem. Soc. Perkin Trans.1*, **1995**, *18*, 2293-2308.
- ⁵² Blanco, O.M., Castedo, L.; *Synlett*, **1999**, *5*, 557-558.
- ⁵³ Grubbs, R.H., Louie, J.; *Angew. Chem. Int. Ed.*, **2001**, *40*, 247-249.
- ⁵⁴ Wallace, T.W., Wardell, I., Li, K-D., Leeming, P., Redhouse, A.D., Challand, S.R.; *J. Chem. Soc. Perkin Trans.1*, **1995**, *18*, 2293-2308.
- ⁵⁵ Kwong, H-L.; *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L.A. (Ed.), John Wiley and Sons: Chichester, **1995**, Vol. 6, pp. 4218-4220.
- ⁵⁶ Devine, P.N., Oh, T.; *Tetrahedron Lett.*, **1991**, *32*, 883-886.
- ⁵⁷ Danheiser, R.L., Morin Jr., J.M., Salaski, E.J.; *J. Am. Chem. Soc.*, **1985**, *107*, 8066-8073.
- ⁵⁸ Kwon, H.B., McKee, B.H., Stille, J.K.; *J. Org. Chem.*, **1990**, *55*, 3114-3118.
- ⁵⁹ Banwell, M.G., Cameron, J.M., Corbett, M., Dupuche, J.R., Hamel, E., Lambert, J.N., Lin, C.M., Mackay, M.F.; *Aust. J. Chem.*, **1992**, *45*, 1967-1982.
- ⁶⁰ Rottländer, M., Boymond, L., Cahiez, G., Knochel, P.; *J. Org. Chem.*, **1999**, *64*, 1080-1081.
- ⁶¹ Yamamura, K., Murahashi, S.; *Tetrahedron Lett.*, **1977**, *50*, 4429-4430.
- ⁶² Boldt, P., Schulz, L., Etzemüller, J.; *Chem. Ber.*, **1967**, *100*, 1281-1288.
- ⁶³ Boldt, P., Schulz, L., Klinsmann, U., Köster, H., Thielecke, W.; *Tetrahedron*, **1970**, *26*, 3591-3615.
- ⁶⁴ Banwell, M.G., Collis, M. P., Mackay, M.F., Richards, S. L.; *J. Chem. Soc., Perkin Trans.1*, **1993**, 1913-1920.
- ⁶⁵ Ponticello, G.S., Baldwin, J.J.; *J. Org. Chem.*, **1979**, *44*, 4003-4005.
- ⁶⁶ Oster, T.A., Harris, T.M.; *Tetrahedron Lett.*, **1983**, *24*, 1851-1854.
- ⁶⁷ Nahm, S., Weinreb, S.M.; *Tetrahedron Lett.*, **1981**, *22*, 3815-3818.
- ⁶⁸ Danheiser, R.L., Morin Jr., J.M., Salaski, E.J.; *J. Am. Chem. Soc.*, **1985**, *107*, 8066-8073.
- ⁶⁹ Petasis, N.A., Bzowej, E.I.; *J. Am. Chem. Soc.*, **1990**, *112*, 6392-6394.
- ⁷⁰ Fukuyama, T., Chen, X.; *J. Am. Chem. Soc.*, **1994**, *116*, 3125-3126.
- ⁷¹ Baran, P.S., Richter, J.M.; *J. Am. Chem. Soc.*, **2004**, *126*, 7450-7451.
- ⁷² Nakatsuka, S., Asano, O., Goto, T.; *Heterocycles*, **1986**, *24*, 2791-2792.

Intramolecular Nucleophilic Trapping of π -Allyl Cations Derived From the Electrocyclic Ring-Opening of *gem*-Dibromocyclopropanes

4.1 Introduction

The research work described thus far has centred on investigating the ability of the π -allyl cations derived from the electrocyclic ring-opening of *gem*-dibromocyclopropanes to undergo intermolecular trapping with the most nucleophilic carbon of various heteroaromatic systems and, thereby, leading to the formation of a new carbon-carbon bond. As mentioned in the introductory Chapter, extensive work has been carried out within the Banwell group on the construction of ring-fused *gem*-dihalocyclopropanes containing a range of tethered nucleophiles and the subsequent capacity they offer for intramolecular trapping of the derived π -allyl cation.¹ The development of related cyclisation reactions involving tethered carbon nucleophiles as the π -allyl cation trapping agent was considered a highly desirable extension of such work. Not only would successful execution of such ideas provide alternative methods for the formation of carbon-carbon bonds but the intramolecular trapping process should deliver new polycyclic compounds incorporating a cycloalkenyl bromide moiety. As noted earlier, this functionality should be capable of participating in further reactions, thus setting the stage for the development of new strategies for natural product synthesis.

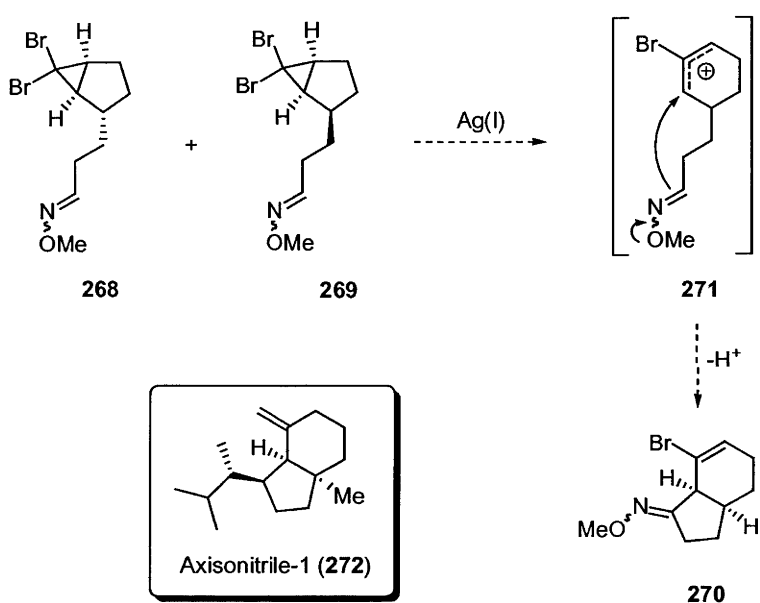
4.2 Oximes as Trapping Nucleophiles

4.2.1 Overview

Initial studies in this area began with an investigation of the potential for an oxime to act as a trapping nucleophile in the abovementioned process. Thus, it was anticipated that by

subjecting a *gem*-dihalocyclopropane containing a suitably tethered oxime, as seen in compounds **268** and **269**, to silver(I)-promoted ring-opening conditions a perhydroindane framework **270** would be formed *via* cyclisation of the intermediate cation **271**. As illustrated in Figure 4.1, this compound bears some structural relationship to the marine natural product azisonitrile-1 (**272**), thus highlighting the potential synthetic utility of the proposed process. Of course, the expectation here was that the C-atom associated with the oxime would be the most nucleophilic entity within this functional group.

Figure 4.1: Examining Oximes as Trapping Nucleophiles



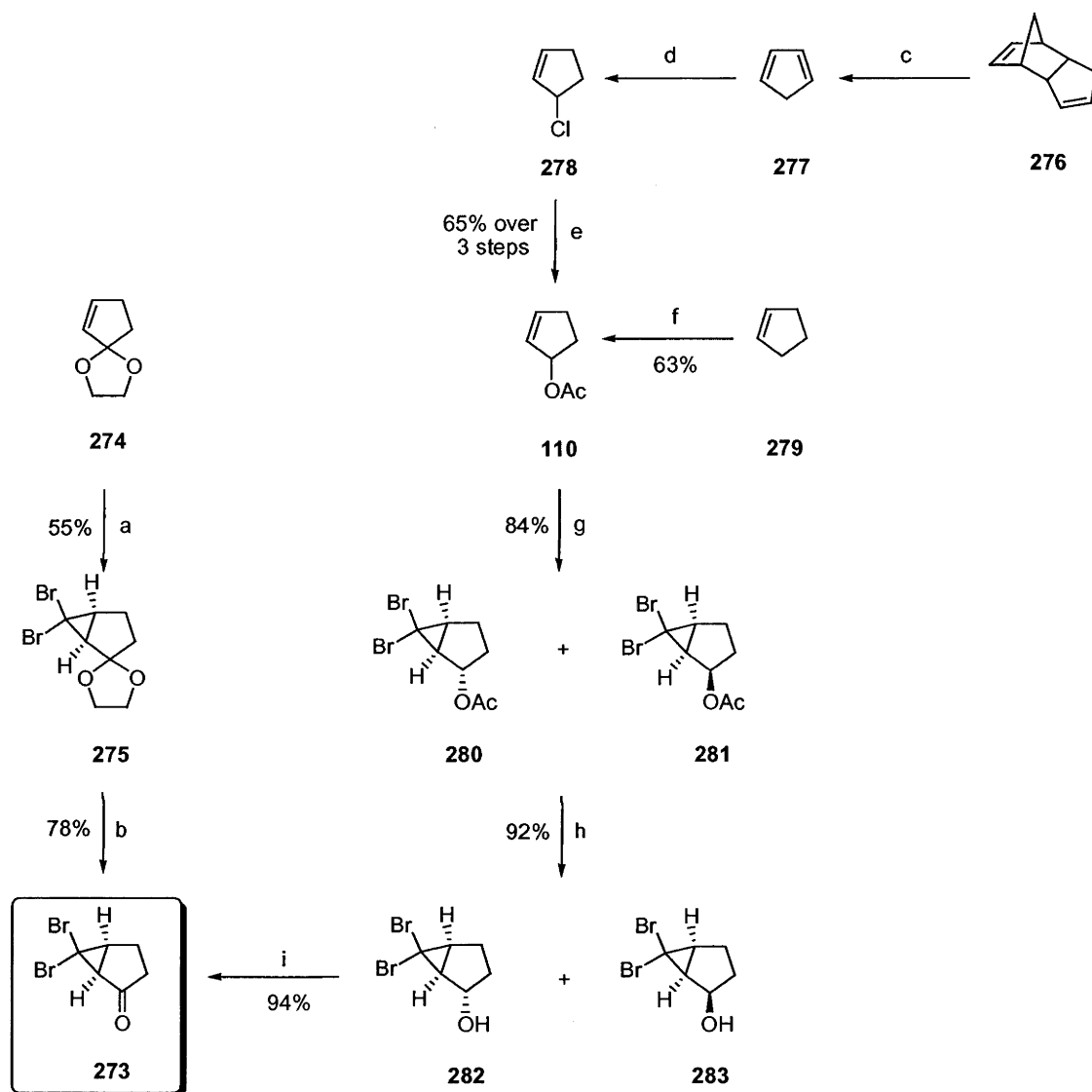
4.2.2 Synthesis of the Requisite Cyclopropanes **268** and **269**

The primary challenge associated with efforts to explore the ideas proposed in Figure 4.1 was the synthesis of tethered oximes **268** and **269**. Of course these should be readily derived from the corresponding aldehydes by standard methods. Therefore, these carbonyl-containing precursors became the initial synthetic targets. The application of standard Wittig chemistry to attach the requisite three-carbon side-chain onto a 6,6-dibromobicyclo[3.1.0]hexanone core was the first approach to be investigated.

4.2.2.1 Synthesis of the Required 6,6-Dibromobicyclo[3.1.0]hexan-2-one (**273**) System

Initial work targeted the previously synthesised 6,6-dibromobicyclo[3.1.0]hexan-2-one (**273**) system *via* an alternate, and more efficient, route. Thus, commercially available 2-cyclopenten-1-one ethylene ketal (**274**) was subjected to dibromocarbene addition utilising the phase-transfer conditions described earlier (Scheme 4.1). Both the ^1H and ^{13}C NMR spectra of product **275** lacked resonances in the olefinic region. The appearance of a complex multiplet at δ 4.05-3.74 in the ^1H NMR spectrum also confirmed that the desired carbene addition reaction had occurred without cleavage of the ketal moiety. The 70 eV EI mass spectrum showed the anticipated molecular ions at m/z 300, 298 and 296 and, as is expected for a dibrominated compound, these ions were observed in a 1:2:1 ratio. Due to the instability of this cyclopropane and the low intensity of the molecular ion cluster an accurate mass measurement was only able to be acquired on the informative fragment ion $[\text{M-HBr}]^+$ which was of the expected composition.

It was observed that the rate at which the aforementioned reaction proceeded was significantly slower than that seen for previously discussed systems. This is presumably due to the steric bulk of the ketal group which is immediately adjacent to the site of carbene addition. This factor could also contribute to the moderate yield observed although this is thought to be due mainly to the instability of compound **275** and its propensity to either decompose or undergo spontaneous ring-opening during the purification process. For this reason, therefore, after initial characterisation subsequent syntheses of compound **273** involved immediate deprotection of the precursor ketal **275**. By such means the relatively stable and previously reported² ketone **273** was obtained as a low melting solid, albeit in modest overall yield. The derived spectral data were in full accord with previous reports.³

Scheme 4.1: Alternative Routes to 6,6-Dibromobicyclo[3.1.0]hexan-2-one (**273**)

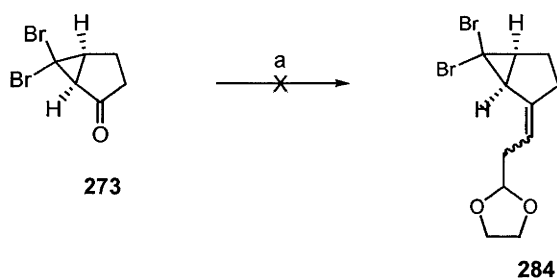
Reagents and conditions: (a) CHBr_3 , TEAC, NaOH, CH_2Cl_2 , 3 h; (b) HCl (2 M aqueous solution), THF, 18 °C, 18 h; (c) iron filings, 180 °C; (d) dry HCl (g), < 0 °C; (e) NaOAc, AcOH, 0 to 18 °C, 15 h; (f) $\text{Pd}(\text{OAc})_2$, MnO_2 , benzoquinone, AcOH, 50 °C, 0.5 h then **279**, 50 °C, 16 h; (g) CHBr_3 , TEAC, NaOH, CH_2Cl_2 , 3 h; (h) K_2CO_3 , MeOH, 18 °C, 16 h; (i) PCC, CH_2Cl_2 , 0 °C to 18 °C, 7 h.

The low yields and practical difficulties associated with accumulating large quantities of material *via* the seemingly direct route mentioned above prompted an investigation of alternative approaches to ketone **273**. Therefore, a modification of the sequence reported by

Banwell and co-workers⁴ was examined next (see right hand side of Scheme 4.1). Thus, commercially available dicyclopentadiene (**276**) was cracked in the presence of iron filings to deliver cyclopentadiene (**277**) which was immediately treated, at 0 °C, with one equivalent of dry hydrogen chloride gas to afford the desired, but highly unstable, 3-chlorocyclopentene (**278**). This compound was then immediately converted into the corresponding 3-acetoxycyclopentene (**110**) *via* reaction with anhydrous sodium acetate in glacial acetic acid. Whilst, in agreement with the previously reported preparations of this compound, the overall yield for this sequence was relatively low no attempts were made to improve upon this. This was because these reactions were performed on such a scale that a sufficient amount of starting material could be obtained for the next step in the reaction sequence. Subsequent investigations also established that compound **110** could be synthesised more efficiently and in only one step, albeit in slightly lower yield, from commercially available cyclopentene (**279**) *via* a palladium(II)-catalysed acetoxylation reaction⁵ (Scheme 4.1). This latter method, therefore, became the one of choice for the synthesis of compound **110**. As was the case with the previously discussed method, the data obtained were in full accord with those reported earlier for this compound. Dibromocarbene addition to acetate **110** then afforded a 4:1 mixture of cyclopropanes **280** and **281** which were hydrolysed to the corresponding alcohols **282** and **283**. These were, in turn, oxidised with PCC to furnish the requisite ketone **273**. All of the physical and spectral data acquired on these materials were in complete agreement with those reported earlier.⁶

4.2.2.2 Initial Approach to the Synthesis of Key Intermediate **284**

With compound **273** in hand efforts were then directed towards installing the requisite three-carbon side-chain utilising Wittig chemistry (Scheme 4.2). Unfortunately, however, the steric bulk of the cyclopropyl group appeared to hinder the desired reaction, thus suggesting that side-chain installation should precede the carbene addition step.

Scheme 4.2: Initial Approach to Key Intermediate 284

Reagents and conditions: (a) 2-(1,3-dioxan-2-yl)-ethyltriphenylphosphonium bromide, KHMDS, THF, 0 °C, 0.5 h then **273**, THF, 0 to 18 °C, 44 h.

4.2.2.3 Revised Synthetic Strategy

The appropriately modified and ultimately successful route to oximes **268** and **269** is depicted in Scheme 4.3 and involved, in the opening stages, reaction of a C3-substituted cyclopentene with a three-carbon Grignard reagent so as to install the required side-chain. The cyclopentenyl acetate, bromide and chloride were all trialed as substrates for this purpose. Despite catalysis by dilithiumtetrachlorocuprate,⁷ the allylic acetate failed to afford any of the desired compound. Whilst the allylic bromide (readily formed through reaction of cyclopentene with *N*-bromosuccinimide in the presence of AIBN⁸) afforded some of the desired product the most useful outcomes, by far, were achieved by employing the previously synthesised 3-chlorocyclopentene (**278**) in the manner indicated. Thus, after basic work-up, to remove excess HCl, a solution of freshly prepared compound **278** in 1:10 v/v DMPU/THF was immediately subjected to reaction with the Grignard reagent derived, *in situ*, from commercially available 2-(2-bromoethyl)-1,3-dioxolane and, in this manner, the desired product **285** was obtained in 98% yield. It should be noted that in the absence of DMPU, which presumably increases the electrophilicity of allyl chloride **278**, the observed yields were dramatically lower. The ¹H NMR spectrum of a purified sample of compound **285** matched that reported⁹ and featured a distinctive multiplet, integrating to two protons, in the olefinic region (δ 5.69) and a characteristic four-proton multiplet, at δ 3.90, attributable to the methylene protons of the acetal moiety. As expected, the ¹³C NMR spectrum (Figure 4.2)

showed signals assignable as C-1, C-2 and C-9/10 at δ 134.5 (CH), 130.3 (CH) and 64.6 (2 x CH₂), respectively. EI mass spectrometry and an accurate mass measurement established that product **285** was of the correct composition, viz. C₁₀H₁₆O₂.

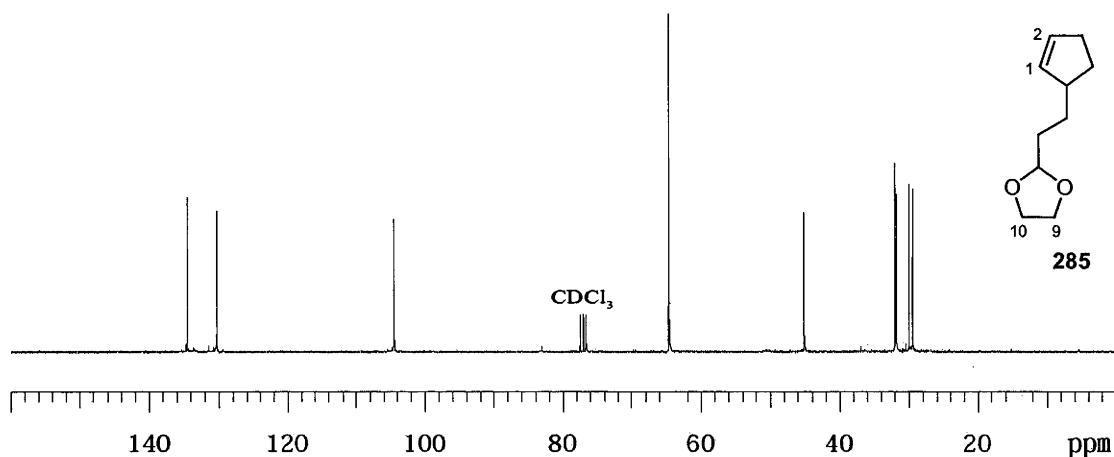
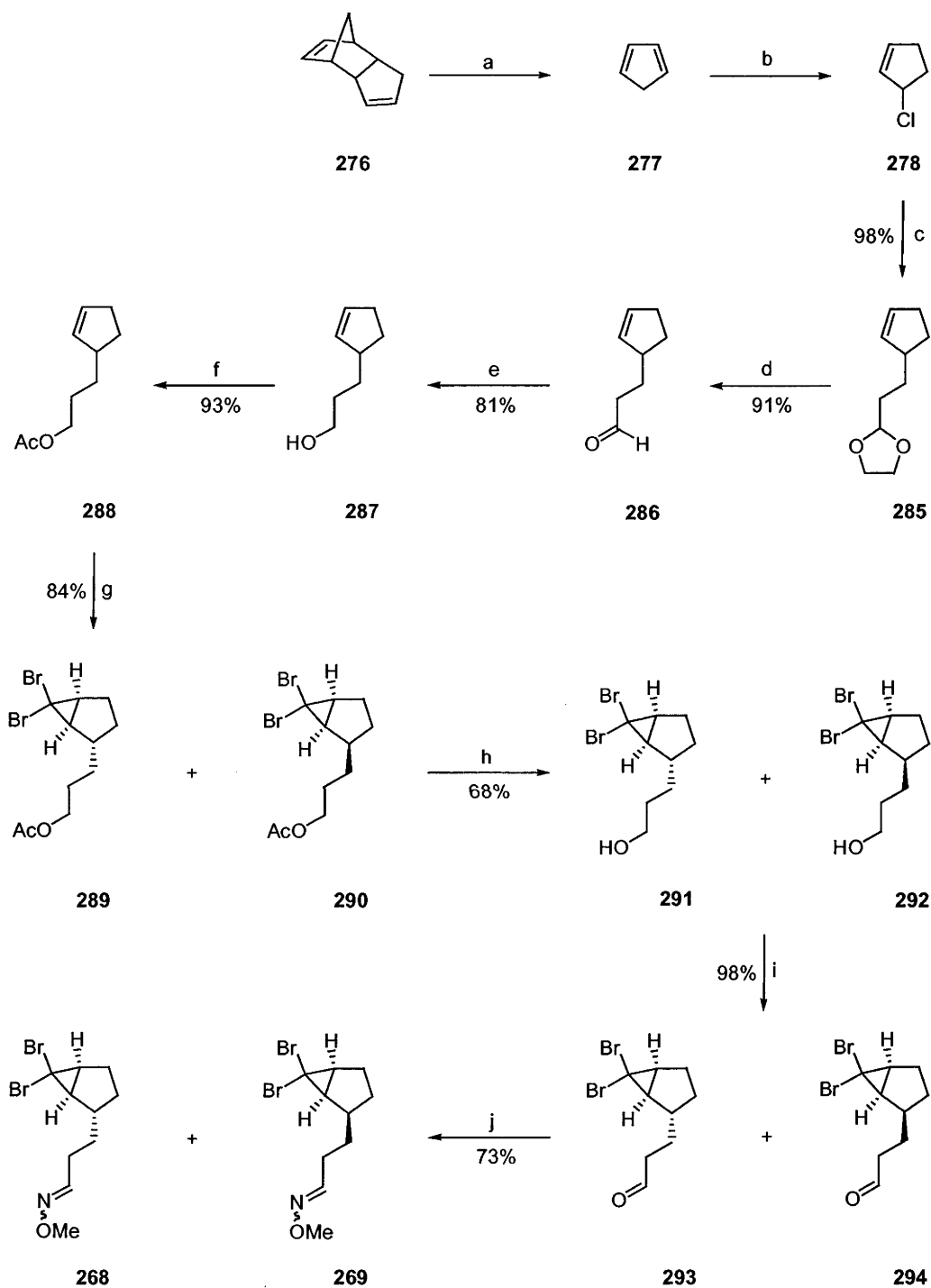


Figure 4.2: 75 MHz ¹³C NMR Spectrum of Acetal **285** in CDCl₃

As the next step in the reaction sequence, the acetal moiety within compound **285** was cleaved through exposure to a 1:1 v/v mixture of 1 M aqueous HCl and THF. In this manner aldehyde **286** was obtained as a pale-yellow oil in 91% yield. The most distinctive features in both the ¹H and ¹³C NMR spectra of compound **286** were signals due to the aldehyde moiety at δ_{H} 9.78 and δ_{C} 202.8, respectively. The infrared spectrum also displayed a typical non-conjugated aldehyde carbonyl absorption band at 1727 cm⁻¹. 70 eV EI mass spectral analysis and a subsequent accurate mass measurement on the observed molecular ion established that the compound was of the composition C₈H₁₂O.

Scheme 4.3: Synthesis of the Requisite Oximes 268 and 269



Reagents and conditions: (a) iron filings, 180 °C; (b) dry HCl (g), < 0 °C; (c) Mg turnings, 2-(2-bromoethyl)-1,3-dioxolane, THF, 20 °C, 1 h then 278, DMPU, THF, 18 °C, 18 h; (d) HCl (1 M aqueous solution), THF, 18 °C, 18 h; (e) NaBH₄, MeOH, 18 °C, 40 min; (f) Ac₂O, pyridine, 18 °C, 3.5 h; (g) CHBr₃, TEBAC, NaOH, CH₂Cl₂,)), 3 h; (h) K₂CO₃, MeOH, 18 °C, 16 h; (i) DMP, CH₂Cl₂, 0 to 18 °C, 1.5 h; (j) CH₃ONH₂·HCl, pyridine, 18 °C, 16 h.

Reduction of aldehyde **286** to the corresponding alcohol **287** was achieved under standard conditions using NaBH_4 . The derived ^1H NMR spectrum (Figure 4.3) was in full accord with the assigned structure. A diagnostic resonance for an sp^3 -hybridised carbon bearing an OH group was observed at δ 63.0 in the ^{13}C NMR spectrum and the infrared spectrum showed a characteristic O-H stretching band at 3339 cm^{-1} . Accompanying O-H bending and C-O stretching bands were apparent at 1361 cm^{-1} and 1055 cm^{-1} , respectively.

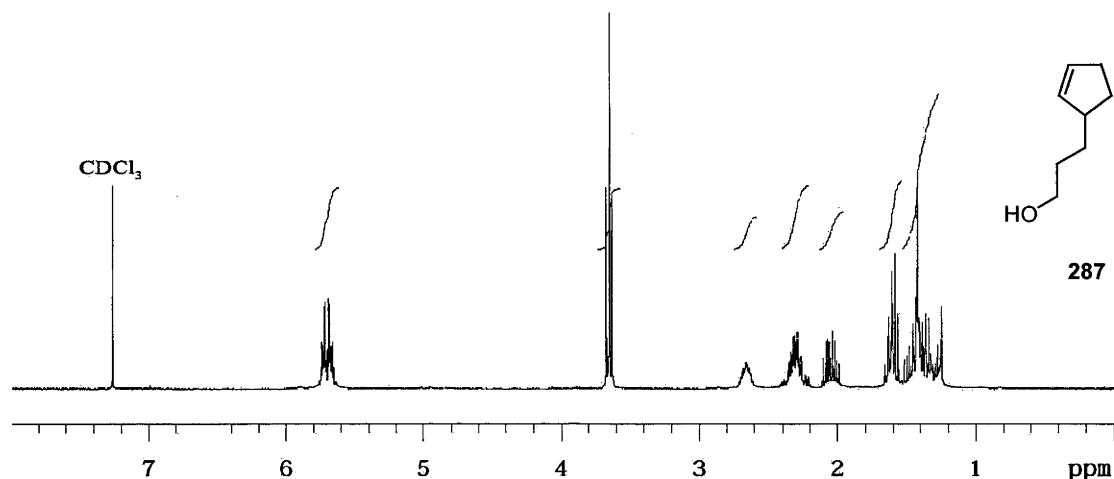


Figure 4.3: 300 MHz ^1H NMR Spectrum of Alcohol **287** in CDCl_3

Protection of alcohol **287** as the corresponding acetate was required as a prelude to the carbene addition step. To this end, a solution of alcohol **287** in pyridine was treated, at ambient temperature, with acetic anhydride. After three and a half hours, TLC analysis indicated that the reaction had gone to completion and, following purification, an analytically pure sample of acetate **288** was obtained as a yellow oil. The derived spectral data were in full accord with the assigned structure.

With compound **288** in hand, the requisite dibromocarbene addition step could be attempted (Scheme 4.3). Classical Makosza conditions¹⁰ were initially investigated. However, an inability to achieve full conversion to the desired product eventually led to the use of the newer and slightly more vigorous Brinker conditions, which also employ benzyltriethylammonium chloride (TEBAC) as the phase transfer catalyst.¹¹ On completion, this reaction afforded the *gem*-dibromocyclopropanes **289** and **290** as a 4:1 mixture of

diastereomers. Whilst previous work,¹² as mentioned earlier, has indicated that the stereochemical relationship between the *gem*-dihalocyclopropane and the tethered nucleophile is not important in determining the success of electrocyclic ring-opening/ π -allyl cation trapping processes of the types being contemplated, for the purposes of characterisation the two diastereomers were separated by column chromatography and characterised independently. Due to the almost identical nature of the data sets obtained for these epimers no definitive judgements could be made regarding stereochemistry. However, assignment of the major product as that involving an *anti*-relationship between the cyclopropane ring and the side-chain is proposed based on the reasonable assumption that dibromocarbene would add, preferentially, to the less-hindered face of the double bond within precursor **288**. All physical, analytical and spectroscopic data acquired on these compounds were in full accord with the assigned structures. The 70 eV EI mass spectra of adducts **289** and **290** each showed molecular ion clusters in the ratio expected for a dibromo-containing compound. Further, an accurate mass measurement on the $[M-H]^+$ fragment ion appearing at m/z 337 (in both instances) implied the molecular formula to be $C_{11}H_{16}^{79}Br_2O_2$. Eleven resonances were observed in each ^{13}C NMR spectrum, the most notable features of which were the absence of any signals in the olefinic region (δ 110-150). Similarly, the 1H NMR spectrum of each diastereomer displayed an absence of signals in the olefinic region and the appearance of an upfield and two-proton multiplet, corresponding to the newly introduced cyclopropyl protons. Such data left no doubt that the desired carbene adducts **289** and **290** had been obtained.

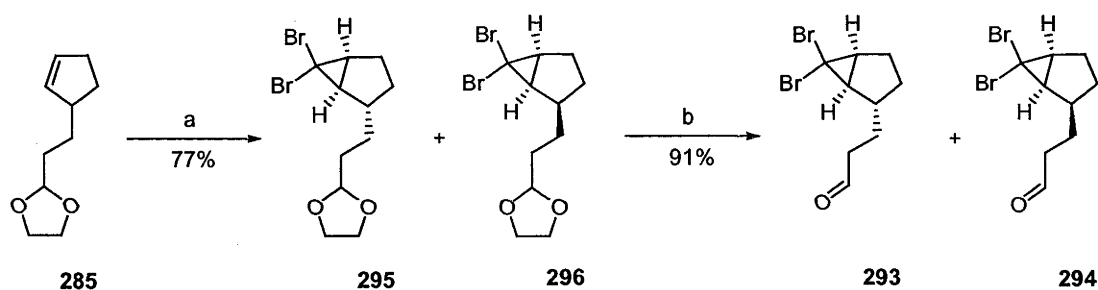
Hydrolysis of the acetate moiety contained within the diastereomeric mixture of compounds **289** and **290** was readily effected with potassium carbonate in methanol. Again, whilst not important in terms of the chemistry to be pursued, the 4:1 diastereomeric mixture of products was separated, utilising column chromatography, and each diastereomer subjected to full characterisation. As before, all of the spectral data acquired on compounds **291** and **292** were in full accord with the assigned structures.

The penultimate transformation required in the studies directed towards the synthesis of key oximes **268** and **269**, was oxidation of the pendant alcohol functionality within compounds **291** and **292**. This conversion proceeded smoothly using the Dess-Martin periodinane and a

small amount of water¹³ to deliver a 4:1 mixture of the target aldehydes **293** and **294** as a yellow oil in 98% combined yield. The chromatographically separable and epimeric aldehydes were again characterised by the usual means and all data obtained were completely consistent with the illustrated structures.

Subsequent to the establishment of the aforementioned sequence, optimisation studies later revealed that aldehydes **293** and **294** could be readily synthesised in two steps and 84% overall yield from acetal **285** via the reaction sequence depicted in Scheme 4.4. This route had not been pursued originally because of (clearly unfounded) concerns that carbene insertion into the C-H bond of the acetal moiety would be problematic.

Scheme 4.4: Alternate Route to Aldehydes 293 and 294



Reagents and conditions: (a) CHBr_3 , TEBAC, NaOH, CH_2Cl_2 , 3 h; (b) HCl (1 M aqueous solution), THF, 18 °C, 16 h.

With requisite aldehydes **293** and **294** in hand, completion of the sequence directed towards the necessary cyclisation precursors **268** and **269** could be pursued. Thus, utilising the straightforward conditions reported by Keana and co-workers,¹⁴ aldehydes **293** and **294** were readily converted into the *O*-methyl oximes **268** and **269** – these being obtained in 73% yield. The resulting 4:1 mixture of epimers could be separated chromatographically and characterised independently. Each epimer was obtained as an inseparable 1:1 mixture of the corresponding *E*- and *Z*-isomers about the C=N bond. A clear indication that the ensuing aldehydes **294** and **293** had undergone conversion into the corresponding oximes **268** and **269**

was evident from the ^1H NMR spectra wherein the resonance due to the proton in the aldehydic precursor had now moved upfield in the derived imine. The appearance of two sets of imine signals also indicated the presence of 1:1 mixture of *E*- and *Z*-isomers. A final characteristic, which aided in the confirmation of the assignment of structures **268** and **269**, was the appearance of two sharp singlets, at δ 3.88 and 3.82, each integrating to three protons and attributable to the OMe-group protons of the *E*- and *Z*-isomers associated with each epimer. As anticipated, twenty resonances were observed in each ^{13}C NMR spectrum. Infrared analysis indicated the absence of any remaining aldehydic functionality, while the 70 eV EI mass spectrum showed molecular ions at m/z 327, 325 and 323 in the 1:2:1 ratio expected for a dibrominated species.

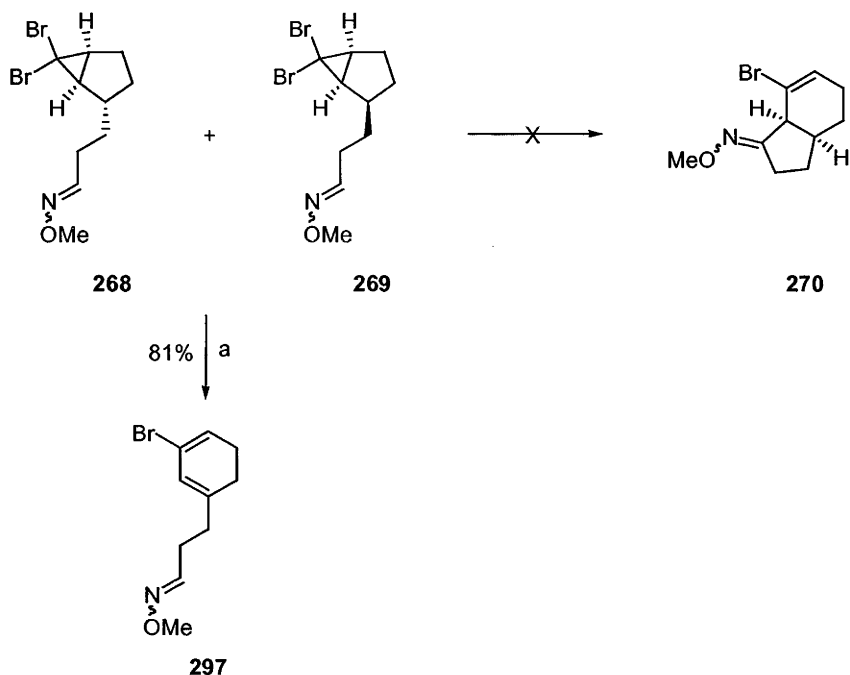
4.2.3 Attempts to Effect Cyclisation of Oximes **268** and **269**

With preparatively useful quantities of oximes **268** and **269** in hand investigations could begin on the originally proposed and key cyclisation reaction. Thus, a solution of these compounds in anhydrous THF was treated, in one portion, with silver tetrafluoroborate. However, despite investigating a variety of conditions, the only isolable product identified was diene **297** (Scheme 4.5) which was obtained in 81% yield. Key features in the ^1H NMR spectrum, which indicated that the illustrated product **297** had indeed been formed, were the presence of the cycloalkenyl bromide proton (δ 6.05), another new olefinic signal at δ 5.46 and, most informatively, the retention of signals due to the *E*- and *Z*-isomeric forms of the aldehyde-derived oxime unit. These spectral features clearly indicated that the desired trapping reaction had not occurred. All of the expected twenty resonances were observed in the APT ^{13}C NMR spectrum and GC-MS analysis of the product revealed the expected pair of molecular ions at m/z 245 and 243.

Compounds related to diene **297** have been observed previously during attempts to implement analogous cyclopropane cleavage/intramolecular cation trapping sequences¹⁵ and, therefore even if rather disappointing, this result could not be considered entirely surprising. It would appear that the sp^2 -hybridised carbons of the oxime moiety within compounds **268** and **269**

were not nucleophilic enough to capture the derived π -allyl cation which, as a consequence, underwent deprotonation to give the observed dienic product **297**.

Scheme 4.5: Cyclisation of Oximes **268** and **269**



Reagents and conditions: (a) AgBF_4 , THF, 18 °C, 5 h.

4.3 Malonates as Trapping Nucleophiles

4.3.1 Overview

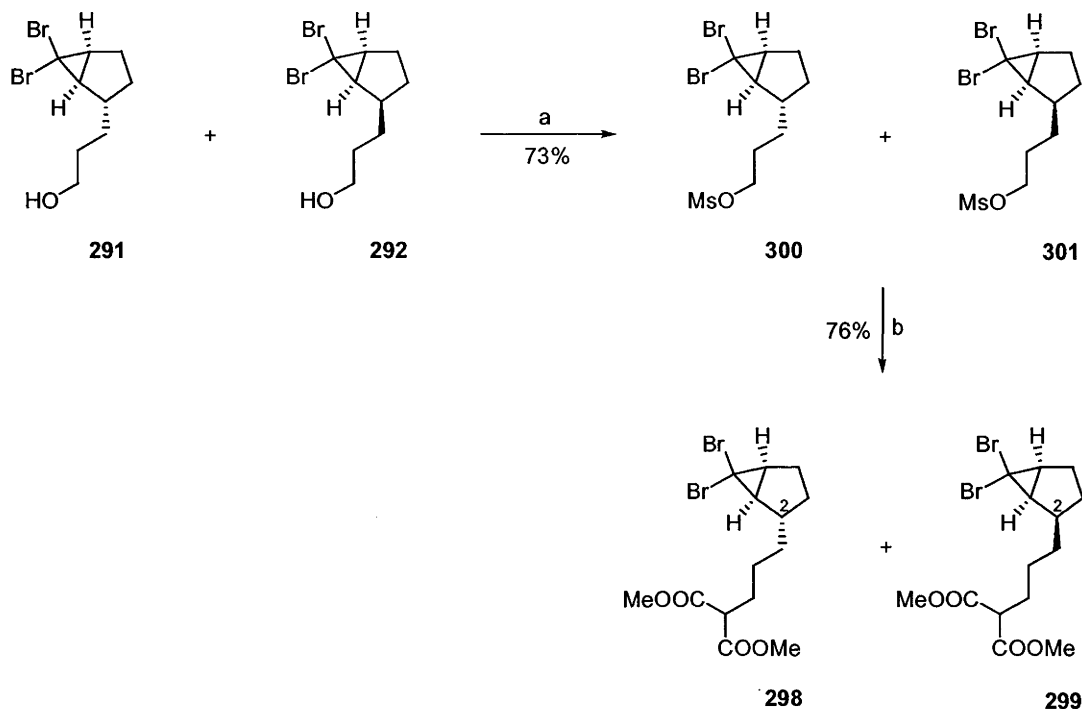
Following the disappointing outcomes detailed in the preceding section it was thought that there could be some merit in investigating alternative *C*-centred nucleophiles in an effort to achieve the desired carbon-carbon bond forming and associated cyclisation reaction. As such, efforts were directed towards utilising a malonate anion as the internal nucleophile. Not only was the use of this functional group attractive because of its increased nucleophilic properties

(relative to an oxime carbon) but its synthesis could also be readily achieved by exploiting the previously discussed chemistry.

4.3.2 Synthesis of the Required Cyclopropanes 298 and 299

The desired malonates **298** and **299** were prepared (Scheme 4.6) by first converting the previously reported alcohols **291** and **292** into the corresponding mesylates **300** and **301** under standard conditions. A diagnostic feature in the ^1H NMR spectra of compounds **300** and **301** was the presence of two three-proton singlets assignable to the methyl groups of the newly introduced sulfonyl moieties. Furthermore, a characteristic sulfonyl group absorbance was observed at 1353 cm^{-1} in the infrared spectrum. Low resolution EI mass spectrometry, together with an accurate mass measurement established the expected molecular formula, *viz.* $\text{C}_{10}\text{H}_{16}\text{Br}_2\text{O}_3\text{S}$, and thus confirmed the formation of the desired product.

The mesylates **300** and **301** then underwent reaction with sodium dimethyl malonate¹⁶ to afford the corresponding, and inseparable, 4:1 mixture of malonate derivatives **298** and **299** as a clear, colourless oil. Characterisation of these compounds was facilitated by a number of pertinent features visible in the ^1H and ^{13}C NMR spectra. The two diastereomeric forms of the newly installed methyl esters gave rise to six-proton singlets at δ 3.75 and 3.78 in the ^1H NMR spectrum of the mixture while the associated methine proton at C-2 led to signals at δ 3.40 and 3.37. All of the expected resonances were observed in the ^{13}C NMR spectrum, with the most informative being those at δ 52.4 and 51.9 and corresponding to the diastereotopic methoxy methyl carbons of compounds **298** and **299**. An absorption maximum visible at 1736 cm^{-1} in the infrared spectrum of the mixture is assigned as the ester carbonyl stretching band. The mass spectral data derived from this mixture served to establish the expected molecular formula, *viz.* $\text{C}_{14}\text{H}_{20}\text{Br}_2\text{O}_4$.

Scheme 4.6: Synthesis of Malonates **298** and **299**

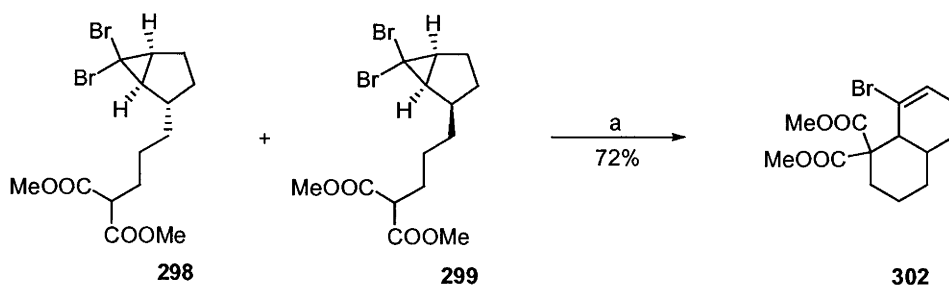
Reagents and conditions: (a) MsCl, Et₃N, CH₂Cl₂, -10 to 0 °C, 2 h; (b) NaH, THF, CH₂(CO₂CH₃)₂, 0 to 18 °C, 1.5 h then X15 and X16, 0 to 80 °C, 18 h.

4.3.3 Cyclisation Studies

Successful attainment of compounds **298** and **299** then allowed for investigation of the pivotal cyclisation reaction (Scheme 4.7). Obviously if the π -allyl cation derived from the ring-opening of cyclopropanes **298** and **299** was to be captured by the tethered malonate residue this would most likely need to be deprotonated first. Accordingly, a 4:1 mixture of malonates **298** and **299** was reacted with sodium hydride in THF at 0 °C for one and a half hours before being treated with silver tetrafluoroborate. Whilst variations in the reaction stoichiometry and temperature were investigated, the optimal results were obtained when six equivalents of silver(I)-salt was added at 0 °C and the temperature maintained at this level for approximately thirty minutes before the reaction mixture was allowed to warm to ambient temperature. After a further sixteen hours the reaction mixture was worked up and, following chromatography,

compound **302** was obtained (72%) as a single diastereomer and the sole isolable product of reaction.

Scheme 4.7: Cyclisation of Malonates **298** and **299**



Reagents and conditions: (a) NaH, THF, 0 °C to 18 °C, 1.5 h then AgBF₄, 0 to 18 °C, 16 h.

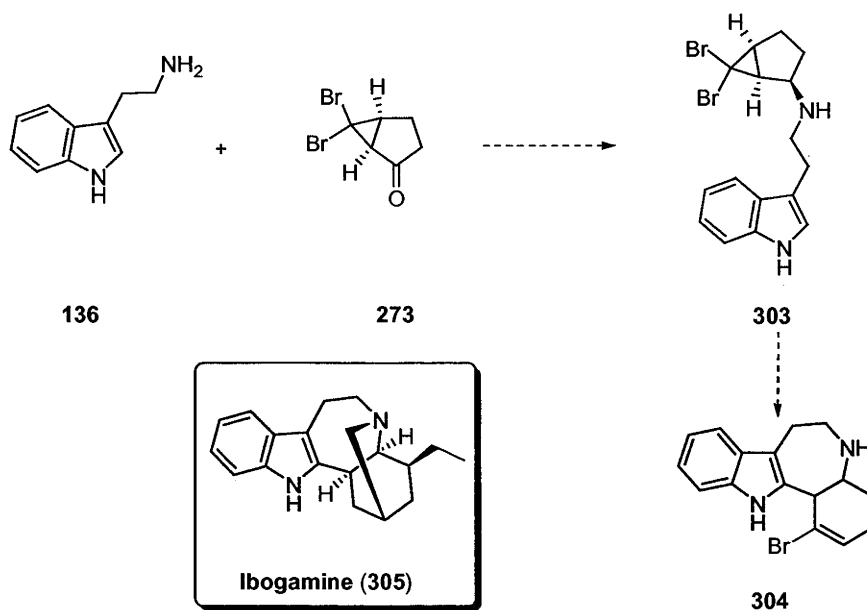
The ¹H NMR spectrum of decalin **302** revealed various features indicating that the desired intramolecular trapping reaction had occurred. Firstly, the characteristic cycloalkenyl bromide resonance was present at δ 6.08 indicating that the cyclopropane ring associated with the precursors **298** and **299** had been cleaved. The absence of a signal due to a methine proton α-related to the two methyl ester groups suggested that, as desired, trapping has occurred at this position. The three-proton singlets observed at δ 3.75 and 3.73 are assigned to the methoxymethyl protons of the diastereotopic ester moieties. The ¹³C NMR spectrum displayed carbonyl group signals at δ 169.8 and 169.6, as well as resonances attributable to the cycloalkenyl bromide functionality at δ 136.5 (CH) and 124.6 (C), while the two methoxymethyl carbon resonances appeared at δ 52.3 and 51.4. 70 eV EI mass spectral analysis revealed that the anticipated molecular ions were present at *m/z* 332 and 330 and in the 1:1 ratio typical of a monobrominated compound. An accurate mass measurement on these ions then confirmed the composition of compound **302** to be C₁₄H₁₉BrO₄. To date no conclusive assignment has been made regarding the stereochemistry of this product.

4.4 Trapping Studies Involving the C-2 Position of Indole

4.4.1 Overview

As discussed in Chapter Two, new methodologies for the functionalisation of the indole ring system remains a topic of considerable interest because of the wide range of biologically useful properties attributed to compounds, including natural products, incorporating this common heterocyclic ring system. On this basis, it was considered desirable to attempt to extend the results detailed in Chapter Two, wherein the π -allyl cation derived from ring-opening of the relevant *gem*-dihalocyclopropane was trapped in an intermolecular fashion by indole (128). Thus it was thought that initial studies could focus on tethering commercially available tryptamine (136) onto the previously synthesised ring-fused *gem*-dibromocyclopropane 273 using a reductive amination process and thus affording the novel construct 303 (Figure 4.4). If obtained, it was anticipated that the π -allyl cation derived from compound 303 should undergo trapping at the most nucleophilic site of the tethered indole, namely C-2, thereby affording product 304. This is structurally very similar to intermediates which have been employed in previously reported syntheses of natural products such as ibogamine (305).

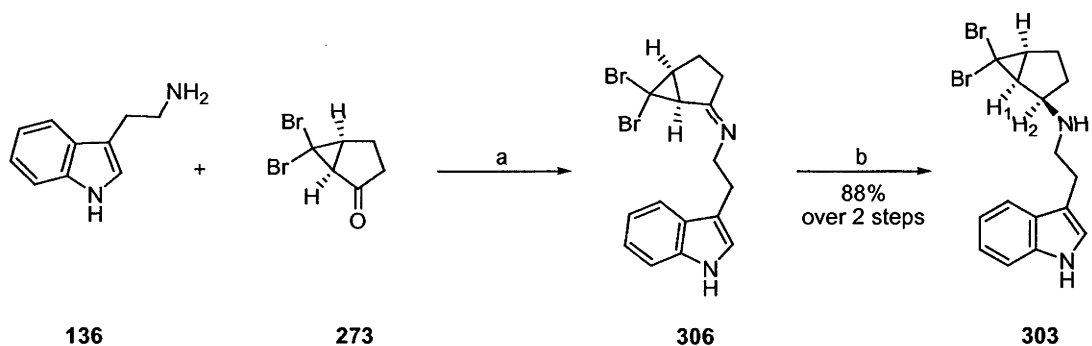
Figure 4.4: Proposed Sequence for Trapping Studies Involving the C-2 Position of Indole



4.4.2 Synthesis of the Required Cyclisation Precursors

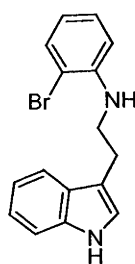
It was hoped that the synthesis of the required cyclisation precursor **303** could be achieved *via* a reductive amination reaction between the previously synthesised ketone **273** and commercially available tryptamine (**136**) (Scheme 4.8). Various conditions were trialed to effect this reaction. However, in all cases, none of the desired product was obtained. It was then found that condensation of compounds **136** and **273** could be successfully achieved upon applying extended reaction times and using methanol as the reaction solvent. This process afforded imine **306** which, on independent subjection to NaBH₄, underwent the desired reduction to furnish the originally targeted compound **303**, as a single diastereomer, in 88% yield.

Scheme 4.8: Synthesis of the Desired Cyclisation Precursor **303**



Reagents and conditions: (a) MeOH, 18 °C, 48 h; (b) NaBH₄, MeOH, 18 °C, 25 min.

Interestingly, if compound **306** was subjected to reaction with NaBH₄ for a period exceeding *ca.* 25 minutes then ring-opening, proton loss and accompanying aromatisation occurred to afford compound **307** as the exclusive product of reaction. However, this situation could be avoided by careful monitoring of the reaction mixture using TLC techniques.



307

The ^1H NMR spectrum (Figure 4.5) acquired on a purified sample of compound **303** displayed all of the expected resonances. The methylene protons on the tryptamine side-chain appeared further downfield than those in the starting material implying that substitution had occurred at the side-chain nitrogen. The ^{13}C NMR spectrum showed sixteen resonances, the most distinctive of which were at δ 39.6 (CH), 38.3 (CH) and 34.7 (C). These are attributed to the carbons of the newly introduced three-membered ring. A 70 eV EI mass spectrum revealed molecular ions at m/z 400, 398 and 396 and in the 1:2:1 ratio expected for a dibromo-compound. An accurate mass measurement then established that the molecular formula was, as anticipated, $\text{C}_{16}\text{H}_{18}\text{Br}_2\text{N}_2$. The illustrated stereochemistry is that predicted based on steric considerations and also by virtue of the presence of a *vicinal*-coupling of 5.7 Hz between H-1 and H-2 in the ^1H NMR spectrum. This value is suggestive (Karplus' rule) of a 0°C dihedral angle for H1-C1-C2-H2 and hence a *cis*-relationship between H-1 and H-2.

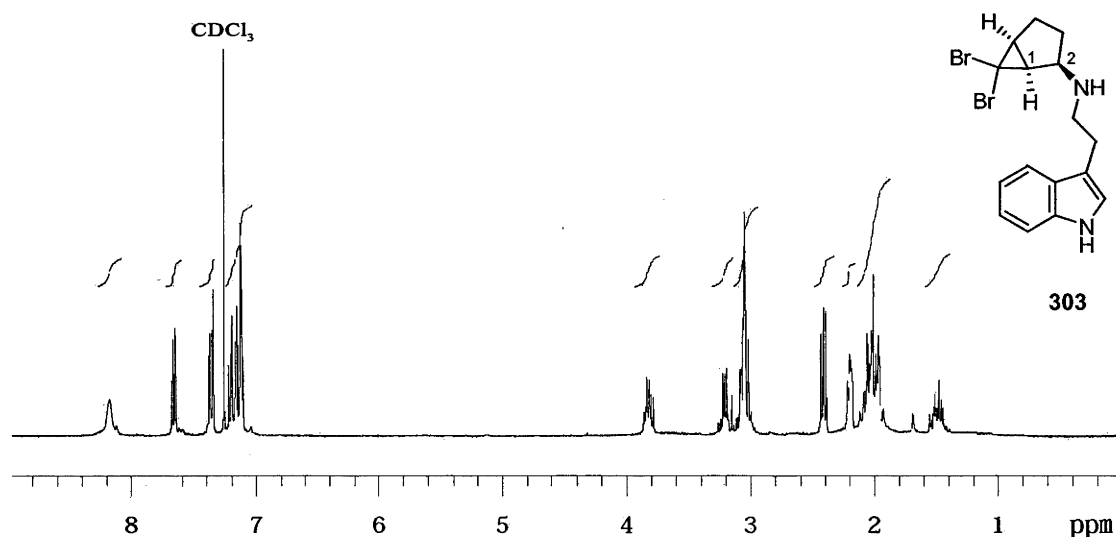
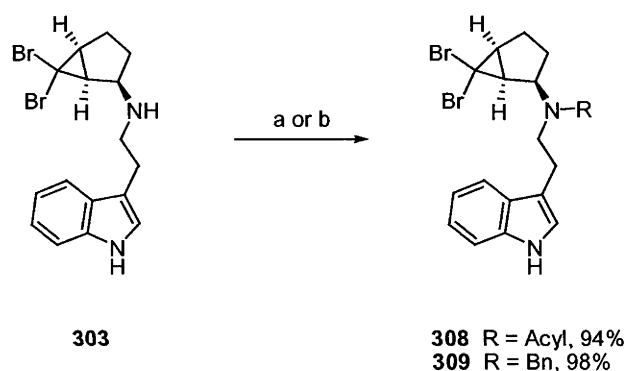


Figure 4.5: 300 MHz ^1H NMR Spectrum of Cyclopropane **303** in CDCl_3

Two protected forms of compound **303** were also synthesised so as to ascertain how they would behave on subjection to the foreshadowed electrocyclic ring-opening conditions. Thus, as shown in Scheme 4.9, the acyl- and benzyl-protected systems were generated by standard methods. Spectroscopic evidence clearly supported the assignment of the illustrated structures for both compounds **308** and **309**. Accurate mass measurements on the molecular ions observed in the 70 eV EI mass spectra of these materials established the molecular formulae as $C_{18}H_{20}Br_2N_2O$ and $C_{23}H_{24}Br_2N_2$ for **308** and **309**, respectively.

Scheme 4.9: *Synthesis of the Cyclisation Precursors 308 and 309*

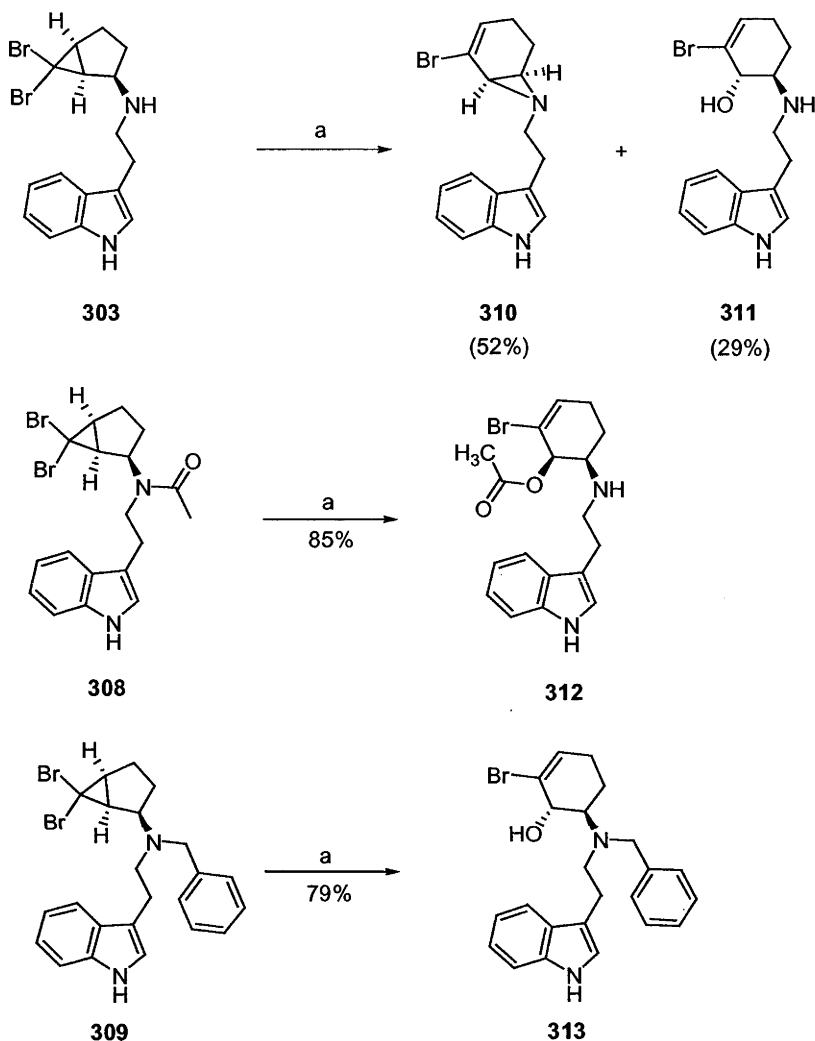


Reagents and conditions: (a) Ac_2O , pyridine, 18 °C, 2 h; (b) Na_2CO_3 (2 M aqueous solution), CH_2Cl_2 , 18 °C, 5 min then benzyl bromide, reflux, 12 h.

4.4.3 Cyclisation Studies

With compounds **303**, **308** and **309** to hand, the pivotal cyclisation reactions could be undertaken. In the event, solutions of cyclopropanes **303**, **308** and **309** in anhydrous dimethoxyethane were each treated with four equivalents of silver tetrafluoroborate and the resulting mixtures then stirred at ambient temperature for seven hours. After this time, TLC analysis indicated that the starting materials had been consumed and the products so-obtained were assigned the structures **310**, **311**, **312** and **313**, as shown in Scheme 4.10.

Scheme 4.10: Cyclisation Studies



Reagents and conditions: (a) AgBF_4 , DME, 18 °C, 7h then aqueous work up.

Evidence for the formation of aziridine **310** was obtained from the ^1H NMR spectrum (Figure 4.6). All of the protons associated with a C3-substituted indole ring system could be accounted for, hence indicating that the hoped-for trapping at the C-2 position of indole had not occurred. Another feature that supported this conclusion was the appearance of resonances corresponding to two protons significantly downfield from where the comparable signals of precursor **303** were observed and assignable as the methylene protons adjacent to nitrogen on the tryptamine side-chain. A characteristic signal for the proton associated with

the cycloalkenyl bromide was visible at δ 6.00. The ^{13}C NMR and APT spectra displayed the required sixteen resonances as expected for the illustrated aziridine structure **310**. Verification of the molecular formula came in the form of an accurate mass measurement which confirmed the composition to be $\text{C}_{16}\text{H}_{17}\text{BrN}_2$. The formation of product **310** over the desired one, *viz.* **304**, no doubt arises because cyclisation leading to a three-membered ring is kinetically more favoured than the analogous processes leading to a seven-membered ring.

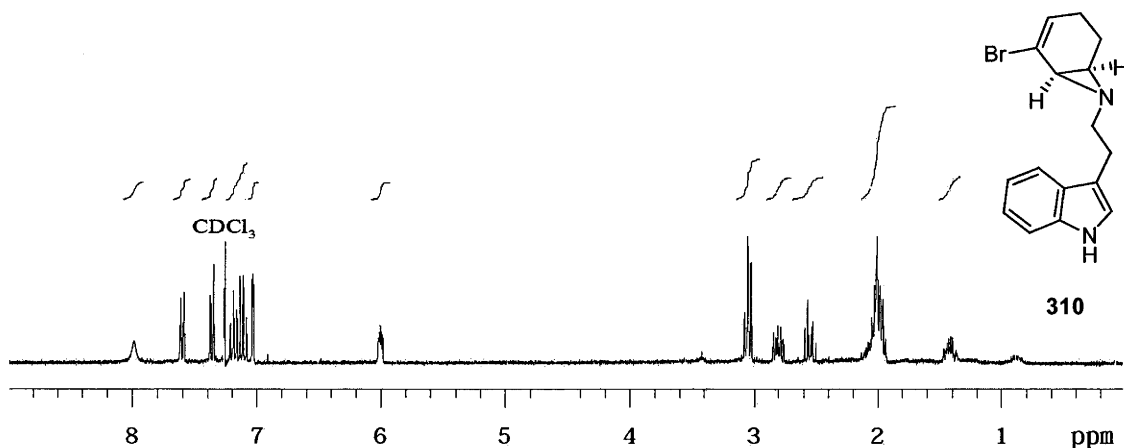


Figure 4.6: 300 MHz ^1H NMR Spectrum of Aziridine **310** in CDCl_3

The other product observed upon reaction of substrate **303** with silver tetrafluoroborate was alcohol **311**. This was obtained in 29% yield and as a single diastereomer. The most diagnostic feature in the ^1H NMR spectrum of alcohol **311** was the appearance of two signals at δ 4.95 and 4.78 which inferred the presence of oxygen in the molecule. An accurate mass measurement on both of the molecular ions, along with the dominant $[\text{M}-\text{H}_2\text{O}]^+$ fragment ions, confirmed the composition to be $\text{C}_{16}\text{H}_{19}\text{BrN}_2\text{O}$. It would appear that formation of product **311** is most likely due to the presence of adventitious water in the reaction mixture which reacted with the π -allyl cation arising from ring-opening of **303**. Although this reaction was performed under notionally anhydrous conditions the small scale of the operation coupled with the hygroscopic nature of silver tetrafluoroborate may have created difficulties in maintaining a strictly water-free environment. Whilst the stereochemistry of this product has not been rigorously proven it is assumed to be that illustrated on the basis of steric effects which should lead to a *trans*-arrangement of substituents about the cyclohexene ring.

Substrate **308**, in which the possibility for aziridine formation is blocked by the presence of the *N*-acyl group, reacted with silver tetrafluoroborate to afford an unexpected product as a pale-yellow oil in excellent yield. Based on the spectroscopic data acquired this compound could be assigned structure **312**.

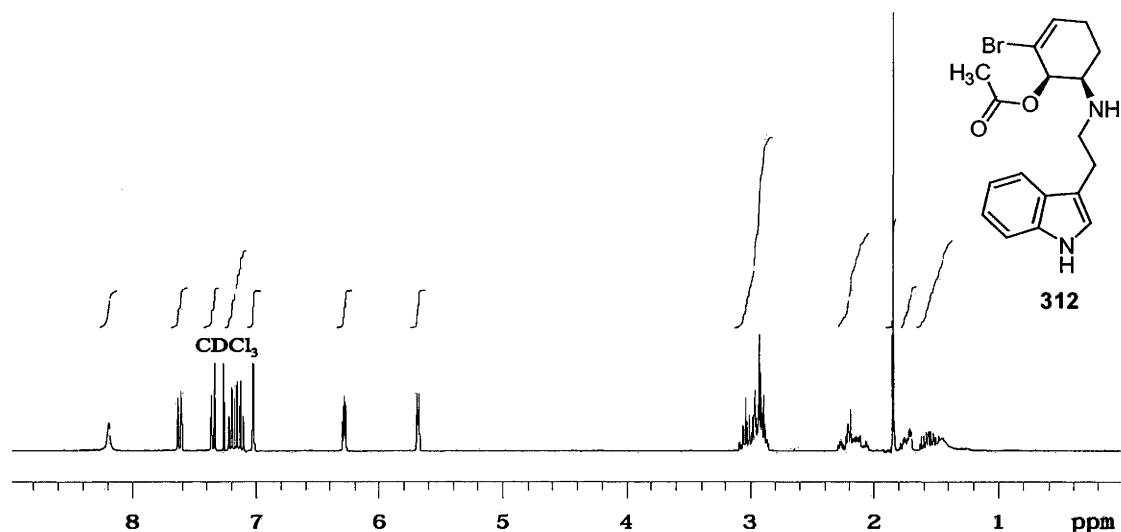
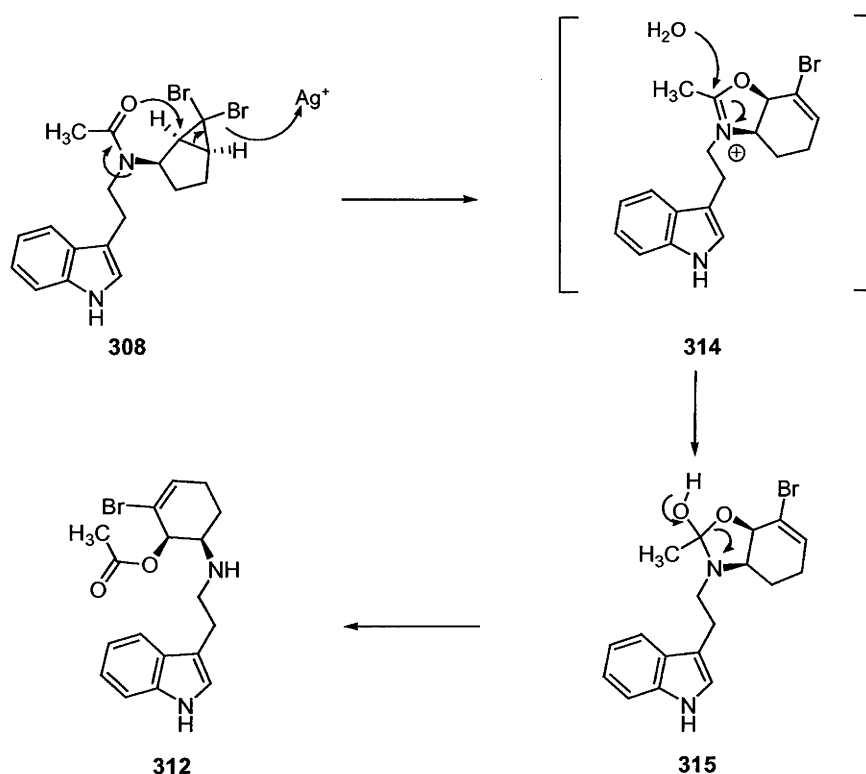
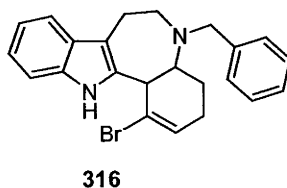


Figure 4.7: 300 MHz ¹H NMR Spectrum of Acetate **312** in CDCl₃

It would appear that following the ring-opening process neighbouring group participation occurred with the intermediate π -allyl cation ultimately being trapped by the carbonyl of the adjacent acetamide unit. Mechanistically it is proposed that the observed product **312** arose from a process such as that depicted in Figure 4.8. Thus, upon treatment with the silver(I)-salt the cyclopropane unit underwent the usual ring-opening process to form the corresponding π -allyl cation which is subsequently trapped by the carbonyl moiety of the acetamide group. This affords the 4,5-dihydrooxazole-type intermediate **314**. Although the reaction was performed under notionally anhydrous conditions a small amount of adventitious water was obviously present and this reacts with the iminium ion to produce intermediate **315** which undergoes ring-opening in the manner indicated to deliver the observed compound **312**.

Figure 4.8: Proposed Mechanism for the Formation of Compound **312**

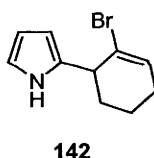
Upon subjection to a variety of silver(I)-promoted ring-opening conditions the third substrate, compound **309** underwent ring-opening and hence, as observed in the unprotected example discussed previously, alcohol **313** was isolated. As expected the derived spectral data obtained on this material were very similar to those recorded for the debenzylated equivalent **311** and the formation of product **313** is no doubt formed by an analogous process involving trapping of the intermediate π -allyl cation by adventitious water. Despite the apparently disfavoured nature of the desired seven-membered ring formation a trace amount of another product was obtained and this has been tentatively assigned as the *N*-benzyl derivative **316** of the targeted cyclised product **304**. It is, therefore, anticipated that an increase in the desired product may be obtained by attempting to effect the analogous, and more favoured, six-*endo* cyclisation. Strategies directed towards achieving this end are discussed further in Chapter Six.



4.5 Intramolecular π -Allyl Cation Trapping Studies with Pyrrole (141)

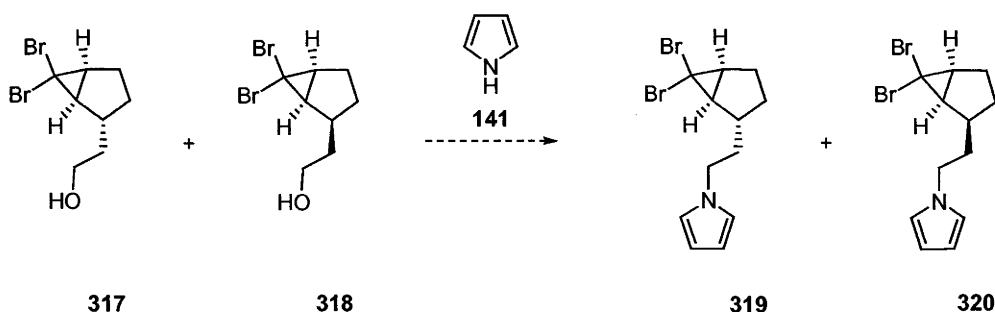
4.5.1 Overview

Whilst some success was observed during previous attempts to trap, in an intramolecular fashion, the π -allyl cation with various nucleophiles it was thought that there could be merit in investigating the behaviour of other heteroaromatic systems as nucleophiles under these conditions. This notion was based on the success that was observed in the equivalent intermolecular trapping studies discussed in Chapter Two. The nucleophile of choice for these initial studies was pyrrole (141). This was based on two main factors. Firstly, alkylation of the nitrogen could be performed with ease under well-established procedures, hence providing a convenient method for attaching the pyrrole nucleophile to the tethered cyclopropane unit. Secondly, studies discussed in Chapter Two have unequivocally proven that the C-2 of pyrrole (141) readily undergoes reaction with the π -allyl cation derived from the electrocyclic ring-opening of a *gem*-dibromocyclopropane unit to give compound 142.



Therefore, the initial studies associated with the present work centred on targeting cyclopropanes **317** and **318**. With these compounds in hand, a Mitsunobu reaction between the tethered alcohol functionality and the nitrogen of pyrrole¹⁷ (141) was envisaged as being likely to afford the requisite cyclisation precursor **319** and its C-2 epimer **320**.

Figure 4.9: Proposed Strategy for the Synthesis of Cyclisation Precursors **319** and **320**



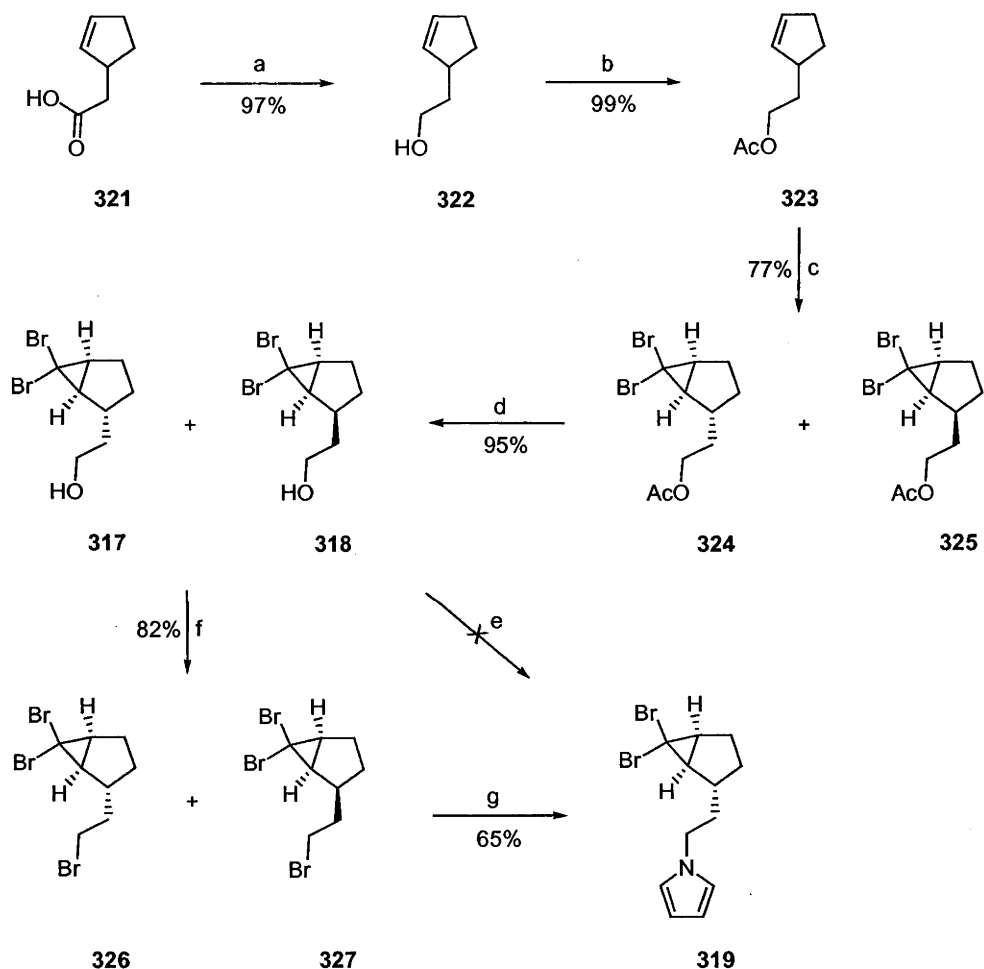
4.5.2 Synthesis of Cyclisation Precursor 319

Cyclopropanes **317** and **318** could be readily synthesised in four steps *via* a modification of the procedure reported by Banwell and co-workers (Scheme 4.11).¹⁸ Thus, commercially available 2-cyclopentene-1-acetic acid (**321**) was reduced to the corresponding and previously reported¹⁹ alcohol **322** using lithium aluminium hydride. The key features associated with the spectroscopic data derived from product **322**, which indicated that the desired reduction had occurred, revolved around loss of the carbonyl moiety associated with the starting material and the appearance of resonances associated with the new methylene unit adjacent to the oxygen functionality. A prominent O-H stretching absorption observed at 3338 cm^{-1} in the infrared spectrum of the product lent further support to the presence of an alcohol moiety within the molecule. It should also be noted that these data were in full accord with previous spectroscopic data reported¹⁸ for compound **322**. Protection of alcohol **322** as the corresponding acetate was then required as a prelude to the carbene addition step. To this end, alcohol **322** was reacted under standard conditions utilising acetic anhydride and pyridine for sixteen hours. After this time, compound **323** was obtained as a clear, colourless oil and the derived spectral data were in full accord with the assigned structure.

With this acetate in hand the pivotal carbene addition step could be performed. Hence, compound **323** was subjected to reaction with dibromocarbene, generated under sonication conditions from bromoform/sodium hydroxide and using benzyltriethylammonium chloride (TEBAC) as the phase transfer catalyst. After 1.5 hours the by now dark-brown reaction mixture was worked up to give a *ca.* 3:1 and chromatographically inseparable mixture of compound (\pm)-**324** and its C-2 epimer (\pm)-**325**. As was discussed earlier in this Chapter for related systems, the assignment of compound (\pm)-**324** as the major product of this reaction is based on the reasonable assumption that dibromocarbene would add, preferentially, to the less hindered face of the double bond within precursor **323**. In the mass spectrum the expected molecular ions were observed at m/z 328, 326 and 324 and in a 1:2:1 ratio, thus indicating the presence of two bromines in the products. Whilst the molecular ions proved too weak to obtain accurate mass measurements on, measurements on the $[(M-\text{CH}_3\text{COOH})^+]$ fragment ions confirmed the composition of these to be $\text{C}_8\text{H}_{10}\text{Br}_2$. Whilst compounds (\pm)-**324** and (\pm)-

325 were chromatographically inseparable, each epimer could be individually assigned with ease from the derived spectroscopic data. However, as expected, the data acquired were very similar.

Scheme 4.11: Synthesis of the Requisite Cyclisation Precursor **319**



Reagents and conditions: (a) LiAlH_4 , THF, 18 °C, 5 h; (b) Ac_2O , pyridine, 18 °C, 16 h; (c) CHBr_3 , TEBAC, NaOH, CH_2Cl_2 ,), 1.5 h; (d) K_2CO_3 , MeOH, 18 °C, 20 h; (e) pyrrole, PPh_3 , DEAD, THF, 18 °C, 18 h; (f) CBr_4 , PPh_3 , CH_2Cl_2 , 18 °C, 0.5 h; (g) KOH, DMSO, pyrrole, 18 °C, 1 h then **326** and **327**, 18 °C, 3 h.

The penultimate step associated with the initial strategy employed for targeting the requisite cyclisation precursors **319** and **320** was the attainment of alcohols **317** and **318**. Thus, the

diastereomeric mixture of acetates (\pm)-**324** and (\pm)-**325** was treated with potassium carbonate in methanol under standard hydrolysis conditions. After the resulting suspension had been stirred at ambient temperature for twenty hours TLC analysis indicated that the reaction had reached completion. After work up and purification, a 3:1 and chromatographically inseparable mixture of the desired products (\pm)-**317** and (\pm)-**318** was obtained. The derived spectral data were in full accord with the assigned structures.

With these compounds in hand, Mitsunobu coupling of cyclopropanes **317** and **318** and pyrrole (**141**) was attempted.²⁰ Unfortunately, however, the desired reaction did not occur. As a consequence alcohols **317** and **318** were converted into the corresponding bromides **326** and **327** with a view to subsequently using these electrophilic species in the *N*-alkylation of pyrrole (**141**). The first step of this proposed sequence was expediently achieved using carbon tetrabromide and triphenylphosphine in dichloromethane (Scheme 4.11).²¹ As expected the spectroscopic data obtained on the resulting material were almost identical to those of congeners **317** and **318**. However, notable features indicating that the desired functional group interconversion had occurred were the absence of the previously assigned and broad O-H singlet in the ^1H NMR spectrum and the upfield shift in the ^{13}C NMR spectrum of the signal attributed to the carbon adjacent to the discussed functionality. The 70 eV EI mass spectrum confirmed the presence of three bromine atoms through the appearance of the appropriate cluster of molecular ions at m/z 350, 348, 346 and 344 in a 1:3:3:1 ratio. An accurate mass measurement on the species appearing at m/z 348 and 346 confirmed that the composition of products **326** and **327** was $\text{C}_8\text{H}_{11}\text{Br}_3$.

With compounds **326** and **327** to hand the synthesis of the targeted cyclisation precursors **319** and **320** could be completed. Pyrrole (**141**) was treated with powdered potassium hydroxide in DMSO²² and after one hour tribromides **326** and **327** were added into the reaction mixture. After a further three hours product **319** was obtained as a pale-yellow oil in 65% yield and as a single diastereomer (Scheme 4.11). All of the spectroscopic data acquired on this material were in complete accord with the assigned structure. The 300 MHz ^1H NMR spectrum is shown in Figure 4.10.

Based on the ratio of the starting bromides and the yield of product **319** obtained it is believed this compound has the illustrated structure in which the side-chain is *anti*-related to the ring-fused cyclopropyl moiety.

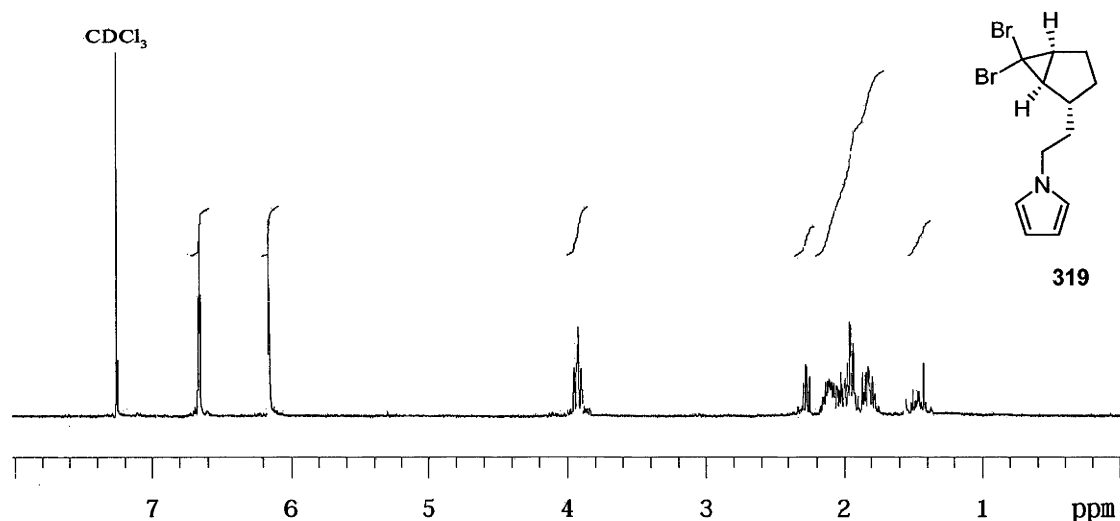


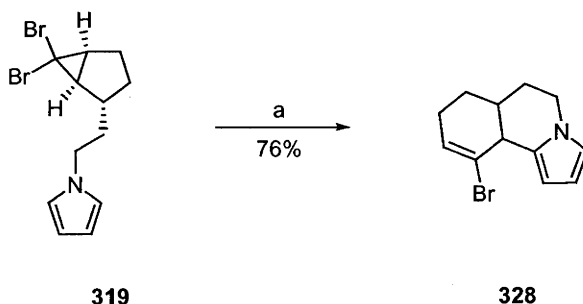
Figure 4.10: 300 MHz ^1H NMR Spectrum of Cyclopropane **319** in CDCl_3

4.5.3 Cyclisation Studies

With the key compound **319** to hand, the pivotal cyclisation reaction could now be investigated. In the event, treatment of precursor **319** with silver tetrafluoroborate under the previously articulated conditions delivered the desired compound **328** as the sole isolable product and in diastereoisomerically pure form (Scheme 4.12). Whilst purification of this compound initially proved difficult full characterisation was eventually accomplished. Several key features associated with the spectroscopic data obtained led to the assignment of structure **328** as the reaction product. Firstly, four resonances due to olefinic protons were now apparent. These are assigned as the three non-equivalent pyrrolic protons (δ 6.41, 6.25 and 6.23-6.16) as would be expected for a 1,2-disubstituted pyrrole. A single cycloalkenyl bromide proton was also observed at δ 6.10. The ^{13}C NMR spectrum displayed twelve resonances, including four (at δ 129.3, 123.8, 115.0 and 105.8) due to protonated sp^2 -hybridised carbons and two (at δ 132.7 and 120.2) due to non-protonated carbons of the same type. The 70 eV EI mass spectrum revealed two equally intense molecular ions at m/z 253

and 251, the compositions of which were established as $C_{12}H_{14}BrN$ through accurate mass measurement. To date no conclusive assignment has been made regarding the stereochemistry of this product.

Scheme 4.12: Cyclisation of Precursor 319



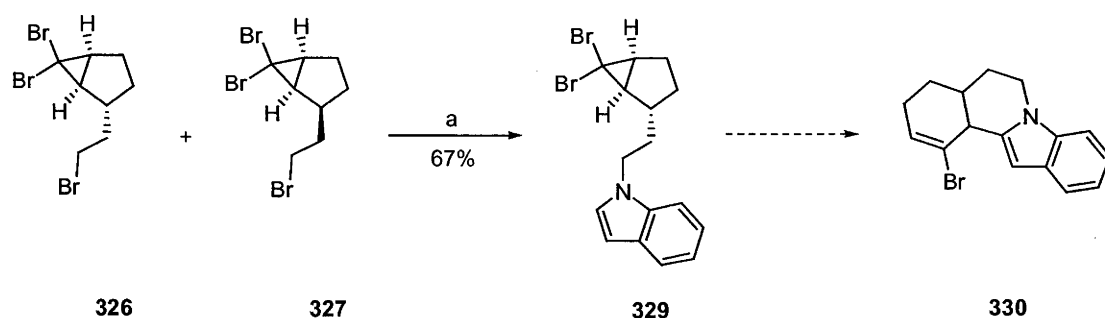
Reagents and conditions: (a) $AgBF_4$, DME, 18 °C, 6.5 h.

4.5.4 Extension of Trapping Studies to Incorporate Indole (128)

On the basis of the results detailed immediately above an exploration began into the feasibility of performing a comparable cyclisation process exploiting the C-2 of indole (**128**) as the tethered nucleophile. Therefore, initial work centred on the synthesis of a relevant cyclisation precursor, namely compound **329** in the expectation that upon cyclisation of this material the azasteroid-like compound **330** would result (Scheme 4.13).

In targeting precursor **329** a parallel approach to that discussed above was employed. Thus, reaction of tribromides **326** and **327** with potassium hydroxide and indole (**128**) yielded cyclopropane **329** as a yellow oil in 67% yield. Again, as was the case in the corresponding pyrrole example, only one diastereomer was observed and this has been assigned the stereochemistry depicted for the previously discussed reasons. The spectroscopic data obtained on this material were in complete accord with the assigned structure.

Scheme 4.13: Synthesis of the Requisite Cyclisation Precursor 329



Reagents and conditions: (a) KOH, DMSO, indole, 18 °C, 1 h then **326** and **327**, 18 °C, 4 h.

To date only preliminary studies have been conducted on the cyclisation of compound **329**. Thus, on subjection of this material to the standard silver(I)-promoted ring-opening conditions a single isolable product was obtained. Difficulties with purification, hence affording low yields of characterisable material, has meant that a conclusive statement about the structure of the obtained product cannot be made at present. However, ^1H NMR analysis of the crude reaction mixture provides good indications that the desired cyclisation has indeed occurred. Work in this area is ongoing.

4.6 Conclusions

Throughout the course of this Chapter discussions have centred on studies which were undertaken in order to investigate the potential of *gem*-dibromocyclopropanes to engage in electrocyclic ring-opening/intramolecular trapping sequences with a variety of *C*-centred nucleophiles. Key nucleophiles exploited in this manner were malonate and pyrrole (**141**). As was the case with the related intermolecular studies, occasionally preference for trapping of the derived π -allyl cation by oxygen- or nitrogen-based functionality was observed. It also became apparent during the course of this work that significant activation (e.g. through deprotonation of a carbon acid such as malonate) of the *C*-centred nucleophile was sometimes required before the desired trapping reaction would occur. Nevertheless, successful new

methods for carbon-carbon bond formation have been developed and a number of novel frameworks have been assembled by such means. Furthermore, a wide array of possibilities exist for the elaboration of such frameworks to a range of natural products. As such the work detailed above serves to confirm the immense potential for *gem*-dihalocyclopropanes in organic synthesis.

4.7 References

- ¹ For a representative example see: Banwell, M.G., Harvey, J.E., Jolliffe, K.A.; *J. Chem. Soc., Perkin Trans. 1*, **2001**, *17*, 2002-2005.
- ² Washburn, W.N., Zahker, R., Chen, I.; *J. Am. Chem. Soc.*, **1978**, *100*, 5863-5874.
- ³ Banwell, M.G., Harvey, J.E., Hockless, D.C.R., Wu, A.W.; *J. Org. Chem.*, **2000**, *65*, 4241-4250.
- ⁴ Banwell, M.G., Wu, A.; *J. Chem. Soc. Perkin. Trans. 1.*, **1994**, *19*, 2671-2672.
- ⁵ Hansson, S., Heumann, A., Rein, T., Abermark, B.; *J. Org. Chem.*, **1990**, *55*, 975-984.
- ⁶ Alder, K., Flock, F.H.; *Chem. Ber.*, **1956**, *89*, 1732-1737.
- ⁷ Kochi, J.K.; *Organometallic Mechanisms and Catalysis*, Academic Press: New York, **1978**.
- ⁸ Gerdil, R., Liu, H., Bernardinelli, G.; *Helv. Chim. Acta*, **1999**, *82*, 418-434.
- ⁹ Dondas, H.A., Grigg, R., Thibault, S.; *Tetrahedron*, **2001**, *57*, 7035-7045.
- ¹⁰ Makosza, M., Wawrzyniewicz, W.; *Tetrahedron Lett.*, **1969**, *10*, 4659-4662.
- ¹¹ Xu, L., Brinker, U.H.; in *Synthetic Organic Sonochemistry*, Luche, J.L. (Ed.), Plenum Press: New York, **1998**, pp. 344-345.
- ¹² Banwell, M.G., Harvey, J.E., Hockless, D.C.R., Wu, A.W.; *J. Org. Chem.*, **2000**, *65*, 4241-4250.
- ¹³ Meyer, S.D., Schreiber, S.L.; *J. Org. Chem.*, **1994**, *59*, 7549-7552.
- ¹⁴ Gee, K.R., Lu, Y., Barmettler, P., Rhodes, M.R., Reddy, N.L., Fischer, J.B., Cotter, R.E., Weber, E., Keana, J.F.W.; *J. Org. Chem.*, **1994**, *59*, 1492-1498.
- ¹⁵ Banwell, M.G., Reum, M.E.; in *Advances in Strain in Organic Chemistry*, Halton, B. (Ed.), JAI Press Ltd: London, **1991**, Vol. 1, pp. 19-64.
- ¹⁶ Destabel, C., Kilburn, J.D., Knight, J.; *Tetrahedron*, **1994**, *50*, 11289-11302.
- ¹⁷ Kreipl, A.T., Reid, C., Steglich, W.; *Org. Lett.*, **2002**, *19*, 3287-3288.
- ¹⁸ Banwell, M.G., Harvey, J.E., Hockless, D.C.R., Wu, A.W.; *J. Org. Chem.*, **2000**, *65*, 4241-4250.
- ¹⁹ Balme, G., Bouyssi, D., Faure, R., Gore, J., Van Hemelryck, B.; *Tetrahedron*, **1992**, *48*, 3891-3902.
- ²⁰ Kreipl, A.T., Reid, C., Steglich, W.; *Org. Lett.*, **2002**, *19*, 3287-3288.
- ²¹ Sripha, K., Zlotos, D.P.; *Tetrahedron*, **2003**, *59*, 391-394.

²² Lazzaroni, R., Settambolo, R., Caiazzo, A., Pontorno, L.; *J. Organomet. Chem.*, **2000**, *601*, 320-323.

Studies Directed Towards the Synthesis of 13-Azasteroids

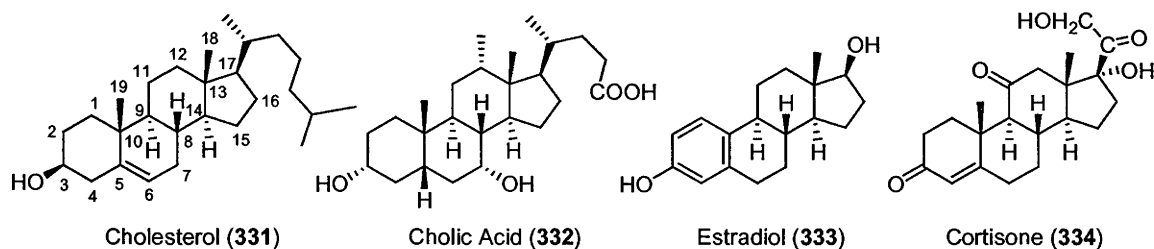
5.1 Introduction

The chemistry of steroids has attracted intense interest for many decades. Not only are these compounds one of the most fascinating, widespread and complex classes of natural products known but they are also estimated to be present in approximately one third of all prescription drugs marketed today. Without a doubt it is their immense physiological and pharmacological importance which has brought them so much attention as synthetic targets.

5.1.1 The Steroid Class of Natural Products

The term steroid is typically used to denote substances that are structurally related to the extent of possessing the characteristic tetracyclic cyclopentanoperhydrophenanthrene ring system ($C_{17}H_{28}$). Nevertheless, an enormous degree of structural diversity is seen within this class of natural products. Representative examples of some of the structural variations that are possible are depicted in Figure 5.1.

Figure 5.1: Representative Examples of Steroids with Important Physiological Roles/Properties



Generally, four major approaches are employed to obtain steroids. These involve isolation from natural sources, microbiological production (fermentation), partial synthesis and total synthesis. One of the main advantages of the latter two approaches, but especially the last, is that numerous modifications of the basic steroid framework are likely to be available, as is often required in the identification of new therapeutic agents with improved bioactivity. The vast majority of pharmaceutically useful steroids are obtained by partial synthesis, traditionally involving degradation of inexpensive and naturally occurring compounds followed by reconstruction with incorporation of the desired functionality. This method is used primarily because of its economic viability. However, various drawbacks do exist. The most notable of these is the fact that limited supplies of commonly used starting materials endangers the future sustainability of this approach. Another important factor is that steroids which exhibit interesting biological activities often possess highly unusual functionality and obtaining these compounds from the limited library of naturally occurring steroidal building blocks can be an arduous task. In contrast, steroid total synthesis has a distinct advantage in that a range of functionalities can be readily, and often more efficiently, incorporated into the target of interest. Furthermore, natural and 'unnatural' enantiomers can often be obtained and, therefore, tested for biological activity.

An enormous amount of effort has been directed into this field of research and for that reason it is impossible to provide a full review of the strategies which have been applied in all of the total synthesis studies undertaken to date. Consequently, the following section merely attempts to highlight some of the key methods which have been employed in this area.

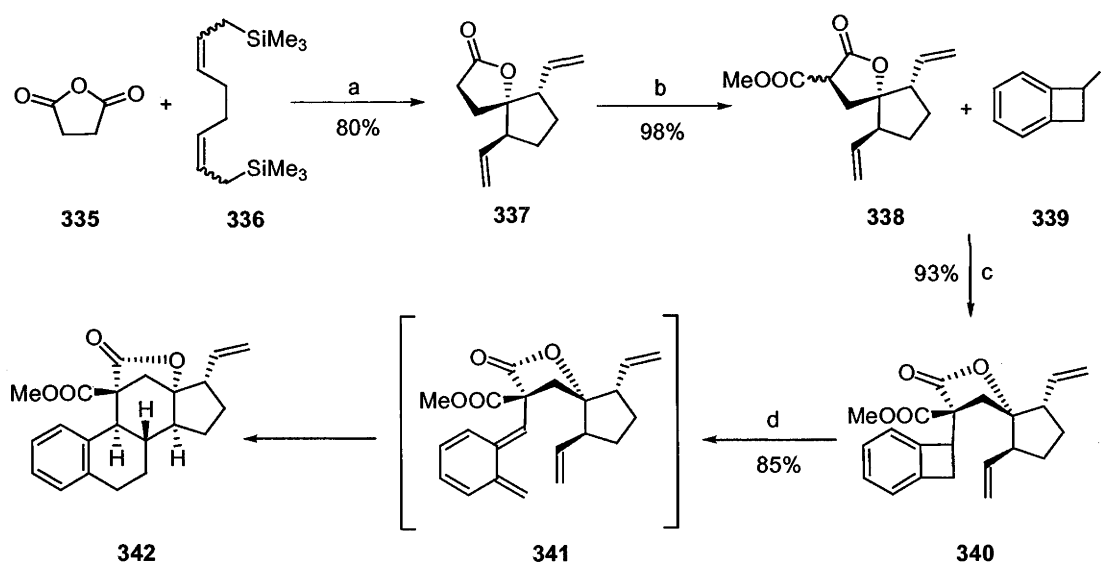
5.1.2 Common Strategies Employed in Steroid Total Synthesis

5.1.2.1 Intramolecular Diels-Alder Approach

There are many examples of the use of intramolecular Diels-Alder reactions in the assembly of steroid frameworks. Unstable dienes such as *o*-quinodimethanes, which can be generated *in situ* in the presence of a dienophile, are exceedingly reactive and, as such, are a popular choice for intramolecular Diels-Alder reactions in general.¹ Not surprisingly, therefore, they

have also become one of the most prominent and convenient methods for the synthesis of steroids which possess an aromatic A-ring.^{2,3} Whilst the requisite *o*-quinodimethane has been generated in a variety of ways the general principle remains the same. Kametani and co-workers were the first to exploit this approach in the synthesis of a range of complex natural products and their 1976 synthesis of D-homoesterone methyl ester is regarded as a landmark in the synthesis of steroids.^{4,5} More recently, using both the aforementioned approach in conjunction with similar methodology developed by Oppolzer,⁶ Santelli and co-workers described highly efficient syntheses of a variety of steroids from 1,3-butadiene and benzocyclobutenes⁷ (Scheme 5.1).

Scheme 5.1: Santelli's Steroid Synthesis – an Intramolecular Diels-Alder Approach



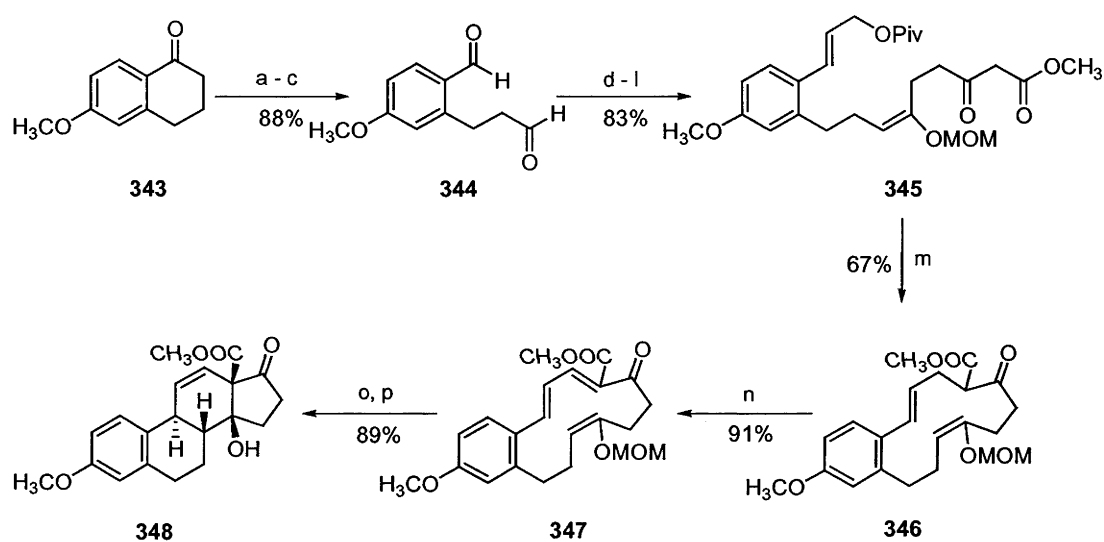
Reagents and conditions: (a) TiCl_4 , MeNO_2 , CH_2Cl_2 , -60 to -90 °C; (b) LiHMDS , THF, -78 °C then $(\text{MeO})_2\text{CO}$, THF, -40 °C; (c) K_2CO_3 , acetone, reflux; (d) 1,2,4-trichlorobenzene, reflux.

5.1.2.2 Transannular Diels-Alder Approach

Another variation on the intramolecular Diels-Alder reaction that has led to steroid skeleta involves a transannular cycloaddition process. In this case, however, the diene and dienophile are both present within a macrocyclic system and this method has emerged as an extremely

robust way of targeting various polycyclic diterpenes including steroids. Numerous model studies have been effective in clearly defining the scope of this approach. One of the main advantages that this method has to offer is the high degree of chemo-, regio- and diastereoselectivity available. Deslongchamps and co-workers have conducted much of the pivotal work in this area and been responsible for the development of a detailed understanding of the stereochemical features of this reaction. Furthermore, they have also been successful in applying this methodology to the total synthesis of a variety of steroids (Scheme 5.2).^{8,9}

Scheme 5.2: Deslongchamps' Steroid Synthesis – a Transannular Diels-Alder Approach



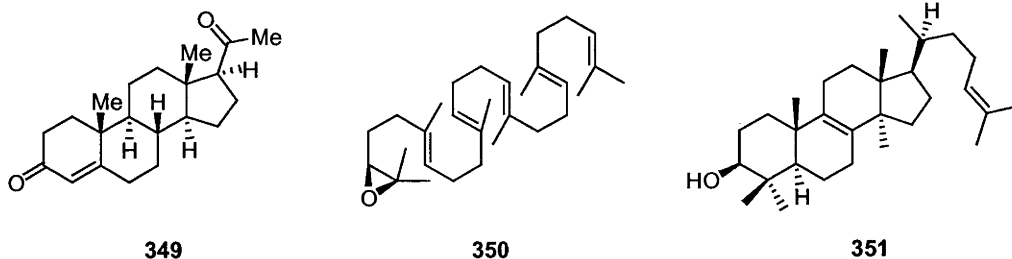
Reagents and conditions: (a) LiAlH_4 , THF, $-78\text{ }^\circ\text{C}$; (b) TsOH, benzene, $-\text{H}_2\text{O}$, reflux; (c) O_3 , MeOH, $-78\text{ }^\circ\text{C}$, then DMS, $18\text{ }^\circ\text{C}$; (d) *n*-BuLi, $(\text{CH}_3\text{O})_2\text{P}(\text{O})\text{CH}(\text{OMOM})\text{COOCH}_3$, THF, $0\text{ }^\circ\text{C}$; (e) *n*-BuLi, $(\text{CH}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{C}(\text{O})\text{N}(\text{OCH}_3)\text{CH}_3$, THF, $0\text{ }^\circ\text{C}$; (f) LiAlH_4 , THF, -78 to $0\text{ }^\circ\text{C}$; (g) MsCl, Et_3N , CH_2Cl_2 , $0\text{ }^\circ\text{C}$ then HMPA, LiCl, $18\text{ }^\circ\text{C}$; (h) NaBH_4 , MeOH, $18\text{ }^\circ\text{C}$; (i) TBDMSCl, imidazole, THF, $18\text{ }^\circ\text{C}$; (j) NaH, *n*-BuLi, $\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{OCH}_3$, THF, $0\text{ }^\circ\text{C}$; (k) TBAF, THF, $18\text{ }^\circ\text{C}$; (l) PivCl, 2,6-lutidine, CH_2Cl_2 , $0\text{ }^\circ\text{C}$; (m) *N,O*-bis(trimethylsilyl)acetamide, THF, reflux then $[(\text{Ph})_3\text{P}]_4\text{Pd}$, $(\text{Ph})_2\text{P}(\text{CH}_2)_3\text{P}(\text{Ph})_2$, THF, reflux; (n) $(\text{PhSeO})_2\text{O}$, Et_3N , CH_2Cl_2 , $18\text{ }^\circ\text{C}$; (o) Et_3N , xylene, reflux; (p) HCl, MeOH, $18\text{ }^\circ\text{C}$.

5.1.2.3 Biomimetic-Type Syntheses

In the case of steroids, the term ‘biomimetic-type syntheses’ applies to strategies in which open-chain or monocyclic systems incorporating an appropriate side-chain are stereoselectively cyclised in a one-pot operation to give a tri- or tetra-cyclic ring system.¹⁰ This methodology represents the ultimate in synthetic efficiency and, as such, has been widely investigated. Four main approaches have been applied under the broad heading of biomimetic-type syntheses and these are (i) cascade biomimetic cationic cyclisations, (ii) cascade biomimetic radical cyclisations, (iii) metal-mediated cyclisations and (iv) domino intramolecular Diels-Alder reactions. All of these are discussed below.

Cascade Biomimetic Cationic Cyclisations

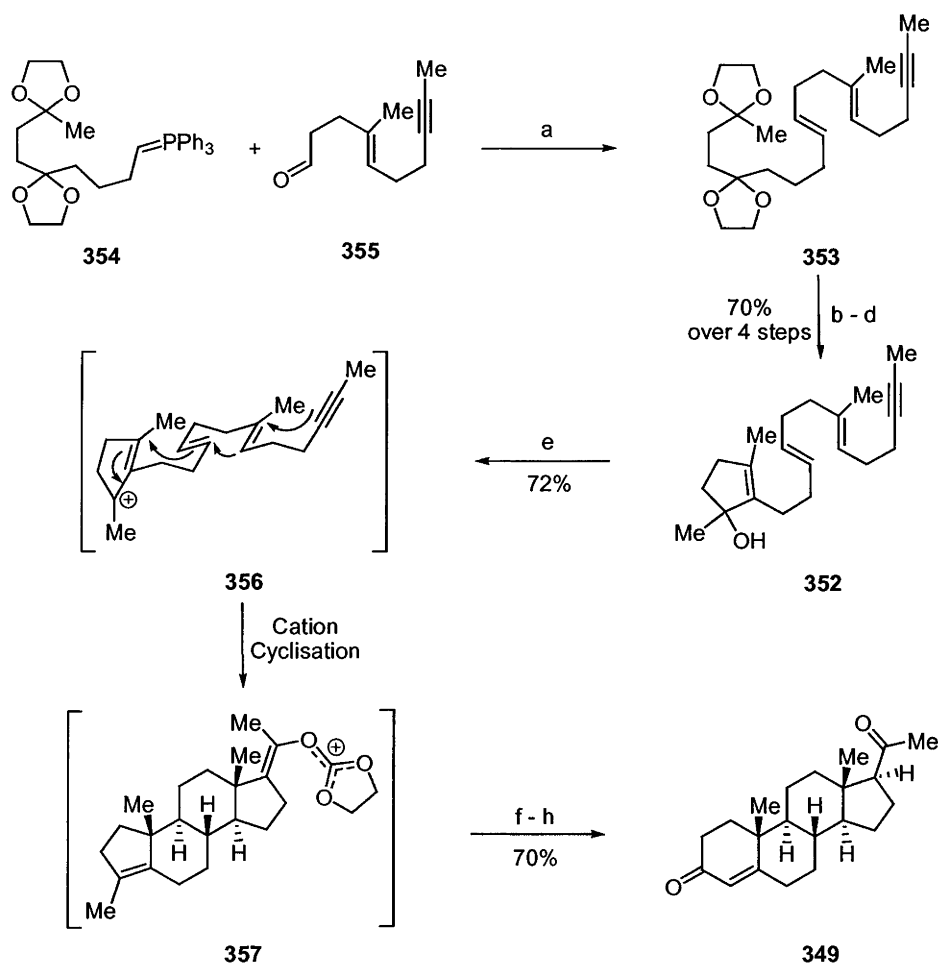
The seminal contribution in this area came from the group of W.S. Johnson and in which a cationic cyclisation approach was utilised to synthesise progesterone (**349**).^{11,12} This work was inspired by the Stork-Eschenmoser hypothesis which proposes that an enzyme-catalysed process is involved in the conversion of squalene oxide (**350**) into lanosterol¹³ (**351**) and dammaradienol.¹⁴ The hypothesis was advanced in 1955 to rationalise the stereochemical outcomes of the biochemical cyclisation of squalene oxide (**350**).^{15,16} This postulate predicted that polyunsaturated molecules possessing *trans*-configured olefinic linkages would cyclise in a stereoselective fashion to afford a polycyclic molecule embodying *trans*-, *anti*-, *trans*-ring fusion as seen in compound **351**.



The validity of this hypothesis was established by Johnson in his elegant biomimetic total synthesis of progesterone (**349**) (Scheme 5.3). In this instance, tertiary allylic alcohol **352**, derived from compound **353** *via* hydrolysis of the ketal protecting groups, aldol cyclodehydration and treatment of the resulting enone with methylolithium, served as the

initiator for the polyolefin cascade. Subsequently it has been shown that acetals and epoxides can also act as effective initiators in the presence of a Lewis acid. Termination of the cyclisation was achieved by the methylacetylenic functionality, which allowed for the formation of a *trans*-fused five-membered ring. In more recent studies propargylic silanes,^{17,18} allylic silanes¹⁹ and vinyl fluorides²⁰ have all been found to be equally effective in terminating such polyene cyclisations. Pioneering contributions in this area, complementing those discussed above, were also made by van Tamelen²¹ and since its inception this methodology has been widely used in the synthesis of a variety of steroids.

Scheme 5.3: Johnson's Steroid Synthesis – a Cationic Cyclisation and Biomimetic Approach



Reagents and conditions: (a) PhLi, THF, -70 to -30 °C then PhLi, MeOH, -30 °C; (b) 0.1 M HCl, H₂O/MeOH (3:10), 40 °C; (c) EtOH, 2% NaOH in H₂O, reflux; (d) MeLi, EtO₂; (e) TFA, Cl(CH₂)₂Cl, ethylene carbonate, 0 °C; (f) K₂CO₃, MeOH, 23 °C; (g) O₃, MeOH, CH₂Cl₂, -70 °C then Zn, AcOH, H₂O, -15 to 23 °C; (h) H₂O/5% KOH (5:2), 23 °C.

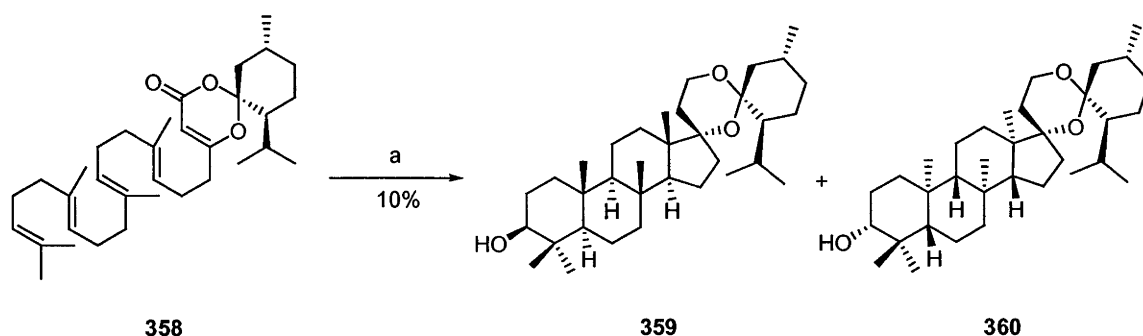
Cascade Biomimetic Radical Cyclisations

Polyene cyclisations, such as those described above, are not limited to cationic cascades and more recently several groups have utilised radical chemistry in a similar one-pot approach to assemble the tetracyclic steroid framework from open-chain and unsaturated precursors. Three distinct modes of initiation for such processes have been reported and these are detailed, through key examples, below.

Photo-Induced Electron Transfer Approach

Demuth and co-workers have reported^{22,23,24} that non-oxidative biosynthetic transformations can be mimicked and a highly stereo- and regio-selective approach to the steroid framework achieved in this sort of manner by application of a photo-induced electron transfer process of terpenoid polyalkenes containing a (-)-menthone-based auxiliary. During this process the radical cation initially generated engages in a sequence of three 6-*endo-trig* and one 5-*exo-trig* cyclisation reactions. The cation is then intercepted by a nucleophile, for example water, which adds exclusively in an equatorial manner. For example, compound **358** underwent a cascade of cyclisation reactions of the types just mentioned upon photolysis to afford, albeit in only 10% combined yield, a 7:1 mixture of products **359** and **360**, each of which embodies the steroid skeleton (Scheme 5.4).

Scheme 5.4: Demuth's Steroid Synthesis – a Photo-Induced Electron Transfer Approach

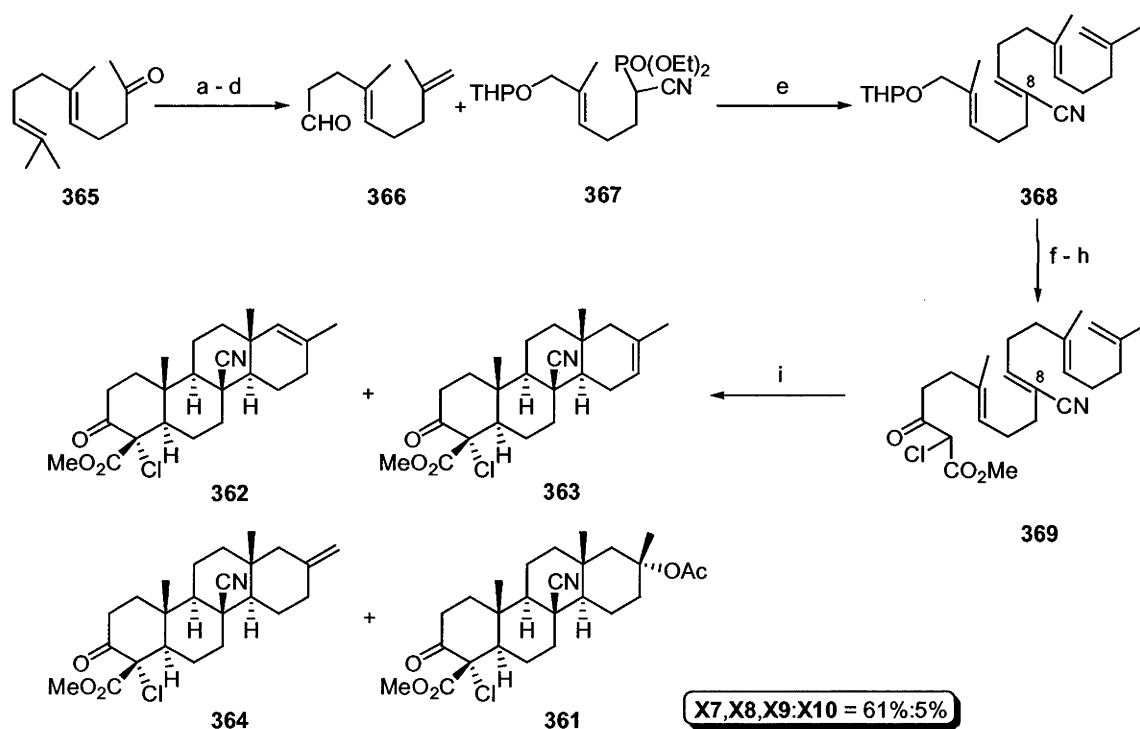


Reagents and conditions: (a) biphenyl, 1,4-dicyano-2,3,5,6-tetramethylbenzene, $h\nu$ (300 nm), MeOH/H₂O (10:1), -25 °C.

Oxidative Free-Radical Approach

The so-called oxidative free-radical approach, reported by Zoretic and co-workers,^{25,26} involves four contiguous *6-endo-trig* cyclisation reactions from an initially generated electrophilic radical. Installation of a cyano-substituent at the *pro*-C8 position enabled control of the regiochemistry of the second cyclisation process and the radical-chain reaction was eventually terminated by oxidation of the tetracyclic tertiary radical to afford the corresponding cation. Subsequent proton loss or, in the case of the process leading to product **361**, acetate trapping then provided a *ca.* 12:1 mixture of the D-homosteroid tetracycles **362**, **363** and **364** to **361** (Scheme 5.5).

Scheme 5.5: Zoretic's Steroid Synthesis – an Oxidative Free Radical Approach

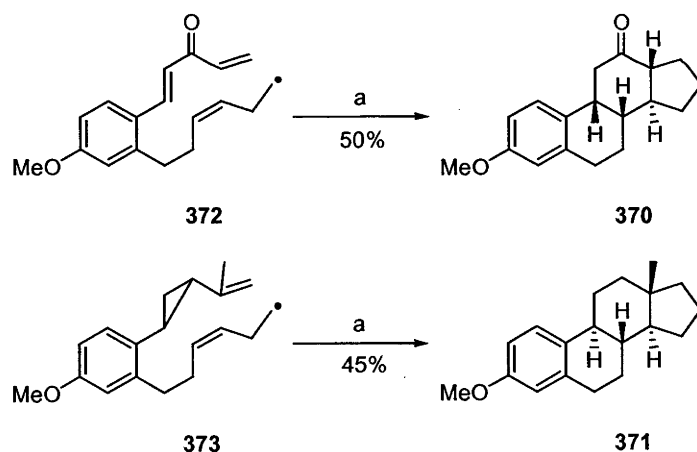


Reagents and conditions: (a) NBS, THF, H₂O, 0 °C, 3 h; (b) K₂CO₃, MeOH, 18 °C, 30 min; (c) Ph₃P=CH₂, THF, -78 °C, 3 h; (d) H₃IO₆, THF, H₂O, 0 °C, 2.5 h; (e) KN(SiMe₃)₂, toluene, -78 °C then **367**, -78 to 18 °C, 4 h; (f) MeOH, *p*-TsOH·H₂O, 18 °C, 3 h; (g) CBr₄, Ph₃P, CH₂Cl₂, 18 °C, 3 h then 40-50 °C, 15 min; (h) LiCH₂C(O)CCl(Na)CO₂Me, THF, HMPA, 0 °C, 1 h then 10% HCl (aq.); (i) Mn(OAc)₃·2H₂O, Cu(OAc)₂·H₂O, HOAc, 18 °C, overnight.

Reductive Free Radical Approach

A plethora of reports have emerged over the last decade whereby a reductive free radical approach has been adopted in the synthesis of the steroid framework. The majority of these have come from the group of Pattenden and have involved consecutive *6-endo-trig*²⁷ and transannular radical cyclisations²⁸ using polyene selenyl ester precursors. In mid-2004 an extension of these studies was reported²⁹ whereby a radical-mediated macrocyclisation reaction was used in tandem with consecutive transannulations of *ortho*-disubstituted aryl-polyene precursors. As shown in Scheme 5.6, two conceptually different and novel examples of such cascade reactions were successfully deployed in constructing the structurally related steroid backbones **370** and **371**. These could then be elaborated to afford two structurally related A-ring aromatic steroids.

Scheme 5.6: *Pattenden's Steroid Synthesis – a Reductive Free Radical Approach*



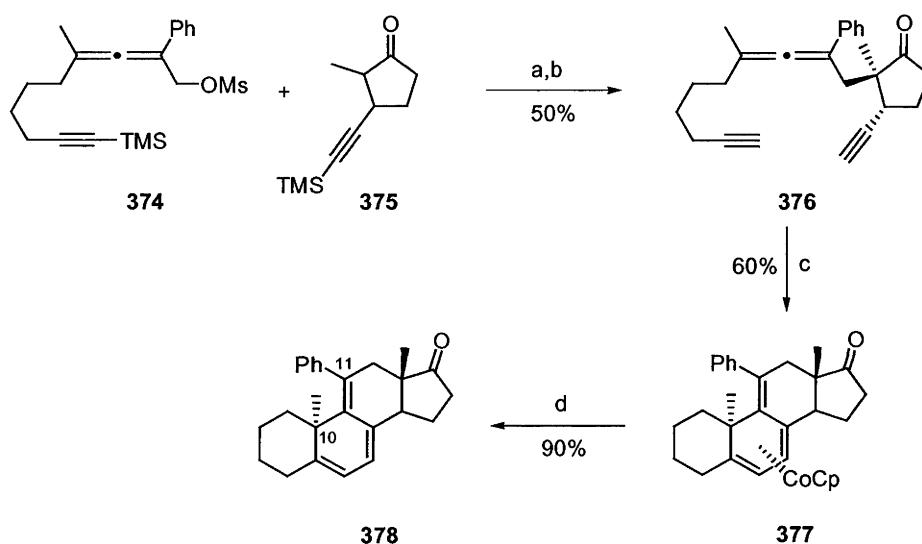
Reagents and conditions: (a) Bu_3SnH , AIBN, benzene, reflux.

Metal-Mediated Cyclisations

A number of elegant steroid total syntheses have utilised transition metal-catalysed cyclisation cascades. A range of metals have been applied in these processes, the most common being

palladium, and a comprehensive review of this topic was published in 2003.³⁰ The most recent contribution in this area was reported in mid-2004 by Aubert and co-workers.³¹ As depicted in Scheme 5.7, this work utilised an intramolecular and cobalt(II)-mediated [2+2+2] cyclisation of allenediynes in the synthesis of an 11-aryl steroid skeleton. Not only was this one-pot process effective in generating the ABCD-ring steroid framework but it also simultaneously incorporated synthetically relevant functionality at the C-10 and C-11 positions.

Scheme 5.7: Aubert's Steroid Synthesis – a Transition Metal-Catalysed Approach



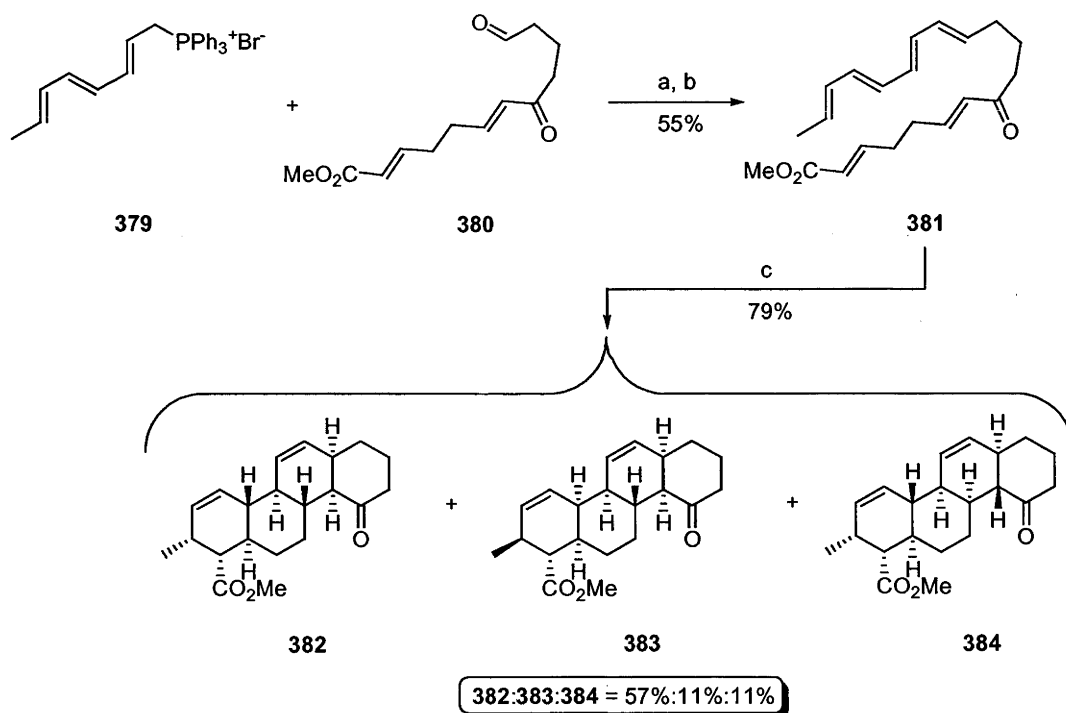
Reagents and conditions: (a) 375, KHMDS, THF, -15 °C then 374, THF, -50 °C; (b) K₂CO₃, MeOH, 18 °C; (c) CpCo(CO)₂, xylenes, *hν*, reflux; (d) SiO₂, CH₂Cl₂, 18 °C.

Domino Intramolecular Diels-Alder Reactions

The literature is replete with examples of the application of domino intramolecular Diels-Alder or domino transannular Diels-Alder reactions in the synthesis of various complex natural products. In 2001 Sherburn and co-workers reported a “proof-of-principle” study that exploited such methodology in the synthesis of the steroid framework. In this work, an unprecedented Lewis acid-promoted domino sequence, involving a simple achiral, acyclic

precursor, was shown to generate, in the one operation, four rings, four new carbon-carbon bonds and eight contiguous stereocentres associated with the tetracyclic D-homosteroid framework. As depicted in Scheme 5.8, only three of the possible eight diastereoisomeric tetracyclic adducts were obtained. More recent reports from this group have demonstrated that this methodology can also be applied to steroid-type frameworks and that both the relative and absolute stereochemistries can be controlled by attachment of a sugar-derived chiral auxiliary onto the chain linking the *bis*-diene and *bis*-dienophile components.

Scheme 5.8: Sherburn's Steroid Synthesis – a Domino Diels-Alder Approach



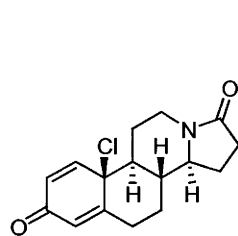
Reagents and conditions: (a) *n*-BuLi, THF, -78 °C, 2 h; (b) I₂, CH₂Cl₂, 18 °C, 2 h; (c) Et₂AlCl, CH₂Cl₂, 40 °C, 30 min.

5.1.3 Possible Structural Variations and Their Effect on Biological Activity

The introduction of heteroatoms at various sites within the steroid ring system has led to the identification of a number of highly interesting structure-activity relationships within this

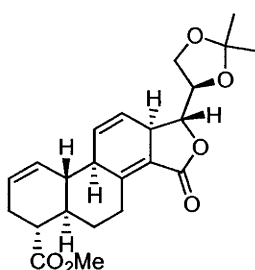
framework and the development of various useful therapeutic agents. Whilst the vast majority of the work undertaken to date has centred around the synthesis and biological evaluation of azasteroids, details of which will be discussed further in the following section, the incorporation of oxygen, sulfur, selenium and tellurium into the steroid nucleus has also been investigated.³²

Replacement of a carbon atom in the steroid framework has not been limited to one heteroatom. In fact there are many examples where two and even three such heteroatoms have been incorporated. As discussed in the following section, these structural variations have been highly useful in the development of new and biologically active compounds.



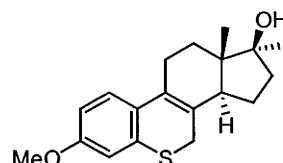
385

13-Azasteroid



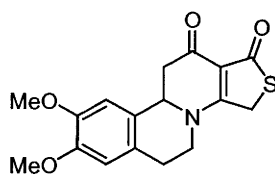
386

16-Oxasteroid



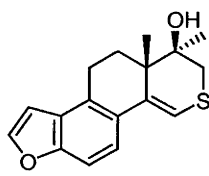
387

6-Thiasteroid



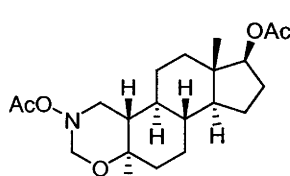
388

8-Aza-16-thiasteroid



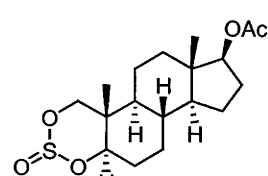
389

3-Oxa-16-thiasteroid



390

2-Aza-4-oxasteroid



391

2,4-Dioxa-3-thiasteroid

5.1.4 Azasteroids and Their Synthesis

A fascinating array of steroid analogues have been reported and synthetic work continues to reveal novel sub-classes which exhibit interesting biological activities. As alluded to above, one such group is the azasteroids. These compounds display a broad spectrum of biological activities, ranging from antifungal,^{33,34} antibacterial,^{35,36} hypocholesterolemic,³⁷ hypotensive,³⁷ antimycotic³⁷ and neuromuscular blocking^{38,39,40} activities to the treatment of benign prostatic hypotrophy,⁴¹ acne and male baldness.^{42,43} It is likely that many of these properties result from formation of stable substrate-enzyme complexes facilitated by the presence of nitrogen

within the molecule.⁴⁴ However, there is a need for diversity in azasteroid synthesis so as to produce compounds which lack the hormonal activity frequently responsible for complicating their application in medicine.⁴⁵

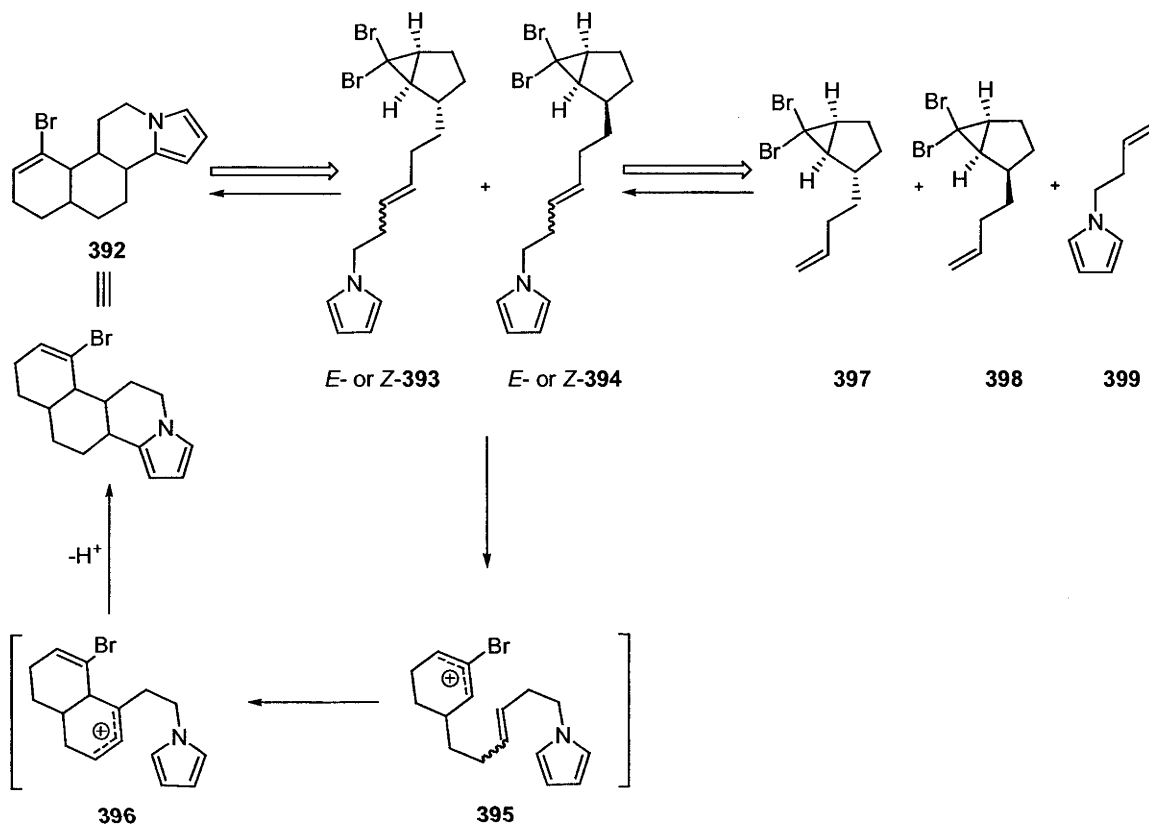
5.2 Retrosynthetic Analysis Associated with the Present Studies

13-Azasteroids occupy a central area in so-called heterosteroidal research and numerous approaches to their synthesis have been reported.^{46,47,48} It was thought that the chemistry discussed in the previous chapter, whereby the π -allyl cation resulting from the electrocyclic ring-opening of a cyclopropane containing a nucleophilic tether was trapped by the C-2 of pyrrole (**141**) to furnish compound **328**, could be exploited in the synthesis of the 13-azasteroid skeleton **392**.



The relevant retrosynthetic analysis of the 13-azasteroid framework **392** is shown in Figure 5.2. Thus, it was anticipated that the pyrrole-tethered cyclopropanes **393** and **394** would undergo silver(I)-promoted electrocyclic ring-opening of the cyclopropane unit to afford π -allyl cation **395** which would then engage in the illustrated cationic cyclisation reaction to produce the targeted framework **392**. The precursors to compounds **393** and **394** would be olefins **397** and **398** and 1-(but-3-enyl)-pyrrole (**399**) which it was envisaged would engage in an olefin cross-metathesis reaction between the two terminal olefins to provide access to these pyrrole-tethered cyclopropyl compounds. Compounds **397** and **398** should, in turn, be readily synthesised by methylenation of the corresponding aldehydes **293** and **294**, which were obtained in multigram quantities *via* a sequence outlined in Chapter 4 (see Scheme 4.3). The other “starting material”, *viz.* 1-(but-3-enyl)-pyrrole (**399**), is readily accessible through procedures reported in the literature and as detailed in the following section.

Figure 5.2: Retrosynthetic Analysis of the 13-Azasteroid Skeleton 392

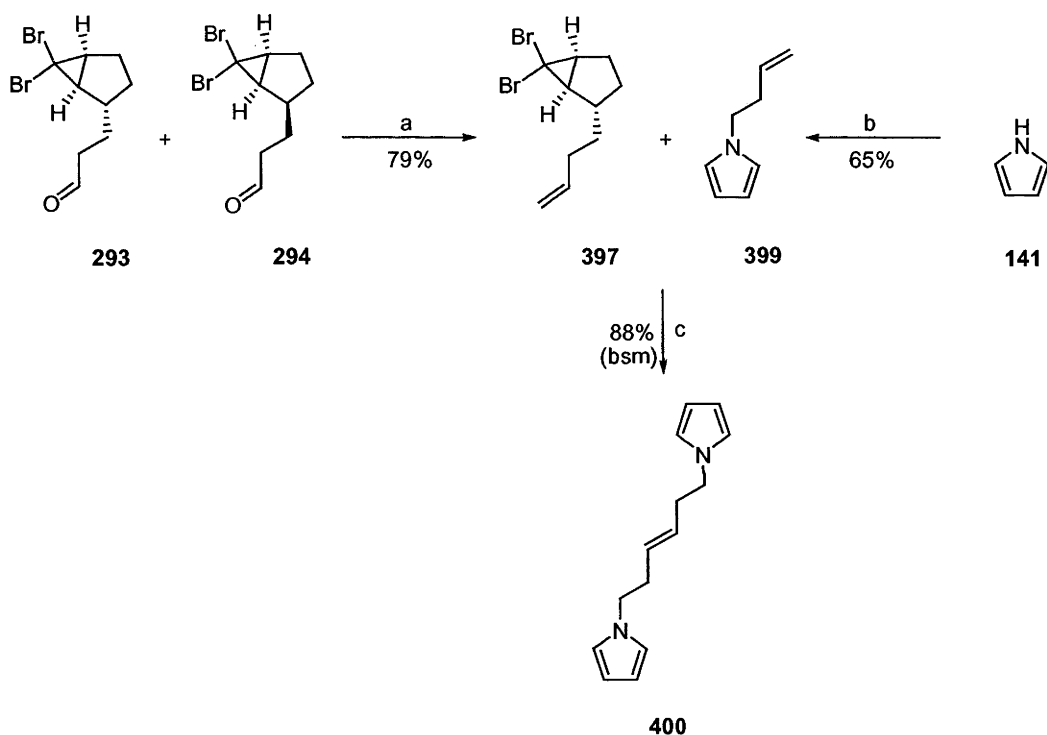


5.3 Initial Approach to Cyclisation Precursors 393 and 394

As foreshadowed in the previous section, methylenation of the 4:1 mixture of the previously obtained aldehydes **293** and **294** was undertaken and readily accomplished by Wittig olefination, utilising the ylide derived from treatment of methyl triphenylphosphonium bromide with NaHMDS. From the spectral data acquired on the product so-formed it was apparent that only one diastereomer had been obtained and this is assumed to be compound **397**. The observance of only one product in this instance is most likely due to the chromatographic instability of the minor epimer or selective reaction of the major diastereomer. As expected, the salient features in both the ^1H and ^{13}C NMR spectra, indicating methylenation had occurred, were the replacement of the aldehydic signals associated with the precursor with resonances attributable to a terminal olefin. In the ^1H NMR spectrum, signals associated with the terminal double bond were visible as a one-proton

multiplet and a complex two-proton multiplet at δ 5.82 and 5.07-4.95, respectively. Similarly, in the APT ^{13}C NMR spectrum the corresponding resonances were visible at δ 138.2 and 114.8. The absence of a carbonyl absorption band in the infrared spectrum also suggested that the desired transformation had occurred and the expected molecular ions, viz. those at m/z 296, 294 and 292, were observed using GC-MS analysis of compound **397**.

Scheme 5.9: Olefin Cross-Metathesis Approach



Reagents and conditions: (a) NaHMDS, methyltriphenylphosphonium bromide, THF, $-78\text{ }^{\circ}\text{C}$, 30 min then **293** and **294**, THF, -78 to $18\text{ }^{\circ}\text{C}$, 16 h; (b) KOH, DMSO, $18\text{ }^{\circ}\text{C}$, 45 min then 4-bromo-1-butene, $18\text{ }^{\circ}\text{C}$, 30 min; (c) Grubbs' I cat. 5 mol %, CH_2Cl_2 , reflux, 18 h.

The proposed OCM coupling partner **399** was readily obtained in one step following a literature procedure for the synthesis of the corresponding three-carbon homologue.⁴⁹ Thus, treatment of a solution of pyrrole (**141**) in DMSO with powdered KOH and 1.3 molar equivalents of 4-bromo-1-butene afforded the desired *N*-alkylation product as a clear, colourless oil and in 65% yield.

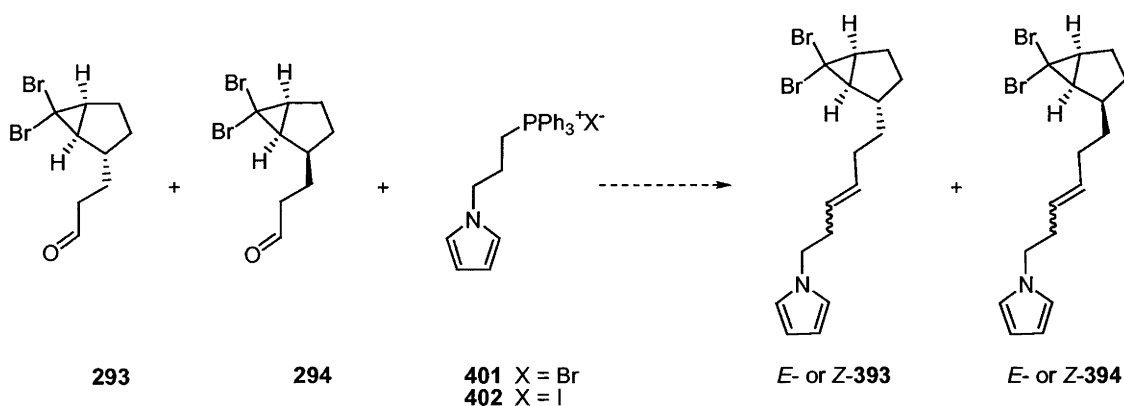
The ^1H and ^{13}C NMR spectral data obtained on product **399** were in full accord with the assigned structure and similar to those recorded for the lower homologue.⁴⁹ Distinctive features in the ^1H NMR spectrum were characteristic pyrrole proton resonances at δ 6.67 and 6.15 as well as signals due to the protons associated with the newly installed olefin which appeared at δ 5.78 and 5.13-5.05. The ^{13}C NMR spectrum displayed the expected eight resonances. GC-MS analysis confirmed that the product was pure and displayed the molecular ion at m/z 121.

Compounds **397** and **399** were subjected to standard olefin cross-metathesis procedures utilising Grubbs' I catalyst. However, none of the desired product was obtained (Scheme 5.9). Instead only self-metathesis of 1-(but-3-enyl)-pyrrole (**399**) was observed and this process produced the *bis*-pyrrole **400** in 88% yield. The same result was also observed with the Grubbs' II catalyst.

5.4 Second Approach to Cyclisation Precursors **393** and **394**

Despite the rather discouraging results detailed in the preceding section it was thought that the requisite cyclisation precursors **393** and **394** could be constructed by alternate means that still exploited some of the building blocks already synthesised. Therefore, the revised synthetic plan involved employing a Wittig reaction for the purposes of "coupling" aldehydes **293** and **294** with a suitable phosphonium salt incorporating a pyrrole subunit as embodied in compound **401** or **402** (Figure 5.3).

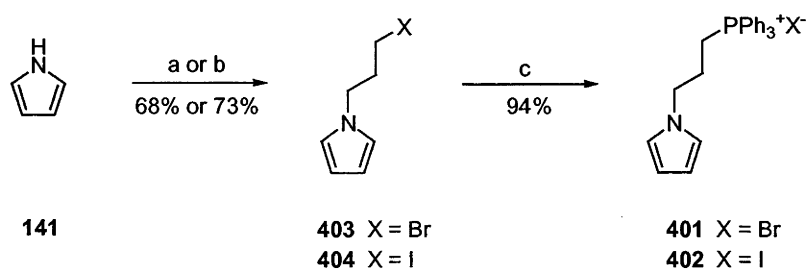
Figure 5.3: Revised Synthetic Strategy



5.4.1 Synthesis of Phosphonium Salts **401** and **402**

Initial studies centred on the synthesis of *N*-(3-bromopropyl)pyrrole (**403**) *via* a literature procedure.⁵⁰ It was then anticipated that reaction of this compound with triphenylphosphine in a suitable solvent would afford the corresponding phosphonium salt **401** (Scheme 5.10). However, upon trialling this reaction in a variety of solvents it was observed that only a very small amount of the desired product was obtained. Therefore, the more reactive, and known,⁵¹ iodo-congener **404** was targeted. In a procedure analogous to that utilised for the synthesis of the corresponding bromo-derivative, the successful alkylation of pyrrole (**141**) was affected with 1,3-diiodopropane, hence affording the previously reported⁵¹ iodide **404**. As anticipated, the ¹H NMR spectrum was almost indistinguishable from that previously acquired for the bromo-analogue. However, in the ¹³C NMR spectrum a large variation was observed between the resonances attributed to the carbon bearing the halide in each case. This was not surprising and is due to the difference in electronegativity between these two halogens. 70 eV Mass spectral analysis revealed a molecular ion of *m/z* 235 and confirmation of the molecular formula, namely C₇H₁₀NI, was achieved *via* an accurate mass measurement.

Scheme 5.10: Synthesis of Phosphonium Salts **401 and **402****



Reagents and conditions: (a) KOH, 1,3-dibromopropane, DMF, 18 °C, 16 h; (b) KOH, 1,3-diiodopropane, DMF, 18 °C, 13 h; (c) PPh₃, toluene, reflux, 5 h.

Iodide **404** was converted into the corresponding phosphonium salt in excellent yield (94%) by heating equimolar amounts of the former material with triphenylphosphine in refluxing

toluene. Not surprisingly, salt **402** precipitated out of solution during the course of the reaction and, hence, could be readily isolated and then purified by recrystallisation from a mixture of diethyl ether and hexane. The most salient feature in the ^1H NMR spectrum of this salt (Figure 5.4) was the appearance of a complex multiplet, integrating to fifteen protons, at δ 7.81-7.64. This suggested inclusion of the elements of a triphenylphosphine moiety in the product. Similarly, the ^{13}C NMR spectrum revealed new aromatic signals. Elemental analysis then served to confirm the expected empirical formula for compound **402**.

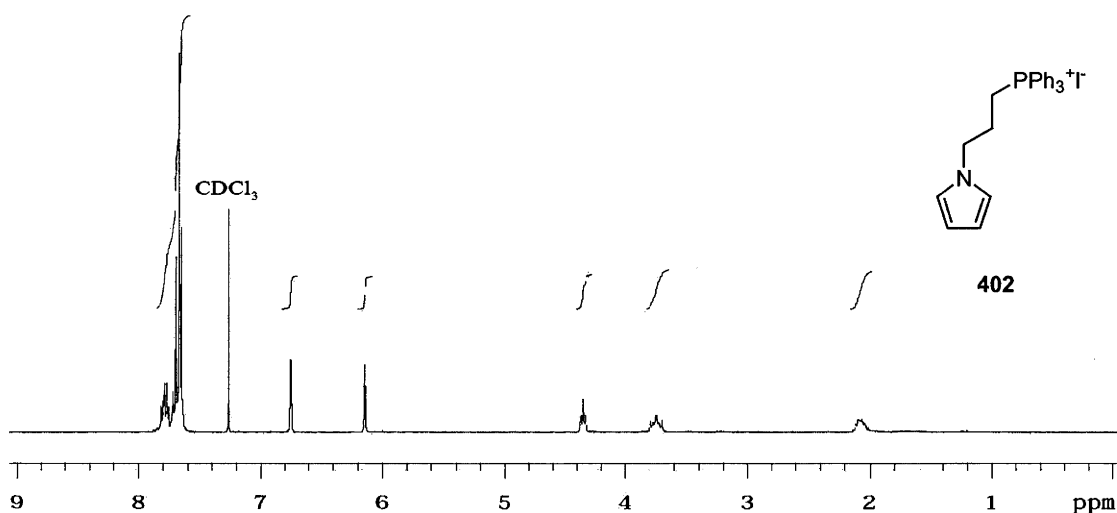


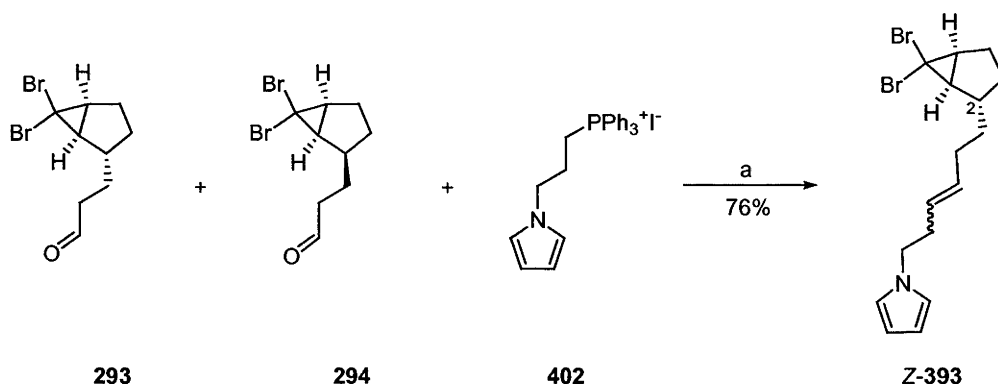
Figure 5.4: 300 MHz ^1H NMR Spectrum of Salt **402** in CDCl_3

5.4.2 Synthesis of Cationic Cyclisation Precursor **393**

With aldehydes **293** and **294** and phosphonium salt **402** in hand efforts were now directed towards coupling the two partners utilising Wittig chemistry. Thus, reaction of salt **402** with sodium hexamethyldisilazide provided the corresponding ylide which, upon reaction with aldehydes **293** and **294**, afforded the requisite cyclisation precursor **393** as the sole isolable product and in 76% yield. Characteristic features in the ^1H NMR spectrum, which supported this assignment, were the symmetrical pyrrolic resonances, observed as triplets at δ 6.67 and 6.14, along with a signal at δ 5.42 due to the newly formed alkenyl protons. Similarly in the ^{13}C NMR spectrum the pyrrolic resonances were apparent at δ 120.4 and 107.9 with the alkenyl signals appearing at δ 131.9 and 125.7. As expected, the remaining ten resonances were visible in the aliphatic region of the spectrum. Low and high-resolution EI mass

spectrometry confirmed that the compound had the anticipated composition, namely $C_{16}H_{21}Br_2N$.

Scheme 5.11: Synthesis of Cyclisation Precursor 393



Reagents and conditions: (a) 402, NaHMDS, THF, $-78\text{ }^{\circ}\text{C}$, 30 min then 293 and 294, THF, -78 to $0\text{ }^{\circ}\text{C}$, 30 min then 0 to $18\text{ }^{\circ}\text{C}$, 16 h.

There are four possible stereochemical outcomes from this reaction, with two possible epimers being formed at C-2 and the newly installed double bond being able to possess either an *E*- or *Z*-configuration. However, it was apparent from the spectral data acquired that only one compound had been obtained. No conclusive comments can be made regarding the configuration about the C=C in this compound but based on the conditions employed, it is expected that the *Z*-stereochemistry would be obtained. This is largely based on the precedence that reaction of unstabilised ylides, such as that utilised, with aldehydes generally afford the *Z*-configured alkene.⁵² Regardless of the stereochemistry obtained however it is not anticipated that this will have an influence on the outcome of the proposed cyclisation. For reasons similar to those enunciated earlier, it is assumed that there is an *anti*-relationship between the cyclopropyl ring and the side-chain associated with the central five-membered ring.

5.4.3 Cationic Cyclisation

In an attempt to effect the desired cyclisation, and hence form the azasteroid core skeleton **392**, compound **393** was subjected to the previously discussed silver(I)-promoted electrocyclic ring-opening conditions. One isolable product was obtained from the reaction mixture. However, the low yields of material as well as purification difficulties have meant that, to date, a conclusive comment cannot be made about the structure of the obtained product. Work in this area is ongoing and details describing possible future approaches to the 13-azasteroid skeleton are discussed in Chapter Six.

5.5 Conclusions

This Chapter has detailed the establishment of an efficient route to the desired cyclisation precursor **393**. Whilst, unfortunately, no conclusive comment can be made to date regarding the outcome of the key cyclisation reaction, the observance of only one isolable product is indeed encouraging. Consequently, it is believed that substrate *Z*-**393** or some simple modification there-of will ultimately serve as a precursor to the 13-azasteroid skeleton.

5.6 References

- ¹ Segura, L.J., Martin, N.; *Chem. Rev.*, **1999**, *99*, 3199-3246.
- ² Funk, R.L., Volhardt, K.P.C.; *Chem. Soc. Rev.*, **1980**, *9*, 41-61.
- ³ Kametani, T., Nemoto, H.; *Tetrahedron*, **1981**, *37*, 3-16.
- ⁴ Kametani, T., Nemoto, H., Ishikawa, H., Shiroyama, K., Fukumoto, K.; *J. Am. Chem. Soc.*, **1976**, *98*, 3378-3379.
- ⁵ Kametani, T., Nemoto, H., Ishikawa, H., Shiroyama, K., Matsumoto, H., Fukumoto, K.; *J. Am. Chem. Soc.*, **1977**, *99*, 3461-3466.
- ⁶ Oppolzer, W., Roberts, D.A.; *Helv. Chim. Acta*, **1980**, *63*, 1703-1705.
- ⁷ Michellys, P-Y., Maurin, P., Toupet, L., Pellissier, H., Santelli, M.; *J. Org. Chem.*, **2001**, *66*, 115-122.
- ⁸ Oullet, L., Langlois, P., Deslongchamps, P.; *Synlett*, **1997**, *6*, 689-690.
- ⁹ Marsault, E., Toró, A., Nowak, P., Deslongchamps, P.; *Tetrahedron*, **2001**, *57*, 4243-4260.
- ¹⁰ Fuhrhop, J.H., Li, G.; *Organic Synthesis: Concepts and Methods*, Wiley-VCH: Weinheim, **2003**.
- ¹¹ Johnson, W.S., Gravestock, M.B., McCarry, B.E.; *J. Am. Chem. Soc.*, **1971**, *93*, 4332-4334.
- ¹² Johnson, W.S., DuBois, G.E.; *J. Am. Chem. Soc.*, **1976**, *98*, 1038-1039.
- ¹³ Van Tamelen, E.E., Willet, J.D., Clayton, R.B.; *J. Am. Chem. Soc.*, **1966**, *88*, 4752-4754.
- ¹⁴ Johnson, W.S.; *Angew. Chem. Int. Ed. Engl.*, **1976**, *15*, 9-17.
- ¹⁵ Stork, G., Burgstahler, A.W.; *J. Am. Chem. Soc.*, **1955**, *77*, 5068-5077.
- ¹⁶ Eschenmoser, A., Riuzicka, L., Jeger, O., Arigoni, D.; *Helv. Chim. Acta*, **1955**, *38*, 1890-1904.
- ¹⁷ Johnson, W.S., Yarnell, T.M., Myers, R.F., Morton, D.R.; *Tetrahedron Lett.*, **1978**, *19*, 2549-2552.
- ¹⁸ Johnson, W.S., Yarnell, T.M., Myers, R.F., Morton, D.R., Boots, S.G.; *J. Org. Chem.*, **1980**, *45*, 1254-1259.
- ¹⁹ Johnson, W.S., Chen, Y.Q., Kellogg, M.S.; *J. Am. Chem. Soc.*, **1983**, *105*, 6653-6656.
- ²⁰ Johnson, W.S., Daub, G.W., Lyle, T.A., Niwa, M.; *J. Am. Chem. Soc.*, **1980**, *102*, 7800-7802.

- ²¹ Sutherland, J.K.; in *Comprehensive Organic Synthesis*, Trost B.M. (Ed.), Pergamon Press: Oxford, **1991**, Vol. 3, pp. 341-377.
- ²² Heinemann, C., Demuth, M.; *J. Am. Chem. Soc.*, **1997**, *119*, 1129-1130.
- ²³ Heinemann, C., Demuth, M.; *J. Am. Chem. Soc.*, **1999**, *121*, 4894-4895.
- ²⁴ Goeller, F., Heinemann, C., Demuth, M.; *Synthesis*, **2001**, *8*, 1114-1116.
- ²⁵ Zoretic, P.A., Chen, Z., Zhang, Y.; *Tetrahedron Lett.*, **1996**, *37*, 7909-7912.
- ²⁶ Zoretic, P.A., Fang, H., Ribeiro, A.A.; *J. Org. Chem.*, **1998**, *63*, 7213-7217.
- ²⁷ Batsanov, A., Chen, L., Gill, G.B., Pattenden, G.; *J. Chem. Soc., Perkin Trans. 1*, **1996**, *1*, 45-55 and references therein.
- ²⁸ Handa, S., Pattenden, G., Li, W-S.; *J. Chem. Soc., Chem. Commun.*, **1998**, *3*, 311-312.
- ²⁹ Pattenden, G., Gonzalez, M.A., McCulloch, S., Walter, A., Woodhead, S.J.; *PNAS*, **2004**, *101*, 12024-12029.
- ³⁰ Skoda-Földes, R., Kollár, L.; *Chem. Rev.*, **2003**, *103*, 4095-4129.
- ³¹ Petit, M., Aubert, C., Malacria, M.; *Org. Lett.*, **2004**, *6*, 3937-3940.
- ³² Suginome, H., Yamada, S., Wang, J.B.; *J. Org. Chem.*, **1990**, *55*, 2170-2176.
- ³³ Solomons, W.E., Doorenbos, N.J.; *J. Pharm. Sci.*, **1973**, *62*, 638-640.
- ³⁴ Doorenbos, N.J., Solomons, W.E.; *J. Pharm. Sci.*, **1974**, *63*, 19-23.
- ³⁵ Dolle, R.E., Allaudeen, H.S., Kruse, L.I.; *J. Med. Chem.*, **1990**, *33*, 877-880.
- ³⁶ Chesnut, R.W., Durham, N.N., Brown, R.A., Mawdsley, E.A., Berlin, R.A.; *Steroids*, **1976**, *27*, 525-541.
- ³⁷ Dolle, R.E., Allaudeen, H.S., Kruse, L.I.; *J. Med. Chem.*, **1990**, *33*, 877-880.
- ³⁸ Singh, H., Paul, D., Parashar, V.V.J.; *J. Chem. Soc., Perkin Trans. 1*, **1973**, *11*, 1204-1206.
- ³⁹ Singh, H., Paul, D.; *J. Chem. Soc., Perkin Trans. 1*, **1974**, *12*, 1475-1479.
- ⁴⁰ Singh, H., Bhardwaj, T.R., Ahuja, N.K., Paul, D.; *J. Chem. Soc., Perkin Trans. 1*, **1979**, *12*, 305-307.
- ⁴¹ Rasmusson, G.H., Reynolds, G.F., Utne, T., Jobson, R.B., Primka, R.L., Berman, C., Brooks, J.R.; *J. Med. Chem.*, **1984**, *27*, 1690-1701.
- ⁴² Brooks, J.R., Berman, C., Primka, R.L., Reynolds, G.F., Rasmusson, G.H.; *Steroids*, **1986**, *47*, 1-19.

- ⁴³ Brooks, J.R., Berman, C., Garnes, D., Giltinan, D., Gordon, L.R., Malatesta, P.F., Primka, R.L., Reynolds, G.F., Rasmusson, G.H.; *Prostate*, **1986**, *9*, 65-75.
- ⁴⁴ Romero, A.G., Leiby, J.A., Mizsak, S.A.; *J. Org. Chem.*, **1996**, *61*, 6974-6979.
- ⁴⁵ Marson, C.M., Pink, J.H., Smith, C.; *Tetrahedron*, **2003**, *59*, 10019-10023.
- ⁴⁶ Birch, A.J., Subba Rao, G.S.R.; *J. Chem. Soc.*, **1965**, *46*, 3007-3008.
- ⁴⁷ Hubert, J.C., Speckamp, W.N., Huisman, H.O.; *Tetrahedron Lett.*, **1969**, *20*, 1553-1556.
- ⁴⁸ Dijink, J., Speckamp, W.N.; *Tetrahedron Lett.*, **1977**, *11*, 935-938.
- ⁴⁹ Lazzaroni, R., Settambolo, R., Caiazzo, A., Pontorno, L.; *J. Organomet. Chem.*, **2000**, *601*, 320-323.
- ⁵⁰ Dehaen, W., Hassner, A.; *J. Org. Chem.*, **1991**, *56*, 896-900.
- ⁵¹ Ozaki, S., Mitoh, S., Ohmori, H.; *Chem. Pharm. Bull.*, **1996**, *44*, 2020-2024.
- ⁵² Lawrence, N.J.; in *Preparation of Alkenes*, Lawrence, N.J. (Ed.), **1996**, Oxford University Press: Oxford, pp. 19-55.

Future Directions

6.1 Possibilities for Future Work Arising from the Research Described in Chapter Two

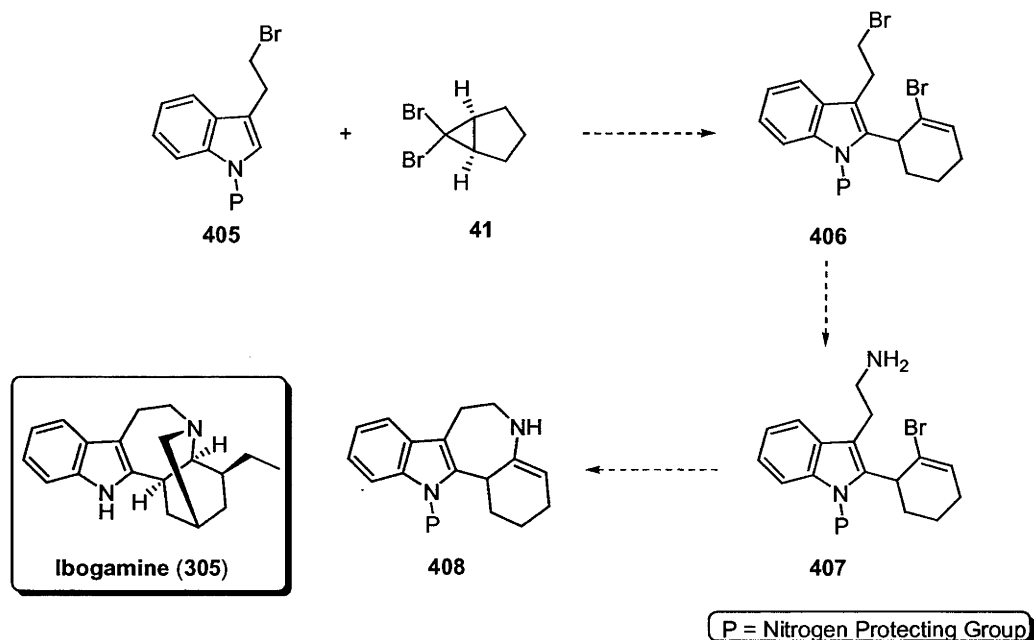
The work detailed in Chapter Two served to showcase the potential of *gem*-dihalocyclopropanes as building blocks in chemical synthesis and the significant potential that exists for extending such work to the construction of natural products and related materials of biological interest. A few examples of these possibilities are discussed in some detail in the following sections.

6.1.1 Attempts at Trapping the π -Allyl Cation at the C-2 Position of Indole (128)

Section 2.2.1.2 detailed attempts to extend the results observed for the successful trapping of the π -allyl cation at the C-3 position of indole (**128**) to the C-2 position of the same heterocyclic system. In particular, the *bis*-*N*-Boc protected tryptamine **137** was initially selected as the nucleophile but it was discovered that the exocyclic nitrogen was too reactive and hence the desired carbon-carbon bond forming reaction did not take place. It was also established that the Boc-protecting group was not entirely stable to the required conditions. Therefore, to rectify this problem and as part of a program to synthesise ibogaine alkaloids such as ibogamine (Figure 6.1), efforts could be directed towards trapping the π -allyl cation generated from the electrocyclic ring-opening of cyclopropane **41** with a compound such as the protected 3-(2-bromoethyl)indole **405**. If such a reaction was successful various applications of the resulting compound **406** are envisaged. For example, conversion of this bromide into the corresponding primary amine **407** and subsequent intramolecular and Pd[0]-

catalysed amination, of the type recently described by Buchwald,¹ should result in the formation of compound **408**.

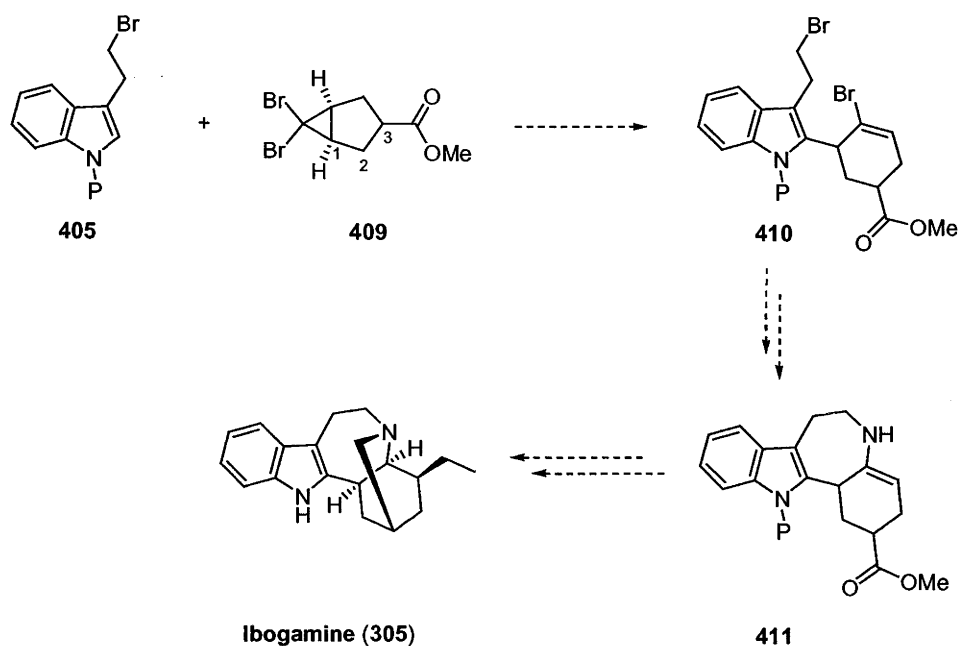
Figure 6.1: Towards the Ibogaine Alkaloid Framework



Compound **408** embodies a tetracyclic ring system that resembles intermediates previously used in the synthesis of various ibogaine alkaloids including ibogamine (**305**). Therefore, it is conceivable that by incorporating additional functionality onto the cyclopropane ring a total synthesis of compounds of this type could be established. For example, it might be expected that cyclopropane **409** (Figure 6.2), which contains a carbomethoxy group attached at the C-3 position, should react with the protected 3-(2-bromoethyl)indole **405**, in the previously suggested manner, to afford conjugate **410**. Then, following procedures analogous to those described above, it is anticipated that compound **411** could be obtained. Attainment of this compound, followed by installation of the ethyl group and deprotection of the indole nitrogen would then complete a formal total synthesis of ibogamine (**305**). Following literature procedures,² which include pyrolytically-promoted lactamisation and reduction of the lactam

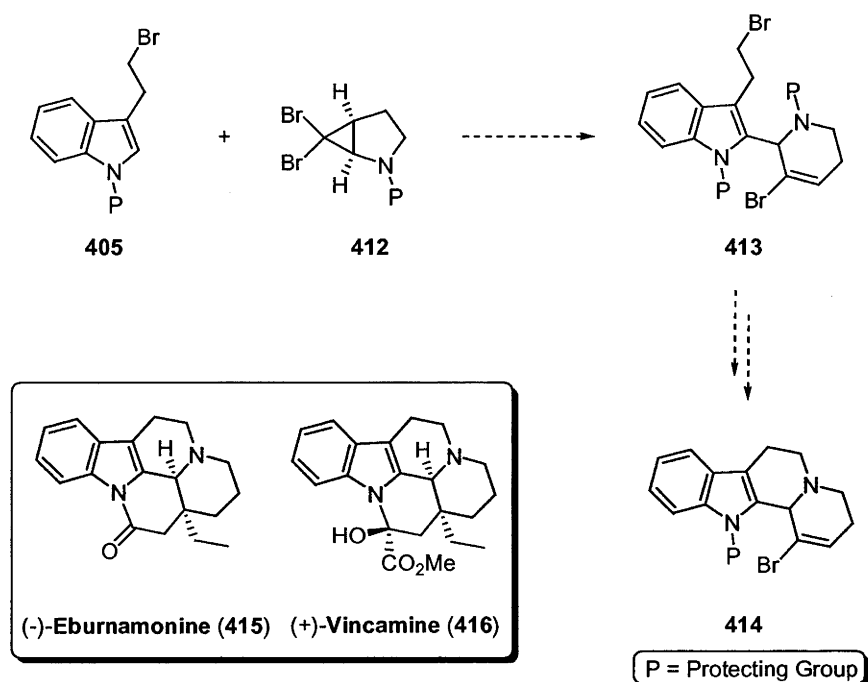
so-formed with lithium aluminium hydride, a total synthesis of ibogamine (**305**) could also be accomplished.

Figure 6.2: Towards Ibogamine (**305**)



Further extensions of this idea could also be pursued by employing, for example, *gem*-dibromocyclopropane **412**, a structurally similar compound to the previously synthesised 2-azabicyclo[3.1.0]hexane **150**, in an analogous reaction sequence (Figure 6.3). If compound **413** was obtained by such means, it is expected that deprotection of the newly attached nitrogen followed by a subsequent intramolecular alkylation, utilising the bromoethyl moiety, would afford compound **414**. This adduct represents a substructure incorporated within a large number of natural products including, for example, the biologically important Vinca-Eburna alkaloids, such as the illustrated (-)-eburnamonine (**415**) and (+)-vincamine (**416**). It is envisaged that elaboration of trapping product **414** to the aforementioned targets could be achieved in an expeditious manner.

Figure 6.3: A Possible Approach to the Ring System Associated with the Vinca-Eburna Alkaloids



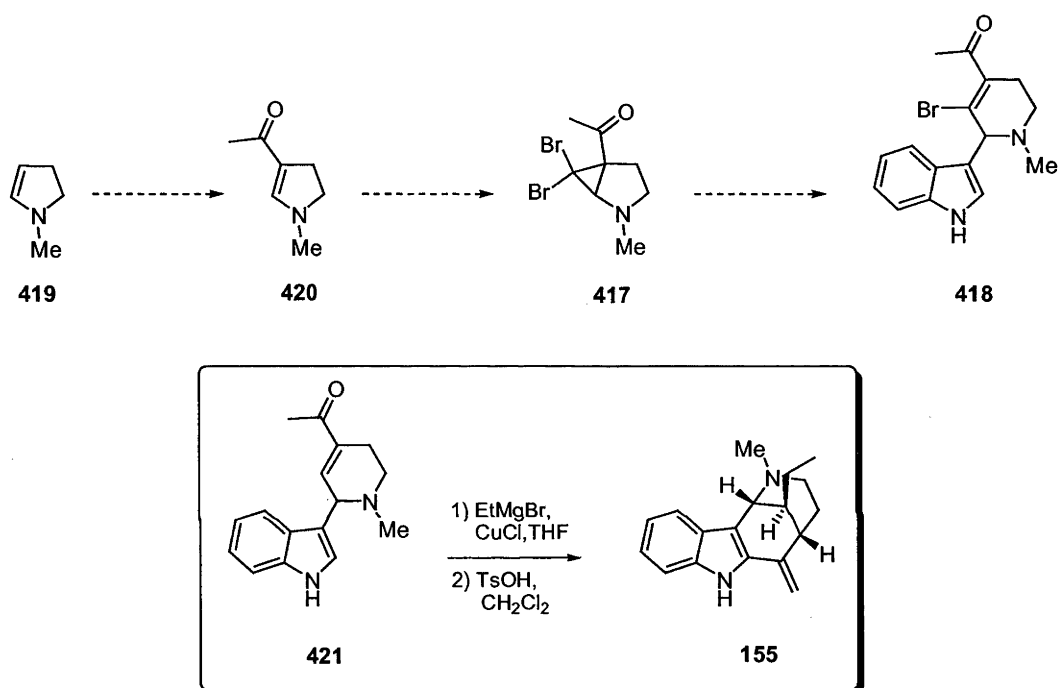
6.1.2 Synthetic Potential of the 3-(2-Piperidyl)indole Moiety

As noted in Chapter Two, the 3-(2-piperidyl)indole moiety is present in, *inter alia*, alkaloids of the Strychnan, Aspidospermatan and Plumeran classes, as well as those of the Uleine group.³ Results discussed in Section 2.3 have established that a moiety such as this can be obtained *via* the electrocyclic ring-opening of the relevant cyclopropane **150** and subsequent trapping of the ensuing π -allyl cation with indole (**128**). Following on from these observations, it seems apparent that a total synthesis of various natural products from the abovementioned alkaloid groups could be targeted.

Figure 6.4 shows a synthetic plan for exploiting this methodology in a synthesis of (\pm) 20-epiuleine (**155**), a representative member of the Uleine alkaloid class of compounds. Installation of an acyl group onto an enamine similar to that previously synthesised is an

established process⁴ and this could be followed by a dibromocarbene addition reaction to provide cyclopropane **417**. It is then anticipated that this compound will undergo electrocyclic ring-opening to afford a π -allyl cation that could be attacked by the C-3 position of indole (**128**) to deliver product **418**.

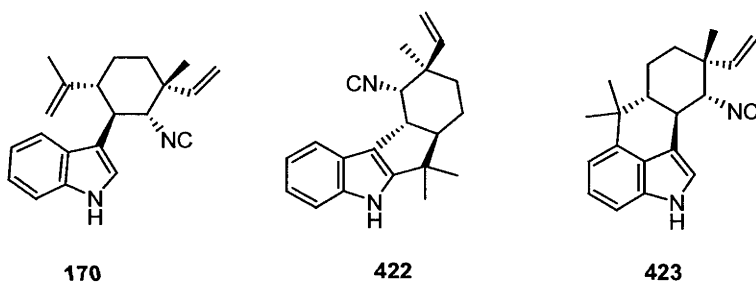
Figure 6.4: Towards the Synthesis of (\pm) 20-Epiuleine (**155**)



This last compound bears a strong resemblance to adduct **421**, an established and key intermediate associated with previously reported syntheses of epiuleine.^{5,6} It is also anticipated that inclusion of a chiral auxiliary at the ring-nitrogen of cyclopropane **417** may allow for the development of an enantioselective synthesis of the natural product **155**.

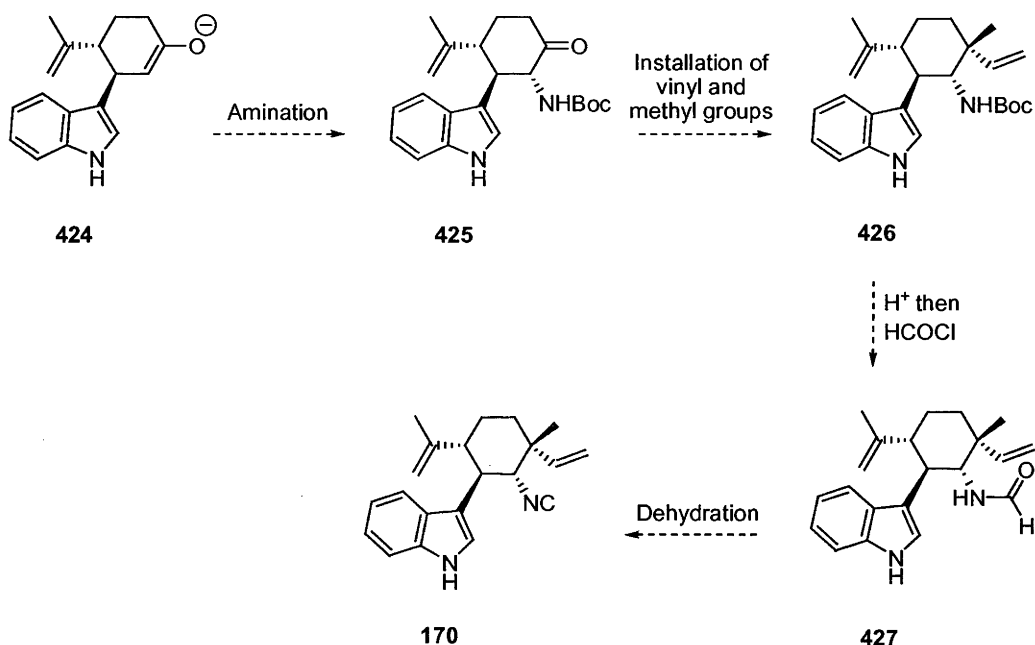
6.2 Possibilities for Future Work Arising from the Research Described in Chapter Three

The work detailed in Chapter Three has provided a viable method for the concise assembly of frameworks associated with the hapalindole and fischerindole alkaloids. Not only is this route efficient, but it is also sufficiently flexible to allow for incorporation of the additional functionality required for the total synthesis of the aforementioned natural products. Future aspects of this work, therefore, will be directed towards implementing a total synthesis of hapalindoles **170** and **422** as well as investigating the possibilities of extending this approach so as to establish a synthesis of the corresponding tetracyclic hapalindole alkaloid **423**. The following sections detail possible methods for achieving such outcomes.



6.2.1 Incorporation of the Isonitrile Functionality

Prior to the installation of the geminally-related vinyl and methyl functionalities required in preparing targets **170** and **422** it is conceivable that a regioselective amination of enolate **424**, derived from the corresponding ketone could be carried out (Figure 6.5). Whilst it is anticipated that the stereochemistry already present within the molecule would cause the amination to occur from the less hindered (and desired) α -face, regiochemical issues will also need to be addressed. It is hoped that, by the use of appropriate bases, deprotonation could be effected at the desired position with some level of control.

Figure 6.5: Plan for Conversion of Enolate **424** into Natural Product **170**

With compound **425** in hand the proposed sequence for the introduction of the geminally-related vinyl and methyl groups, as discussed in the following section, could be examined before the carbamate-protected amine is converted into the corresponding formamide **427**. Dehydration of this system would then be expected to provide the required isonitrile moiety, hence completing the installation of all of the necessary functionality around the cyclohexyl ring system of target **170**.

6.2.2 Proposed Strategy for Installation of the Geminally-Related Vinyl and Methyl Groups of **170**

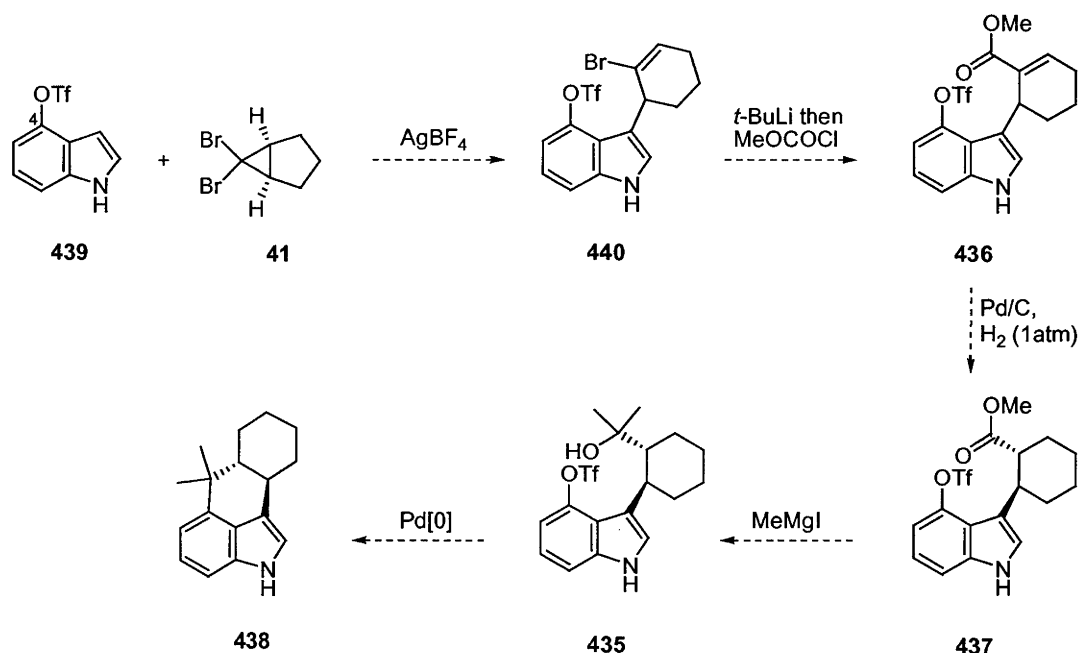
As shown in retrosynthetic form in Figure 6.6, deprotection of the chiral auxiliary incorporated on the newly coupled cyclohexyl ring in compound **214** would deliver ketone **428** which could serve as a platform for installation of the required and geminally-related vinyl and methyl substituents seen at C-12 in **170**.

It is anticipated that subjection of cyclopropane **429** to Barton-McCombie deoxygenation conditions would result in ring-cleavage to deliver product **433**. It is acknowledged that two possible products, **433** and **434**, may arise from such a process. However, it is hoped that the already established stereochemistry within the actual hapalindole/fischerindole system will exert some control over the pathway followed in this radical process. For this reason, therefore, the discussed reaction has not been trialled on the model system. It should be noted however that these studies were successful in establishing a more efficient and higher yielding sequence leading to **429** than that reported previously⁹ and will, therefore, be of benefit when applied to the “real” system.

6.2.3 Towards the Tetracyclic Hapalindole Framework

The chemistry detailed in the preceding section should also be capable of adaptation to the synthesis of at least one of the tetracyclic hapalindole alkaloids (Figure 6.7). Thus, incorporation of a triflate moiety onto the C-4 position of indole, as seen in compound **439**, would provide, following trapping of the π -allyl cation derived from the ring-opening of cyclopropane **41**, a means for effecting the required ring closure as depicted in the proposed conversion **435** \rightarrow **438**. Installation of the necessary methyl ester functionality, as seen in compound **436**, and subsequent hydrogenation would be performed in an identical manner to that described previously (Section 3.5.4.4) so as to afford the saturated system **437**. The desired cyclisation could be successfully achieved utilising either palladium-catalysed cross-coupling chemistry or analogous conditions to those described by Rapoport *et al.* in their synthesis of an advanced intermediate *en route* to the ergot alkaloids.¹⁰ These latter conditions involved the cyclisation of a tethered alcohol onto a bromide incorporated at the C-4 position of indole *via* lithium-for-halogen exchange chemistry. In the absence of the triflate moiety and with a bulky protecting group present it is also conceivable that Friedel-Crafts cyclisation conditions, such as those utilised for the synthesis of Uhle’s ketone,¹¹ would deliver target **438**. Of course, once the framework has been successfully constructed a total synthesis of the corresponding natural product should be achievable by employing the sequences described previously for the installation of the necessary functionality.

Figure 6.7: Proposed Reaction Sequence for the Synthesis of the Tetracyclic Hapalindole Framework **438**



6.3 Possibilities for Future Work Arising from the Research Described in Chapter Four

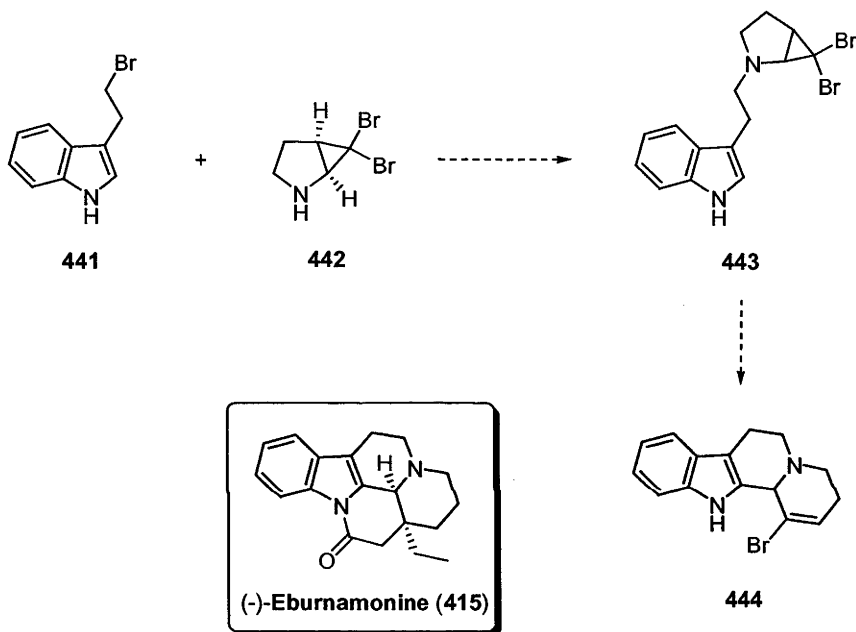
Investigations on the use of various carbon-centred nucleophiles for the intramolecular trapping of π -allyl cations were discussed throughout Chapter Four. Some of the nucleophiles employed proved significantly more effective than others such that clear directions can be formulated in regard to the approach that should be taken with any future work in the area. Some such directions are highlighted in the following section.

6.3.1 Extension on Trapping of the π -Allyl Cation at the C-2 position of Indole (128)

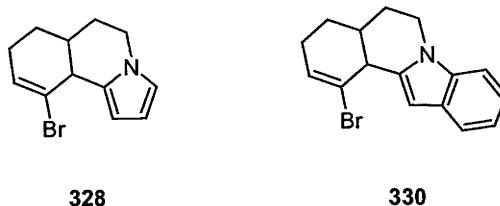
It is anticipated that reaction of commercially available 3-(2-bromoethyl)indole (**441**) with cyclopropane **442** would afford compound **443** (Figure 6.8). This adduct is structurally similar to that utilised in the studies detailed in Chapter Four although it has the distinct

advantage that cyclisation in the desired manner is more highly favoured and hence would be more likely to result in formation of the illustrated six-membered ring. If this cyclisation was successful, tetracycle **444** would be rapidly obtained and it seems reasonable to argue that this tetracyclic compound could be readily elaborated to natural products of the eburnane family, for example (-)-eburnamonine (**415**) as depicted below.

Figure 6.8: Strategy for the Synthesis of the Tetracyclic Framework **444**



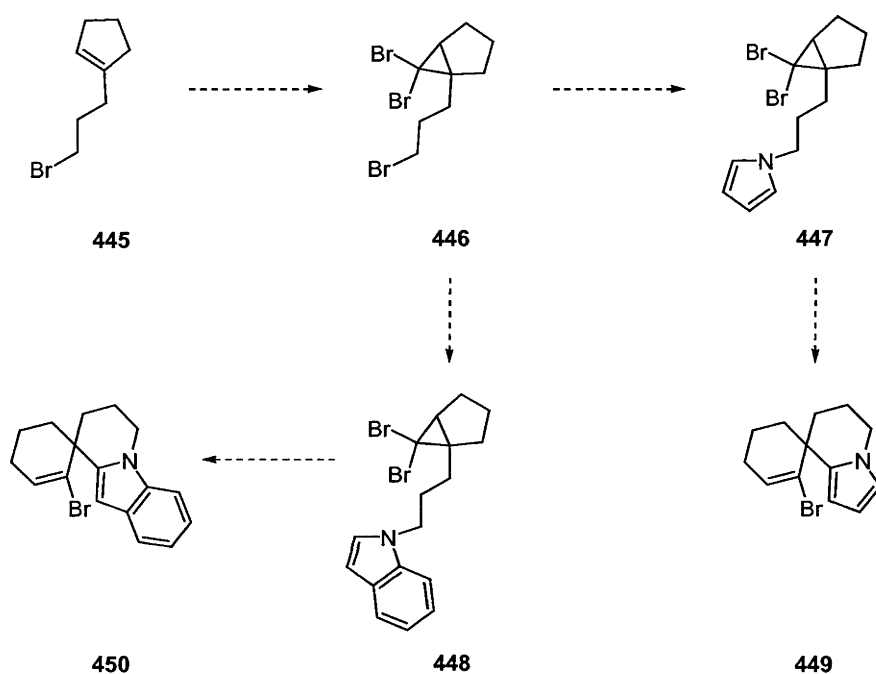
One of the other major successes described in Chapter Four was the intramolecular trapping of a π -allyl cation by the C-2 of pyrrole to furnish compound **328**.



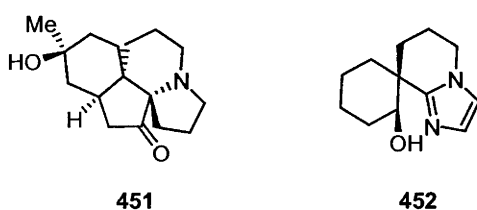
Whilst work is continuing in an effort to apply this methodology to the synthesis of the corresponding indole congener **330** other extensions are also possible. For example, as depicted in Figure 6.9, it is envisaged that compound **445** would react with dibromocarbene to

afford tribromide **446**, which could be converted into cyclisation precursors **447** and **448** upon treatment with pyrrole (**141**) and indole (**128**), respectively. It is anticipated that spirocycles such as **449** and **450** could then be obtained by reaction of compounds **447** and **448** with silver tetrafluoroborate.

Figure 6.9: Extension to Spirocyclic Systems



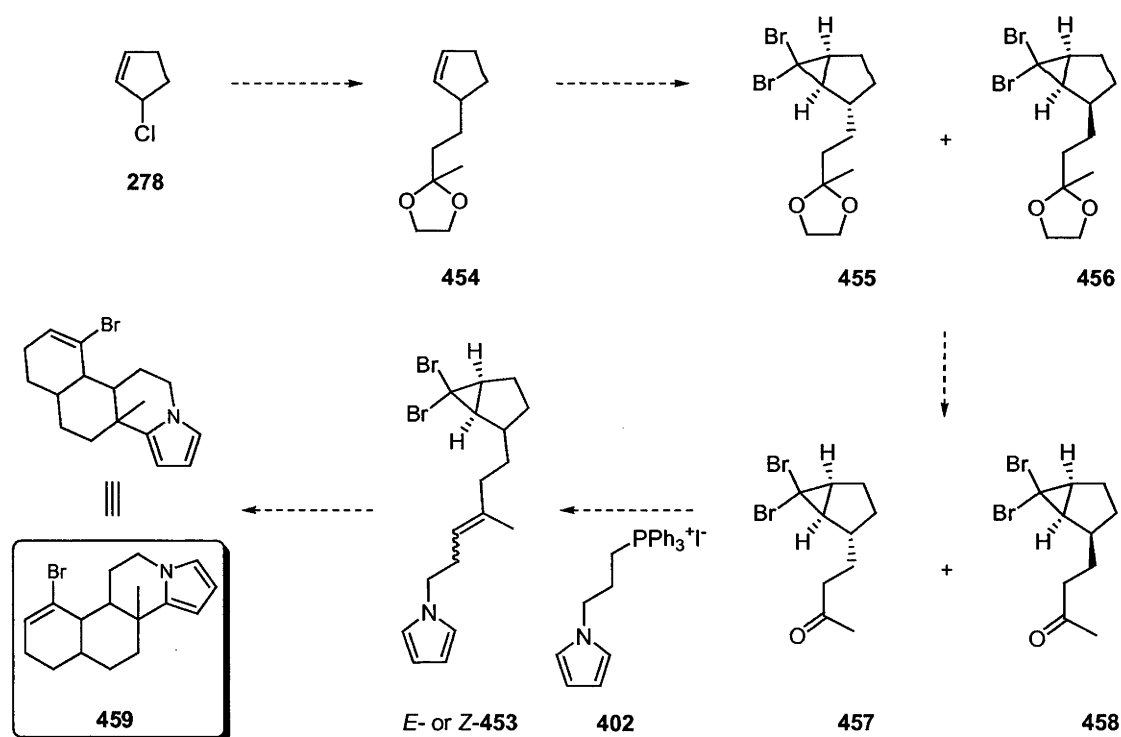
The interest in compounds **449** and **450** again arises from their structural similarities to various natural products. For example, it is envisaged that product **449** could be exploited in the construction of compounds such as the biologically significant lycopodium alkaloid 13-deoxyserratine (**451**), whilst the imidazole analogue of substrate **449** could be treated with a silver(I)-salt and elaborated in a straightforward fashion to the unusual natural product nitrabirine (**452**).



6.4 Possibilities for Future Work Arising from the Research Described in Chapter Five

Chapter Five detailed the establishment of an efficient route to compound **393**. As noted earlier, studies on the cyclisation of this material have been inconclusive in determining whether or not the azasteroid framework **392** can be obtained *via* the anticipated cationic cascade. The primary objective of future work in this area, therefore, will be repetition of such cyclisation studies and analysis of the product(s) so-obtained. If such studies do not deliver target **392** then enhancing the nucleophilicity of the double bond linking the pyrrole and cyclopropane substructures will be investigated. In particular, and as illustrated in Figure 6.10, the methyl-substituted analogue, **453**, of compound **393**, could be prepared by the route indicated and subsequently subjected to reaction with silver tetrafluoroborate.

Figure 6.10: Strategy for the Synthesis of Alternative Cyclisation Precursor **453**



6.5 Conclusions

Based on the foregoing proposals, there would appear to be an extensive array of possibilities for exploiting *gem*-dibromocyclopropanes in the construction of alkaloid and related frameworks. As such it is quite clear that the application of these novel three-membered ring-containing building blocks has a rich future. Not only has this Chapter served to further emphasise the potential of this methodology but it has also highlighted some of the prospective applications of this research in the field of total synthesis. Undoubtedly one of the highlights presented above is the possibility that exists for the rapid construction of key sub-targets associated with a range of structurally and biologically interesting natural products.

6.6 References

- ¹ Wolfe, J.P., Buchwald, S.L.; *Tetrahedron Lett.*, **1997**, *38*, 6359-6362.
- ² Henry Jr, K.J., Grieco, P.A., DuBay, W.J.; *Tetrahedron Lett.*, **1996**, *37*, 8289-8292.
- ³ Kiskürek, M.V., Leeuwenberg, A.J.M., Heese, M.; in *Alkaloids: Chemical and Biological Perspectives*, Pelletier, S.W. (Ed.), John Wiley & Sons: New York, **1983**, Chapter 5.
- ⁴ Shono, T., Matsumura, Y., Tsubata, K., Sugihara, Y., Tamane, S., Kanazawa, T., Aoki, T.; *J. Am. Chem. Soc.*, **1982**, *104*, 6697-6703.
- ⁵ Harris, M., Besselièvre, R., Grierson, D.S., Husson, H.P.; *Tetrahedron Lett.*, **1981**, *22*, 331-334.
- ⁶ Tanaka, K., Katsumura, S.; *J. Am. Chem. Soc.*, **2002**, *124*, 9660-9661.
- ⁷ Huang, H., Forsyth, C.J.; *Tetrahedron*, **1997**, *53*, 16341-16348.
- ⁸ Bonadies, F., Cardilli, A., Lattanzi, A., Orielli, L.R., Scettri, A.; *Tetrahedron Lett.*, **1994**, *35*, 3383-3386.
- ⁹ Yang, Z., Lorenz, J.C., Shi, Y.; *Tetrahedron Lett.*, **1998**, *39*, 8621-8624.
- ¹⁰ Hurt, C.R., Lin, R., Rapoport, H.; *J. Org. Chem.*, **1999**, *64*, 225-233.
- ¹¹ Teranishi, K., Hayashi, S., Nakatsuka, S., Goto, T.; *Synthesis*, **1995**, *5*, 506-508.

Experimental Procedures Associated with Work Described in Chapters Two to Five

7.1 General Procedures

Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. In certain cases, either a Varian Inova 500 spectrometer, operating at 500 MHz for proton and 125 MHz for carbon, or a Varian Inova 600 spectrometer, operating at 600 MHz for proton and 150 MHz for carbon, was used. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuteriochloroform (CDCl_3) at 20 °C unless stated otherwise. For ^1H NMR spectra recorded in this solvent, the peak due to residual CHCl_3 (δ 7.26) was used as the internal reference. ^1H NMR data are presented as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral], where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The central peak (δ 77.0) of the CDCl_3 triplet was used as the internal reference for proton-decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra the data are presented as follows: chemical shift (δ) (protonicity), where protonicity is defined as: C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl. The assignment of signals observed in various NMR spectra were often assisted by conducting attached proton test (APT), homonuclear ($^1\text{H}/^1\text{H}$) correlation spectroscopy (COSY) and/or heteronuclear ($^1\text{H}/^{13}\text{C}$) correlation spectroscopy (HETCOR) experiments.

Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer Spectrum *One* instrument. Samples were analysed as KBr disks (for solids) or as thin films on KBr plates (for liquids/oils).

Low and high resolution mass spectra were recorded on a VG Fisons AutoSpec three sector (E/B/E) double-focussing mass spectrometer using, unless otherwise specified, positive-ion electron impact techniques at the voltages indicated. Low resolution electrospray mass spectra were obtained on a VG Quattro II triple quadrupole MS instrument operating in the positive ion mode. GC-MS analyses was conducted on an Agilent/HP 6890/5973 GC-MS spectrometer. Mass spectral data are listed as follows: mass-to-charge ratio (m/z), assignment (where possible) and intensity [relative to the base peak – (100%)].

Optical rotations were measured with a Perkin-Elmer 241 polarimeter at the sodium D-line (589 nm) using the spectroscopic grade solvents specified at 20 °C and at concentrations (c) (g/100 mL) indicated. The measurements were carried out in a cell with a path length (l) of 1 dm. Specific rotations $\{[\alpha]_D\}$ were calculated using the equation $[\alpha]_D = (100 \cdot \alpha) / (c \cdot l)$ and are given in $10^{-1} \cdot \text{deg} \cdot \text{cm}^2 \cdot \text{g}^{-1}$.

Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected.

Elemental analyses were performed by the Australian National University Microanalytical Services Unit based in the Research School of Chemistry, The Australian National University, Canberra, Australia.

Analytical thin layer chromatography (TLC) was conducted on glass-backed 2.5 x 7.5 cm silica gel 60 F₂₅₄ plates (Merck) and the chromatograms visualised under a 254 nm UV lamp and/or treated with an anisaldehyde/sulphuric acid/ethanol (3 mL : 4.5 mL : 200 mL) dip or, occasionally, with a phosphomolybdic acid/ceric sulfate/sulphuric acid/water (37.5 g : 7 g : 37.5 mL : 720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g : 20 g : 5 mL : 300 mL) dip, followed by heating. The retention factor (R_f) quoted is rounded to the nearest 0.1. Flash column chromatography was conducted using silica gel 60 (mesh size 0.040-0.063 mm) as the stationary phase and the analytical reagent (AR) grade solvents indicated. Preparative thin layer chromatography (PTLC) was conducted on glass-backed 20 x 20 cm silica gel 60 F₂₅₄ plates (Merck), of the thickness

specified. HPLC analysis and separations were performed on the instruments specified in the relevant entries associated with this Chapter.

Reactions requiring subjection to sonication conditions were carried out in a Branson 2200 sonicator with a 60 W power output and 47 kHz operating frequency. In accordance with previous reports in the literature,¹ the water level of the sonicator bath was kept equivalent to that of the reaction mixture throughout. In all cases the reaction flask was positioned directly above the emitter and *ca.* 0.5 cm from the base of the sonicator bath.

Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied or, in the case of some liquids, distilled. Drying agents and other inorganic salts were purchased from AJAX or BDH Chemicals. Reactions employing air- and/or moisture-sensitive reagents and intermediates were carried out under an atmosphere of dry, oxygen-free nitrogen in flame-dried apparatus.

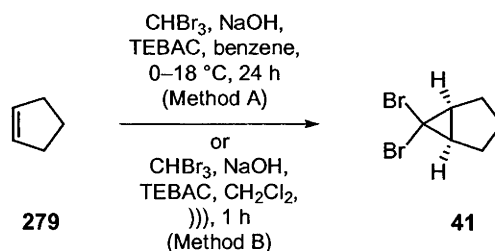
Room temperature is assumed to be *ca.* 18 °C.

Tetrahydrofuran (THF) and diethyl ether were dried using sodium metal and then distilled, as required, from sodium benzophenone ketyl. Methanol (MeOH) was distilled from magnesium methoxide. Benzene, toluene, dichloromethane (CH₂Cl₂) and hexane were distilled from calcium hydride. Ethylene glycol dimethyl ether (DME) was heated at reflux over calcium hydride and then distilled, as required, from sodium benzophenone ketyl. *N,N*-dimethylformamide (DMF) was heated at reflux over calcium hydride for 16 h then distilled and stored over 3Å molecular sieves.

Organic solutions obtained from work-up of reaction mixtures were dried with magnesium sulfate (MgSO₄) or sodium sulfate (Na₂SO₄), as specified. Organic solutions were concentrated under reduced pressure on a rotary evaporator with the temperature of the water bath generally not exceeding 40 °C.

7.2 Experimental Section for Chapter Two

6,6-Dibromobicyclo[3.1.0]hexane (**41**)



Method A:

Sodium hydroxide (75 mL of a 50% w/v aqueous solution) was added to a vigorously stirred solution of cyclopentene (**279**) (18.6 mL, 14.3 g, 0.21 mol), benzyltriethylammonium chloride (190 mg, 0.83 mmol) and bromoform (30 mL, 87.0 g, 0.34 mol) in benzene (45 mL) which was maintained at *ca.* 0 °C (ice-water bath). After the addition was complete the reaction mixture was placed under a nitrogen atmosphere and allowed to warm to room temperature over a period of several hours. After 8 hours a further aliquot of sodium hydroxide (10 mL of a 50% w/v aqueous solution) was added and stirring continued for an additional 16 hours. The reaction mixture was then partitioned between hexane (100 mL) and brine (100 mL) and the resulting phases separated. The aqueous layer was extracted with additional ethyl acetate (3 x 66 mL) and the combined organic fractions washed with brine (1 x 100 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure to provide an orange-brown oil. Vacuum distillation of this material afforded the title compound **41** (45.3 g, 90%) as a clear, colourless oil, b.p. 54–56 °C/4 mmHg (lit.² b.p. 63 °C/2.9 mmHg).

Method B:

A flask containing a suspension of powdered sodium hydroxide (17.6 g, 0.44 mol), benzyltriethylammonium chloride (300 mg, 1.40 mmol), cyclopentene (**279**) (6.5 mL, 5.0 g, 70 mmol) and bromoform (12.3 mL, 35.4 g, 0.14 mol) in dichloromethane (42 mL) was fitted with a reflux condenser and subjected to sonication without external temperature control.

After 1 hour TLC analysis indicated that the reaction had reached completion. Consequently, a small amount of Celite™ was added to the reaction mixture and the ensuing suspension then filtered through a 1 cm plug of Celite™ which was washed with CH₂Cl₂ (300 mL). Concentration of the combined filtrates provided a brown oil that was subjected to flash column chromatography (silica, hexane elution). Concentration of the appropriate fractions (*R_f* = 0.7) then delivered the title cyclopropane **41**² (16.1 g, 96%) as a clear, colourless oil. This material was spectroscopically identical to that prepared *via* Method A.

¹H NMR (300 MHz) δ 2.24 (m, 2H), 2.10-1.99 (complex m, 2H), 1.93-1.84 (complex m, 2H), 1.78-1.69 (complex m, 2H).

¹³C NMR (75 MHz) δ 40.5 (C), 39.6 (2 x CH, overlapping), 29.2 (2 x CH₂, overlapping), 25.7 (CH₂).

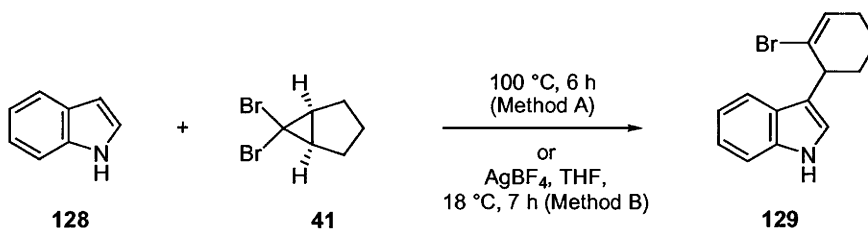
IR (neat) ν_{\max} 3030, 2952, 2930, 2860, 1467, 1441, 1318, 1285, 1227, 1189, 1074, 1005, 970, 889, 745, 639 cm⁻¹.

Mass Spectrum (EI, 70 eV) *m/z* 242, 240 and 238 [M⁺, 3, 6 and 3%], 201, 199 and 197 (10, 20 and 10), 161 and 159 [(M-Br)⁺, 31 and 33], 80 (32), 79 (100), 57 (17).

HRMS Found M⁺, 239.8958. C₆H₈⁸¹Br₂ requires M⁺, 239.8972.

Found M⁺, 237.8994. C₆H₈⁷⁹Br₂ requires M⁺, 237.8993.

3-(2-Bromocyclohex-2-enyl)-1*H*-indole (**129**)



Method A:

A magnetically stirred mixture of 6,6-dibromobicyclo[3.1.0]hexane (**41**) (1.0 g, 4.17 mmol) and indole (**128**) (480 mg, 4.17 mmol) was heated at 100 °C for 6 hours in a flask fitted with an air condenser. The resulting dark-purple and viscous reaction mixture was cooled and then subjected to flash column chromatography (silica, 1:4 v/v dichloromethane/hexane elution). Concentration of the appropriate fractions ($R_f = 0.2$) then afforded the *title compound 129* (890 mg, 77%) as a clear, colourless oil.

Method B:

Silver tetrafluoroborate (1.6 g, 8.40 mmol) was added, in one portion, to a magnetically stirred solution of 6,6-dibromobicyclo[3.1.0]hexane (**41**) (1.0 g, 4.17 mmol) and indole (**128**) (480 mg, 4.17 mmol) in anhydrous THF (21 mL). The resulting solution was protected from light and then stirred at ambient temperature for 7 hours. After this time the reaction mixture was filtered through a plug of CeliteTM which was washed with ethyl acetate (250 mL). Concentration of the combined filtrates under reduced pressure provided a viscous and dark-maroon coloured solution that was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions ($R_f = 0.3$) afforded *product 129* (970 mg, 84%) as a clear, colourless oil. This material was identical, in all respects, with that obtained *via* Method A.

¹H NMR (300 MHz) δ 8.02 (broad s, 1H, NH), 7.62 (d, $J = 7.8$ Hz, 1H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.22 (t, $J = 7.8$ Hz, 1H), 7.14 (t, $J = 7.8$ Hz, 1H), 7.03 (s, 1H), 6.32 (t, $J = 3.9$ Hz, 1H), 4.02 (broad s, 1H), 2.23-2.18 (complex m, 2H), 2.14-2.06 (complex m, 2H), 1.69-1.56 (complex m, 2H).

¹³C NMR (75 MHz) δ 136.4 (C), 130.9 (CH), 126.4 (C), 124.7 (C), 122.8 (CH), 121.9 (CH), 119.3 (CH), 118.7 (CH), 117.4 (C), 111.3 (CH), 41.2 (CH), 31.3 (CH₂), 29.7 (CH₂), 27.7 (CH₂).

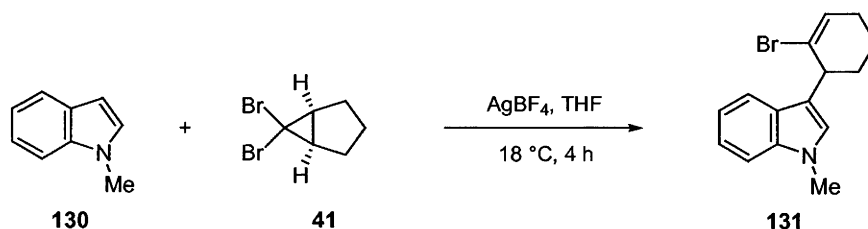
IR (neat) ν_{\max} 3416, 3051, 2926, 2854, 1643, 1510, 1458, 1335, 1308, 1215, 1149, 1091, 984, 895, 846, 739 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 277 and 275 [$\text{M}^{+\cdot}$, 52 and 54%], 249 and 247 (both 8), 196 [$(\text{M}-\text{Br})^{+\cdot}$, 28], 168 (57), 130 (16), 117 (100).

HRMS Found $\text{M}^{+\cdot}$, 277.0291. Calculated for $\text{C}_{14}\text{H}_{14}^{81}\text{BrN}$ $\text{M}^{+\cdot}$, 277.0289.

Found $\text{M}^{+\cdot}$, 275.0308. Calculated for $\text{C}_{14}\text{H}_{14}^{79}\text{BrN}$ $\text{M}^{+\cdot}$, 275.0310.

1-Methyl-3-(2-bromocyclohex-2-enyl)-1*H*-indole (**131**)



A magnetically stirred solution of 6,6-dibromobicyclo[3.1.0]hexane (**41**) (200 mg, 0.83 mmol), 1-methylindole (**130**) (110 mg, 0.83 mmol) and silver tetrafluoroborate (320 mg, 1.67 mmol) in anhydrous THF (8 mL) was protected from light and stirred at room temperature under a nitrogen atmosphere for 4 hours. The ensuing mixture was then filtered through a plug of CeliteTM which was washed with ethyl acetate (60 mL). Concentration of the combined filtrates under reduced pressure provided an orange-red oil that was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions ($R_f = 0.6$) then afforded *compound 131* (210 mg, 87%) as a clear, colourless oil.

¹**H NMR** (300 MHz) δ 7.63 (d, $J = 7.8$ Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 1H), 7.26 (t, $J = 7.8$ Hz, 1H), 7.14 (t, $J = 7.8$ Hz, 1H), 6.91 (s, 1H), 6.32 (dt, $J = 3.9$ and 0.9 Hz, 1H), 4.03 (broad s, 1H), 3.79 (s, 3H), 2.23-2.18 (complex m, 2H), 2.13-2.02 (complex m, 2H), 1.67-1.56 (complex m, 2H).

^{13}C NMR (75 MHz) δ 137.2 (C), 130.8 (CH), 127.5 (CH), 126.9 (C), 124.8 (C), 121.5 (CH), 118.8 (CH), 118.7 (CH), 115.9 (C), 109.3 (CH), 41.1 (CH), 32.7 (CH₃), 31.5 (CH₂), 27.7 (CH₂), 17.7 (CH₂).

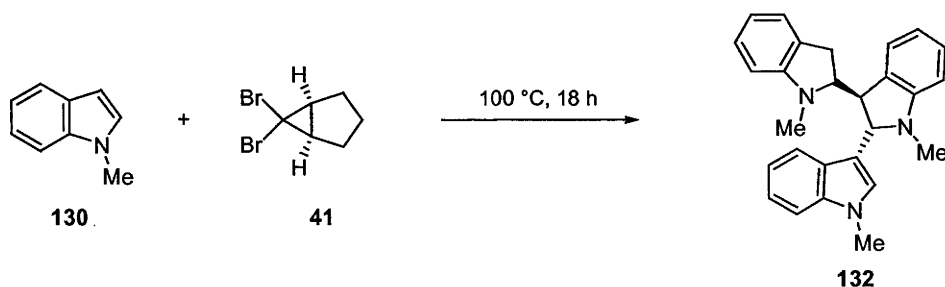
IR (neat) ν_{max} 3052, 2934, 2875, 2834, 1641, 1615, 1548, 1472, 1424, 1374, 1329, 1233, 1203, 1154, 982, 738 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 291 and 289 [$\text{M}^{+\cdot}$, both 55%], 263 and 261 (both 23), 210 [$(\text{M}-\text{Br})^{+\cdot}$, 36], 182 (54), 167 (40), 157 (18), 139 (18), 131 (100), 115 (20), 105 (8), 91 (25), 77 (25).

HRMS Found $\text{M}^{+\cdot}$, 291.0450. $\text{C}_{15}\text{H}_{16}^{81}\text{BrN}$ requires $\text{M}^{+\cdot}$, 291.0446.

Found $\text{M}^{+\cdot}$, 289.0470. $\text{C}_{15}\text{H}_{16}^{79}\text{BrN}$ requires $\text{M}^{+\cdot}$, 289.0466.

1-Methyl-3-[(2*SR*,3*RS*)-1-methyl-3-(1-methylindolin-2-yl)indolin-2-yl]-1*H*-indole (132)



A round-bottomed flask containing a magnetically stirred solution of 6,6-dibromobicyclo[3.1.0]hexane (**41**) (500 mg, 2.08 mmol) and 1-methylindole (**130**) (0.5 mL, 500 mg, 3.81 mmol) was fitted with an air condenser and calcium chloride drying tube and heated at 100 °C for 18 hours. The cooled reaction mixture was subjected to flash column chromatography (silica, 1:4 v/v dichloromethane/hexane elution). Concentration of the appropriate fractions ($R_f = 0.3$) under reduced pressure then delivered the *title compound* **132** (390 mg, 79%) as a clear, colourless oil.

$^1\text{H NMR}$ (300 MHz) δ 7.60 (dq, $J = 7.8$ and 0.6 Hz, 1H), 7.29-7.07 (complex m, 7H), 6.97-6.92 (complex m, 2H), 6.66 (s, 1H), 6.60 (dt, $J = 7.2$ and 1.2 Hz, 1H), 6.49 (dd, $J = 7.8$ and 1.2 Hz, 1H), 4.67 (t, $J = 7.2$ Hz, 1H), 3.87-3.75 (complex m, 1H), 3.69 (s, 3H), 3.46-3.28 (complex m, 3H), 3.37 (s, 3H), 2.40 (s, 3H).

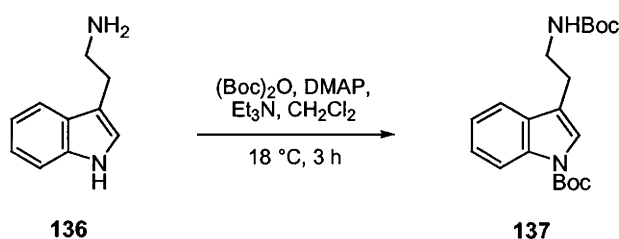
$^{13}\text{C NMR}$ (75 MHz) δ 143.5 (C), 137.3 (C), 136.9 (C), 130.1 (CH), 127.5 (C), 127.4 (CH), 126.9 (CH), 126.6 (C), 121.7 (C), 121.6 (CH), 120.7 (CH), 120.0 (CH), 119.1 (CH), 119.0 (CH), 118.9 (2 x CH), 116.2 (C), 109.0 (CH), 108.8 (CH), 98.7 (CH), 37.8 (CH₃), 35.1 (CH₃), 32.8 (CH₃), 32.0 (CH), 31.7 (CH), 31.1 (CH), 29.6 (CH₂).

IR (neat) ν_{max} 3409, 3049, 2930, 2812, 1604, 1584, 1509, 1468, 1424, 1371, 1328, 1313, 1264, 1154, 1131, 1013, 741 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 393 [M^+ , 22%], 273 (100), 257 (18), 217 (10), 144 (16).

HRMS Found M^+ , 393.2209. $\text{C}_{27}\text{H}_{27}\text{N}_3$ requires M^+ , 393.2205.

tert-Butyl 2-[1-(*tert*-butoxycarbonyl)-indol-3-yl]ethylcarbamate (**137**)



Di-*tert*-butyl dicarbonate (1.3 g, 5.76 mmol), DMAP (700 mg, 5.76 mmol) and triethylamine (0.8 mL, 580 mg, 5.76 mmol) were added to a magnetically stirred solution of tryptamine (**136**) (500 mg, 1.92 mmol) in anhydrous CH₂Cl₂ (10 mL). The resultant orange solution was then stirred under a nitrogen atmosphere at 18 °C for 3 hours before being poured into brine (30 mL). The separated aqueous phase was extracted with CH₂Cl₂ (1 x 40 mL) and the combined organic fractions washed with brine (1 x 50 mL) before being dried (MgSO₄),

filtered and concentrated under reduced pressure to afford a yellow oil. This material was then subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.2$) provided the desired product **137**³ (650 mg, 94%) as a pale-cream flaky solid, m.p. 95-97 °C.

¹H NMR (300 MHz) δ 8.14 (d, $J = 7.2$ Hz, 1H), 7.54 (d, $J = 7.2$ Hz, 1H), 7.42 (s, 1H), 7.32 (dt, $J = 7.2$ and 1.2 Hz, 1H), 7.23 (dt, $J = 7.2$ and 1.2 Hz, 1H), 4.75 (broad s, 1H, NH), 3.46 (q, $J = 6.3$ Hz, 2H), 2.89 (t, $J = 6.6$ Hz, 2H), 1.67 (s, 9H, 3 x CH₃), 1.44 (s, 9H, 3 x CH₃).

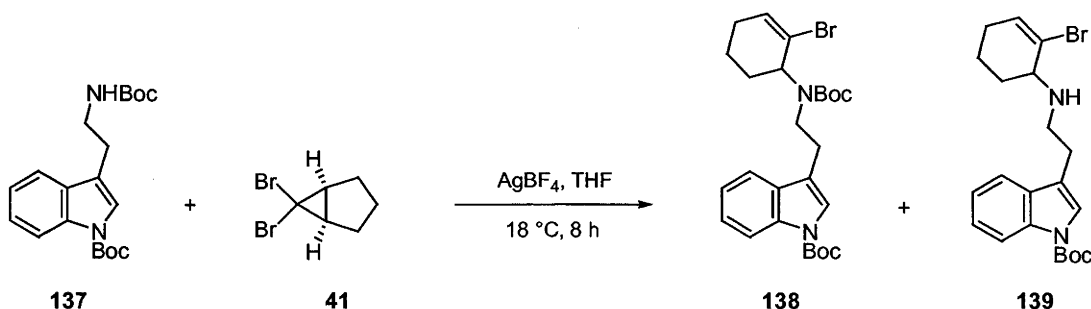
¹³C NMR (75 MHz) δ 155.8 (C), 149.6 (C), 135.5 (C), 130.3 (C), 124.3 (CH), 123.0 (CH), 122.4 (CH), 118.9 (CH), 117.7 (CH), 115.2 (C), 83.4 (C), 79.1 (C), 40.1 (CH₂), 31.5 (CH₂), 28.3 (3 x CH₃), 28.1 (3 x CH₃).

IR (neat) ν_{\max} 3366, 2978, 2932, 1732, 1514, 1454, 1381, 1368, 1308, 1254, 1162, 1091, 768, 746 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 360 [M^+ , 10%], 259 (4), 248 (5), 230 (3), 204 (22), 187 (22), 174 (8), 159 (5), 143 (36), 130 (83), 57 (100).

HRMS Found M^+ , 360.2052. C₂₀H₂₈N₂O₂ requires M^+ , 360.2049.

***tert*-Butyl 2-[1-(*tert*-butoxycarbonyl)-indol-3-yl]ethyl-2-bromocyclohex-2-enyl carbamate (138) and *tert*-Butyl 3-[2-(2-bromocyclohex-2-enylamino)ethyl]-indole-1-carboxylate (139)**



Silver tetrafluoroborate (320 mg, 1.67 mmol) was added to a magnetically stirred solution of 6,6-dibromobicyclo[3.1.0]hexane (**41**) (200 mg, 0.84 mmol) and carbamate **137** (300 mg, 0.84 mmol) in anhydrous THF (8 mL). The resulting grey solution was protected from light and then allowed to stir at ambient temperatures for 8 hours. After this time, the reaction mixture was filtered through a plug of CeliteTM that was washed with ethyl acetate (60 mL). The combined filtrates were concentrated under reduced pressure to provide a dark-yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f = 0.5$) afforded the *title compound 138* (270 mg, 63%) as a yellow oil.

¹H NMR (300 MHz) δ 8.13 (broad d, $J = 7.2$ Hz, 1H), 7.54 (d, $J = 7.2$ Hz, 1H), 7.42 (s, 1H), 7.32 (dt, $J = 7.2$ and 1.5 Hz, 1H), 7.26 (dt, $J = 7.2$ and 0.9 Hz, 1H), 6.20 (t, $J = 3.9$ Hz, 1H), 4.67 (broad s, 1H), 3.46 (q, $J = 6.6$ Hz, 2H), 2.89 (t, $J = 6.6$ Hz, 2H), 2.21-1.84 (complex m, 4H), 1.82-1.50 (complex m, 2H), 1.67 (s, 9H, 3 x CH₃), 1.44 (s, 9H, 3 x CH₃).

¹³C NMR (75 MHz) δ 155.9 (C), 149.7 (C), 135.5 (C), 132.5 (CH), 130.4 (C), 124.4 (CH), 123.1 (C), 122.4 (CH), 118.9 (CH), 117.7 (CH), 115.2 (C), 114.0 (CH), 83.5 (C), 79.2 (C), 69.8 (CH), 40.1 (CH₂), 34.2 (CH₂), 33.8 (CH₂), 31.9 (CH₂), 30.2 (3 x CH₃, overlapping), 27.7 (3 x CH₃, overlapping), 25.5 (CH₂).

IR (neat) ν_{\max} 3370, 2921, 2855, 1732, 1513, 1454, 1368, 1308, 1254, 1161, 1091, 1017, 858, 767, 746 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 520 and 518 [M^+ , both <1%], 464 and 462 [($M-C_4H_8$)⁺, both <1], 360 (62), 304 (12), 260 (30), 248 (38), 204 (94), 187 (96), 174 (45), 159 (25), 143 (88), 130 (86), 102 (15), 77 (14), 57 (85), 41 (86).

HRMS Found ($M-C_4H_8$)⁺, 462.1156. Calculated for C₂₂H₂₇⁷⁹BrN₂O₄ ($M-C_4H_8$)⁺, 462.1154.

Concentration of fraction B ($R_f = 0.4$) furnished the *title compound 139* (50 mg, 15%) as a yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 8.14 (broad d, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 7.5$ Hz, 1H), 7.43 (s, 1H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 6.32 (t, $J = 3.9$ Hz, 1H), 5.32 (broad s, 1H), 3.58-3.50 (complex m, 2H), 2.94 (t, $J = 6.6$ Hz, 2H), 2.19-1.84 (complex m, 5H), 1.67 (s, 9H, 3 x CH_3), 1.65-1.60 (complex m, 1H).

$^{13}\text{C NMR}$ (75 MHz) δ 155.8 (C), 135.0 (CH), 130.3 (C), 124.8 (C), 124.5 (CH), 123.3 (CH), 122.5 (CH), 120.5 (C), 118.9 (CH), 117.4 (C), 115.3 (CH), 83.5 (C), 71.7 (CH), 40.6 (CH_2), 31.9 (CH_2), 30.3 (CH_2), 28.9 (3 x CH_3 , overlapping), 27.5 (CH_2), 25.5 (CH_2).

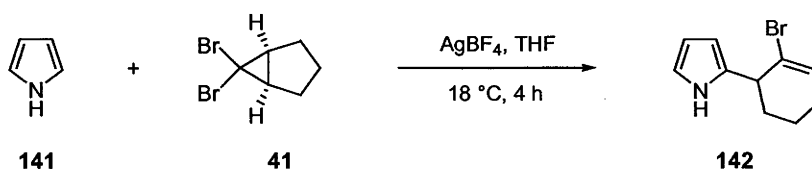
IR (neat) ν_{max} 3352, 2926, 2854, 1730, 1519, 1454, 1381, 1255, 1160, 1091, 746 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 420 and 418 [M^+ , both <1%], 364 and 362 [$(\text{M}-\text{C}_4\text{H}_8)^+$, both <1], 327 (40), 316 (10), 264 and 262 (both 20), 247 (11), 203 (35), 187 (23), 174 (10), 159 (42), 143 (68), 130 (90), 111 (45), 97 (45), 83 (31), 69 (30), 57 (100), 43 (47).

HRMS Found M^+ , 420.1248. $\text{C}_{21}\text{H}_{27}^{81}\text{BrN}_2\text{O}_2$ requires M^+ , 420.1235.

Found M^+ , 418.1266. $\text{C}_{21}\text{H}_{27}^{79}\text{BrN}_2\text{O}_2$ requires M^+ , 418.1256.

2-(2-Bromocyclohex-2-enyl)-1H-pyrrole (**142**)



Silver tetrafluoroborate (320 mg, 1.67 mmol) was added, in one portion, to a magnetically stirred solution of pyrrole (**141**) (58 μL , 560 mg, 0.84 mmol) and 6,6-dibromobicyclo[3.1.0]hexane (**41**) (200 mg, 0.84 mmol) in anhydrous THF (8 mL). Upon addition of the silver(I)-salt the originally clear pale-yellow solution immediately became

cloudy. The reaction mixture was then protected from light and stirred at 18 °C under a nitrogen atmosphere for 4 hours. The resulting purple and highly-viscous reaction mixture was then filtered through a plug of Celite™ that was washed with ethyl acetate (60 mL). Concentration of the filtrate under reduced pressure gave a purple oil that was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions ($R_f = 0.4$) then afforded the *title compound 142* (170 mg, 90%) as a clear, colourless oil.

¹H NMR (300 MHz) δ 8.10 (broad s, 1H, NH), 6.72 (t, $J = 1.2$ Hz, 1H), 6.27 (t, $J = 4.2$ Hz, 1H), 6.27 (d, $J = 2.4$ Hz, 1H), 6.03 (s, 1H), 3.74 (s, 1H), 2.20-1.90 (complex m, 4H), 1.66-1.62 (complex m, 2H).

¹³C NMR (75 MHz) δ 132.9 (CH), 131.6 (C), 123.2 (C), 116.6 (CH), 108.4 (CH), 106.0 (CH), 42.9 (CH), 32.2 (CH₂), 27.6 (CH₂), 18.2 (CH₂).

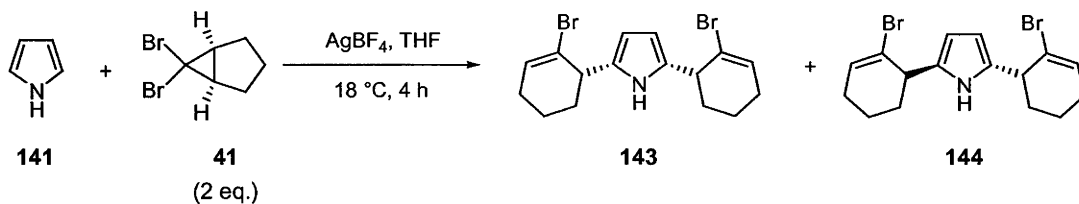
IR (CH₂Cl₂) ν_{\max} 3418, 2935, 2860, 2835, 1674, 1645, 1563, 1444, 1429, 1350, 1330, 1279, 1116, 1094, 1027, 991, 936, 914, 889, 843, 762, 718 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 227 and 225 [M^+ , 40 and 41%], 198 and 196 (11 and 13), 160 and 158 (9 and 10), 146 [(M-Br)⁺, 37], 130 (15), 118 (86), 104 (22), 91 (29), 79 (58), 67 (100), 39 (45).

HRMS Found M^+ , 227.0135. C₁₀H₁₂⁸¹BrN requires M^+ , 227.0133.

Found M^+ , 225.0148. C₁₀H₁₂⁸¹BrN requires M^+ , 225.0153.

***d,l*-2,5-bis-(2-Bromocyclohex-2-enyl)-1*H*-pyrrole (143) and *meso*-2,5-bis-(2-Bromocyclohex-2-enyl)-1*H*-pyrrole (144)**



A magnetically stirred solution of 6,6-dibromobicyclo[3.1.0]hexane (**41**) (400 mg, 1.67 mmol) and pyrrole (**141**) (60 μ L, 56 mg, 0.84 mmol) in anhydrous THF (8 mL) was treated, in one portion, with silver tetrafluoroborate (320 mg, 1.67 mmol). The resulting mixture was protected from light and stirring continued under a nitrogen atmosphere for 4 hours. The ensuing purple-grey reaction mixture was then filtered through a plug of CeliteTM that was washed with ethyl acetate (60 mL). Concentration of the combined filtrates under reduced pressure delivered a green-brown oil that was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). In this manner two fractions, A and B, were obtained.

Concentration of fraction A ($R_f = 0.5$) furnished a 1:1 and inseparable mixture of the *illustrated products 143 and 144* (230 mg, 73%) as a clear, colourless oil.

¹H NMR (300 MHz) δ 7.94 (broad s, 2H, 2 x NH), 6.25 (m, 2H), 6.22-6.19 (complex m, 2H), 5.95 (dd, $J = 2.7$ and 0.9 Hz, 4H), 3.70 (m, 4H), 2.25-1.84 (complex m, 4H), 1.78-1.61 (complex m, 12H), 1.78-1.61 (complex m, 8H).

¹³C NMR (75 MHz) δ 131.7 (4 x CH), 131.4 (4 x C), 123.5 (2 x C), 123.4 (2 x C), 105.9 (4 x CH), 42.9 (2 x CH), 42.8 (2 x CH), 32.3 (2 x CH₂), 32.2 (2 x CH₂), 27.6 (2 x CH₂), 27.4 (2 x CH₂), 18.3 (4 x CH₂).

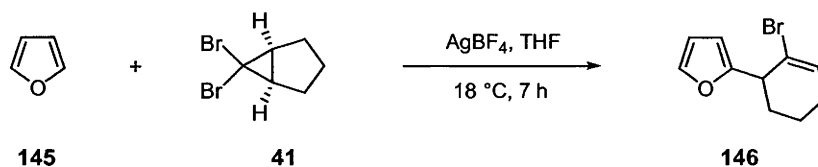
IR (CH₂Cl₂) ν_{\max} 3432, 3037, 2930, 2857, 1642, 1580, 1444, 1429, 1349, 1331, 1280, 1159, 1078, 1036, 979, 937, 914, 890, 843, 807, 765, 712, 638 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 387, 385 and 383 [M^+ , 48, 87 and 49%], 359, 357 and 355 (4, 10 and 5), 306 and 304 [$(M-Br)^+$, 25 and 27], 278 and 276 (both 8), 227 and 225 (62 and 63), 198 and 196 (21 and 20), 180 (13), 168 (26), 144 (38), 130 (21), 117 (89), 97 (98), 79 (100), 67 (38).

HRMS Found M^+ , 382.9886. Calculated for $C_{16}H_{19}^{79}Br_2N M^+$, 382.9884.

Concentration of fraction B ($R_f = 0.4$) afforded the mono-substituted *product 142* (19 mg, 10%) that was identical, in all respects, with authentic material.

2-(2-Bromocyclohex-2-enyl)furan (**146**)



A magnetically stirred solution of 6,6-dibromobicyclo[3.1.0]hexane (**41**) (200 mg, 0.84 mmol) and furan (**145**) (60 μL , 57 mg, 0.84 mmol) in anhydrous THF (8 mL) was treated with silver tetrafluoroborate (320 mg, 1.67 mmol), protected from light and stirred at ambient temperatures under a nitrogen atmosphere for 7 hours. The resulting mixture was then filtered through a plug of CeliteTM that was washed with ethyl acetate (60 mL). Concentration of the combined filtrates under reduced pressure then subjection of the resulting yellow oil to flash column chromatography (silica, hexane \rightarrow 1:19 v/v ethyl acetate/hexane gradient elution) provided, after concentration of the relevant fractions ($R_f = 0.9$ in 1:19 v/v ethyl acetate/hexane), the *title compound 146* (150 mg, 83 %) as a clear, colourless oil.

¹H NMR (300 MHz) δ 7.34 (dd, $J = 2.1$ and 0.9 Hz, 1H), 6.33 (dd, $J = 3.3$ and 0.9 Hz, 1H), 6.28 (dt, $J = 3.9$ and 1.2 Hz, 1H), 6.15 (dt, $J = 3.3$ and 0.9 Hz, 1H), 3.75 (broad s, 1H), 2.23-2.10 (complex m, 2H), 2.07-1.94 (complex m, 2H), 1.69-1.58 (complex m, 2H).

^{13}C NMR (75 MHz) δ 155.7 (C), 141.4 (CH), 131.8 (CH), 121.5 (C), 110.1 (CH), 106.9 (CH), 43.4 (CH), 30.1 (CH_2), 27.5 (CH_2), 17.9 (CH_2).

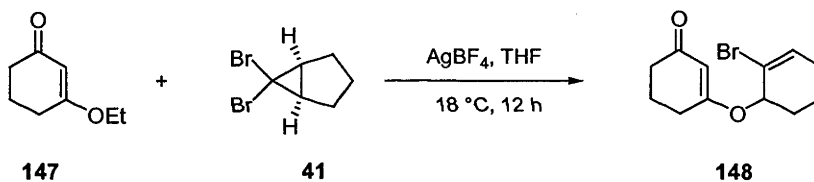
IR (CH_2Cl_2) ν_{max} 3372, 2926, 2855, 1712, 1456, 1377, 1260, 1186, 1081, 1057 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 228 and 226 [M^+ , 79 and 80%], 200 and 198 (both 24), 160 and 158 (67 and 69), 147 [$(\text{M}-\text{Br})^+$, 100], 129 (21), 119 (60), 105 (15), 91 (90), 79 (76), 65 (37).

HRMS Found M^+ , 227.9969. Calculated for $\text{C}_{10}\text{H}_{11}^{81}\text{BrO}$ M^+ , 227.9973.

Found M^+ , 225.9991. Calculated for $\text{C}_{10}\text{H}_{11}^{79}\text{BrO}$ M^+ , 225.9993.

3-(2-Bromocyclohex-2-enyloxy)cyclohex-2-enone (148)



A magnetically stirred solution of 6,6-dibromobicyclo[3.1.0]hexane (**41**) (200 mg, 0.84 mmol) and 2-ethoxy-2-cyclohexen-1-one (**147**) (0.1 mL, 120 mg, 0.84 mmol) in anhydrous THF (8 mL) was treated, in one portion, with silver tetrafluoroborate (320 mg, 1.67 mmol). The resulting suspension was immediately protected from light and stirring continued at ambient temperatures under a nitrogen atmosphere for 12 hours. The reaction mixture was then filtered through a plug of CeliteTM that was washed with ethyl acetate (60 mL). After concentration of the combined filtrates under reduced pressure the resulting light-yellow oil was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A ($R_f = 0.3$) furnished the starting enone **147** (48 mg, 40%). This material was identical, in all respects, to an authentic sample.

Concentration of fraction B ($R_f = 0.3$) afforded the *title compound 148* (110 mg, 46% - at 60% conversion) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 6.40 (dd, $J = 5.1$ and 3 Hz, 1H), 5.38 (s, 1H), 4.68 (broad s, 1H), 2.51-2.34 (complex m, 2H), 2.25-1.93 (complex m, 6H), 1.70-1.61 (complex m, 4H).

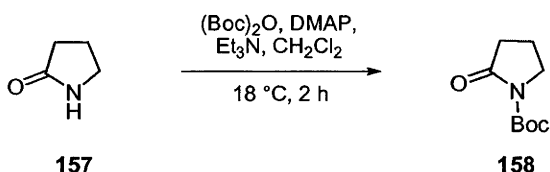
$^{13}\text{C NMR}$ (75 MHz) δ 200.1 (C), 176.8 (C), 135.9 (CH), 118.9 (C), 103.2 (CH), 75.6 (CH), 36.6 (CH₂), 28.3 (CH₂), 27.7 (CH₂), 27.5 (CH₂), 21.0 (CH₂), 16.7 (CH₂).

IR (neat) ν_{max} 3436, 2930, 2867, 1733, 1652, 1600, 1455, 1427, 1383, 1349, 1328, 1214, 1183, 1135, 1059, 996, 961, 918, 864, 825, 769, 745, 524 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 191 [(M-Br)⁺, 62%], 161 and 159 (both 40), 113 (60), 84 (26), 79 (100).

HRMS Found (M-Br)⁺, 191.1075. Calculated for C₁₂H₁₅O₂ (M-Br)⁺, 191.1072.

N-(*tert*-Butoxycarbonyl)-2-pyrrolidinone (**158**)



Di-*tert*-butyl dicarbonate (11.7 g, 54 mmol), DMAP (6.6 g, 54 mmol) and triethylamine (7.5 mL, 5.5 g, 54 mmol) were added to a magnetically stirred solution of 2-pyrrolidinone (**157**) (3.0 g, 36 mmol) in anhydrous CH₂Cl₂ (180 mL). The resulting orange solution was stirred under a nitrogen atmosphere at 18 °C for 2 hours before being poured into brine (200 mL) and extracted with CH₂Cl₂ (3 x 300 mL). The combined organic phases were washed with brine (1 x 500 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure to provide a yellow-coloured and oily solid. This material was subjected to flash column

chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.2$) delivered the title compound **158**⁴ (6.2 g, 93%) as a pale-yellow oil.

¹H NMR (300 MHz) δ 3.72 (t, $J = 7.2$ Hz, 2H), 2.48 (t, $J = 7.2$ Hz, 2H), 1.97 (quintet, $J = 7.2$ Hz, 2H), 1.49 (s, 9H, 3 x CH₃).

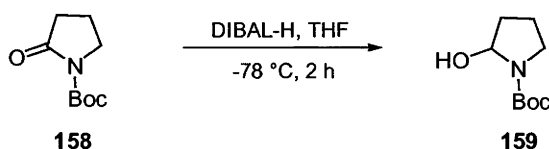
¹³C NMR (75 MHz) δ 173.9 (C), 149.6 (C), 82.0 (C), 46.0 (CH₂), 32.4 (CH₂), 27.5 (3 x CH₃), 16.9 (CH₂).

IR (neat) ν_{\max} 3610, 2980, 1785, 1752, 1713, 1459, 1422, 1368, 1314, 1258, 1153, 1044, 1019, 940, 892, 847, 814, 778, 756, 700, 638, 589 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 185 [M⁺, <1%], 170 [(M-CH₃)⁺, 1], 130 (48), 126 (12), 112 (50), 98 (10), 86 (45), 84 (16), 69 (27), 57 (100).

HRMS Found M⁺, 185.1048. C₉H₁₅NO₃ requires M⁺, 185.1052.

N-(*tert*-Butoxycarbonyl)-2-pyrrolidinol (**159**)



Using a modification of the procedure reported by Deiter and Sharma⁵ for the preparation of lactamols from Boc-protected lactams, DIBAL-H (49 mL of a 1 M solution in hexane, 49 mmol) was slowly added to a magnetically stirred solution of carbamate **158** (6.0 g, 30 mmol) in anhydrous THF (100 mL) which was maintained, under a nitrogen atmosphere at -78 °C (dry ice/acetone cooling bath). After 2 hours the reaction mixture was quenched, at -78 °C, by the sequential addition of NH₄Cl (150 mL of a saturated aqueous solution) and Na₂CO₃ (100 mL of a 10% w/v aqueous solution). Stirring was then continued at ambient temperature

for 20 minutes and then the ensuing cloudy-white reaction mixture was extracted with dichloromethane (3 x 300 mL). The combined organic fractions were washed with brine (1 x 500 mL), then dried (MgSO₄), filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.3$) afforded the title compound **159**⁶ (5.1 g, 90%) as a clear, colourless oil.

¹H NMR (300 MHz) δ 5.50-5.36 (complex m, 1H), 3.57-3.45 (complex m, 2H), 3.32-3.21 (complex m, 2H), 2.10-1.76 (complex m, 2H), 1.60 (broad s, 1H, OH), 1.50 (1.47) (s, 9H, 3 x CH₃, pair of rotamers).

¹³C NMR (75 MHz) δ 154.8 (C), 81.1 (81.0) (CH), 79.6 (79.9) (C), 45.6 (45.4) (CH₂), 32.6 (33.4) (CH₂), 28.2 (28.1) (3 x CH₃ – overlapping), 22.4 (21.7) (CH₂), (pair of rotamers).

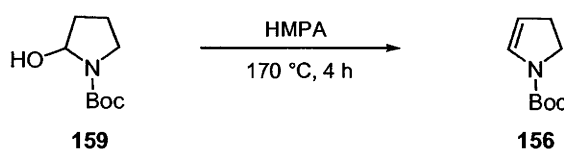
IR (neat) ν_{\max} 3432, 2977, 2884, 1703, 1685, 1478, 1395, 1367, 1299, 1256, 1165, 1126, 110, 1034, 988, 956, 916, 875, 774, 564 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 187 [M⁺, 2%], 186 [(M-H)⁺, 8], 170 [(M-HO)⁺, 43], 130 (72), 114 (92), 96 (7), 86 (10), 70 (90), 57 (100).

HRMS Found M⁺, 187.1204. C₉H₁₇NO₃ requires M⁺, 187.1208.

Found (M-H)⁺, 186.1130. C₉H₁₆NO₃ requires (M-H)⁺, 186.1130.

N-(*tert*-Butoxycarbonyl)-2-pyrroline (**156**)



Following the procedure of Mori *et al.*,⁶ hexamethylphosphoramide (27 mL) was added, *via* syringe, to lactamol **159** (1.0 g, 5.38 mmol) under a nitrogen atmosphere. The resulting

solution was then heated, in an oil bath, at 170 °C for 4 hours after which time TLC analysis indicated that the starting material had been consumed. Consequently the reaction mixture was allowed to cool to room temperature then NH₄Cl (80 mL of a saturated aqueous solution) was added. The separated aqueous layer was extracted with diethyl ether (4 x 150 mL) and the combined organic fractions then washed with NH₄Cl (4 x 150 mL of a saturated aqueous solution) before being dried (K₂CO₃), filtered and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f = 0.5) afforded the desired product **156**⁷ (720 mg, 79%, lit.⁷ 70%) as a clear, colourless oil.

¹H NMR (300 MHz) δ 6.45 (6.58) (broad s, 1H), 4.99 (broad d, *J* = 12.6 Hz, 1H), 3.75-3.64 (complex m, 2H), 2.67-2.56 (complex m, 2H), 1.47 (s, 9H, 3 x CH₃).

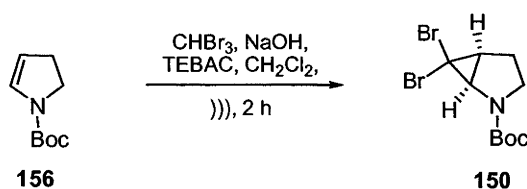
¹³C NMR (75 MHz) δ 151.8 (151.1) (C), 129.4 (CH), 107.0 (CH), 79.3 (C), 44.3 (44.8) (CH₂), 29.3 (CH₂), 28.0 (28.2) (3 x CH₃ – overlapping), (pair of rotamers).

IR (neat) ν_{max} 2977, 2931, 2864, 1703, 1618, 1478, 1451, 1411, 1366, 1351, 1256, 1224, 1180, 1134, 1091, 984, 883, 810, 762, 702 cm⁻¹.

Mass Spectrum (EI, 70 eV) *m/z* 170 [(M+H)⁺, 18%], 169 [M⁺, 53], 113 [(M-C₄H₈)⁺, 84], 96 (72), 84 (23), 69 (88), 68 (89), 57 (90), 49 (28), 41 (100), 39 (48).

HRMS Found (M+H)⁺, 170.1183. C₉H₁₆NO₂ requires (M+H)⁺, 170.1181.

tert-Butyl 6,6-Dibromo-2-aza-bicyclo[3.1.0]hexane-2-carboxylate (**150**)



Bromoform (0.4 mL, 1.2 g, 4.73 mmol) was added to a solution of enamine **156** (400 mg, 2.37 mmol), benzyltriethylammonium chloride (11 mg, 0.05 mmol) and finely ground sodium hydroxide (570 mg, 14 mmol) in CH₂Cl₂ (1.4 mL). The resulting dark-brown suspension was then sonicated without external temperature control. After 2 hours TLC analysis indicated that the reaction had reached completion and consequently a small amount of Celite™ was added to the reaction mixture. Filtration of the ensuing mixture through a 1 cm plug of Celite™ followed by washing of this plug with CH₂Cl₂ (25 mL) and concentration of the combined filtrates under reduced pressure afforded a dark-brown liquid. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (*R_f* = 0.4) then provided the *desired product 150* (480 mg, 60%) as a yellow oil and a *ca.* 4:1 mixture of rotamers (as judged by ¹H and ¹³C NMR analysis).

¹H NMR (300 MHz) δ (major rotamer) 3.72-3.52 (complex m, 2H), 2.34-1.94 (complex m, 4H), 1.47 (s, 9H, 3 x CH₃); δ (minor rotamer) 3.44-3.36 (complex m, 2H), 2.34-1.94 (complex m, 4H), 1.44 (s, 9H, 3 x CH₃).

¹³C NMR (75 MHz) δ (major rotamer) 154.9 (C), 80.4 (C), 49.1 (CH₂), 48.8 (CH), 36.1 (CH), 34.8 (C), 28.2 (3 x CH₃ – overlapping), 25.3 (CH₂); δ (minor rotamer) 154.0 (C), 80.3 (C), 49.0 (CH₂), 48.5 (CH), 35.7 (CH), 34.1 (C), 28.0 (3 x CH₃ – overlapping), 24.5 (CH₂).

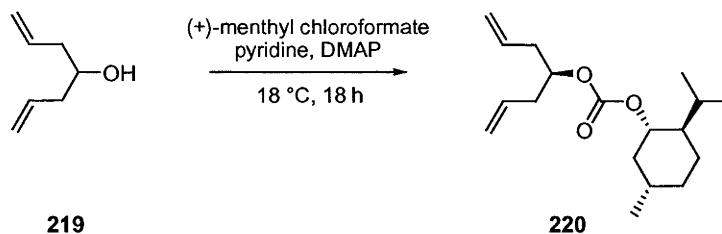
IR (neat) ν_{\max} 3396, 2976, 2932, 1704, 1477, 1455, 1393, 1367, 1343, 1288, 1254, 1163, 1125, 1082, 1058, 1022, 996, 909, 862, 784, 768, 709, 577, 519 cm⁻¹.

Mass Spectrum (EI, 70 eV) *m/z* 343, 341 and 339 [M⁺, all <1%], 297, 295 and 293 (3, 5 and 3), 262 and 260 [(M-Br)⁺, both 3], 240 and 238 (4 and 3), 206 and 204 (15 and 13), 162 and 160 (22 and 25), 118 and 116 (both 26), 80 (8), 57 (100), 41 (57).

HRMS Found [M-Br]⁺, 260.0283. C₁₀H₁₅⁷⁹BrNO₂ requires [M-Br]⁺, 260.0286.

7.3 Experimental Section for Chapter Three

Hepta-1,6-dien-4-yl (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl Carbonate (220)



(+)-Menthyl chloroformate (2.9 mL, 2.9 g, 13.0 mmol) and DMAP (110 mg, 0.89 mmol) were added to a magnetically stirred solution of alcohol **219** (1.2 mL, 1.0 g, 8.93 mmol) in pyridine (1.5 mL, 1.4 g, 18.0 mmol) maintained at 0 °C (ice/water bath) under a nitrogen atmosphere. The resulting dark-yellow solution was allowed to warm to room temperature and stirred magnetically for a further 18 hours during which time a cream precipitate formed. The entire reaction mixture was then subjected directly to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions ($R_f = 0.4$) then provided the *title carbonate* **220** (2.6 g, 98%) as a clear, colourless oil.

$^1\text{H NMR}$ (300 MHz) δ 5.72 (m, 2H), 5.10-5.00 (complex m, 4H), 4.80 (quintet, $J = 6.3$ Hz, 1H), 4.49 (dt, $J = 10.8$ and 4.5 Hz, 1H), 2.39-2.33 (complex m, 4H), 2.03 (m, 1H), 1.94 (dt, $J = 6.9$ and 2.7 Hz, 1H), 1.69-1.63 (complex m, 2H), 1.58 (complex m, 1H), 1.53-1.39 (complex m, 1H), 1.36 (t, $J = 2.7$ Hz, 1H), 1.10-0.97 (complex m, 2H), 0.91 (d, $J = 6.9$ Hz, 3H, CH₃), 0.88 (d, $J = 6.9$ Hz, 3H, CH₃), 0.77 (d, $J = 6.9$ Hz, 3H, CH₃).

$^{13}\text{C NMR}$ (75 MHz) δ 154.5 (C), 133.2 (overlapping signals, 2 x CH), 118.1 (CH₂), 118.0 (CH₂), 78.0 (CH), 76.0 (CH), 47.0 (CH), 40.7 (CH₂), 38.1 (2 x CH₂, overlapping), 34.1 (CH₂), 31.4 (CH), 26.0 (CH), 23.3 (CH₂), 21.9 (CH₃), 20.6 (CH₃), 16.2 (CH₃).

IR (neat) ν_{max} 3080, 2957, 2929, 2871, 1738, 1643, 1456, 1370, 1259, 1181, 981, 957, 917, 787 cm^{-1} .

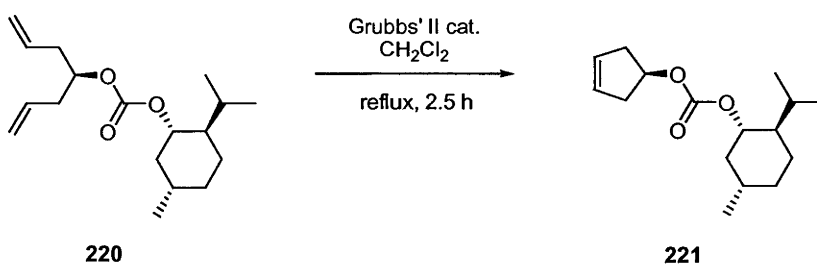
Mass Spectrum (EI, 70 eV) m/z 156 [(M-C₁₀H₁₈)⁺, 16%], 139 (77), 123 (26), 112 (78), 95 (63), 83 (100), 69 (50).

Mass Spectrum (ESI) m/z 317 [(M+Na)⁺, 10%], 295 [(M+H)⁺, 6], 157 (6), 139 (100), 95 (14), 83 (27), 57 (7).

HRMS Found (M-C₁₀H₁₈)⁺, 156.0787. Calculated for C₈H₁₂O₃ (M-C₁₀H₁₈)⁺, 156.0786.

Specific Rotation [α_D] + 53 (c 0.5, CHCl₃).

Cyclopent-3-enyl (1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl Carbonate (221)



A deoxygenated solution of diene **220** (2.5 g, 8.50 mmol) in anhydrous CH₂Cl₂ (85 mL) maintained under a nitrogen atmosphere was treated with Grubbs' II catalyst (360 mg, 0.43 mmol) and the resulting purple solution heated under reflux conditions for 2.5 hours. The cooled reaction mixture was then treated with DMSO (3.0 mL, 3.3 g, 43.0 mmol) and stirred for a further 18 hours at room temperature. The reaction mixture was then concentrated under reduced pressure and the residue so-obtained subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions ($R_f = 0.5$) then afforded the *title carbonate* **221** (3.6 g, 96%) as a clear, colourless oil.

¹H NMR (300 MHz) δ 5.70 (s, 2H), 5.27 (m, 1H), 4.51 (dt, $J = 10.8$ and 4.5 Hz, 1H), 2.78 (dd, $J = 6.9$ and 0.6 Hz, 1H), 2.72 (dd, $J = 6.9$ and 0.6 Hz, 1H), 2.51-2.48 (complex m, 1H), 2.45-2.42 (complex m, 1H), 2.31 (m, 1H), 2.09-2.03 (complex m, 1H), 1.98-1.90 (complex m, 1H), 1.69-1.64 (complex m, 2H), 1.54-1.36 (complex m, 1H), 1.34 (t, $J = 2.7$ Hz, 1H), 1.09-

0.97 (complex m, 2H), 0.90 (d, $J = 7.2$ Hz, 3H, CH₃), 0.79 (d, $J = 7.2$ Hz, 3H, CH₃), 0.78 (d, $J = 7.2$ Hz, 3H, CH₃).

¹³C NMR (75 MHz) δ 154.8 (C), 128.0 (2 x CH – overlapping signals), 83.7 (CH), 78.0 (CH), 47.0 (CH₂), 46.9 (CH), 40.8 (CH₂), 39.6 (CH₂), 34.1 (CH₂), 31.4 (CH), 26.0 (CH), 23.2 (CH₂), 22.0 (CH₃), 20.7 (CH₃), 16.1 (CH₃).

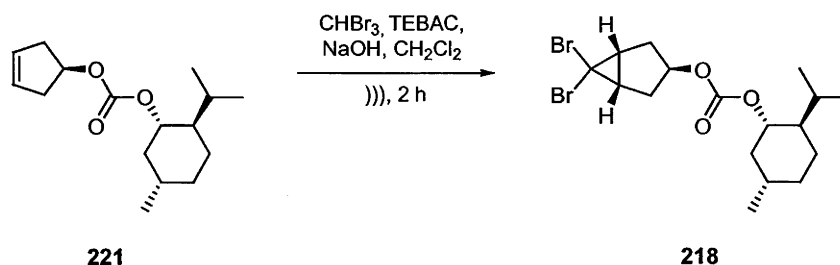
IR (neat) ν_{\max} 3065, 2955, 2870, 1737, 1465, 1370, 1341, 1300, 1259, 1196, 1182, 1156, 1099, 1078, 1029, 1008, 981, 964, 884, 861, 837, 793, 677 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 266 [M⁺, 8%], 239 [(M-C₂H₃)⁺, 1], 201 (6), 186 (51), 139 (84), 128 [(M-C₁₀H₁₈)⁺, 62], 114 (70), 97 (39), 83 (75), 67 (100).

HRMS Found (M-C₁₀H₁₈)⁺, 128.0470. C₆H₈O₃ requires (M-C₁₀H₁₈)⁺, 128.0473.

Specific Rotation $[\alpha]_{\text{D}} +47$ (c 0.4, CHCl₃).

(1*R*,3*S*,5*S*)-6,6-Dibromobicyclo[3.1.0]hexan-3-yl (1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl Carbonate (218)



A suspension of bromoform (1.7 mL 5.0 g, 20.0 mmol), benzyltriethylammonium chloride (50 mg, 0.23 mmol), freshly ground sodium hydroxide (2.4 g, 60.0 mmol) and compound **221** (3.0 g, 10.0 mmol) in dichloromethane (6 mL) was subjected to sonication without external temperature control for 2 hours. After this time, CeliteTM was added to the reaction mixture

and the resulting suspension filtered through a 1 cm plug of CeliteTM which was washed with CH₂Cl₂ (25 mL). The combined filtrates were then concentrated under reduced pressure. Subjection of this material to flash chromatography (silica, 1:19 v/v ethyl/hexane elution) and concentration of the appropriate fractions ($R_f = 0.4$) then afforded the *title compound 218* (3.3 g, 76%) as a yellow oil.

¹H NMR (300 MHz) δ 5.18 (quintet, $J = 8.7$ Hz, 1H), 4.47 (dt, $J = 10.8$ and 4.2 Hz, 1H), 2.66 (m, 2H), 2.14 (m, 2H), 2.03 (m, 2H), 1.92 (dt, $J = 6.9$ and 2.7 Hz, 1H), 1.84 (s, 1H), 1.75 (s, 1H), 1.71-1.60 (complex m, 2H), 1.51-1.33 (complex m, 2H), 1.10-0.97 (complex m, 2H), 0.89 (t, $J = 7.2$ Hz, 6 H, 2 x CH₃ overlapping), 0.76 (d, $J = 7.2$ Hz, 3 H, CH₃).

¹³C NMR (75 MHz) δ 154.3 (C), 82.0 (CH), 78.5 (CH), 46.9 (CH₂), 43.4 (CH₂), 40.7 (CH₂), 35.8 (2 x CH, overlapping), 34.9 (CH₂), 34.0 (CH₂), 31.4 (C), 29.7 (CH), 26.0 (CH), 23.2 (CH₃), 21.9 (CH), 20.7 (CH₃), 16.2 (CH₃).

IR (neat) ν_{\max} 3456, 2956, 2929, 2870, 1737, 1648, 1455, 1385, 1370, 1285, 1262, 1182, 1080, 1009, 981, 959, 791, 743 cm⁻¹.

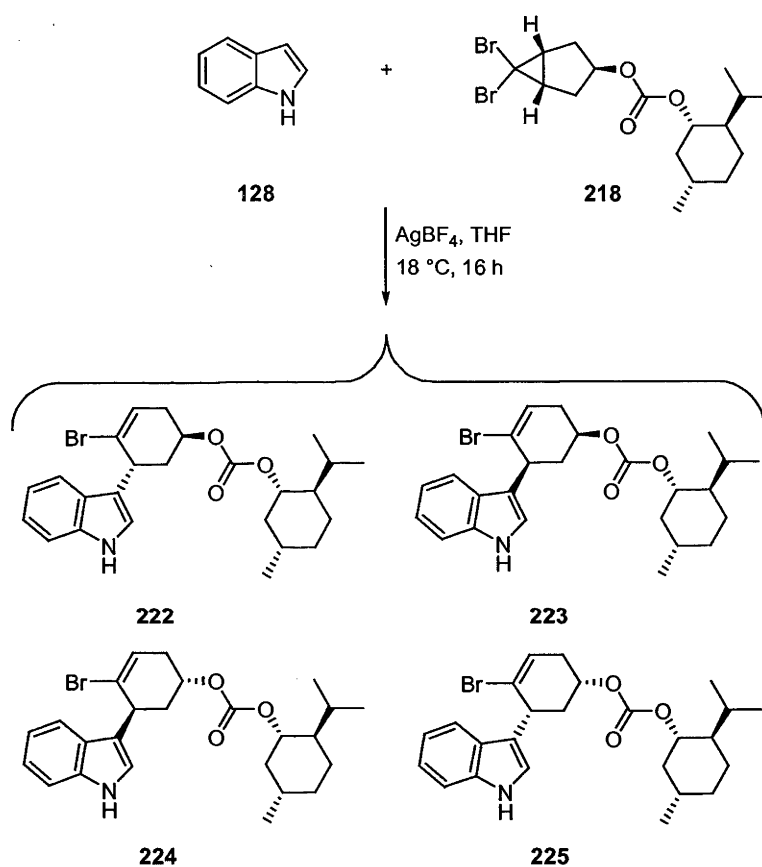
Mass Spectrum (EI, 70 eV) m/z 440, 438 and 438 [M^+ , 1, 2 and 1%], 302, 300 and 298 [($M-C_{10}H_{18}$)⁺, 8, 15 and 8], 240, 238 and 236 (57, 81 and 57), 159 and 157 (83 and 84), 139 (96), 123 (63), 109 (18), 95 (91), 83 (100), 81 (91), 77 (87), 55 (88).

HRMS Found ($M-C_{10}H_{18}$)⁺, 299.8813. C₇H₈⁸¹Br⁷⁹BrO₃ requires ($M-C_{10}H_{18}$)⁺, 299.8820.

Found ($M-C_{10}H_{18}$)⁺, 297.8830. C₇H₈⁷⁹Br₂O₃ requires ($M-C_{10}H_{18}$)⁺, 297.8840.

Specific Rotation [α]_D +20 (c 0.2, CHCl₃).

(1*S*,5*R*)-4-Bromo-5-(indol-3-yl)cyclohex-3-enyl (2*R*,5*S*) 2-Isopropyl-5-methylcyclohexyl Carbonate (**222**), (1*S*,5*S*)-4-Bromo-5-(indol-3-yl)cyclohex-3-enyl (2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl Carbonate (**223**), (1*R*,5*S*)-4-Bromo-5-(indol-3-yl)cyclohex-3-enyl (2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl Carbonate (**224**) and (1*R*,5*S*)-4-Bromo-5-(indol-3-yl)cyclohex-3-enyl(2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl Carbonate (**225**)



A magnetically stirred mixture of cyclopropane **218** (540 mg, 1.23 mmol) and indole (**128**) (140 mg, 1.23 mmol) in anhydrous THF (12 mL) and maintained under a nitrogen atmosphere was treated, in one portion, with silver tetrafluoroborate (480 mg, 2.46 mmol). The resulting dark-pink and opaque solution was protected from light and stirring continued at room temperature for 16 hours. The reaction mixture was then filtered through a plug of CeliteTM that was washed with ethyl acetate (100 mL). Concentration of the combined filtrates under reduced pressure provided a dark-maroon and viscous oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the

relevant fractions ($R_f = 0.2$) afforded a *ca.* 1:1:1:1 mixture (as determined by HPLC analysis[#]) of the *title compounds* 222-225 (450 mg, 77%) as a pale-orange oil.

¹H NMR (300 MHz) δ 8.11 (broad s, 2H), 8.06 (broad s, 2H), 7.59 (d, $J = 8.1$ Hz, 4H), 7.40-7.35 (complex m, 4H), 7.26-7.05 (complex m, 12H), 6.19 (t, $J = 6.9$ Hz, 4H), 5.08-4.94 (complex m, 2H), 4.93-4.85 (complex m, 2H), 4.45 (m, 4H), 4.22-4.16 (complex m, 2H), 4.12-4.03 (complex m, 2H), 3.41 (m, 4H), 2.77-2.37 (complex m, 4H), 2.37-2.21 (complex m, 8H), 2.05-1.84 (complex m, 16H), 1.67-1.61 (complex m, 16H), 1.42-1.28 (complex m, 4H), 0.89 (m, 36H, 12 x CH₃).

¹³C NMR (75 MHz) δ 154.3 (2 x C), 154.2 (2 x C), 139.3 (4 x C, overlapping), 136.5 (4 x CH, overlapping), 127.2 (4 x C), 124.0 (4 x CH), 122.8 (2 x C), 122.7 (2 x C), 122.6 (2 x CH), 122.2 (2 x CH), 119.6 (2 x CH), 119.1 (2 x CH), 118.6 (4 x CH, overlapping), 116.4 (4 x C, overlapping), 111.4 (4 x CH, overlapping), 71.8 (2 x CH), 70.8 (2 x CH), 70.1 (4 x CH), 47.1 (4 x CH₂), 40.9 (4 x CH), 34.2 (2 x CH₂), 33.4 (2 x CH₂), 32.2 (2 x CH₂), 31.9 (2 x CH₂), 26.2 (2 x CH₂), 26.1 (2 x CH₂), 24.2 (4 x CH), 23.4 (4 x CH), 22.9 (2 x CH), 22.5 (2 x CH), 22.2 (4 x CH₃, overlapping), 21.3 (4 x CH, overlapping), 21.0 (4 x CH₃, overlapping), 16.9 (2 x CH₃), 16.4 (2 x CH₃).

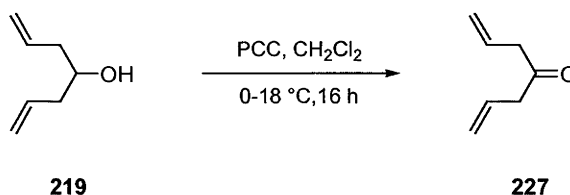
IR (neat) ν_{\max} 3368, 2956, 2926, 2870, 1737, 1456, 1331, 1262, 1098, 980, 958, 791, 741 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 475 and 473 [M^+ , both 50%], 337 and 335 [(M-C₁₀H₁₈)⁺, both 10], 275 and 273 (both 96), 194 (100), 167 (23), 148 (88), 133 (36), 117 (25), 95 (33), 83 (55), 69 (34), 55 (41), 43 (37).

HRMS Found M^+ , 475.1549. C₂₅H₃₂⁸¹BrNO₃ requires M^+ , 475.1545.

Found M^+ , 473.1560. C₂₅H₃₂⁷⁹BrNO₃ requires M^+ , 473.1566.

[#] Waters 3.9 x 300 mm 10 micron silica column with 5:95 v/v isopropanol:hexane as the eluting solvent. (R_f 41.77, 43.56, 57.00, 58.52)

Hepta-1,6-dien-4-one (227)

Pyridinium chlorochromate (38.0 g, 0.27 mol) was added, in twelve roughly equal portions, over one hour to a magnetically stirred solution of 1,6-heptadiene-4-ol (**219**) (11.6 mL, 10.0 g, 0.09 mol) in dichloromethane (180 mL) maintained at 0 °C (ice/water bath) under a nitrogen atmosphere. Upon completion of addition the resultant solution was protected from light and allowed to warm to ambient temperature. Stirring continued for a further 16 hours. After this time the reaction mixture was filtered through a plug of silica gel that was washed with diethyl ether (800 mL) and the combined filtrates concentrated under reduced pressure to provide a yellow oil. Subjection of this compound to flash chromatography (silica gel, 1:9 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions ($R_f = 0.5$), the desired product **227**⁸ (8.9 g, 91%) as a clear, colourless oil.

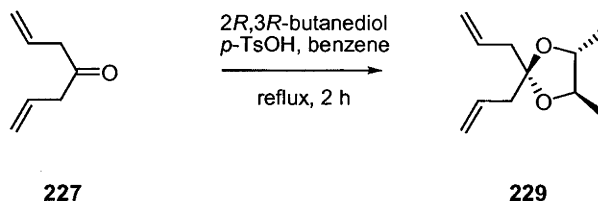
¹H NMR (300 MHz) δ 5.92 (ddt, $J = 17.2, 10.2$ and 7.2 Hz, 2H), 5.21 (q, $J = 1.5$ Hz, 1H), 5.18 (quintet, $J = 1.5$ Hz, 2H), 5.12 (q, $J = 1.5$ Hz, 1H), 3.21 (dt, $J = 6.9$ and 1.5 Hz, 4H).

¹³C NMR (75 MHz) δ 206.0 (C), 130.1 (2 x CH, overlapping), 118.6 (2 x CH₂, overlapping), 46.8 (2 x CH₂, overlapping).

IR (neat) ν_{max} 3417, 3082, 2983, 2922, 1717, 1640, 1425, 1396, 1330, 1138, 1050, 994, 920, 692, 591 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 110 [M^+ , 26%], 69 [($M - C_3H_5$)⁺, 100].

HRMS Found M^+ , 110.0731. Calculated for C₇H₁₀O M^+ , 110.0732.

(4*R*,5*R*)-2,2-Diallyl-4,5-dimethyl-[1,3]dioxolane (229)

p-Toluenesulfonic acid (7 mg, 0.04 mmol) was added to a solution of ketone **227** (1.0 g, 9.09 mmol) and 2*R*,3*R*-butanediol (1.2 mL, 1.2 g, 14.0 mmol) in benzene (20 mL) contained in a flask fitted with a Dean-Stark trap, dry ice condenser and calcium chloride drying tube. The ensuing mixture was heated at reflux for 2 hours then cooled and washed with sodium hydroxide (1 x 30 mL of a 10% w/v aqueous solution). The separated organic phase was then washed with water (5 x 30 mL) and brine (1 x 100 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (*R_f* = 0.6) afforded the *title ketal 229* (1.2 g, 75%) as a pale-yellow oil.

¹H NMR (300 MHz) δ 5.85 (ddt, *J* = 15.6, 9.3 and 7.2 Hz, 2H), 5.12 (m, 2H), 5.08 (m, 2H), 3.64 (m, 2H), 2.39 (d, *J* = 7.2 Hz, 4H), 1.24-1.23 (dd, *J* = 5.7 and 2.1 Hz, 6H, 2 x CH₃).

¹³C NMR (75 MHz) δ 133.2 (2 x CH, overlapping), 118.2 (2 x CH₂, overlapping), 109.4 (C), 78.8 (2 x CH, overlapping), 43.3 (2 x CH₂, overlapping), 16.5 (2 x CH₃, overlapping).

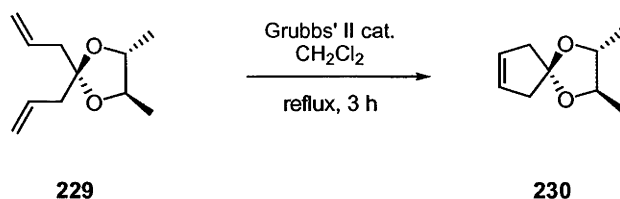
IR (neat) ν_{max} 3078, 2979, 2931, 1642, 1432, 1377, 1316, 1293, 1262, 1097, 999, 914, 842, 810, 701, 659 cm⁻¹.

Mass Spectrum (EI, 70 eV) *m/z* 182 [*M*⁺, 16%], 167 (22), 141 [(*M*-C₃H₅)⁺, 100], 69 (63).

HRMS Found (*M*-C₃H₅)⁺, 141.0913. C₈H₁₃O₂ requires (*M*-C₃H₅)⁺, 141.0916.

Specific Rotation $[\alpha]_{\text{D}} -19$ (c 1.2, CHCl_3).

(2*R*,3*R*)-2,3-Dimethyl-1,4-dioxaspiro[4.4]non-7-ene (230)



A deoxygenated solution of ketal **229** (400 mg, 2.20 mmol) in anhydrous dichloromethane (22 mL) was treated with Grubbs' II catalyst (90 mg, 0.11 mmol) and the resulting solution heated at reflux for 3 hours whilst being maintained under a nitrogen atmosphere. Upon cooling of the resulting dark-purple reaction mixture to room temperature, DMSO (0.8 mL, 11.0 mmol) was added and stirring then continued overnight. The solvent was then removed under reduced pressure and the residue so-obtained subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions ($R_f = 0.4$) then delivered the *title compound* **230** (240 mg, 70%) as a clear, colourless oil.

^1H NMR (300 MHz) δ 5.68 (t, $J = 0.9$ Hz, 2H), 3.62 (m, 2H), 2.58 (t, $J = 0.9$ Hz, 4H), 1.26 (dd, $J = 5.7$ and 2.4 Hz, 6H, 2 x CH_3).

^{13}C NMR (75 MHz) δ 128.1 (2 x CH, overlapping), 116.6 (C), 78.4 (2 x CH, overlapping), 44.7 (2 x CH_2 , overlapping), 17.0 (2 x CH_3 , overlapping).

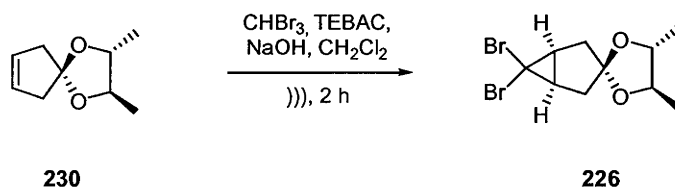
IR (neat) ν_{max} 2970, 2929, 2871, 1734, 1455, 1376, 1316, 1290, 1263, 1093, 967, 857, 746, 697, 660 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 155 [(M+H)⁺, 27%], 141 (100), 127 (12), 115 (8), 97 (11), 83 (14), 69 (69), 55 (36).

HRMS Found (M+H)⁺, 155.1072. C₉H₁₅O₂ requires (M+H)⁺, 155.1072.

Specific Rotation [α]_D -15 (c 0.2, CHCl₃).

6,6-Dibromobicyclo[3.1.0]hexane-3-one (2*R*,3*R*)-2,3-Dimethyl ethylene ketal (226)



A round bottomed flask containing a solution of (2*R*,3*R*)-2,3-dimethyl-1,4-dioxaspiro[4.4]non-7-ene (**230**) (50 mg, 0.32 mmol) in dichloromethane (1 mL) was charged with benzyltriethylammonium chloride (1.5 μg , 6.50 μmol), bromoform (60 μL) and powdered sodium hydroxide (78 mg, 1.95 mmol). The flask was then fitted with a reflux condenser and the resulting mixture subjected to sonication, without external temperature control, for 2 hours. After this time a small amount of CeliteTM was added to the reaction vessel and the resultant suspension filtered through a 1 cm plug of CeliteTM which was then washed with CH₂Cl₂ (25 mL). Concentration of the combined filtrates under reduced pressure provided a brown liquid that was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions then delivered the *title cyclopropane* **226** (89 mg, 85%) as a light-yellow oil.

¹H NMR (300 MHz) δ 3.53 (m, 2H), 2.36-2.18 (complex m, 4H), 1.86-1.70 (complex m, 2H), 1.25 (broad d, $J = 5.7$ Hz, 3H, CH₃), 1.19 (broad d, $J = 5.7$ Hz, 3H, CH₃).

¹³C NMR (75 MHz) δ 122.7 (C), 79.1 (CH), 77.8 (CH), 44.9 (C), 41.0 (CH), 40.9 (CH), 35.2 (CH₂), 35.1 (CH₂), 16.9 (CH₃), 16.6 (CH₃).

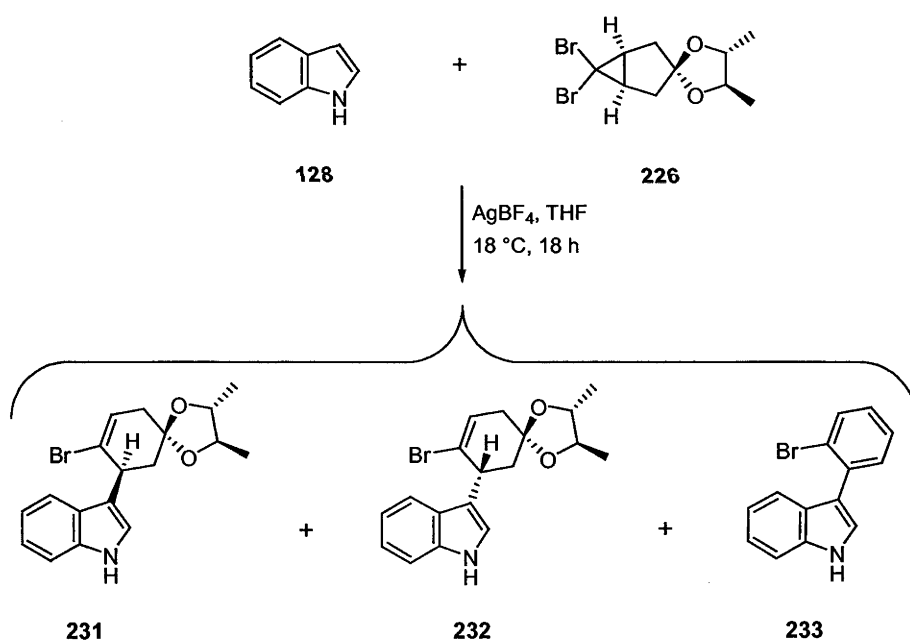
IR (CH₂Cl₂) ν_{max} 3331, 2924, 2853, 1734, 1606, 1457, 1377, 1260, 1086 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 328, 326 and 324 [M^+ , 15, 30 and 15%], 284, 282 and 280 (13, 26 and 13), 247 and 245 [($M-Br$) $^+$, both 53], 227, 225 and 223 (6, 13 and 6), 201 and 199 (both 6), 175 and 173 (21 and 23), 161 and 159 (both 18), 147 and 145 (57 and 58), 127 (35), 114 (49), 99 (19), 94 (35), 77 (56), 69 (62), 55 (63), 55 (100), 43 (57).

HRMS Found M^+ , 325.9341. $C_{10}H_{14}^{79}Br^{81}BrO_2$ requires M^+ , 325.9340.

Specific Rotation $[\alpha]_D -14$ (c 0.1, $CHCl_3$).

(2'*R*,3'*R*,7'*S*)-3-(8'-Bromo-2',3'-dimethyl-1',4'-dioxaspiro[4.5]dec-8'-en-7'-yl)-indole (**231**), (2'*R*,3'*R*,7'*R*)-3-(8'-Bromo-2',3'-dimethyl-1',4'-dioxaspiro[4.5]dec-8'-en-7'-yl)-indole (**232**) and 3-(2-Bromophenyl)-indole (**233**)



Silver tetrafluoroborate (84 mg, 0.43 mmol) was added, in one portion, to a magnetically stirred solution of ketal **226** (70 mg, 0.22 mmol) and indole (**128**) (25 mg, 0.22 mmol) in anhydrous THF (5 mL) maintained under a nitrogen atmosphere. The resulting solution was immediately protected from light and stirring continued at room temperature for 18 hours. The reaction mixture was then filtered through a plug of CeliteTM that was washed with ethyl

acetate (25 mL) and the combined filtrates concentrated under reduced pressure. Subjection of this material to flash column chromatography (silica, elution with 1:4 v/v ethyl acetate/hexane containing 1% triethylamine) furnished two fractions, A and B.

Concentration of fraction A ($R_f = 0.3$) delivered an inseparable mixture of the *title compounds 231 and 232* (50 mg, 64%) as a pale-yellow oil. Subjection of this material to HPLC (Alltima 250 x 46 mm 5 micron C18 column with guard cartridge utilising 3:7 v/v MeOH/H₂O as the eluting solvent) afforded two fractions, A' and A''.

Concentration of fraction A' (R_t 27.54 min) afforded the *title compound 231* (40 mg, 51%) as a clear, colourless oil.

¹H NMR (600 MHz, CD₃COCD₃) δ 10.09 (broad s, 1H, NH), 7.57 (dd, $J = 7.8$ and 1.2 Hz, 1H), 7.38 (dd, $J = 7.8$ and 1.2 Hz, 1H), 7.23 (d, $J = 2.4$ Hz, 1H), 7.07 (dt, $J = 7.8$ and 1.2 Hz, 1H), 6.99 (dt, $J = 7.8$ and 1.2 Hz, 1H), 6.15 (dt, $J = 6.0$ and 2.4 Hz, 1H), 4.12 (m, 1H), 3.72 (m, 2H), 2.63 (ddd, $J = 6.0, 3.6$ and 2.4 Hz, 1H), 2.37 (m, 1H), 2.35 (m, 1H), 2.14 (ddd, $J = 8.4, 6.0$ and 2.4 Hz, 1H), 1.26 (d, $J = 6.0$ Hz, 3H, CH₃), 1.16 (d, $J = 6.0$ Hz, 3H, CH₃).

¹³C NMR (150 MHz, CD₃COCD₃) δ 137.9 (C), 128.0 (CH), 127.5 (C), 127.3 (C), 124.2 (CH), 122.0 (CH), 119.7 (CH), 119.4 (CH), 117.2 (C), 112.3 (CH), 106.7 (C), 79.3 (CH), 79.2 (CH), 42.7 (CH₂), 42.3 (CH), 40.3 (CH₂), 17.5 (CH₃), 17.2 (CH₃).

IR (CH₂Cl₂) ν_{\max} 3584, 3294, 2925, 2854, 1712, 1618, 1458, 1260, 1101, 799 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 363 and 361 [M^+ , 60 and 58%], 304 and 302 (7 and 8), 290 and 288 (both 12), 249 and 247 (76 and 77), 210 (12), 180 (32), 168 (100), 149 (37), 115 (77), 105 (49), 83 (21), 77 (27), 55 (32), 43 (52).

HRMS Found M^+ , 363.0657. C₁₈H₂₀⁸¹BrNO₂ requires M^+ , 363.0657.

Found M^+ , 361.0671. C₁₈H₂₀⁷⁹BrNO₂ requires M^+ , 361.0677.

Specific Rotation $[\alpha]_D -21$ (c 0.4, CHCl_3).

Concentration of fraction A'' (R_t 28.54 min) afforded the *title compound 232* (10 mg, 13%) as a clear, colourless oil.

^1H NMR (600 MHz, CD_3COCD_3) δ 10.10 (broad s, 1H, NH), 7.56 (dd, $J = 7.2$ and 1.2 Hz, 1H), 7.38 (dd, $J = 7.2$ and 1.2 Hz, 1H), 7.23 (d, $J = 2.4$ Hz, 1H), 7.07 (dt, $J = 7.2$ and 1.2 Hz, 1H), 6.99 (dt, $J = 7.2$ and 1.2 Hz, 1H), 6.13 (dt, $J = 6.0$ and 2.4 Hz, 1H), 4.13 (m, 1H), 3.65 (m, 2H), 2.57 (ddd, $J = 6.0$, 3.6 and 2.4 Hz, 1H), 2.32 (m, 1H), 2.29 (m, 1H), 2.06 (m, 1H), 1.26 (d, $J = 6.0$ Hz, 3H, CH_3), 1.20 (d, $J = 6.0$ Hz, 3H, CH_3).

^{13}C NMR (150 MHz, CD_3COCD_3) δ 137.9 (C), 128.4 (CH), 127.8 (C), 127.2 (C), 124.0 (CH), 122.0 (CH), 119.7 (CH), 119.4 (CH), 117.2 (C), 112.4 (CH), 106.6 (C), 79.0 (CH), 78.8 (CH), 43.4 (CH_2), 42.1 (CH), 39.6 (CH_2), 17.0 (2 x CH_3 , overlapping).

IR (CH_2Cl_2) ν_{max} 3352, 2927, 2855, 1712, 1620, 1457, 1376, 1357, 1293, 1262, 1142, 1112, 1023, 805, 741 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 363 and 361 [M^+ , 45 and 46%], 249 and 247 (59 and 60), 210 (6), 180 (18), 168 (100), 149 (27), 115 (62), 83 (14), 69 (19), 55 (35).

HRMS Found M^+ , 363.0661. $\text{C}_{18}\text{H}_{20}^{81}\text{BrNO}_2$ requires M^+ , 363.0657.

Found M^+ , 361.0677. $\text{C}_{18}\text{H}_{20}^{79}\text{BrNO}_2$ requires M^+ , 361.0677.

Specific Rotation $[\alpha]_D +30$ (c 0.1, CHCl_3).

Concentration of fraction B ($R_f = 0.5$) afforded *compound 233* (15 mg, 25%) as a pale-orange oil.

^1H NMR (300 MHz) δ 8.29 (broad s, 1H), 7.89 (dd, $J = 7.8$ and 0.6 Hz, 1H), 7.56 (d, $J = 1.2$ Hz, 1H), 7.45 (dt, $J = 7.8$ and 1.2 Hz, 1H), 7.37 (d, $J = 2.7$ Hz, 1H), 7.35 (s, 1H), 7.32 (d, $J =$

1.2 Hz, 1H), 7.24 (dd, $J = 3.3$ and 1.5 Hz, 1H), 6.74 (d, $J = 1.2$ Hz, 1H), 6.71 (d, $J = 1.2$ Hz, 1H).

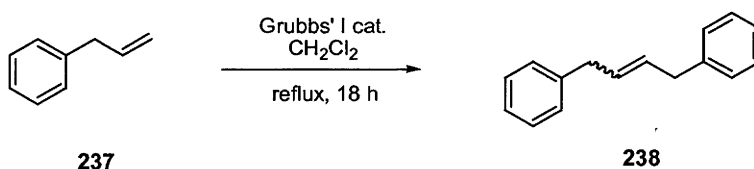
^{13}C NMR (75 MHz) δ 134.9 (C), 132.3 (C), 132.3 (CH), 131.7 (CH), 128.8 (CH), 125.9 (C), 122.8 (C), 122.5 (CH), 121.8 (CH), 120.5 (CH), 119.5 (C), 119.4 (CH), 117.1 (CH), 111.4 (CH).

IR (CH_2Cl_2) ν_{max} 3412, 3379, 2921, 1587, 1541, 1487, 1455, 1236, 1104, 1070, 1007, 815, 747 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 273 and 271 [M^+ , both 100%], 191 [$(\text{M}-\text{HBr})^+$, 32], 165 (15), 96 (14), 82 (15).

HRMS Found M^+ , 270.9993. $\text{C}_{14}\text{H}_{10}^{79}\text{BrN}$ requires M^+ , 270.9997.

E- and *Z*-1,4-Diphenyl-2-butene (**238**)



Grubbs' I catalyst (1.4 g, 1.69 mmol) was added to a deoxygenated solution of allyl benzene (**237**) (4.5 mL, 4.0 g, 34.0 mmol) in anhydrous CH_2Cl_2 (68 mL) maintained under a nitrogen atmosphere. The resulting solution was subsequently heated at reflux for 18 hours. The cooled reaction mixture was then treated with DMSO (12.2 mL, 13.4 g, 0.17 mol) and stirring continued under a nitrogen atmosphere for a further 18 hours. The solvent was then removed under reduced pressure and the residue so-obtained subjected to flash column chromatography (silica, hexane elution) to provide, after concentration of the appropriate fractions ($R_f = 0.3$), a 5.6:1 mixture (as judged by ^1H and ^{13}C NMR analysis) of the *E*- and *Z*-isomeric forms of the title alkene **238** (6.6 g, 93%) which was obtained as a clear, colourless oil. On standing

portions of this material slowly crystallised and the solid could be removed by filtration to give pure samples of the *E*-isomer of compound **238**, m.p. 39–42 °C (lit.⁹ 40.5–42 °C).

¹H NMR (300 MHz) (mixture of *E*- and *Z*-isomers) δ 7.35–7.30 (complex m, 8H), 7.27–7.20 (complex m, 12H), 5.78 (dt, $J = 5.1$ and 1.2 Hz, 2H, *Z*), 5.71 (m, 2H, *E*), 3.53 (d, $J = 5.1$ Hz, 4H, *Z*), 3.39 (d, $J = 4.5$, 4H, *E*).

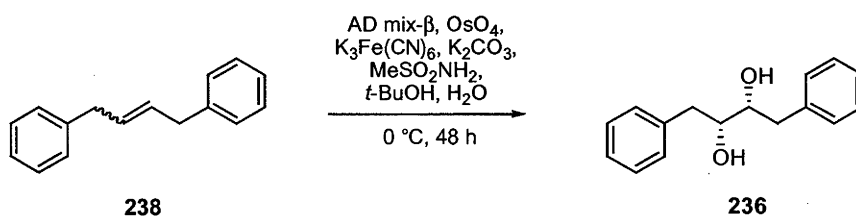
¹³C NMR (75 MHz) (mixture of *E*- and *Z*-isomers) δ 140.6 (2 x C) (*E*), 140.4 (2 x C) (*Z*), 130.2 (4 x CH), 128.9 (4 x CH), 128.4 (4 x CH), 128.3 (4 x CH), 128.2 (4 x CH), 125.8 (4 x CH), 38.8 (2 x CH₂) (*E*), 33.3 (2 x CH₂) (*Z*).

IR (CH₂Cl₂) (mixture of *E*- and *Z*-isomers) ν_{\max} 3084, 3062, 3027, 2967, 2901, 2837, 1602, 1493, 1452, 1074, 1029, 969, 738, 697 cm⁻¹.

Mass Spectrum (EI, 70 eV) (mixture of *E*- and *Z*-isomers) m/z 208 [M⁺, 36%], 194 (6), 178 (6), 165 (7), 152 (3), 139 (1), 130 (21), 117 (100), 104 (28), 91 (44), 77 (16), 65 (18).

HRMS Found M⁺, 208.1254. Calculated for C₁₆H₁₆ M⁺, 208.1252.

(*R,R*)-1,4-Diphenyl-butane-2,3-diol (**236**)



Following a procedure reported by Wallace and co-workers,¹⁰ a powdered mixture of potassium ferricyanide (18.8 g, 57.0 mmol), potassium carbonate (7.8 g, 57.0 mmol), and AD mix- β (150 mg, 0.19 mmol) was added, along with osmium tetroxide (0.6 mL of a 0.1 M solution in *t*-butanol, 1.90 mmol), to a 1:1 v/v mixture of *t*-butanol and water (96 mL). After

stirring for a few minutes, powdered methanesulfonamide (1.8 g, 19.0 mmol) was added and the resulting solution cooled to 0 °C. Alkene **238** (4.0 g, 19.0 mmol, 5.6:1 mixture of *E*- and *Z*-isomers) was then added in one portion and the ensuing mixture vigorously stirred at 0 °C for 48 hours. Sodium thiosulfate (26.9 g, 11.0 mmol) was then added and the resulting mixture stirred at 0 °C for a further one hour. The aqueous phase was then extracted with ethyl acetate (3 x 500 mL) and the combined organic fractions were washed with sodium hydroxide (1 x 500 mL of a 2 M aqueous solution), before being dried (MgSO₄), filtered and concentrated under reduced pressure to provide a white solid. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.4$ in 2:3 ethyl acetate/hexane) then gave a white solid. Recrystallisation of this material (hexane/acetone) afforded the title diol **236** (3.5 g, 76%) as a white crystalline solid, m.p. 126-130 °C (lit.¹¹ m.p. 126-128 °C)

¹H NMR (300 MHz) δ 7.34-7.29 (complex m, 5H), 7.26-7.21 (complex m, 5H), 3.76 (m, 2H), 2.96-2.81 (2 overlapping dd, $J = 13.8$ and 4.5 Hz, 4H), 2.04 (br d, $J = 3.9$ Hz, 2H, 2 x OH).

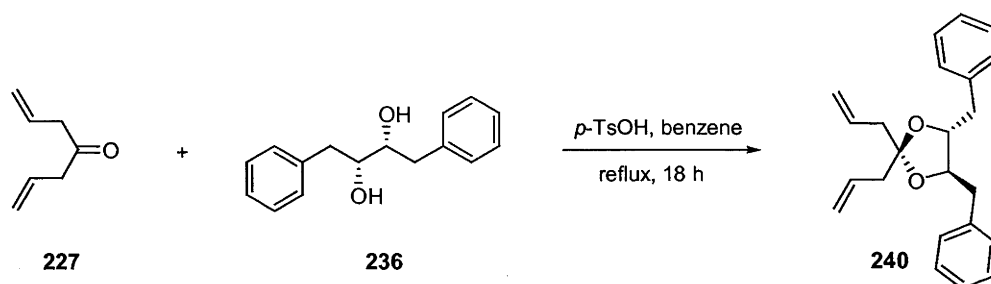
¹³C NMR (75 MHz) δ 138.0 (2 x C), 129.4 (4 x CH), 128.6 (4 x CH), 126.6 (2 x CH), 74.0 (2 x CH), 40.3 (2 x CH₂).

IR (CH₂Cl₂) ν_{\max} 3325, 3025, 2923, 2852, 1741, 1600, 1454, 1152, 1103, 1041, 1012, 932, 749, 700.

Mass Spectrum (EI, 70 eV) m/z 242 [M^+ , 2%], 150 (47), 133 (54), 121 (49), 103 (41), 91 (100), 77 (32), 65 (65).

HRMS Found M^+ , 242.1309. C₁₆H₁₈O₂ requires M^+ , 242.1307.

Specific Rotation $[\alpha]_D -2$ (c 0.5, CHCl₃).

(2*R*,3*R*)-2,2-Diallyl-4,5-dibenzyl-[1,3]-dioxolane (240)

p-Toluenesulfonic acid (6 mg, 0.03 mmol) was added to a solution of ketone **227** (1.8 g, 16.0 mmol) and (*R,R*)-1,4-diphenylbutane-2,3-diol (**236**) (2.0 g, 8.26 mmol) in benzene (40 mL). The resulting solution was then heated at reflux under Dean-stark conditions for 18 hours. Upon cooling the reaction mixture was washed with sodium hydroxide (1 x 40 mL of a 10% w/v aqueous solution), water (5 x 50 mL) and brine (1 x 50 mL), then dried (K_2CO_3), filtered and concentrated under reduced pressure to provide a cream solid. Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.7$) then delivered the *title ketal* **240** (3.4 g, 64%) as a pale-yellow oil.

1H NMR (300 MHz) δ 7.31-7.19 (complex m, 5H), 7.16-7.12 (complex m, 5H), 5.87-5.74 (complex m, 2H), 5.10 (m, 2H), 5.06 (m, 2H), 3.93 (t, $J = 3.6$ Hz, 2H), 2.81 (dd, $J = 14.1$ and 6.0 Hz, 2H), 2.60 (dd, $J = 14.1$ and 4.2 Hz, 2H), 2.34 (d, $J = 7.2$ Hz, 4H).

^{13}C NMR (75 MHz) δ 137.4 (2 x C), 133.3 (2 x CH), 129.5 (4 x CH), 128.3 (2 x CH), 126.5 (2 x CH), 118.1 (2 x CH_2), 110.0 (C), 81.1 (2 x CH), 43.1 (2 x CH_2), 38.8 (2 x CH_2).

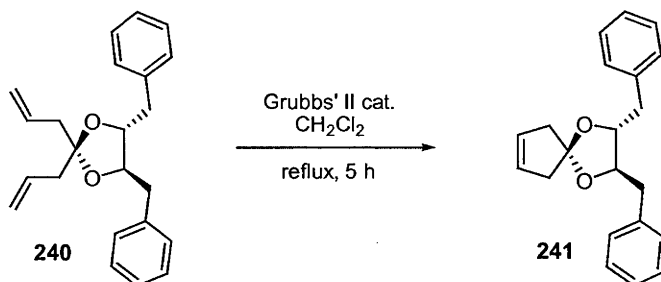
IR (neat) ν_{max} 3345, 3064, 3028, 2923, 2858, 2098, 1728, 1641, 1604, 1496, 1454, 1431, 1324, 1289, 1240, 1190, 1080, 1059, 998, 915, 755, 699 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 334 [M^+ , 3%], 293 [$(M-C_3H_5)^+$, 100], 243 (12), 207 (36), 129 (45), 117 (15), 105 (22), 91 (99), 77 (16), 65 (12).

HRMS Found M^+ , 334.1936. Calculated for $C_{23}H_{26}O_2 M^+$, 334.1933.

Specific Rotation $[\alpha]_D -5$ (c 0.2, $CHCl_3$).

(2*R*,3*R*)-2,3-Dibenzyl-1,4-dioxaspiro[4.4]non-7-ene (241)



A deoxygenated solution of diene **240** (100 mg, 0.30 mmol) in dichloromethane (3 mL) was treated with Grubbs' II catalyst (13 mg, 0.02 mmol) and subsequently heated at reflux for 5 hours. DMSO (0.1 mL, 120 mg, 1.50 mmol) was then added to the cooled reaction mixture and stirring continued at room temperature for 18 hours. After this time the solvent was removed under reduced pressure and the ensuing residue subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions ($R_f = 0.2$) then furnished the *title cyclopentene* **241** (74 mg, 81%) as a pale-yellow oil.

1H NMR (300 MHz) δ 7.31-7.22 (complex m, 5H), 7.15-7.12 (complex m, 5H), 5.67 (s, 2H), 3.96 (m, 2H), 2.84 (dd, $J = 13.8$ and 6.3 Hz, 2H), 2.61 (dd, $J = 13.8$ and 4.8 Hz, 2H), 2.57 (s, 4H).

^{13}C NMR (75 MHz) δ 137.4 (2 x C), 129.4 (4 x CH), 128.5 (4 x CH), 128.0 (2 x CH), 126.5 (2 x CH), 117.2 (C), 80.9 (2 x CH), 44.6 (2 x CH_2), 39.3 (2 x CH_2).

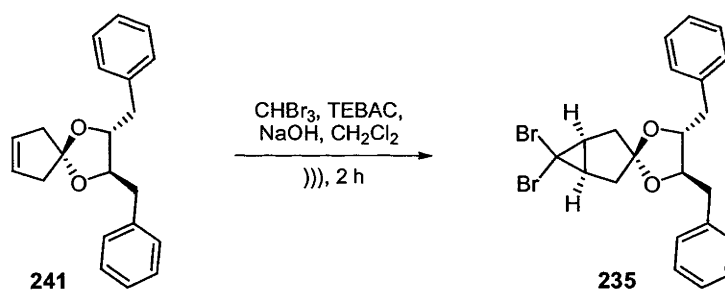
IR (neat) ν_{max} 3062, 3028, 2925, 2856, 1496, 1454, 1321, 1263, 1219, 1136, 1101, 1078, 1031, 967, 954, 746, 699, 662 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 306 [M^+ , 84%], 293 (20), 279 (2), 215 (8), 207 (14), 192 (5), 133 (75), 129 (51), 117 (32), 105 (45), 91 (100), 84 (45), 77 (23), 64 (28), 54 (48), 39 (20).

HRMS Found M^+ , 306.1616. Calculated for $C_{21}H_{22}O_2$ M^+ , 306.1620.

Specific Rotation $[\alpha]_D -4$ (c 0.3, $CHCl_3$).

(2*R*,3*R*)-2,3-Dibenzyl-6,6-dibromobicyclo[3.1.0]hexan-3-one Ethylene Ketal (235)



Benzyltriethylammonium chloride (1 mg, 5.20 μ mol), sodium hydroxide (63 mg, 1.57 mmol) and bromoform (50 μ L, 130 mg, 0.52 mmol) were added to a solution of ketal **241** (80 mg, 0.26 mmol) in dichloromethane (0.5 mL). The flask containing the resulting yellow solution was then fitted with a reflux condenser and subjected to sonication, without external temperature control, for 2 hours. Upon completion, a small amount of CeliteTM was added in to the reaction mixture which was filtered through a 1 cm plug of CeliteTM. This plug was washed with dichloromethane (25 mL) and concentration of the combined filtrates under reduced pressure afforded a brown oil. Subjection of this material to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.4$ in 1:9 v/v ethyl acetate/hexane) then delivered the *title compound* **235** (95 mg, 77%) as a pale-yellow oil.

^1H NMR (300 MHz) δ 7.32–7.21 (complex m, 5H), 7.16–7.07 (complex m, 5H), 3.86–3.83 (complex m, 2H), 2.82–2.37 (complex m, 4H), 2.26–2.10 (complex m, 4H), 1.83–1.72 (complex m, 2H).

^{13}C NMR (75 MHz) δ 137.1 (C), 136.9 (C), 129.5 (2 x CH, overlapping), 129.4 (2 x CH, overlapping), 128.4 (4 x CH, overlapping), 126.7 (CH), 126.6 (CH), 123.2 (C), 81.3 (CH), 80.1 (CH), 44.7 (C), 41.0 (CH₂), 40.9 (CH₂), 39.1 (CH₂), 38.8 (CH₂), 35.5 (CH), 35.1 (CH).

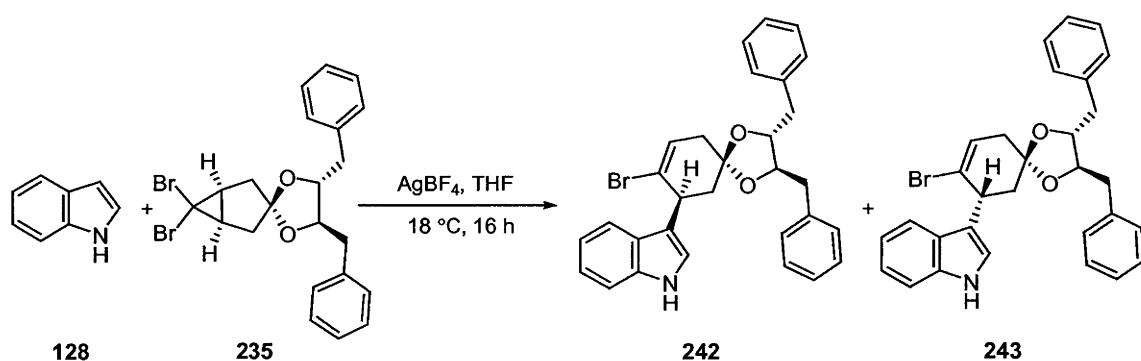
IR (neat) ν_{max} 3027, 2925, 2853, 1734, 1603, 1495, 1454, 1304, 1191, 1117, 1078, 745, 700, 535 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 480, 478 and 476 [M^+ , all <1%], 399 and 397 [($\text{M}-\text{Br}$) $^+$, both 35], 293 (5), 266 (22), 207 (14), 145 (8), 133 (28), 129 (23), 105 (13), 91 (100), 67 (24).

HRMS Found M^+ , 479.9945. Calculated for $\text{C}_{22}\text{H}_{23}^{81}\text{Br}_2\text{O}_2$ M^+ , 479.9944.

Specific Rotation $[\alpha]_{\text{D}} -3$ (c 0.2, CHCl_3).

(2'*R*,3'*R*,7'*S*)-3-(8'-Bromo-2,3-dibenzyl-1',4'-dioxaspiro[4.5]dec-8'-en-7'-yl)-indole (242) and (2'*R*,3'*R*,7'*R*)-3-(8'-Bromo-2,3-dibenzyl-1',4'-dioxaspiro[4.5]dec-8'-en-7'-yl)-indole (243)



A magnetically stirred solution of cyclopropane **235** (55 mg, 0.12 mmol) and indole (**128**) (13 mg, 0.12 mmol) in anhydrous THF (2 mL) and maintained under a nitrogen atmosphere was treated, in one portion, with silver tetrafluoroborate (45 mg, 0.23 mmol). The ensuing mixture was protected from light and stirring continued at room temperature for 12 hours. The resulting suspension was filtered through a plug of Celite™ which was washed with ethyl acetate (25 mL). Concentration of the combined filtrates under reduced pressure and subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions ($R_f = 0.2$), an inseparable mixture[§] of the *title compounds* **242** and **243** (44 mg, 72%) as a pale-yellow oil.

¹H NMR (300 MHz, CD₃COCD₃) δ 10.11 (s, 1H), 10.07 (s, 1H), 7.71 (d, $J = 7.8$ Hz, 2H), 7.56 (d, $J = 7.8$ Hz, 2H), 7.41-7.08 (complex m, 22H), 7.01 (dq, $J = 1.2$ Hz, 2H), 6.82 (s, 1H), 6.79 (s, 1H), 6.13 (m, 1H), 6.00-5.97 (complex m, 1H), 4.32-3.90 (complex m, 6H), 3.04-2.52 (complex m, 8H), 2.52-1.83 (complex m, 8H).

¹³C NMR (75 MHz, CD₃COCD₃) δ 138.3 (2 x C, overlapping), 132.7 (2 x C, overlapping), 130.2 (CH), 130.2 (CH), 130.0 (4 x CH, overlapping), 129.8 (4 x CH, overlapping), 128.7 (4 x CH, overlapping), 127.9 (4 x CH, overlapping), 127.7 (4 x CH, overlapping), 126.9 (2 x C, overlapping), 126.7 (2 x C, overlapping), 124.0 (C), 123.8 (C), 121.7 (2 x CH, overlapping), 119.3 (2 x CH, overlapping), 119.1 (2 x CH, overlapping), 118.6 (2 x CH, overlapping), 112.0 (2 x CH, overlapping), 107.7 (2 x C, overlapping), 107.0 (2 x C, overlapping), 81.5 (CH), 81.4 (CH), 81.2 (CH), 80.8 (CH), 42.8 (CH₂), 42.7 (CH₂), 42.4 (CH), 42.3 (CH), 41.9 (CH₂), 41.7 (CH₂), 39.7 (CH₂), 39.4 (CH₂), 39.3 (CH₂), 39.1 (CH₂).

IR (CH₂Cl₂) ν_{\max} 3426, 3061, 3028, 2925, 2854, 1716, 1603, 1495, 1454, 1362, 1243, 1108, 1075, 913, 822, 743, 700 cm⁻¹.

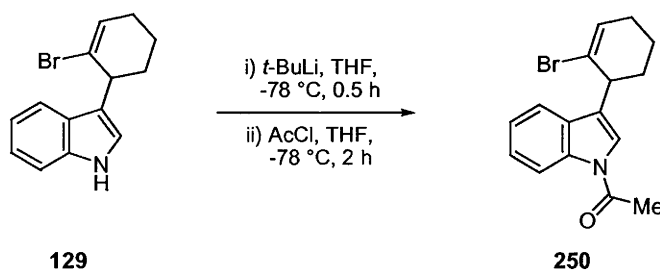
[§] HPLC analysis of this compound was conducted utilising the following: Alltima 250 x 46 mm 5 micron C18 column with guard cartridge and with 3:7 v/v MeCN:H₂O as the eluting solvent, (R_t 42.67 and 44.63 min).

Mass Spectrum (EI, 70 eV) m/z 515 and 513 [M^+ , both 2%], 207 (8), 167 (15), 149 (38), 135 (50), 111 (16), 105 (34), 81 (46), 69 (100), 57 (82), 43 (98).

HRMS Found M^+ , 515.1260. Calculated for $C_{30}H_{28}^{81}BrNO_2 M^+$, 515.1283.

Found M^+ , 513.1306. Calculated for $C_{30}H_{28}^{79}BrNO_2 M^+$, 513.1303.

1-[3'-(2''-Bromocyclohex-2''-enyl)-indol-1'-yl]ethanone (**250**)



t-BuLi (0.6 mL of a 1.7 M solution in pentane, 1.08 mmol) was added, dropwise, to a magnetically stirred solution of bromoalkene **129** (100 mg, 0.36 mmol) in anhydrous THF (2 mL) whilst being maintained at $-78\text{ }^{\circ}\text{C}$ (dry ice/acetone cooling bath) under a nitrogen atmosphere. The resulting solution was stirred for 1 hour before being transferred, *via* cannula, into a magnetically stirred solution of acetyl chloride (30 μL , 28 mg, 0.36 mol) in THF (1 mL), also maintained under a nitrogen atmosphere. After a further 2 hours TLC analysis indicated that the reaction had reached completion so it was quenched, at $-78\text{ }^{\circ}\text{C}$, with NH_4Cl (4 mL of a saturated aqueous solution). The ensuing mixture was allowed to stir for a further 10 minutes at ambient temperature then poured into water (5 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic phases were washed with brine (1 x 15 mL) then dried (MgSO_4), filtered and concentrated under reduced pressure to provide an orange-yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.6$) afforded the *title compound 250* (95 mg, 83%) as an orange oil.

$^1\text{H NMR}$ (300 MHz) δ 8.45 (d, $J = 7.2$ Hz, 1H), 7.54 (d, $J = 7.2$ Hz, 1H), 7.37 (dt, $J = 7.2$ and 1.2 Hz, 1H), 7.30 (dt, $J = 7.2$ and 1.2 Hz, 1H), 7.21 (s, 1H), 6.37 (dt, $J = 4.2$ and 1.2 Hz, 1H),

3.95 (broad s, 1H), 2.65 (s, 3H), 2.54-2.18 (complex m, 2H), 2.13-2.09 (complex m, 2H), 1.66-1.57 (complex m, 2H).

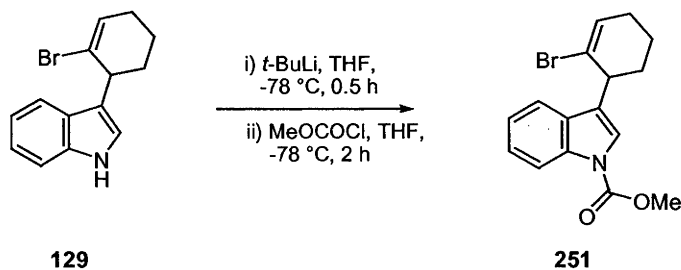
^{13}C NMR (75 MHz) δ 151.7 (C), 131.9 (CH), 131.5 (C), 125.6 (C), 125.2 (CH), 123.6 (C), 123.3 (2 x CH, overlapping), 122.8 (C), 118.7 (CH), 116.8 (CH), 41.0 (CH), 30.5 (CH₂), 27.8 (CH₂), 24.2 (CH₃), 17.8 (CH₂).

IR (neat) ν_{max} 3436, 2936, 2859, 1680, 1641, 1605, 1564, 1454, 1376, 1307, 1259, 1219, 1151, 1091, 1061, 1016, 985, 898, 787, 765, 742, 603, 565 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 319 and 317 [M^+ , both 38%], 277 and 275 (both 21), 249 and 247 (both 6), 196 (30), 167 (44), 139 (12), 117 (100), 77 (10).

HRMS Found M^+ , 317.0409. Calculated for $\text{C}_{16}\text{H}_{16}^{79}\text{BrNO}$ M^+ , 317.0410.

Methyl 3-(2'-Bromocyclohex-2'-enyl)-indole-1-carboxylate (251)



t-BuLi (0.1 mL of a 2.38 M solution in pentane, 0.24 mmol) was added, dropwise, to a magnetically stirred solution of bromoalkene **129** (40 mg, 0.11 mmol) in anhydrous THF (0.8 mL) whilst being maintained at -78 $^\circ\text{C}$ (dry ice/acetone cooling bath) under a nitrogen atmosphere. The resulting solution was stirred for 0.5 hours at -78 $^\circ\text{C}$ then a solution of methyl chloroformate (10 μL , 12 mg, 0.13 mol) in THF (0.1 mL) was added. After a further 2 hours TLC analysis indicated that the reaction had reached completion so it was quenched at -78 $^\circ\text{C}$, with NH_4Cl (1 mL of a 25% w/v aqueous solution which had been buffered to pH 8

with a 25% aqueous NH_4OH solution). The ensuing mixture was allowed to stir for a further 10 minutes at ambient temperatures then was poured into water (5 mL) and extracted with ether (3 x 10 mL). The combined organic fractions were washed with brine (1 x 15 mL) then dried (MgSO_4), filtered and concentrated under reduced pressure to provide an orange-yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) afforded, after concentration of the relevant fractions ($R_f = 0.6$), the *title compound 251* (28 mg, 75%) as a pale-orange oil.

$^1\text{H NMR}$ (300 MHz) δ 8.21 (d, $J = 7.5$ Hz, 1H), 7.56 (dq, $J = 7.5$ and 0.6 Hz, 1H), 7.43 (s, 1H), 7.36 (dt, $J = 7.5$ and 1.2 Hz, 1H), 7.27 (dt, $J = 7.5$ and 1.2 Hz, 1H), 6.35 (dt, $J = 3.6$ and 1.2 Hz, 1H), 4.04 (s, 3H), 3.93 (broad s, 1H), 2.23-2.19 (complex m, 2H), 2.15-1.97 (complex m, 2H), 1.65-1.56 (complex m, 2H).

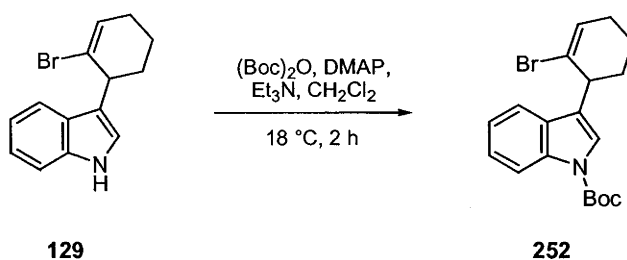
$^{13}\text{C NMR}$ (75 MHz) δ 151.2 (C), 135.7 (C), 131.5 (CH), 129.3 (C), 124.5 (CH), 123.5 (CH), 122.8 (C), 122.6 (CH), 122.5 (C), 118.8 (CH), 115.2 (CH), 53.7 (CH_3), 40.9 (CH), 30.4 (CH_2), 27.6 (CH_2), 17.6 (CH_2).

IR (neat) ν_{max} 3436, 3119, 2937, 2859, 1740, 1641, 1607, 1568, 1455, 1375, 1307, 1257, 1219, 1150, 1091, 1068, 1019, 985, 938, 895, 845, 808, 787, 764, 746, 600, 565 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 335 and 333 [M^+ , both 33%], 277 and 275 (14 and 12), 254 [$(\text{M}-\text{Br})^+$, 31], 226 (8), 194 (26), 175 (100), 154 (6), 130 (12), 117 (46), 79 (8).

HRMS Found M^+ , 335.0340. Calculated for $\text{C}_{16}\text{H}_{16}^{81}\text{BrNO}_2 \text{M}^+$, 335.0344.

Found M^+ , 333.0359. Calculated for $\text{C}_{16}\text{H}_{16}^{79}\text{BrNO}_2 \text{M}^+$, 333.0364.

***tert*-Butyl 3-(2-Bromocyclohex-2-enyl)-indole-1-carboxylate (252)**

Di-*tert*-butyl dicarbonate (1.3 g, 5.20 mmol), DMAP (630 mg, 5.20 mmol) and triethylamine (0.7 mL, 520 mg, 5.20 mmol) were added to a magnetically stirred solution of indole **129** (950 mg, 3.40 mmol) in anhydrous CH_2Cl_2 (17 mL) maintained under a nitrogen atmosphere. The ensuing orange solution was then stirred at 18 °C for 2 hours before being poured into brine (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine (1 x 150 mL), then dried (MgSO_4), filtered and concentrated under reduced pressure to provide a yellow solid. This material was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.4$) delivered the *title carbamate* **252** (1.2 g, 92%) as a clear, colourless oil.

^1H NMR (300 MHz) δ 8.12 (d, $J = 7.2$ Hz, 1H), 7.54 (d, $J = 7.2$ Hz, 1H), 7.41 (s, 1H), 7.31 (dt, $J = 7.2$ and 1.2 Hz, 1H), 7.23 (dt, $J = 7.2$ and 1.2 Hz, 1H), 6.34 (dt, $J = 4.2$ and 1.2 Hz, 1H), 3.92 (broad s, 1H), 2.24-2.18 (complex m, 2H), 2.14-1.97 (complex m, 2H), 1.68 (s, 9H), 1.65-1.59 (complex m, 2H).

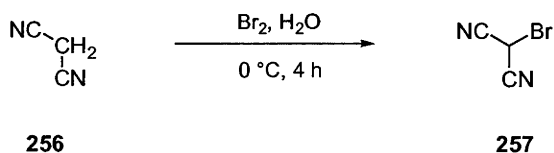
^{13}C NMR (75 MHz) δ 152.1 (C), 135.7 (C), 131.5 (CH), 131.1 (C), 124.2 (CH), 123.3 (C), 122.3 (CH), 121.9 (C), 118.9 (CH), 115.4 (CH), 109.5 (CH), 79.3 (C), 41.0 (CH), 31.2 (CH_2), 30.7 (CH_2), 28.2 (3 x CH_3), 27.6 (CH_2).

IR (neat) ν_{max} 3443, 3052, 2978, 2934, 2862, 1732, 1642, 1607, 1568, 1475, 1452, 1429, 1370, 1308, 1257, 1219, 1158, 1089, 1065, 1043, 1021, 983, 937, 896, 857, 810, 764, 745, 702, 652, 590 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 377 and 375 [M^{+} , both 28%], 321 and 319 (48 and 46), 304 and 302 (both 9), 277 and 275 (25 and 26), 240 (30), 196 (36), 180 (15), 161 (45), 139 (14), 117 (66), 79 (15), 57 (100).

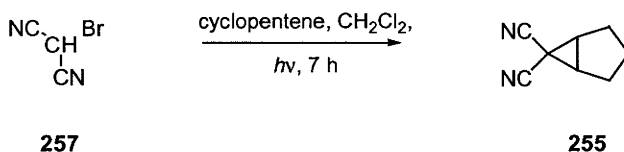
HRMS Found M^{+} , 375.0833. Calculated for $C_{19}H_{22}BrNO_2$ M^{+} , 375.0834.

Bromodicyanomethane (**257**)



Following a procedure reported by Boldt and co-workers,¹² bromine (4 mL, 12.2 g, 76 mmol) was added in small portions to a vigorously stirred suspension of malononitrile (**256**) (5.0 g, 76 mmol) in water (57 mL) maintained at 0 °C (ice-water bath). After stirring had continued for 4 hours the reaction mixture was filtered and the pale-brown crystalline material thus obtained washed with ice-water. The resulting solid was then recrystallised (twice from chloroform) to afford the title halide **257** (2.5 g, 50%) as a colourless crystalline solid, mp. 63-66 °C (lit.¹² mp. 64-65 °C).

6,6-Dicyanobicyclo[3.1.0]hexane (**255**)



Following procedures previously described in the literature for the cyclopropanation of cyclohexene,^{12,13} a solution of cyclopentene (**279**) (300 mg, 4.50 mmol) in degassed CH_2Cl_2 (6 mL) was added, in one portion, to bromodicyanomethane (**257**) (500 mg, 3.50 mmol). The

resulting mixture was deoxygenated and then subjected to irradiation, whilst being maintained under a nitrogen atmosphere, for 7 hours using a Phillips 125 W HPL-N lamp (the lamp was initially placed at a distance of approximately 20 cm from the reaction mixture and varied accordingly to maintain a maximum reaction temperature of 35 °C). The lamp was then switched off and a solution of triethylamine (0.6 mL, 420 mg, 4.10 mmol) in CH₂Cl₂ (3 mL) added to the reaction mixture. Stirring continued for a further 0.5 hours then the reaction mixture was washed with HCl (1 x 8 mL of a 2 M aqueous solution) and water (1 x 8 mL). Sodium hydroxide (8 mL of a 2 M aqueous solution) was then added to the separated organic phase and the ensuing mixture stirred at ambient temperatures for a further 1.5 hours. After this time the separated organic phase was washed with water (1 x 10 mL), sodium hydrogen sulphite (1 x 10 mL of a saturated aqueous solution) and water (1 x 10 mL) before being dried (Na₂SO₄), filtered and concentrated under reduced pressure to provide an orange solid. Recrystallisation (methanol/hexane) of this material afforded the title compound **255** (200 mg, 45%) as pale-orange crystals, mp. 33-35 °C. (lit.¹⁴ mp. 34-35 °C).

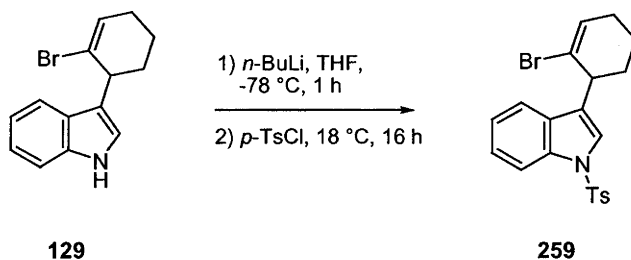
¹H NMR (300 MHz) δ 2.55 (d, *J* = 3.9 Hz, 2H), 2.28-2.08 (complex m, 4H), 1.94-1.64 (complex m, 2H).

¹³C NMR (75 MHz) δ 115.2 (C), 112.9 (C), 38.7 (2 x CH), 26.3 (2 x CH₂), 21.5 (2 x CH₂), 8.8 (C).

IR (CH₂Cl₂) ν_{max} 3064, 2945, 2872, 2244, 1614, 1478, 1447, 1356, 1328, 1291, 1262, 1232, 1164, 1056, 1012, 958, 939, 872, 789, 669, 578 cm⁻¹.

Mass Spectrum (GC-MS) *m/z* 131 [(M-H)⁺, 100%], 104 (73), 92 (13), 78 (40), 67 (57), 51 (20).

3-(2-Bromocyclohex-2-enyl)-1-tosyl-indole (259)



n-BuLi (1.2 mL of a 1.6 M solution in hexane, 1.90 mmol) was added, dropwise, to a magnetically stirred solution of indole **129** (520 mg, 1.90 mmol) in anhydrous THF (8 mL) which was maintained at -78°C (dry ice/acetone bath) under a nitrogen atmosphere. The ensuing mixture was allowed to warm to 0°C , stirred for 1 hour at this temperature then re-cooled to -78°C . *p*-Toluenesulfonyl chloride (390 mg, 2.10 mmol) was then added and the reaction mixture allowed to warm to ambient temperatures and stirred for a further 16 hours. After this time water (8 mL) was added to quench the reaction and the separated organic phase then extracted with diethyl ether (3 x 30 mL). The combined organic phases were washed with brine (1 x 50 mL), then dried (MgSO_4), filtered and concentrated under reduced pressure to afford a brown oil. Subjection of this material to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.3$) then delivered the *title compound* **259** (700 mg, 87%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 8.03 (d, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 8.1$ Hz, 1H), 7.47 (s, 1H), 7.31 (t, $J = 8.1$ Hz, 1H), 7.23 (t, $J = 8.1$ Hz, 1H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.35 (t, $J = 3.6$ Hz, 1H), 3.90 (broad s, 1H), 2.42 (d, $J = 4.8$ Hz, 1H), 2.24 (s, 3H), 2.19-2.18 (complex m, 1H), 2.11-1.90 (complex m, 2H), 1.60-1.48 (complex m, 2H).

$^{13}\text{C NMR}$ (75 MHz) δ 144.6 (C), 135.5 (C), 134.7 (C), 132.0 (C), 129.8 (CH), 129.6 (2 x CH, overlapping), 126.8 (CH), 126.6 (CH), 124.8 (CH), 124.5 (CH), 123.9 (C), 123.1 (CH), 122.3 (C), 119.1 (CH), 113.8 (CH), 40.7 (CH), 29.9 (CH_2), 27.4 (CH_2), 21.3 (CH_2), 17.1 (CH_3).

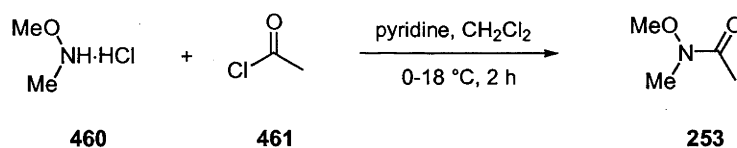
IR (neat) ν_{\max} 3403, 3051, 2960, 2934, 2874, 2590, 1919, 1734, 1642, 1598, 1494, 1447, 1362, 1306, 1292, 1280, 1209, 1188, 1176, 1120, 1097, 1054, 1019, 990, 939, 884, 814, 786, 747, 704, 675, 664, 634, 589, 575, 555, 539, 491 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 431 and 429 [M^+ , 32 and 31%], 271 (43), 194 (35), 173 (73), 155 (64), 117 (9), 91 (100), 77 (9), 65 (29).

HRMS Found M^+ , 431.0372. Calculated for $\text{C}_{21}\text{H}_{20}^{81}\text{BrNO}_2\text{S M}^+$, 431.0378.

Found M^+ , 429.0392. Calculated for $\text{C}_{21}\text{H}_{20}^{79}\text{BrNO}_2\text{S M}^+$, 429.0398.

***N*-methoxy-*N*-methylacetamide (253)**



Following a procedure reported by Oster and Harris,¹⁵ a magnetically stirred solution of acetyl chloride (**461**) (6 mL, 6.6 g, 84 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (**460**) (9.0 g, 92 mmol) in CH_2Cl_2 (125 mL) was cooled to 0 °C (ice/water bath) and slowly treated with pyridine (15 mL, 14.6 g, 0.19 mol). The ensuing mixture was then allowed to warm to 18 °C and the resulting white suspension stirred at this temperature for a further 2 hours. The reaction mixture was then partitioned between brine (200 mL) and diethyl ether (200 mL) and the separated aqueous phase extracted with additional diethyl ether (2 x 250 mL). The combined organic fractions were washed with HCl (2 x 250 mL of a 1 M aqueous solution) and brine (1 x 400 mL), before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash column chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) then provided, after concentration of the relevant fractions ($R_f=0.3$), the title amine **253**¹⁵ (5.5 g, 64%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 3.69 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 2.13 (s, 3H, CH_3).

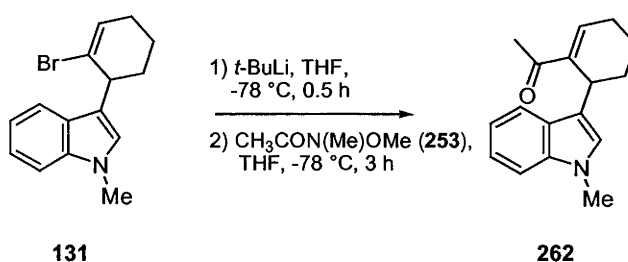
^{13}C NMR (75 MHz) δ 171.3 (C), 60.5 (CH_3), 31.3 (CH_3), 19.2 (CH_3).

IR (neat) ν_{max} 3474, 2941, 1750, 1724, 1667, 1642, 1461, 1439, 1417, 1385, 1244, 1184, 1029, 968, 933, 718, 585, 498 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 104 [$(\text{M}+\text{H})^+$, 17%], 103 [M^+ , 28], 73 (7), 61 (100), 60 (40).

HRMS Found M^+ , 103.0634. Calculated for $\text{C}_4\text{H}_9\text{NO}$ M^+ , 103.0633.

1-[6-(1-Methyl-indol-3-yl)cyclohex-1-enyl]ethanone (262)



t-BuLi (0.6 mL of a 1.5 M solution in pentane, 0.97 mmol) was added, dropwise, to a magnetically stirred solution of indole **131** (140 mg, 0.48 mmol) in anhydrous THF (2.4 mL) maintained, under a nitrogen atmosphere, at -78 °C (dry ice/acetone cooling bath). The resulting orange solution was allowed to stir at -78 °C for 30 minutes before a solution of *N*-methoxy-*N*-methylacetamide (**253**) (60 mg, 0.58 mmol) in THF (1.2 mL) was added as rapidly as possible. The ensuing pale-yellow solution was magnetically stirred at -78 °C for a further 3 hours then quenched, at -78 °C, with NH_4Cl (4 mL of a 25% w/v aqueous solution which had been buffered to pH 8 with a 25% aqueous NH_4OH solution). The reaction mixture was then extracted with ethyl acetate (3 x 20 mL) and the combined organic fractions then washed with brine (1 x 50 mL), before being dried (K_2CO_3), filtered and concentrated under reduced pressure to afford a mustard-coloured oil. Subjection of this material to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the

appropriate fractions ($R_f = 0.2$) delivered the *desired product 262* (80 mg, 67%) as a pale-brown solid.

$^1\text{H NMR}$ (300 MHz) δ 7.68 (d, $J = 7.8$ Hz, 1H), 7.28-7.19 (complex m, 2H), 7.14-7.08 (complex m, 2H), 6.54 (s, 1H), 4.38 (broad s, 1H), 3.70 (s, 3H, CH_3), 2.36-2.30 (complex m, 1H), 2.23 (s, 3H, CH_3), 2.05-1.99 (complex m, 2H), 1.85-1.74 (complex m, 2H), 1.58-1.50 (complex m, 1H).

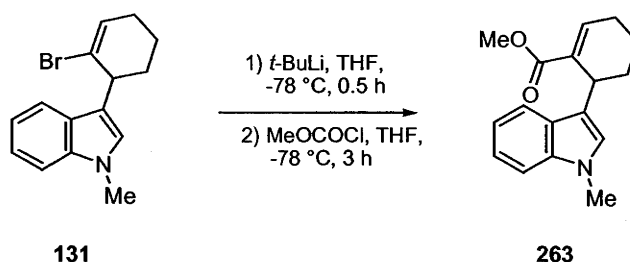
$^{13}\text{C NMR}$ (75 MHz) δ 198.8 (C), 140.8 (C), 140.2 (CH), 137.1 (C), 126.9 (C), 126.5 (CH), 121.2 (CH), 118.8 (CH), 118.3 (CH), 117.6 (C), 109.0 (CH), 32.3 (CH_3), 29.3 (CH_2), 28.4 (CH), 25.8 (CH_2), 25.7 (CH_2), 16.9 (CH_3).

IR (CH_2Cl_2) ν_{max} 3051, 2933, 2855, 2818, 1667, 1636, 1613, 1546, 1472, 1423, 1373, 1350, 1328, 1254, 1232, 1154, 1118, 1061, 1013, 970, 902, 797, 739, 697, 621, 593, 549 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 253 [M^+ , 100%], 238 [($\text{M}-\text{CH}_3$) $^+$, 25], 224 (37), 210 (43), 182 (48), 167 (22), 157 (14), 144 (25), 131 (97), 115 (10), 103 (5), 90 (8), 77 (10), 43 (22).

HRMS Found M^+ , 253.1464. Calculated for $\text{C}_{17}\text{H}_{19}\text{NO}$ M^+ , 253.1467.

Methyl 6-(1'-Methyl-indol-3'-yl)cyclohex-1-ene Carboxylate (**263**)



Following the procedure described above for the synthesis of compound **262**, $t\text{-BuLi}$ (0.7 mL of a 1.5 M solution in pentane, 1.03 mmol) was added, dropwise, to a magnetically stirred

solution of indole **131** (150 mg, 0.52 mmol) in anhydrous THF (3 mL) which was maintained, under a nitrogen atmosphere, at $-78\text{ }^{\circ}\text{C}$ (dry ice/acetone cooling bath). The resulting orange solution was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 0.5 hours then a solution of methyl chloroformate (48 μL , 58 mg, 0.62 mmol) in THF (1 mL) was added as rapidly as possible. The ensuing pale-yellow solution was stirred magnetically at $-78\text{ }^{\circ}\text{C}$ for a further 3 hours then quenched, at $-78\text{ }^{\circ}\text{C}$, with NH_4Cl (4 mL of a 25% w/v aqueous solution which had been buffered to pH 8 with a 25% aqueous NH_4OH solution). The ensuing mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic fractions then washed with brine (1 x 50 mL), before being dried (K_2CO_3), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.3$) delivered the *title ester 263* (110 mg, 79%) as a pale-orange oil.

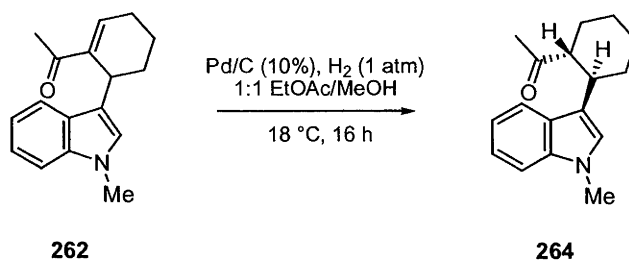
$^1\text{H NMR}$ (300 MHz) δ 7.70 (dq, $J = 8.1$ and 0.6 Hz, 1H), 7.28 (dq, $J = 8.1$ and 0.6 Hz, 1H), 7.23 (dd, $J = 6.6$ and 1.2 Hz, 1H), 7.18 (t, $J = 3.9$ Hz, 1H), 7.12 (dt, $J = 8.1$ and 1.2 Hz, 1H), 6.61 (s, 1H), 4.30 (broad s, 1H), 3.71 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 2.37-2.15 (complex m, 2H), 2.05-1.98 (complex m, 1H), 1.87-1.75 (complex m, 1H), 1.56-1.47 (complex m, 2H).

$^{13}\text{C NMR}$ (75 MHz) δ 168.0 (C), 140.4 (CH), 137.4 (C), 132.3 (C), 127.1 (CH), 126.7 (C), 121.4 (CH), 119.0 (CH), 118.5 (CH), 117.9 (C), 109.1 (CH), 51.5 (CH_3), 32.6 (CH_2), 30.2 (CH), 28.6 (CH_2), 25.7 (CH_2), 16.9 (CH_3).

IR (neat) ν_{max} 3051, 2934, 1714, 1645, 1614, 1547, 1471, 1435, 1372, 1328, 1257, 1242, 1203, 1154, 1131, 1119, 1093, 1068, 1013, 975, 942, 914, 862, 841, 808, 738, 670, 565 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 269 [M^+ , 100%], 240 (45), 209 (81), 181 (69), 167 (32), 131 (98), 90 (18), 77 (17).

HRMS Found M^+ , 269.1407. Calculated for $\text{C}_{17}\text{H}_{19}\text{NO}_2$ M^+ , 269.1416.

(1*RS*,2*SR*)-1-[2-(1'-methyl-indol-3'-yl)cyclohexyl]ethanone (264)

A solution of enone **262** (240 mg, 0.95 mmol) in ethyl acetate/methanol (10 mL of a 1:1 v/v mixture) and treated with 10% Pd/C (120 mg) then stirred magnetically at 18 °C under 1 atmosphere of hydrogen for 16 hours. After this time TLC analysis revealed that all of the starting material had been consumed so the reaction mixture was filtered through a plug of Celite™ which was washed with methanol (50 mL). Concentration of the combined filtrates under reduced pressure provided a yellow oil that was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions ($R_f = 0.5$) then afforded the *title ketone* **264** (220 mg, 90%) as a yellow oil.

¹H NMR (300 MHz) δ 7.61 (d, $J = 8.1$ Hz, 1H), 7.28 (dd, $J = 8.1$ and 0.6 Hz, 1H), 7.22 (dt, $J = 6.9$ and 1.2 Hz, 1H), 7.11 (dt, $J = 6.9$ and 1.2 Hz, 1H), 6.88 (s, 1H), 3.72 (s, 3H, CH₃), 3.04 (m, 1H), 2.20 (m, 1H), 2.05-1.77 (complex m, 4H), 1.86 (s, 3H, CH₃), 1.58-1.35 (complex m, 4H).

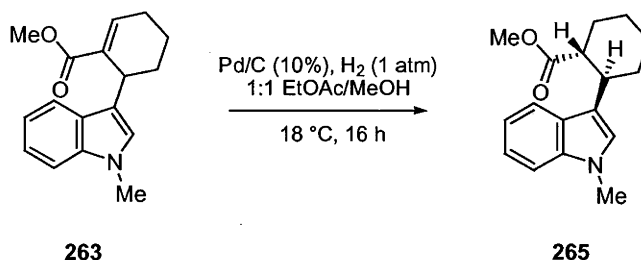
¹³C NMR (75 MHz) δ 211.9 (C), 136.4 (C), 127.6 (C), 126.9 (CH), 121.4 (CH), 118.6 (2 x CH, overlapping), 115.4 (C), 109.1 (CH), 52.5 (CH), 34.2 (CH₃), 32.7 (CH₂), 30.3 (CH), 29.4 (CH₂), 25.3 (CH₂), 23.6 (CH₃), 23.2 (CH₂).

IR (neat) ν_{\max} 2929, 2853, 1703, 1614, 1471, 1447, 1375, 1350, 1247, 1156, 1127, 789 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 255 [M^+ , 89%], 241 (7), 226 (3), 212 (50), 197 (15), 170 (100), 157 (45), 144 (66), 131 (30), 115 (14), 77 (6), 43 (14).

HRMS Found M^+ , 255.1634. Calculated for $C_{17}H_{21}NO M^+$, 255.1623.

(1*RS*,2*SR*)-Methyl 2-(1-Methyl-indol-3-yl)cyclohexane Carboxylate (265)



10% Pd/C (30 mg) was added to a solution of compound **263** (60 mg, 0.22 mmol) in ethyl acetate/methanol (2 mL of a 1:1 v/v mixture). The resulting black solution was then magnetically stirred at 18 °C under 1 atmosphere of hydrogen for 16 hours. After this time, the reaction mixture was filtered through a plug of Celite™ which was washed with methanol (30 mL). Concentration of the filtrates under reduced pressure provided a yellow oil which was purified by preparative thick layer chromatography (silica, 0.50 mm, 60F-254, 1:4 v/v ethyl acetate/hexane elution). In this manner two bands, A and B, were obtained.

Extraction and concentration of band A ($R_f = 0.5$) afforded the *desired compound* **265** (30 mg, 50% - at 57% conversion).

¹H NMR (300 MHz) δ 7.57 (d, $J = 7.8$ Hz, 1H), 7.27 (d, $J = 7.8$ Hz, 1H), 7.19 (dt, $J = 7.2$ and 1.2 Hz, 1H), 7.08 (dt, $J = 7.2$ and 1.2 Hz, 1H), 6.95 (s, 1H), 3.73 (s, 3H, CH₃), 3.40 (s, 3H, CH₃), 3.01 (m, 1H), 2.35-2.24 (complex m, 1H), 1.88-1.60 (complex m, 6H), 1.56-1.44 (complex m, 2H).

¹³C NMR (75 MHz) δ 175.1 (C), 130.9 (C), 126.5 (CH), 125.7 (C), 121.3 (CH), 118.8 (CH), 118.5 (CH), 114.1 (C), 109.0 (CH), 50.9 (CH₃), 45.3 (CH), 37.1 (CH₃), 34.9 (CH), 33.8 (CH₂), 27.2 (CH₂), 24.4 (CH₂), 23.1 (CH₂).

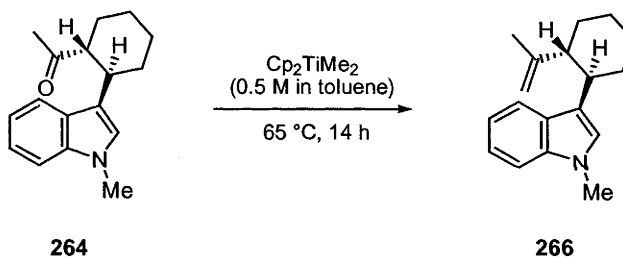
IR (CH₂Cl₂) ν_{\max} 2924, 2854, 1735, 1464, 1376, 1244, 1162, 803, 737 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 271 [M⁺, 35%], 223 (38), 184 (18), 170 (39), 168 (36), 141 (33), 128 (15), 115 (28), 92 (8), 77 (49), 64 (13), 51 (13).

HRMS Found M⁺, 271.1576. Calculated for C₁₇H₂₁NO₂ M⁺, 271.1572.

Extraction and concentration of band B ($R_f = 0.3$ in 1:9 v/v ethyl acetate elution) furnished the starting ester **263** (26 mg, 43%) as a pale-orange oil. This material was identical, in all respects, to an authentic sample.

(1*SR*,2*RS*)-1-Methyl-3-[2'-(propen-2'-yl)cyclohexan-1'-yl]-indole (266)



Following a published procedure¹⁶ for the titanium-mediated methylenation of ketones in general, dimethyltitanocene (3.3 mL of a 0.5 M toluene solution, 1.65 mmol - prepared according to a literature procedure,¹⁷) was added to ketone **264** (140 mg, 0.55 mmol) contained in a round-bottomed flask. The resulting orange solution was protected from light and heated at 65 °C under an argon atmosphere for 14 hours. After this time TLC analysis indicated that the reaction had reached completion so it was diluted with hexane (20 mL). The ensuing yellow-orange precipitate was removed by filtration and the combined filtrates concentrated under reduced pressure to provide a bright-yellow oil. Subjection of this residue to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.3$) then afforded the *title alkene* **266** (120 mg, 86%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 7.60 (d, $J = 7.8$ Hz, 1H), 7.27 (d, $J = 7.8$ Hz, 1H), 7.20 (dt, $J = 6.9$ and 1.2 Hz, 1H), 7.08 (dt, $J = 6.9$ and 1.2 Hz, 1H), 6.99 (s, 1H), 4.68 (d, $J = 7.8$ Hz, 2H), 3.75 (s, 3H), 2.44 (m, 1H), 2.06-1.97 (complex m, 1H), 1.93-1.74 (complex m, 4H), 1.58 (t, $J = 0.6$ Hz, 3H, CH_3), 1.49-1.39 (complex m, 4H).

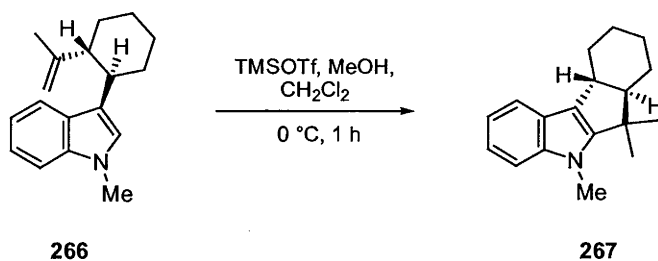
$^{13}\text{C NMR}$ (75 MHz) δ 149.1 (C), 136.1 (C), 128.7 (C), 127.1 (CH), 121.1 (CH), 118.9 (CH), 118.2 (CH), 115.3 (C), 109.3 (CH), 109.8 (CH_2), 46.6 (CH), 33.4 (CH), 32.6 (CH_3), 29.7 (CH_2), 26.9 (CH_2), 26.2 (CH_2), 22.6 (CH_2), 21.8 (CH_3).

IR (neat) ν_{max} 3054, 2926, 2852, 1641, 1613, 1464, 1448, 1423, 1374, 1331, 1310, 1287, 1247, 1208, 1154, 1114, 1050, 1014, 885, 798, 768, 737 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 253 [M^+ , 99%], 238 [$(\text{M}-\text{CH}_3)^+$, 12], 210 (10), 196 (25), 182 (17), 170 (100), 157 (66), 144 (89), 131 (23), 115 (18), 97 (12), 83 (13), 77 (13), 69 (10), 57 (20), 41 (19).

HRMS Found M^+ , 253.1830. Calculated for $\text{C}_{18}\text{H}_{23}\text{N}$ M^+ , 253.1830.

(6c*R*,10a*R*)-1,2,6c,7,8,9,10,10a-Octahydro-1,1,2-trimethylindeno[2,1-*b*]indole
(267)



Following a published procedure¹⁸ concerning the cyclisation of a structurally related system, compound **266** (110 mg, 0.44 mmol) was dissolved in CH_2Cl_2 (4.3 mL) and the resulting, magnetically stirred, solution cooled to 0 °C (ice/water bath). TMSOTf (0.2 mL, 290 mg,

1.30 mmol) was then added, followed by methanol (19 μ L, 0.48 mmol). The ensuing mixture was maintained at 0 °C for a further one hour then quenched, at 0 °C, with NaHCO₃ (4 mL of a 5% w/v aqueous solution) and diluted with ethyl acetate (10 mL). The separated organic layer was washed with water (1 x 5 mL) and brine (1 x 5 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure to provide a pink oil. Subjection of this material to preparative thick layer chromatography (silica, 0.50 mm, 60F-254, 1:9 v/v ethyl acetate/hexane elution) afforded two bands, A and B.

Extraction and concentration of band A ($R_f = 0.8$) furnished the *title compound 267* (52 mg, 47% - at 63% conversion) as a pale-yellow oil.

¹H NMR (300 MHz) δ 7.83 (d, $J = 7.8$ Hz, 1H), 7.26 (d, $J = 7.8$ Hz, 1H), 7.12 (dt, $J = 7.8$ and 1.2 Hz, 1H), 7.05 (dt, $J = 7.8$ and 1.2 Hz, 1H), 3.73 (s, 3H, CH₃), 3.27 (m, 1H), 2.46-2.39 (complex m, 1H), 2.21-2.12 (complex m, 1H), 2.05-1.94 (complex m, 1H), 1.73-1.65 (complex m, 2H), 1.43 (d, $J = 3.9$ Hz, 2H), 1.35 (d, $J = 2.1$ Hz, 3H, CH₃), 1.26 (d, $J = 2.1$ Hz, 3H, CH₃), 1.08-1.05 (complex m, 2H).

¹³C NMR (75 MHz) δ 126.3 (C), 125.5 (C), 121.4 (C), 120.4 (C), 119.8 (CH), 118.8 (CH), 118.4 (CH), 109.1 (CH), 53.6 (CH), 37.0 (CH), 30.3 (C), 29.9 (CH₂), 29.7 (CH₂), 26.9 (CH₃), 24.3 (CH₂), 24.1 (2 x CH₃, overlapping), 23.8 (CH₂).

IR (neat) ν_{\max} 3051, 2925, 2854, 1867, 1736, 1610, 1571, 1540, 1466, 1417, 1378, 1362, 1233, 1197, 1158, 1132, 1082, 1013, 917, 796, 738, 721 cm⁻¹.

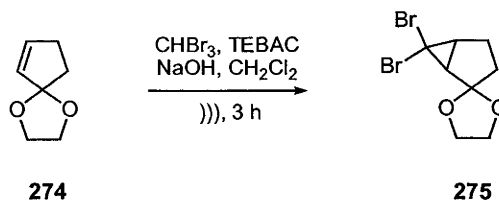
Mass Spectrum (EI, 70 eV) m/z 253 [M^+ , 96%], 238 [(M-CH₃)⁺, 93], 222 (20), 210 (100), 194 (71), 182 (67), 167 (46), 157 (20), 144 (45), 131 (46), 115 (21), 97 (36), 91 (16), 83 (23), 69 (34), 55 (32), 43 (39).

HRMS Found M^+ , 253.1836. Calculated for C₁₈H₂₃N M^+ , 253.1830.

Concentration of band B ($R_f = 0.3$) afforded the starting indole **266** (41 mg, 37% recovery) which was identical, in all respects, to authentic material.

7.4 Experimental Section for Chapter Four

6,6-Dibromobicyclo[3.1.0]hexan-2-one Ethylene Ketal (275)



Benzyltriethylammonium chloride (36 mg, 0.16 mmol), finely ground sodium hydroxide (2.0 g, 50.0 mmol), and bromoform (1.4 mL, 4.0 g, 16.0 mmol) were added, in that order, to a solution of 2-cyclopenten-1-one ethylene ketal (**274**) (0.9 mL, 1.0 g, 7.94 mmol) in dichloromethane (5 mL). The resulting suspension was then subjected to sonication, without external temperature control, for 3 hours after which stage TLC analysis indicated that the reaction had reached completion. Consequently a small amount of Celite™ was added into the reaction mixture and the resulting brown suspension filtered through a 1 cm plug of Celite™ which was washed with dichloromethane (40 mL). Concentration of the combined filtrates under reduced pressure provided a brown oil that was subjected to flash column chromatography (silica, 1:4 → 2:3 v/v ethyl acetate/hexane gradient elution). Concentration of the appropriate fractions ($R_f = 0.5$, 2:3 v/v ethyl acetate/hexane) then afforded the *title cyclopropane 275* (1.1 g, 55%) as a clear, colourless oil.

$^1\text{H NMR}$ (300 MHz) δ 4.05-3.74 (complex m, 4H), 2.90-1.46 (complex m, 6H).

$^{13}\text{C NMR}$ (75 MHz) δ 134.4 (C), 64.1 (CH₂), 64.0 (CH₂), 35.7 (CH), 31.8 (C), 30.2 (CH₂), 26.5 (CH), 21.0 (CH₂).

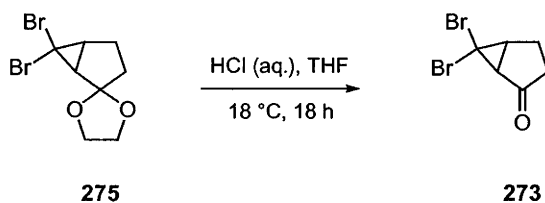
IR (neat) ν_{max} 3458, 2957, 2926, 1738, 1707, 1588, 1458, 1443, 1404, 1342, 1250, 1161, 1121, 1097, 1031, 948, 863, 787, 751 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 300, 298 and 296 [M^+ , all <1%], 256, 254 and 252 (2, 3 and 2), 228, 226 and 224 (3, 6 and 3), 218 and 216 [($\text{M}-\text{HBr}$)⁺, both 10], 214, 212 and 210 (57,

100 and 58), 175 and 173 (both 47), 138 (28), 131 (26), 119 and 117 (both 9), 65 (52), 51 (82), 39 (46).

HRMS Found (M-HBr)⁺, 215.9789. Calculated for C₈H₉⁷⁹BrO₂ (M-HBr)⁺, 215.9786.

6,6-Dibromobicyclo[3.1.0]hexan-2-one (273)



A magnetically stirred solution of ketal **275** (800 mg, 3.14 mmol) in THF (6 mL) was treated with HCl (6 mL of a 2 M aqueous solution). The resulting pale-yellow solution was allowed to stir at ambient temperatures for 18 hours then NaHCO₃ (10 mL of a saturated aqueous solution) was added. Stirring was continued at 18 °C for 10 minutes then the reaction mixture was partitioned between water (20 mL) and diethyl ether (20 mL). The aqueous phase was extracted with diethyl ether (2 x 100 mL) and the combined organic fractions then washed with brine (1 x 100 mL), before being dried (MgSO₄), filtered and concentrated under reduced pressure to provide a pale-yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.2$) then afforded the title compound **273**¹⁹ (630 mg, 78%) as a pale-yellow waxy-like solid, m.p. 5-7 °C.

¹H NMR (300 MHz) δ 2.76 (dt, $J = 6.3$ and 0.6 Hz, 1H), 2.69 (d, $J = 6.3$ Hz, 1H), 2.43-2.08 (complex m, 4H).

¹³C NMR (75 MHz) δ 207.9 (C), 45.4 (CH), 39.7 (C), 36.3 (CH), 28.1 (CH₂), 22.7 (CH₂).

IR (neat) ν_{\max} 3449, 3057, 2940, 2880, 1733, 1581, 1451, 1403, 1297, 1266, 1181, 1146, 1059, 960, 739, 472 cm^{-1} .

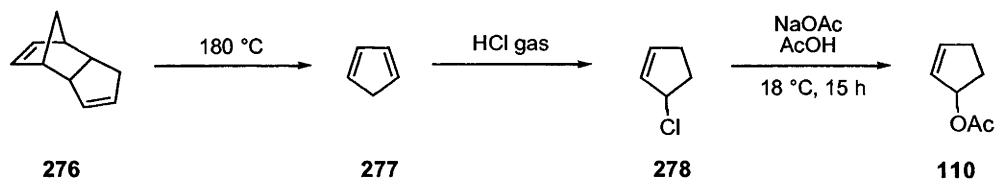
Mass Spectrum (EI, 70 eV) m/z 256, 254 and 252 [M^+ , 2, 3 and 2%], 228, 226 and 224 [(M-CO) $^+$, 1, 2 and 1], 214, 212 and 210 (67, 100 and 69), 175 and 173 [(M-Br) $^+$, both 47], 147 and 145 (13 and 11), 133 and 131 (both 28), 119 and 117 (16 and 15), 65 (69), 51 (30), 39 (49).

HRMS Found (M-CO) $^+$, 227.8788. Calculated for $\text{C}_5\text{H}_6^{81}\text{Br}_2$ (M-CO) $^+$, 227.8795.

Found (M-CO) $^+$, 225.8806. Calculated for $\text{C}_5\text{H}_6^{79}\text{Br}^{81}\text{Br}$ (M-CO) $^+$, 225.8816.

Found (M-CO) $^+$, 223.8834. Calculated for $\text{C}_5\text{H}_6^{79}\text{Br}_2$ (M-CO) $^+$, 223.8836.

3-Acetoxycyclopentene (110)

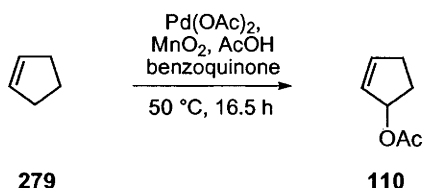


Method A:

The title compound was prepared essentially according to the method of Alder and Flock.²⁰ Thus, dicyclopentadiene (**276**) was cracked over iron filings at 180 °C in a flask fitted with a Vigreux column. Cyclopentadiene (**277**) (23.0 g) distilled over as a clear colourless liquid at 40–46 °C and was collected in a trap cooled to –90 °C (dry ice/methanol bath). HCl gas was then bubbled through the diene, initially held at –90 °C, until one equivalent (12.5 g, 0.35 mol) of the acid had been added. During this process the reaction mixture was maintained below 0 °C and any exiting HCl gas was “scrubbed” by bubbling the exit gases through a bubbler into a saturated aqueous solution of NaHCO_3 . The amount of HCl that had been added was determined by sealing and quickly weighing the flask. Once one equivalent had been added this reaction mixture was immediately poured into an ice-cold suspension of

sodium acetate (37.0 g, 0.45 mol) and glacial acetic acid (156 mL) and the resulting white suspension stirred at 18 °C for 15 hours. The reaction mixture was then poured into water (300 mL) and the organic phase separated. The aqueous phase was then saturated with sodium chloride before being extracted with hexane (3 x 150 mL). Subsequent washing of the combined organic phases with water (2 x 300 mL), NaHCO₃ (2 x 300 mL of a saturated aqueous solution) and brine (1 x 300 mL) led to a solution that was then dried (MgSO₄), filtered and concentrated under reduced pressure to give a yellow liquid. Vacuum distillation (b.p. 26-34 °C/2 mmHg) of this material then afforded the title compound **110** (27.8 g, 63%) as a clear colourless oil (lit.²⁰ b.p. 48 °C/11 mmHg).

Method B:



Following a procedure reported by Hansson *et al.*,²¹ a round-bottom flask containing a magnetically stirred slurry of palladium acetate (560 mg, 2.5 mmol), manganese dioxide (5.2 g, 60.0 mmol) and benzoquinone (1.1 g, 10.0 mmol) in acetic acid (125 mL) was fitted with a reflux condenser and the contents heated at 50 °C for 0.5 hours. Cyclopentene (**279**) (4.4 mL, 3.4 g, 50.0 mmol) was then added and stirring continued at 50 °C for a further 16 hours. The cooled reaction mixture was diluted with pentane/diethyl ether (125 mL of a 1:1 v/v mixture) and the resulting solution stirred at ambient temperatures for 0.5 hours. This solution was then filtered through a CeliteTM pad that was washed with pentane/diethyl ether mix (1 x 125 mL of a 1:1 v/v mixture), water (1 x 125 mL), pentane/diethyl ether mix (1 x 50 mL of a 1:1 v/v mixture) and water (1 x 125 mL). The separated aqueous phase was extracted with pentane/diethyl ether (3 x 250 mL of a 1:1 v/v mixture) and the combined organic fractions were then washed with water (1 x 125 mL) and brine (1 x 500 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure to provide an orange-red oil. Subjection of this material to vacuum distillation (b.p. 26-34 °C/2 mmHg, lit.²¹ b.p. 79-82

$^{\circ}\text{C}/60\text{ mmHg}$) then provided the title acetate **110** (4.1 g, 65%) as a clear, colourless oil. This material was identical, in all respects, with that obtained *via* method A.

$^1\text{H NMR}$ (300 MHz) δ 6.07 (m, 1H), 5.79 (m, 1H), 5.66 (m, 1H), 2.53-2.42 (complex m, 1H), 2.35-2.19 (complex m, 2H), 2.00 (s, 3H, CH_3), 1.84-1.73 (complex m, 1H).

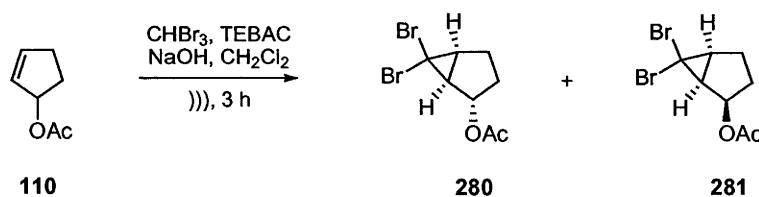
$^{13}\text{C NMR}$ (75 MHz) δ 170.6 (C), 137.2 (CH), 129.0 (CH), 80.1 (CH), 30.8 (CH_2), 29.5 (CH_2), 21.0 (CH_3).

IR (neat) ν_{max} 2928, 1734, 1361, 1241, 1050 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 126 [M^+ , 2%], 83 (29), 67 (52), 66 (79), 55 (15), 43 (100).

HRMS Found M^+ , 126.0683. Calculated for $\text{C}_7\text{H}_{10}\text{O}_2$ M^+ , 126.0681.

(1*SR*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl acetate (280) and (1*SR*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl acetate (281)



Bromoform (10.5 mL, 30.0 g, 0.12 mol) was added to a solution of acetate **110** (7.5 g, 0.06 mol) in CH_2Cl_2 (36 mL) containing benzyltriethylammonium chloride (260 mg, 1.20 mmol) and finely ground sodium hydroxide (14.4 g, 0.36 mol). The resulting dark brown suspension was then subjected to sonication without external temperature control. After 3 hours TLC analysis revealed that all of the starting material had been consumed so a small amount of CeliteTM was added into the reaction mixture. After filtration of this material through a 1 cm plug of CeliteTM and washing of the plug with CH_2Cl_2 (400 mL) the combined filtrates were concentrated under reduced pressure to deliver a dark-brown liquid. Subjection of this

material to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) provided a 4:1 mixture of the desired products **280** and **281**²² (15.0 g, 84%) as a pale-yellow oil. For the purposes of spectroscopic characterisation a small amount of this material was re-subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A [$R_f = 0.3(3)$] afforded compound **280** as a clear, colourless oil.

¹H NMR (300 MHz) δ 5.10 (dd, $J = 6.6$ and 1.8 Hz, 1H), 2.36 (m, 2H), 2.28-2.13 (complex m, 2H), 2.01 (s, 3H, CH₃), 1.90 (m, 1H), 1.70 (m, 1H).

¹³C NMR (75 MHz) δ 170.0 (C), 77.8 (CH), 42.7 (CH), 38.9 (C), 33.5 (CH), 32.8 (CH₂), 27.4 (CH₂), 21.1 (CH₃).

IR (neat) ν_{\max} 3457, 3052, 2937, 2863, 1735, 1455, 1437, 1361, 1313, 1288, 1238, 1172, 1069, 1048, 1020, 994, 885, 753, 604 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 300, 298 and 296 [M^+ , 4, 7 and 4%], 259, 257 and 255 (4, 6 and 3), 241, 239 and 237 (12, 20 and 11), 214, 212 and 210 (9, 17 and 9), 177 and 175 (7 and 9), 159 and 157 (both 34), 133 and 131 (both 2), 119 and 117 (3 and 4), 99 (25), 95 (15), 77 (31), 65 (16), 51 (22), 43 (100).

HRMS Found M^+ , 295.9047. Calculated for C₈H₁₀⁷⁹Br₂O₂ M^+ , 295.9048.

Concentration of fraction B [$R_f = 0.2(7)$] furnished the C-2 epimer **281** as a clear, colourless oil.

¹H NMR (300 MHz) δ 5.45 (dd, $J = 9.3$ and 5.7 Hz, 1H), 2.57 (dd, $J = 7.5$ and 5.7 Hz, 1H), 2.27 (m, 1H), 2.21-2.12 (complex m, 1H), 2.10 (s, 3H, CH₃), 2.08-2.02 (complex m, 2H), 1.90-1.79 (complex m, 1H).

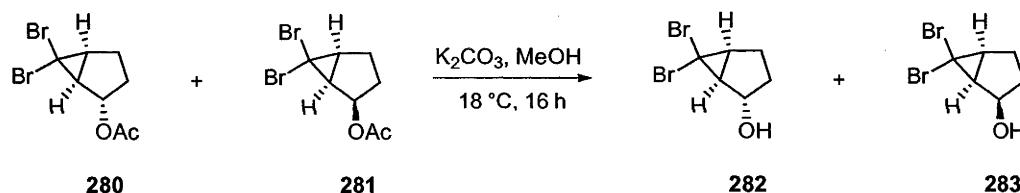
^{13}C NMR (75 MHz) δ 171.0 (C), 77.8 (CH), 39.9 (CH), 38.2 (C), 32.5 (CH), 28.6 (CH₂), 26.5 (CH₂), 21.1 (CH₃).

IR (neat) ν_{max} 3453, 2934, 2862, 1735, 1462, 1441, 1374, 1308, 1240, 1119, 1083, 1054, 1053, 892, 813, 764, 565 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 300, 298 and 296 [M^+ , 3, 6 and 3%], 241, 239 and 237 (12, 31 and 14), 159 and 157 (81 and 83), 77 (93), 43 (100).

HRMS Found M^+ , 295.9032. Calculated for $\text{C}_8\text{H}_{10}^{79}\text{Br}_2\text{O}_2$ M^+ , 295.9048.

(1*SR*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-ol (282) and (1*SR*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-ol (283)



A magnetically stirred solution of a *ca.* 4:1 mixture of acetates (\pm)-**280** and *C2-epi*-(\pm)-**281** (14.5 g, 0.05 mol) in methanol (24.5 mL) was treated, in one portion, with potassium carbonate (11.0 g, 0.08 mol). The resulting solution was stirred at ambient temperatures for 16 hours after which time TLC analysis indicated that the starting materials had been consumed. Consequently the reaction mixture was poured into brine (50 mL) and extracted with CH_2Cl_2 (5 x 150 mL). The combined organic fractions were then washed with water (1 x 300 mL) and brine (1 x 500 mL) before being dried (MgSO_4), filtered and the combined filtrates concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded a *ca.* 4:1 mixture of (\pm)-**282** and (\pm)-**283**²² (9.6 g, 92 %) as a clear colourless oil. This material could be used in the next step in the reaction sequence. For the purposes of spectroscopic

characterisation a small amount of this mixture was re-subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A ($R_f = 0.5$) afforded compound **282** as a clear colourless oil.

$^1\text{H NMR}$ (300 MHz) δ 4.31 (dd, $J = 6.6$ and 1.5 Hz, 1H), 2.40-2.10 (complex m, 4H), 1.91-1.61 (complex m, 3H).

$^{13}\text{C NMR}$ (75 MHz) δ 75.9 (CH), 45.5 (CH), 39.0 (C), 36.3 (CH), 33.9 (CH₂), 27.3 (CH₂).

IR (neat) ν_{max} 3327, 3024, 2930, 2860, 1455, 1438, 1325, 1284, 1184, 1167, 1078, 1043, 99, 951, 856, 747, 658, 520 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 258, 256 and 254 [M^+ , 1, 2 and 1%], 214, 212 and 210 (54, 98 and 55), 201, 199 and 197 (6, 12 and 6), 177 and 175 [(M-Br) $^+$, 70 and 71], 159 and 157 (31 and 32), 149 and 147 (12 and 14), 133 and 131 (22 and 24), 95 (75), 77 (40), 67 (100), 57 (49), 51 (41), 41 (52), 30 (76).

HRMS Found M^+ , 255.8920. Calculated for $\text{C}_6\text{H}_8^{79}\text{Br}^{81}\text{BrO M}^+$, 255.8921.

Found M^+ , 253.8940. Calculated for $\text{C}_6\text{H}_8^{79}\text{Br}_2\text{O M}^+$, 253.8942.

Concentration of fraction B ($R_f = 0.4$) furnished product **283** as a clear colourless oil.

$^1\text{H NMR}$ (300 MHz) δ 4.78 (m, 1H), 2.67 (broad s, 1H), 2.42 (dd, $J = 7.2$ and 5.7 Hz, 1H), 2.29-2.02 (complex m, 4H), 1.80-1.72 (complex m, 1H).

$^{13}\text{C NMR}$ (75 MHz) δ 77.4 (CH), 41.9 (CH), 38.6 (C), 31.9 (CH), 29.6 (CH₂), 26.9 (CH₂).

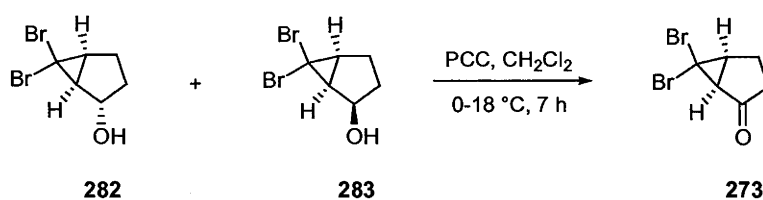
IR (neat) ν_{max} 3453, 2934, 2862, 1735, 1462, 1441, 1374, 1308, 1240, 1119, 1083, 1054, 1053, 892, 813, 764, 565 cm^{-1}

Mass Spectrum (EI, 70 eV) m/z 258, 256 and 254 [M^+ , all <1%], 214, 212 and 210 (22, 43 and 22), 177 and 175 [($M-Br$) $^+$, 45 and 47], 159 and 157 (both 22), 149 and 147 (6 and 7), 133 and 131 (11 and 10), 95 (65), 77 (35), 67 (100), 51 (44), 41 (48), 39 (72).

HRMS Found M^+ , 255.8919. Calculated for $C_6H_8^{79}Br^{81}BrO$ M^+ , 255.8921.

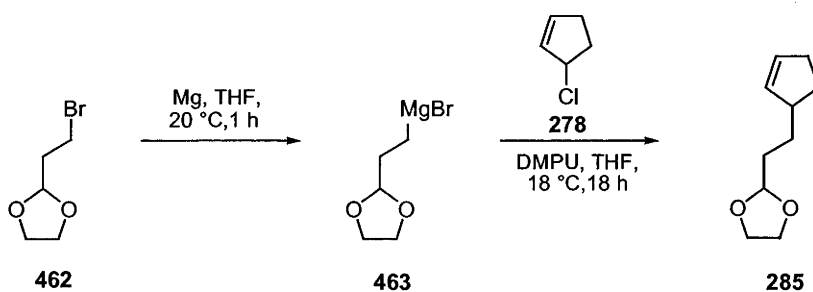
Found M^+ , 253.8948. Calculated for $C_6H_8^{79}Br_2O$ M^+ , 253.8942.

6,6-Dibromobicyclo[3.1.0]hexan-2-one (**273**)



A cooled (0 °C) and magnetically stirred solution of a *ca.* 4:1 mixture of compounds (\pm)-**282** and its C2-epimer (\pm)-**283** (9.1 g, 0.04 mol) in anhydrous dichloromethane (270 mL) was treated in twelve portions, over the period of an hour, with pyridinium chlorochromate (29.3 g, 0.11 mol). The ensuing dark-brown mixture was then protected from light and stirred at ambient temperatures for 7 hours before being filtered through a plug of TLC-grade silica gel which was washed with diethyl ether (800 mL). The combined filtrates were then concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.2$) afforded the title ketone **273**²³ (10.1 g, 94%) as a pale-yellow waxy-like solid, m.p. 5-7 °C. This material was identical, in all respects, with that obtained *via* the procedures detailed on pages 241-242.

2-[2-(Cyclopent-2-enyl)ethyl]-1,3-dioxolane (285)



Several crystals of iodine, a few drops of 1,2-dibromoethane and a few drops of a solution of 2,2-bromoethyl-1,3-dioxolane (**462**) in THF were added to a suspension of magnesium turnings (3.7 g, 0.13 mol) in anhydrous THF (42 mL). The reaction was then gently warmed with a heat gun until the resulting yellow solution became clear. The reaction mixture was then cooled to *ca.* 20 °C (water bath) and the remaining portions of the solution of 2,2-bromoethyl-1,3-dioxolane (**462**) (15 mL, 23.1 g, 0.13 mol) in THF (15 mL) slowly added at this temperature. Vigorous stirring of the resulting suspension at room temperature over 1 hour led to the consumption of all of the magnesium turnings. Subsequently a solution of 3-chlorocyclopentene (**278**) (10.0 g, 0.10 mol) and DMPU (8 mL) in THF (15 mL) was added at 20 °C and the resulting brown mixture stirred at room temperature for 18 hours. After this time TLC analysis indicated complete consumption of the starting chloride so HCl (60 mL of a 1 M aqueous solution) was added to quench the reaction. After a further 10 minutes the reaction mixture was poured into water (200 mL) and extracted with diethyl ether (3 x 300 mL). The combined organic fractions were washed with brine (1 x 500 mL), then dried (MgSO_4), filtered and concentrated under reduced pressure to afford a yellow oil. Subjecting of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions ($R_f = 0.3$), the title compound **285**²⁴ (16.1 g, 98%) as a yellow oil.

¹H NMR (300 MHz) δ 5.69 (m, 2H), 4.84 (t, $J = 4.8$ Hz, 1H), 3.90 (m, 4H), 2.67 (m, 1H), 2.36-2.17 (m, 2H), 2.04 (m, 1H), 1.72-1.65 (m, 2H), 1.58-1.34 (m, 3H).

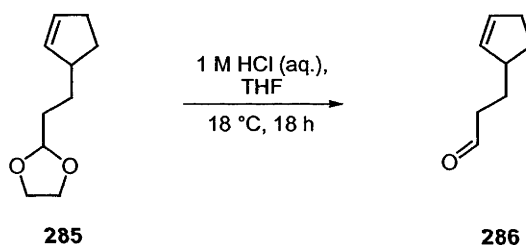
^{13}C NMR (75 MHz) δ 134.5 (CH), 130.3 (CH), 104.5 (CH), 64.6 (2 x CH_2 overlapping), 45.1 (CH), 32.0 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.4 (CH_2).

IR (neat) ν_{max} 3049, 2947, 2856, 1453, 1409, 1361, 1212, 1138, 1037, 943, 913, 721 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 168 [M^+ , <1%], 167 [($\text{M}-\text{H}^+$) $^+$, 4], 137 (3), 125 (2), 106 (25), 99 (34), 80 (100), 73 (83), 67 (58).

HRMS Found M^+ , 168.1148. Calculated for $\text{C}_{10}\text{H}_{16}\text{O}_2 \text{M}^+$, 168.1150.

3-Cyclopent-2-enyl-propionaldehyde (286)



HCl (117 mL of a 1 M aqueous solution) was added, in one portion, to a magnetically stirred solution of 2-[2-(cyclopent-2-enyl)ethyl]-1,3-dioxolane (**285**) (9.8 g, 60.0 mmol) in THF (117 mL) and the resulting yellow solution stirred at ambient temperatures for 18 hours. NaHCO_3 (100 mL of a saturated aqueous solution) was then added and stirring continued at 18 °C for a further 10 minutes. Following this, the reaction mixture was extracted with diethyl ether (3 x 250 mL) and the combined organic fractions washed with brine (1 x 300 mL) before being dried (MgSO_4), filtered and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions ($R_f = 0.3$), the title compound **286**²⁴ (6.8 g, 91%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 9.78 (t, $J = 1.8$ Hz, 1H), 5.71 (m, 2H), 2.87 (t, $J = 7.8$ Hz, 1H), 2.80-2.57 (complex m, 1H), 2.51-2.42 (complex m, 2H), 2.29 (m, 2H), 2.12-1.91 (complex m, 2H), 1.85 (m, 1H).

$^{13}\text{C NMR}$ (75 MHz) δ 202.8 (CH), 132.9 (CH), 130.5 (CH), 42.2 (CH₂), 41.9 (CH), 32.1 (CH₂), 30.3 (CH₂), 28.5 (CH₂).

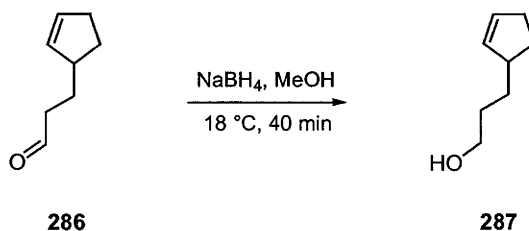
IR (neat) ν_{max} 3049, 2925, 2853, 2715, 1727, 1452, 1410, 1362, 1187, 1141, 1081, 967, 910, 718 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 124 [M^+ , 1%], 123 [($\text{M}-\text{H}\cdot$)⁺, 6], 107 (25), 79 (100), 67 (88).

HRMS Found M^+ , 124.0880. Calculated for $\text{C}_8\text{H}_{12}\text{O M}^+$, 124.0888.

Found ($\text{M}-\text{H}\cdot$)⁺, 123.0810. Calculated for $\text{C}_8\text{H}_{11}\text{O}(\text{M}-\text{H}\cdot)^+$, 123.0810.

3-Cyclopent-2-enyl-propan-1-ol (287)



A magnetically stirred solution of aldehyde **286** (6.0 g, 48.0 mmol) in anhydrous methanol (145 mL) was treated, in one portion, at ambient temperature with sodium borohydride (2.7 g, 73.0 mmol). After 40 minutes the evolution of gas ceased and TLC analysis showed complete conversion of aldehyde **286**. The solvent was then removed under reduced pressure and the resulting residue taken up into diethyl ether (200 mL). This solution was poured into water (200 mL) and the separated aqueous phase extracted with additional diethyl ether (2 x 300 mL). The combined organic phases were then washed with brine (1 x 300 mL), dried (MgSO_4), filtered and concentrated under reduced pressure to provide a yellow oil. Flash

column chromatography of this material (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions ($R_f = 0.3$) then furnished the title alcohol **287**²⁵ (4.9 g, 81%) as a pale-yellow oil.

¹H NMR (300 MHz) δ 5.70 (m, 2H), 3.65 (t, $J = 6.6$ Hz, 2H), 2.66 (m, 1H), 2.36-2.25 (m, 2H), 2.10-1.99 (m, 1H), 1.66-1.56 (m, 2H), 1.52-1.28 (m, 3H).

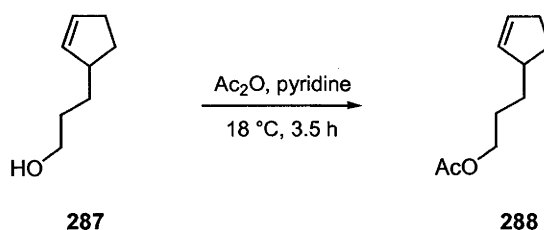
¹³C NMR (75 MHz) δ 134.8 (CH), 130.4 (CH), 63.0 (CH₂), 45.2 (CH), 32.0 (CH₂), 31.9 (CH₂), 31.0 (CH₂), 29.7 (CH₂).

IR (neat) ν_{\max} 3339, 3051, 2931, 2851, 1452, 1361, 1055, 1012, 913, 718 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 126 [M^+ , 6%], 125 [($M-H$)⁺, 10], 108 [($M-H_2O$)⁺, 8], 93 (19), 80 (63), 67 (100).

HRMS Found ($M-H$)⁺, 125.0963. Calculated for C₈H₁₃O ($M-H$)⁺, 125.0966.

Acetic acid 3-Cyclopent-2-enyl-propyl Ester (**288**)



Acetic anhydride (6.7 mL, 7.3 g, 71.0 mmol) was added, in one portion, to a magnetically stirred solution of alcohol **287** (4.5 g, 36.0 mmol) in pyridine (5.7 mL, 5.6 g, 71.0 mmol). The resulting solution was allowed to stir at 18 °C for 3.5 hours after which time TLC analysis indicated that the reaction had reached completion. Consequently, excess acetic anhydride was destroyed by the addition of methanol (10 mL) to the ice-cooled solution. After a further 4 hours the reaction mixture was partitioned between diethyl ether (300 mL) and water (300

mL) and the separated aqueous phase extracted with diethyl ether (3 x 250 mL). The combined organic phases were then washed with HCl (3 x 300 mL of a 1 M aqueous solution), NaHCO₃ (3 x 300 mL of a saturated aqueous solution) and brine (1 x 700 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure. The ensuing orange oil was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.4$) provided the *title acetate 288* (5.6 g, 93%) as a pale-yellow oil.

¹H NMR (300 MHz) δ 5.70 (m, 2H), 4.06 (t, $J = 6.6$ Hz, 2H), 2.65 (m, 1H), 2.36-2.26 (m, 2H), 2.10-1.99 (m, 1H), 2.05 (s, 3H), 1.71-1.61 (m, 2H), 1.59 (s, 1H), 1.51-1.28 (m, 2H).

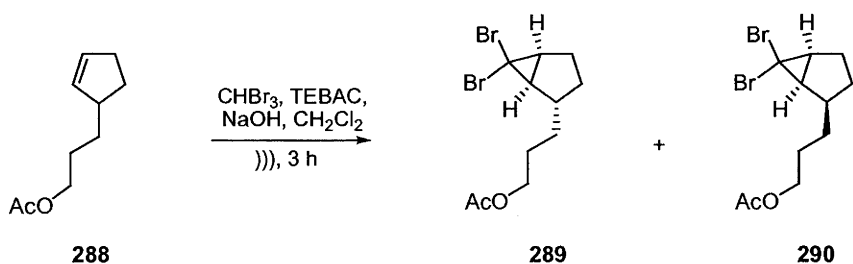
¹³C NMR (75 MHz) δ 171.1 (C), 134.6 (CH), 130.5 (CH), 64.7 (CH₂), 45.1 (CH), 32.1 (CH₂), 31.9 (CH₂), 29.6 (CH₂), 26.9 (CH₂), 20.9 (CH₃).

IR (neat) ν_{\max} 3050, 2928, 2852, 1742, 1452, 1387, 1365, 1241, 1047, 719 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 167 [(M-H)⁺, 1%], 125 (5), 108 (37), 93 (22), 80 (100), 67 (89).

HRMS Found (M-H)⁺, 167.1076. Calculated for C₁₀H₁₅O₂, (M-H)⁺, 167.1072.

3-[(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propyl Acetate (289) and 3-[(1*RS*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propyl Acetate (290)



Bromoform (4.7 mL, 13.6 g, 54.0 mmol) was added to a mixture of acetate **288** (4.6 g, 27.0 mmol), benzyltriethylammonium chloride (120 mg, 0.54 mmol) and powdered sodium hydroxide (6.5 g, 0.16 mol) in dichloromethane (16 mL). The resulting brown suspension was subjected to sonication, without external temperature control, for 3 hours. Celite™ was then added into the reaction and the resulting suspension filtered through a 1 cm plug of Celite™ which was washed with dichloromethane. Concentration of the combined filtrates then delivered a dark-brown liquid that was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). In this manner, two fractions, A and B, were obtained.

Concentration of fraction A ($R_f = 0.2$) afforded the *title compound* **289** (6.2 g, 67%) as a pale-yellow oil.

^1H NMR (300 MHz) δ 4.07 (t, $J = 6.3$ Hz, 2H), 2.58 (dt, $J = 6.3$ and 0.9 Hz, 1H), 2.21-2.09 complex m, 1H), 2.06 (s, 3H), 2.05-1.96 (complex m, 1H), 1.95-1.78 (complex m, 3H), 1.73-1.63 (complex m, 2H), 1.56-1.51 (complex m, 1H), 1.49-1.38 (complex m, 2H).

^{13}C NMR (75 MHz) δ 171.0 (C), 64.3 (CH_2), 44.2 (CH), 42.8 (CH), 39.7 (C), 39.3 (CH), 32.8 (CH_2), 32.2 (CH_2), 28.4 (CH_2), 26.8 (CH_2), 20.9 (CH_3).

IR (neat) ν_{max} 3460, 2927, 2855, 1739, 1464, 1453, 1386, 1364, 1241, 1039, 742, 605 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 341, 339 and 337 [(M-H) $^+$, 9, 16 and 9%], 283, 281 and 279 (5, 11 and 5), 261 and 259 [(M-Br) $^+$, both 4], 173 and 171 (both 12), 159 and 157 (both 17), 119 (35), 99 (16), 91 (36), 79 (47), 73 (40), 57 (37), 43 (100).

HRMS Found (M-H) $^+$, 336.9435. $\text{C}_{11}\text{H}_{15}^{79}\text{Br}_2\text{O}_2$ requires (M-H) $^+$, 336.9439.

Concentration of fraction B ($R_f = 0.2$) afforded the *C-2 epimer* **290** (1.5 g, 17%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 4.06 (dt, $J = 6.6$ and 2.4 Hz, 2H), 2.27-2.13 (complex m, 2H), 2.05 (s, 3H), 2.11-1.37 (complex m, 9H).

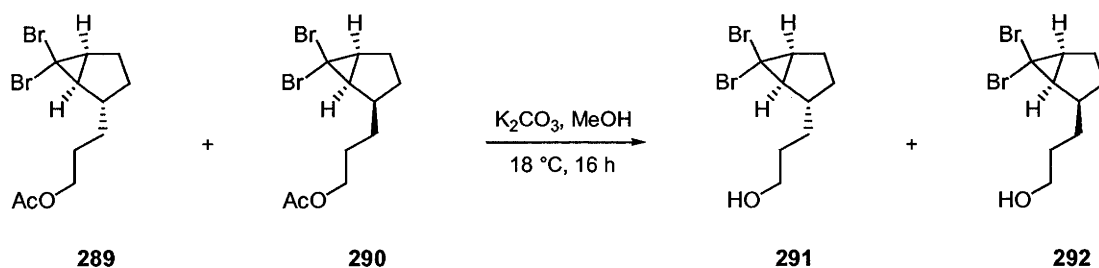
$^{13}\text{C NMR}$ (75 MHz) δ 168.2 (C), 64.9 (CH_2), 44.3 (CH), 42.9 (CH), 39.7 (C), 39.3 (CH), 32.7 (CH_2), 32.0 (CH_2), 30.2 (CH_2), 28.4 (CH_2), 22.7 (CH_3).

IR (neat) ν_{max} 3451, 2926, 2855, 1738, 1454, 1410, 1364, 1241, 1142, 1036, 744 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 341, 339 and 337 [(M-H) $^+$, 3, 5 and 3%], 298, 296 and 294 (3, 5 and 3), 283, 281 and 279 (4, 7 and 4), 261 and 259 [(M-Br) $^+$, both 13], 173 and 171 (both 30), 159 and 157 (both 20), 119 (48), 99 (50), 91 (54), 79 (57), 73 (70), 57 (57), 43 (100).

HRMS Found (M-H) $^+$, 336.9439. $\text{C}_{11}\text{H}_{15}^{79}\text{Br}_2\text{O}_2$ requires (M-H) $^+$, 336.9439.

3-[(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propan-1-ol (291) and 3-[(1*RS*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propan-1-ol (292)



A magnetically stirred solution of a 4:1 mixture of acetates **289** and **290** (5.0 g, 17.0 mmol) in methanol (43 mL) was treated, in one portion, with potassium carbonate (3.3 g, 24.0 mmol) and the resulting suspension stirred at room temperature under an atmosphere of nitrogen for 16 hours. The reaction mixture was then poured into brine (50 mL) and extracted with dichloromethane (5 x 100 mL). The combined organic fractions were washed with water (1 x 200 mL) and brine (1 x 300 mL) before being dried (MgSO_4), filtered and concentrated under

reduced pressure. The resulting orange oil was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) and thus affording a 4:1 mixture of *alcohols* (\pm)-**291** and (\pm)-**292** (3.4 g, 68%). Re-subjection of this material to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f = 0.1$) furnished *compound 291* (2.7 g, 54%) as a pale-orange oil.

$^1\text{H NMR}$ (300 MHz) δ 3.67 (t, $J = 6.3$ Hz, 2H), 2.25 (dt, $J = 6.3$ and 0.9 Hz, 1H), 2.21-2.13 complex m, 1H), 2.11-1.99 (complex m, 2H), 1.96-1.78 (complex m, 2H), 1.67-1.40 (complex m, 5H).

$^{13}\text{C NMR}$ (75 MHz) δ 61.9 (CH_2), 44.0 (CH), 42.7 (CH), 39.8 (C), 39.0 (CH), 32.5 (CH_2), 31.8 (CH_2), 30.4 (CH_2), 28.2 (CH_2).

IR (neat) ν_{max} 3327, 2932, 2861, 1452, 1057, 1017, 742 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 300, 298 and 296 [M^+ , 3, 5 and 3%], 282, 280 and 278 [($\text{M}-\text{H}_2\text{O}$) $^+$, 4, 6 and 4], 254, 252 and 250 (18, 36 and 18), 241, 239 and 237 (23, 50 and 23), 219 and 217 [($\text{M}-\text{Br}$) $^+$, both 30], 214, 212 and 210 (26, 50 and 26), 201, 199 and 197 (45, 91 and 45), 173 and 171 (both 67), 159 and 157 (both 72), 137 (47), 119 (92), 107 (80), 93 (75), 81 (75).

HRMS Found ($\text{M}-\text{H}_2\text{O}$) $^+$, 277.9301. $\text{C}_9\text{H}_{12}^{79}\text{Br}_2$ requires ($\text{M}-\text{H}_2\text{O}$) $^+$, 277.9306.

Concentration of fraction B ($R_f = 0.1$) furnished *compound 292* (680 mg, 14%) as an orange oil.

$^1\text{H NMR}$ (300 MHz) δ 3.66 (dt, $J = 6.0$ and 1.8 Hz, 2H), 2.40-2.00 (complex m, 3H), 1.85-1.44 (complex m, 8H).

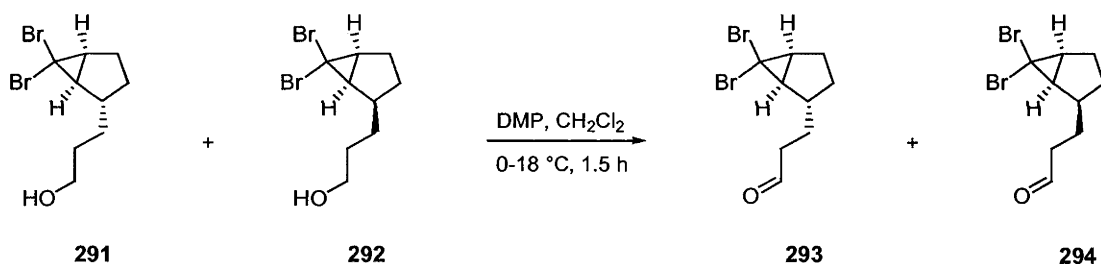
^{13}C NMR (75 MHz) δ 62.6 (CH_2), 42.9 (CH), 40.6 (CH), 39.3 (C), 38.6 (CH), 36.5 (CH_2), 31.3 (CH_2), 30.2 (CH_2), 27.1 (CH_2).

IR (neat) ν_{max} 3351, 2925, 2854, 1451, 1057, 750 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 300, 298 and 296 [M^+ , 1, 3 and 1%], 282, 280 and 278 [$(\text{M}-\text{H}_2\text{O})^+$, 4, 6 and 4], 219 and 217 [$(\text{M}-\text{Br})^+$, both 70], 201, 199 and 197 (16, 32 and 16), 173 and 171 (both 36), 159 and 157 (both 63), 137 (42), 119 (100).

HRMS Found M^+ , 295.9413. $\text{C}_9\text{H}_{14}^{79}\text{Br}_2$ requires M^+ , 295.9411.

3-[(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propanal (293) and 3-[(1*RS*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propanal (294)



A magnetically stirred solution of alcohols **291** and **292** (1.2 g, 4.03 mmol) in moist dichloromethane (67 mL) was cooled to 0 °C (ice/water bath) and treated with Dess-Martin periodinane (3.4 g, 8.06 mmol). The resulting cream suspension was then allowed to warm to ambient temperature and stirring continued for a further 1.5 hours. A 1:1 mixture of NaHCO_3 (30 mL of a saturated aqueous solution) and $\text{Na}_2\text{S}_2\text{O}_3$ (30 mL of a 10% w/v aqueous solution) was then added to the reaction mixture and vigorous stirring continued for 1 hour. After this time, the solvent was removed under reduced pressure and the residue taken up in diethyl ether (80 mL). The separated aqueous phase was then extracted with additional diethyl ether (3 x 80 mL). The combined organic fractions were washed with brine (1 x 300 mL) then dried (MgSO_4), filtered and concentrated under reduced pressure to provide a pale-orange oil.

Subjection of this material to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and subsequent concentration of the appropriate fractions ($R_f = 0.5$) delivered a 4:1 mixture of the *title aldehydes* (\pm)-**293** and (\pm)-**294** (1.1 g, 98%) as a pale-yellow oil. Re-subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f = 0.5$) afforded *aldehyde 293* (850 mg, 78%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 9.80 (t, $J = 1.5$ Hz, 1H), 2.51 (dt, $J = 7.5$ and 1.5 Hz, 2H), 2.26 (dt, $J = 7.5$ and 0.6 Hz, 1H), 2.20-1.89 (complex m, 4H), 1.88-1.62 (complex m, 3H), 1.46-1.36 (complex m, 1H).

$^{13}\text{C NMR}$ (75 MHz) δ 201.2 (CH), 43.7 (CH), 42.1 (CH), 41.7 (CH₂), 39.1 (CH), 38.9 (C), 32.2 (CH₂), 28.0 (CH₂), 27.4 (CH₂).

IR (neat) ν_{max} 3426, 2928, 2722, 1724, 1448, 1389, 747 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 298, 296 and 294 [M^+ , 3, 6 and 3%], 297, 295 and 293 [$(\text{M}-\text{H})^+$, 5, 10 and 5], 280, 278 and 276 [$(\text{M}-\text{H}_2\text{O})^+$, 15, 30 and 15], 254, 252 and 250 (33, 69 and 33), 239, 237 and 235 (8, 19 and 8), 217 and 215 [$(\text{M}-\text{Br})^+$, both 21], 201, 199 and 197 (50, 100 and 50), 189, 187 and 185 (6, 10 and 6), 173 and 171 (both 79), 159 and 157 (both 38), 147 and 145 (both 24), 135 (76), 117 (79), 107 (79), 93 (82), 78 (84), 65 (74).

HRMS Found $(\text{M}-\text{H})^+$, 292.9173. $\text{C}_9\text{H}_{11}^{79}\text{Br}_2\text{O}$ requires $(\text{M}-\text{H})^+$, 292.9177.

Concentration of fraction B ($R_f = 0.4$) afforded *aldehyde 294* (210 mg, 20%) as a pale-yellow oil.

^1H NMR (300 MHz) δ 9.81 (t, $J = 1.5$ Hz, 1H), 2.89-2.68 (complex m, 2H), 2.62-2.35 (complex m, 2H), 2.30-2.12 (complex m, 1H), 2.07-1.92 (complex m, 2H), 1.88-1.75 (complex m, 2H), 1.73-1.57 (complex m, 2H).

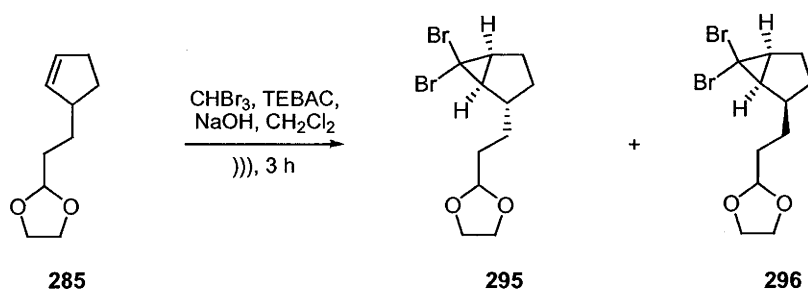
^{13}C NMR (75 MHz) δ 201.7 (CH), 43.3 (CH), 42.9 (CH), 41.4 (CH_2), 39.4 (CH), 38.2 (C), 32.2 (CH_2), 28.9 (CH_2), 28.5 (CH_2).

IR (neat) ν_{max} 3406, 2923, 2852, 1727, 1639, 1464, 1081 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 298, 296 and 294 [M^+ , 6, 11 and 6%], 297, 295 and 293 [$(\text{M}-\text{H})^+$, 7, 15 and 7], 280, 278 and 276 [$(\text{M}-\text{H}_2\text{O})^+$, 35, 73 and 35], 254, 252 and 250 (34, 64 and 34), 239, 237 and 235 (23, 46 and 23), 217 and 215 [$(\text{M}-\text{Br})^+$, both 37], 201, 199 and 197 (52, 85 and 52), 189, 187 and 185 (15, 24 and 15), 173 and 171 (both 67), 159 and 157 (both 61), 147 and 145 (both 52), 135 (69), 117 (87), 107 (76), 93 (74), 78 (75).

HRMS Found $(\text{M}-\text{H})^+$, 292.9166. $\text{C}_9\text{H}_{11}^{79}\text{Br}_2\text{O}$ requires $(\text{M}-\text{H})^+$, 292.9177.

2-{2-[(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]ethyl}-1,3-dioxolane (295) and 2-{2-[(1*RS*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]ethyl}-1,3-dioxolane (296)



Benzyltriethylammonium chloride (30 mg, 0.16 mmol), powdered sodium hydroxide (1.9 g, 7.81 mmol), and bromoform (1.4 mL, 4.0 g, 16.0 mmol) were added to a solution of acetal **285** (1.3 g, 7.81 mmol) in CH_2Cl_2 (4.7 mL). A flask containing the resulting suspension was

then fitted with a reflux condenser and subjected to sonication, without external temperature control, for 3 hours. Upon completion of the reaction a small amount of CeliteTM was added into the reaction flask and the entire contents of the flask then filtered through a 1 cm plug of CeliteTM which was washed with CH₂Cl₂ (40 mL). The resultant brown filtrate was then concentrated under reduced pressure and the ensuing residue subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A ($R_f = 0.4$) furnished *acetal 295* (1.6 g, 62%) as a yellow oil.

¹H NMR (300 MHz) δ 4.84 (t, $J = 4.5$ Hz, 1H), 3.90 (m, 4H), 2.25-2.10 (complex m, 2H), 2.09-1.96 (complex m, 2H), 1.94-1.73 (complex m, 2H), 1.71-1.36 (complex m, 5H).

¹³C NMR (75 MHz) δ 104.2 (CH), 64.8 (2 x CH₂ – overlapping), 44.3 (CH), 42.9 (CH), 39.7 (C), 39.2 (CH₂), 32.7 (CH), 32.0 (CH₂), 29.9 (CH₂), 28.4 (CH₂).

IR (neat) ν_{\max} 3369, 2948, 2883, 1731, 1599, 1452, 1409, 1359, 1287, 1141, 1033, 984, 944, 905, 864, 743 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 341, 339 and 337 [(M-H)⁺, 10, 17 and 10%], 297, 295 and 293 (3, 5 and 3), 280, 278 and 276 (6, 12 and 6), 261 and 259 [(M-Br)⁺, both 15], 199 and 197 (both 17), 173 and 171 (both 24), 141 (12), 117 (18), 99 (36), 73 (100).

HRMS Found (M-H)⁺, 336.9440. C₁₁H₁₅⁷⁹Br₂O₂ requires (M-H)⁺, 336.9439.

Concentration of fraction B ($R_f = 0.3$) delivered *acetal 296* (400 mg, 15%) as a yellow oil.

¹H NMR (300 MHz) δ 4.85 (m, 1H), 3.90 (m, 4H), 2.41-1.99 (complex m, 4H), 1.94-1.36 (complex m, 7H).

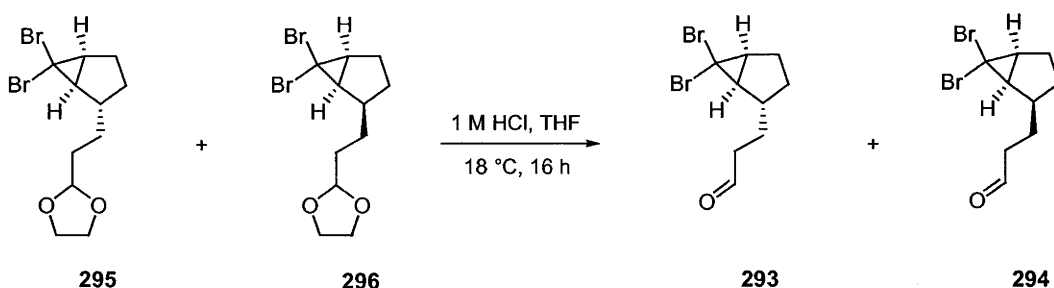
¹³C NMR (75 MHz) δ 104.2 (CH), 64.9 (2 x CH₂ – overlapping), 40.5 (CH), 38.5 (CH), 36.5 (C), 33.5 (CH₂), 30.6 (CH), 29.2 (CH₂), 27.9 (CH₂), 22.8 (CH₂).

IR (neat) ν_{\max} 2928, 2877, 1731, 1631, 1452, 1410, 1321, 1141, 1033, 943, 907, 750, 645 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 341, 339 and 337 [(M-H)⁺, 5, 9 and 5%], 261 and 259 [(M-Br)⁺, both 92], 199 and 197 (both 87), 173 and 171 (both 100), 117 (53).

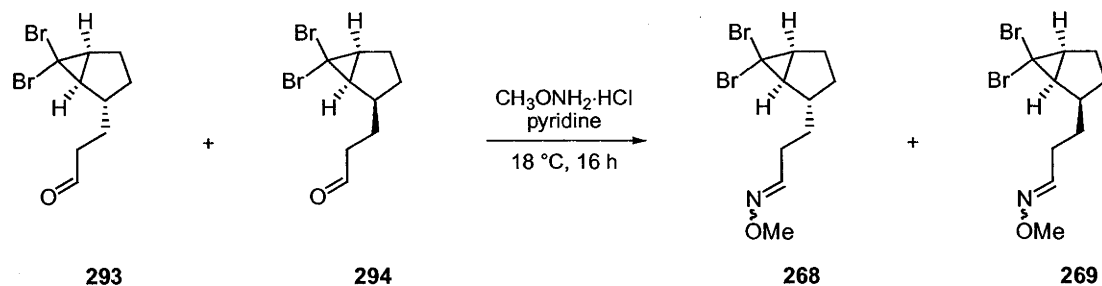
HRMS Found (M-H)⁺, 338.9419. C₁₁H₁₅⁸¹Br⁷⁹BrO₂ requires (M-H)⁺, 338.9418.

3-[(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propanal (293) and 3-[(1*RS*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propanal (294)



HCl (22 mL of a 1 M aqueous solution) was added, in one portion, to a magnetically stirred solution of a 4:1 mixture of acetals **295** and **296** (1.5 g, 4.42 mmol) in THF (22 mL) and the resulting yellow solution stirred at ambient temperatures for 16 hours. NaHCO₃ (20 mL of a saturated aqueous solution) was then added and stirring continued at 18 °C for a further 10 minutes. Following this, the reaction mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic fractions washed with brine (1 x 80 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions ($R_f = 0.5$), a 4:1 mixture of the title compounds **293** and **294** (1.2 g, 91%) as a pale-yellow oil. This material was identical, in all respects, *via* the procedure detailed on pages 257-259.

3-[(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propanal *O*-methyl oxime (268) and 3-[(1*RS*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propanal *O*-methyl oxime (269)



The hydrochloride salt of methoxylamine (840 mg, 10.0 mmol) was added, in one portion, to a magnetically stirred solution of aldehydes **293** and **294** (300 mg, 1.0 mmol) in pyridine (3.4 mL). The resulting orange-yellow solution was then stirred under a nitrogen atmosphere at 18 °C for 16 hours. After this time TLC analysis indicated that the reaction had reached completion. Consequently, the reaction mixture was concentrated under reduced pressure and the residual solids stirred in diethyl ether (4 mL) for 1 hour. Filtration, followed by concentration under reduced pressure delivered a 4:1 mixture of the *desired products* **268** and **269** as a yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) then furnished two fractions, A and B.

Concentration of fraction A ($R_f = 0.3$) afforded a *ca.* 1:1 mixture of the *E*- and *Z*-isomers of oxime (\pm)-**268** (190 mg, 58%) as a clear, colourless oil.

¹H NMR (300 MHz) δ 7.38 (t, $J = 6.3$ Hz, 1H), 6.65 (t, $J = 5.4$ Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 2.39-2.17 (complex m, 6H), 2.10-1.79 (complex m, 8H), 1.72-1.39 (complex m, 8H).

¹³C NMR (75 MHz) δ 150.7 (CH), 149.9 (CH), 61.6 (CH₃), 61.2 (CH₃), 44.1 (CH), 44.0 (CH), 42.8 (CH), 42.6 (CH), 39.5 (2 x C, overlapping), 39.4 (CH), 39.3 (CH), 32.7 (2 x CH₂, overlapping), 32.6 (CH₂), 32.2 (CH₂), 29.6 (CH₂), 29.2 (CH₂), 28.3 (CH₂), 27.8 (CH₂).

IR (neat) ν_{\max} 2935, 2858, 2817, 1464, 1450, 1051, 881, 855, 743 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 327, 325 and 323 [M^+ , 7, 15 and 7%], 296, 294 and 292 (7, 13 and 7), 246 and 244 [($M-Br$) $^+$, both 38], 214 and 212 (both 13), 199 and 197 (both 17), 132 (38), 117 (19), 105 (44), 91 (73).

HRMS Found M^+ , 324.9501. Calculated for $C_{10}H_{15}^{81}Br^{79}BrNO M^+$, 322.9500.

Found M^+ , 322.9529. Calculated for $C_{10}H_{15}^{79}Br_2NO M^+$, 322.9520.

Concentration of fraction B ($R_f = 0.2$) delivered a *ca.* 1:1 mixture of the *E*- and *Z*-isomers of *oxime* (\pm)-**269** (50 mg, 15%) as a clear, colourless oil.

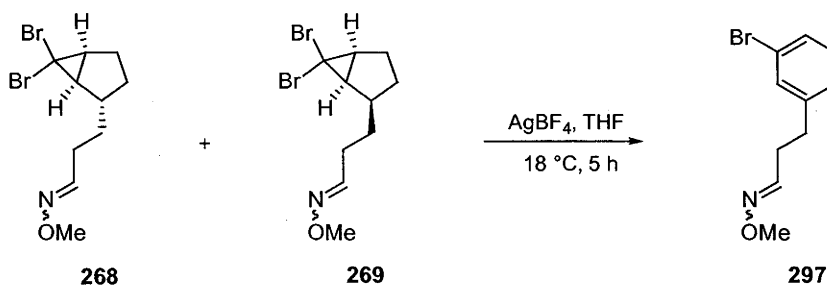
1H NMR (300 MHz) δ 7.38 (t, $J = 6.3$ Hz, 1H), 6.65 (t, $J = 5.4$ Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 2.39-2.31 (complex m, 2H), 2.82-2.13 (complex m, 6H), 2.12-1.78 (complex m, 6H), 1.75-1.39 (complex m, 8H).

^{13}C NMR (75 MHz) δ 150.7 (CH), 149.9 (CH), 61.6 (CH₃), 61.2 (CH₃), 44.1 (CH), 44.0 (CH), 42.9 (CH), 42.6 (CH), 39.5 (2 x C, overlapping), 39.4 (CH), 39.3 (CH), 32.7 (2 x CH₂, overlapping), 32.6 (CH₂), 32.2 (CH₂), 29.6 (CH₂), 28.8 (CH₂), 28.3 (CH₂), 27.8 (CH₂).

IR (neat) ν_{max} 2934, 2857, 2817, 1464, 1450, 1051, 881, 855, 743 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 327, 325 and 323 [M^+ , 19, 33 and 19%], 296, 294 and 292 (32, 58 and 32), 246 and 244 [($M-Br$) $^+$, both 90], 214 and 212 (both 66), 199 and 197 (both 69), 132 (92), 117 (82), 105 (93), 91 (95).

HRMS Found M^+ , 322.9529. Calculated for $C_{10}H_{15}^{79}Br_2NO M^+$, 322.9522.

3-(3-Bromocyclohexa-1,3-dienyl)propanal *O*-methyl oxime (297)

Silver tetrafluoroborate (84 mg, 0.43 mmol) was added, in one portion, to a magnetically stirred solution of a 4:1 mixture of oximes **268** and **269** (70 mg, 0.22 mmol) in anhydrous THF (5 mL). The resulting mixture was immediately protected from light and stirring continued at room temperature for 5 hours. The reaction mixture was then filtered through a plug of CeliteTM which was washed with ethyl acetate (25 mL). Concentration of the combined filtrates under reduced pressure then afforded a viscous yellow oil that was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions ($R_f = 0.4$) then furnished a 1:1 mixture of the *E*- and *Z*-isomeric forms of the *title compound* **297** (43 mg, 81%) as a clear, colourless oil.

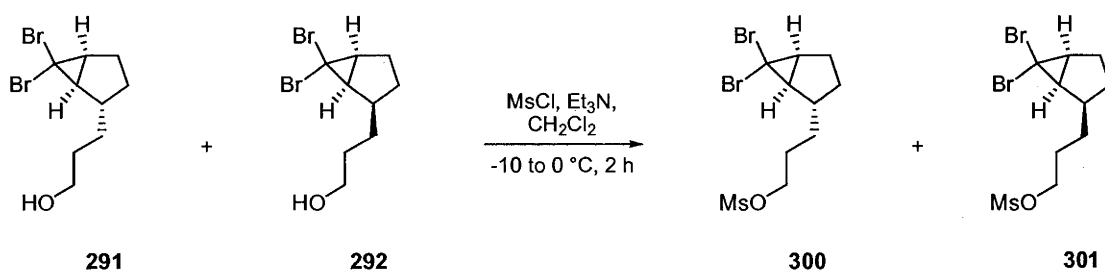
¹H NMR (300 MHz) δ 7.36-7.32 (complex m, 1H), 7.17-7.12 (complex m, 1H), 6.05 (m, 2H), 5.46 (m, 2H), 3.89 (s, 3H, CH₃), 3.87 (s, 3H, CH₃), 2.97 (m, 4H), 2.77 (m, 4H), 2.49-2.43 (complex m, 4H), 2.14 (t, $J = 7.2$ Hz, 4H).

¹³C NMR (75 MHz) δ 150.8 (CH), 150.0 (CH), 133.3 (2 x C, overlapping), 125.8 (2 x CH, overlapping), 118.9 (2 x C, overlapping), 118.1 (CH), 117.9 (CH), 61.7 (CH₃), 61.3 (CH₃), 38.4 (CH₂), 38.3 (CH₂), 32.8 (CH₂), 32.5 (CH₂), 27.3 (2 x CH₂, overlapping), 23.0 (2 x CH₂, overlapping).

IR (CH₂Cl₂) ν_{\max} 2929, 1733, 1436, 1083, 1043, 875, 778 cm⁻¹.

Mass Spectrum (GC-MS) m/z 245 and 243 [M^+ , both 3%], 212 and 210 (both 28), 197 and 195 (both 8), 184 and 182 (both 8), 171 and 169 (both 50), 132 (33), 115 (12), 105 (33), 91 (100), 77 (39), 65 (16), 51 (13).

3-[(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propyl Methanesulfonate (300) and 3-[(1*RS*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propyl Methanesulfonate (301)



Methanesulfonyl chloride (0.2 mL, 23 mg, 2.02 mmol) was added, in one portion, to a magnetically stirred solution of a 4:1 mixture of alcohols **291** and **292** (500 mg, 1.68 mmol) and triethylamine (0.4 mL, 270 mg, 2.69 mmol) in CH_2Cl_2 (16.8 mL) which was maintained at $-10 \text{ } ^\circ\text{C}$ (dry ice/isopropanol bath) under a nitrogen atmosphere. The resultant solution was then stirred for a further 2 hours, during which time it was allowed to warm to $0 \text{ } ^\circ\text{C}$. TLC analysis indicated that the reaction had reached completion after this time so it was diluted with ice-water (1 x 50 mL). The separated organic phase was then washed with HCl (1 x 50 mL of a 2 M aqueous solution), NaHCO_3 (1 x 50 mL of a saturated aqueous solution) and brine (1 x 80 mL) before being dried (MgSO_4), filtered and concentrated under reduced pressure to provide an orange-yellow oil. This material was then subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.2$) then afforded a *ca.* 3:1 mixture of *compounds* (\pm)-**300** and (\pm)-**301** (460 mg, 73%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ [(\pm)-**300**] 4.24 (t, $J = 6.9$ Hz, 2H), 3.03 (s, 3H), 2.27 (dt, $J = 6.9$ and 0.9 Hz, 1H), 2.20-1.98 (complex m, 4H), 1.96-1.78 (complex m, 3H), 1.69-1.38 (complex m,

3H); δ [(±)-**301**] 4.28 (t, $J = 6.9$ Hz, 2H), 3.04 (s, 3H), 2.21-1.98 (complex m, 5H), 1.96-1.78 (complex m, 3H), 1.69-1.38 (complex m, 3H).

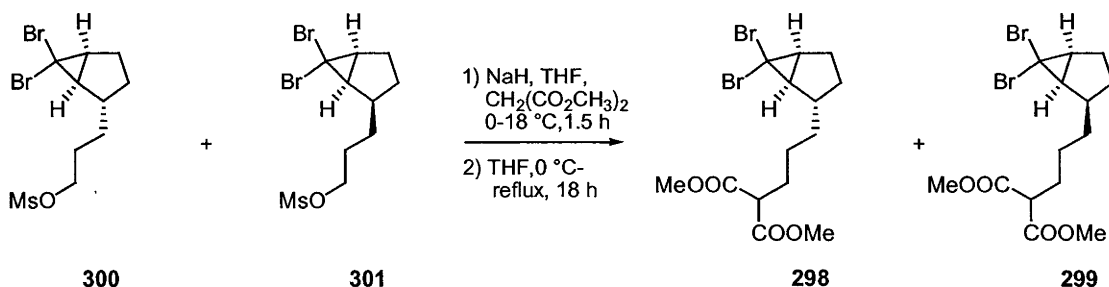
^{13}C NMR (75 MHz) δ [(±)-**300**] 69.7 (CH₂), 44.0 (CH), 42.5 (CH₃), 39.5 (C), 39.2 (CH), 37.2 (CH), 32.7 (CH₂), 31.5 (CH₂), 28.2 (CH₂), 27.3 (CH₂); δ [(±)-**301**] 69.9 (CH₂), 43.7 (CH), 41.7 (CH₃), 39.6 (C), 38.4 (CH), 37.3 (CH), 29.2 (CH₂), 28.7 (CH₂), 28.6 (CH₂), 26.3 (CH₂).

IR (neat) ν_{max} 3027, 2939, 2860, 1466, 1452, 1413, 1353, 1174, 1013, 973, 925, 827, 744, 528 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 378, 376 and 374 [M^+ , all <1%], 282, 280 and 278 [(M-CH₃SO₃H)⁺, 4, 8 and 4], 254, 252 and 250 (6, 12 and 6), 241, 239 and 237 (7, 14 and 7), 201 and 199 (both 55), 173 and 171 (both 41), 159 and 157 (both 41), 119 (79), 91 (74), 79 (100), 65 (34).

HRMS Found (M-H)⁺, 374.9096. Calculated for C₁₀H₁₅⁸¹Br⁷⁹Br O₃S (M-H)⁺, 374.9088.

Dimethyl 2-{3-[(1*RS*,2*SR*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propyl} Malonate (298**) and Dimethyl 2-{3-[(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]propyl} Malonate (**299**)**



A 60% dispersion of sodium hydride in oil was washed with hexane (3 x 8 mL) to remove the excess oil. The remaining solvent which could not be decanted was then removed under reduced pressure. After addition of THF (8 mL) to the washed and dried sodium hydride (36

mg, 1.15 mmol) the suspension was cooled to 0 °C. Dimethyl malonate (0.1 mL, 13 mg, 0.96 mmol) was added, dropwise, and the resulting solution stirred at 0 °C before being allowed to warm to ambient temperature over a further 1.5 hours. The reaction mixture was re-cooled to 0 °C before a solution of a 3:1 mixture of mesylates **300** and **301** (360 mg, 0.96 mmol) in THF (6 mL) was added. The ensuing yellow-orange solution was heated at reflux for 18 hours then cooled, poured into water (30 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic fractions were then washed with brine (1 x 100 mL), before being dried (Na₂SO₄), filtered and concentrated under reduced pressure to provide a dark-yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (*R_f* = 0.3 in 1:4 ethyl acetate/hexane) delivered a *ca.* 3:1 mixture of the *compounds* (±)-**298** and (±)-**299** (300 mg, 76%) as a clear, colourless oil.

¹H NMR (300 MHz) δ [(±)-**298**] 3.75 (d, *J* = 2.7 Hz, 6H, 2 x CH₃), 3.40 d, *J* = 2.7 Hz, 1H), 2.22 (t, *J* = 6.3 Hz, 1H), 2.17-1.73 (complex m, 4H), 1.70-1.60 (complex m, 2H), 1.53-1.22 (complex m, 5H); δ [(±)-**299**] 3.78 (d, *J* = 2.7 Hz, 6H, 2 x CH₃), 3.37 d, *J* = 2.7 Hz, 1H), 2.26-1.73 (complex m, 5H), 1.70-1.60 (complex m, 2H), 1.53-1.22 (complex m, 5H).

¹³C NMR (75 MHz) δ [(±)-**298**] 169.6 (2 x C, overlapping), 52.4 (2 x CH₃, overlapping), 51.4 (CH), 44.2 (CH), 42.9 (CH), 41.0 (C), 39.2 (CH), 35.4 (CH₂), 32.8 (CH₂), 28.7 (CH₂), 28.3 (CH₂), 25.4 (CH₂); δ [(±)-**299**] 166.8 (2 x C, overlapping), 51.9 (2 x CH₃, overlapping), 51.7 (CH), 39.8 (CH), 38.4 (CH), 36.1 (C), 33.4 (CH), 31.4 (CH₂), 30.2 (CH₂), 28.5 (CH₂), 27.2 (CH₂), 22.9 (CH₂).

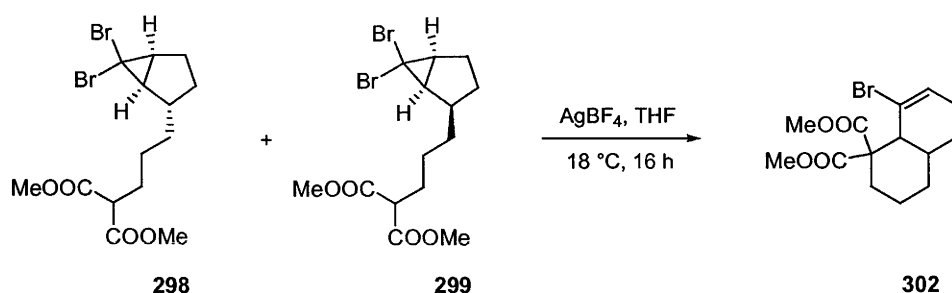
IR (neat) *v*_{max} 2951, 2860, 1736, 1435, 1238, 1154, 1113, 1068, 1024, 743 cm⁻¹.

Mass Spectrum (EI, 70 eV) *m/z* 414, 412 and 410 [M⁺, all <1%], 365, 363 and 361 (6, 14 and 6), 333 and 331 [(M-Br)⁺, both 7], 301 and 299 (both 17), 269 and 267 (both 44), 251 (86), 239 (29), 187 (38), 159 (49), 145 (88), 132 (96), 119 (57), 91 (80).

HRMS Found M⁺, 411.9684. Calculated for C₁₄H₂₀⁸¹Br⁷⁹BrO₄ M⁺, 411.9708.

Found M^{++} , 409.9751. Calculated for $C_{14}H_{20}^{79}Br_2O_4 M^{++}$, 409.9728.

Dimethyl 8-Bromo-2,3,4,4a,5,6-hexahydronaphthalene-1,1(8aH)-dicarboxylate
(302)



A 60% dispersion of sodium hydride in oil was washed with hexane (3 x 3 mL) to remove the excess oil. The residual solvent that could not be decanted was then removed under reduced pressure. After addition of THF (4 mL) to the washed and dried sodium hydride (5 mg, 0.20 mmol) the ensuing suspension was cooled to $0\text{ }^\circ\text{C}$ (ice/water bath) then a 4:1 mixture of dibromocyclopropanes **298** and **299** (80 mg, 0.18 mmol) in THF (0.5 mL) was added, dropwise, and the resulting solution stirred at $0\text{ }^\circ\text{C}$ before being allowed to warm to ambient temperature over a period of 1.5 hours. The reaction mixture was then re-cooled to $0\text{ }^\circ\text{C}$ before being treated, in one portion, with silver tetrafluoroborate (200 mg, 1.00 mmol). The reaction mixture was subsequently protected from light and stirred at ambient temperatures for 16 hours. The resulting suspension was filtered through a plug of CeliteTM which was washed with ethyl acetate (15 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained subjected to flash column (silica, 1:9 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions ($R_f = 0.3$) then afforded the *title decalin* **302** (43 mg, 72%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 6.08 (m, 1H), 4.19 (m, 1H), 3.74 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.36 (t, $J = 7.8\text{ Hz}$, 2H), 2.23-2.01 (complex m, 2H), 1.94-1.80 (complex m, 4H), 1.74-1.58 (complex m, 2H), 1.44-1.28 (complex m, 1H).

^{13}C NMR (75 MHz) δ 169.8 (C), 169.6 (C), 136.5 (CH), 124.6 (C), 69.7 (CH), 67.8 (C), 52.3 (CH₃), 51.4 (CH₃), 38.5 (CH), 34.6 (CH₂), 31.1 (CH₂), 28.7 (CH₂), 24.4 (CH₂), 22.8 (CH₂).

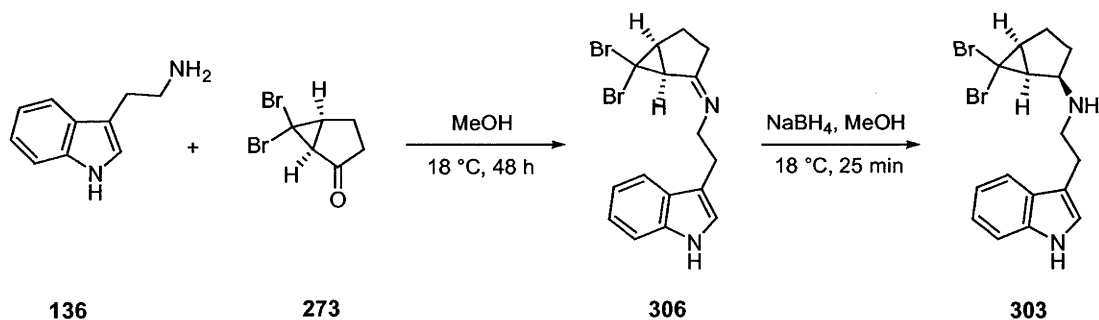
IR (neat) ν_{max} 3506, 2929, 2859, 1735, 1639, 1436, 1244, 1156, 1068, 1022, 964, 761 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 332 and 330 [M^+ , both 4%], 269 and 267 (both 21), 251 [$(\text{M}-\text{Br})^+$, 13], 240 and 238 (both 35), 223 and 221 (both 45), 177 (21), 159 (47), 145 (91), 131 (90), 119 (47), 81 (48), 67 (57), 55 (100), 41 (71).

HRMS Found M^+ , 332.0445. Calculated for $\text{C}_{14}\text{H}_{19}^{81}\text{BrO}_4 \text{M}^+$, 332.0446.

Found M^+ , 330.0460. Calculated for $\text{C}_{14}\text{H}_{19}^{79}\text{BrO}_4 \text{M}^+$, 332.0467.

**(1*SR*,2*RS*,5*SR*)-*N*-[2-(1-Indol-3-yl)ethyl]-6,6-dibromobicyclo[3.1.0]hexan-2-amine
(303)**



A solution of ketone **273** (3.5 g, 14.0 mmol) and tryptamine (**136**) (8.9 g, 56.0 mmol) in methanol (35 mL) was vigorously stirred at ambient temperatures under a nitrogen atmosphere for 48 hours. NaBH_4 (790 mg, 21.0 mmol) was then added to the resulting orange solution and stirring continued for 25 minutes. The solvent was removed under reduced pressure and the residue partitioned between water (40 mL) and diethyl ether (60 mL). The aqueous phase was then extracted with additional diethyl ether (3 x 60 mL). The combined organic phases were washed with brine (1 x 100 mL), then dried (MgSO_4), filtered and concentrated under reduced pressure to provide a cream-brown solid. Subjection of this

material to flash column chromatography (silica, 1:1 v/v acetone/hexane elution) and concentration of the appropriate fractions ($R_f = 0.3$) afforded the *title amine 303* (4.9 g, 88%) as a powdery pale-tan solid. A spectroscopically pure sample of this was by recrystallisation (diethyl ether/dichloromethane), m.p. 118-123 °C.

$^1\text{H NMR}$ (300 MHz) δ 8.22 (broad s, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.39 (d, $J = 7.8$ Hz, 1H), 7.21 (s, 1H), 7.21 (t, $J = 7.2$ Hz, 1H), 7.14 (t, $J = 7.2$ Hz, 1H), 3.94 (m, 1H), 3.31-3.21 (complex m, 3H), 3.18 (s, 1H), 2.44 (dd, $J = 7.8$ and 5.7 Hz, 1H), 2.25-1.92 (complex m, 4H), 1.59-1.48 (complex m, 1H).

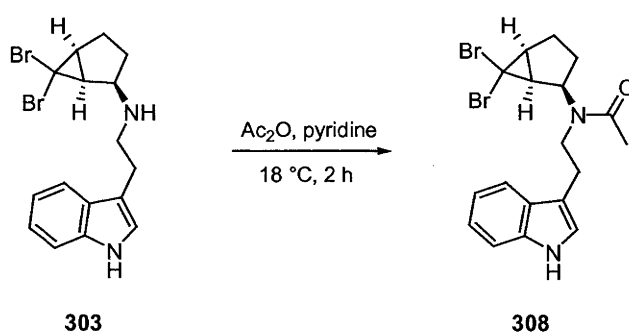
$^{13}\text{C NMR}$ (75 MHz) δ 136.4 (C), 127.4 (C), 122.0 (2 x CH, overlapping), 119.3 (CH), 118.8 (CH), 113.4 (C), 111.1 (CH), 64.1 (CH), 48.9 (CH₂), 39.6 (CH), 38.3 (CH), 34.7 (C), 30.4 (CH₂), 27.0 (CH₂), 26.0 (CH₂).

IR (CH₂Cl₂) ν_{max} 3292, 2919, 2856, 1636, 1456, 1188, 1109, 1050, 752, 738 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 400, 398 and 396 [M^+ , 3, 5 and 3%], 318 and 316 [(M-Br)⁺, both 12], 270, 268 and 266 (20, 42 and 21), 237 (7), 188 and 186 (both 10), 159 and 157 (17 and 16), 144 (40), 130 (100), 115 (10), 103 (13), 77 (29).

HRMS Found M^+ , 395.9833. Calculated for C₁₆H₁₈⁷⁹Br₂N₂ M^+ , 395.9837.

***N*-[2-(Indol-3-yl)-ethyl]-*N*-[(1*SR*,2*RS*,5*SR*)-6,6-dibromobicyclo[3.1.0]hex-2-yl]acetamide (308)**



A magnetically stirred solution of amine **303** (100 mg, 0.25 mmol) in pyridine (1.3 mL) maintained under a nitrogen atmosphere was treated with acetic anhydride (0.9 mL). The resulting dark-orange solution was stirred at ambient temperatures for 2 hours at which point TLC analysis indicated that the reaction had reached completion. Consequently the entire reaction mixture was subjected to flash column chromatography (silica, 7:13 v/v acetone/hexane elution). The appropriate fractions ($R_f = 0.2$) were concentrated and the residue dissolved in ethyl acetate (30 mL). The solution thus obtained was washed with HCl (2 x 25 mL of a 1 M aqueous solution), then NaHCO_3 (2 x 30 mL of a saturated aqueous solution) and brine (1 x 50 mL) before being dried (MgSO_4), filtered and concentrated under reduced pressure to provide a pale-brown solid. Recrystallisation (diethyl ether/ CH_2Cl_2) of this material provided spectroscopically pure *acetamide 308* (100 mg, 94%) as a pale cream solid, m.p. 124-127 °C.

$^1\text{H NMR}$ (300 MHz) δ 8.16 (broad s, 1H), 7.65 (d, $J = 7.5$ Hz, 1H), 7.40 (d, $J = 7.5$ Hz, 1H), 7.29 (t, $J = 7.5$ Hz, 1H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.16 (t, $J = 6.9$ Hz, 1H), 5.21 (m, 1H), 3.89 (m, 2H), 3.15 (m, 2H), 2.40-2.36 (complex m, 1H), 2.30-2.25 (complex m, 1H), 2.21 (s, 3H, CH_3), 2.15-1.95 (complex m, 3H), 1.76-1.62 (complex m, 1H).

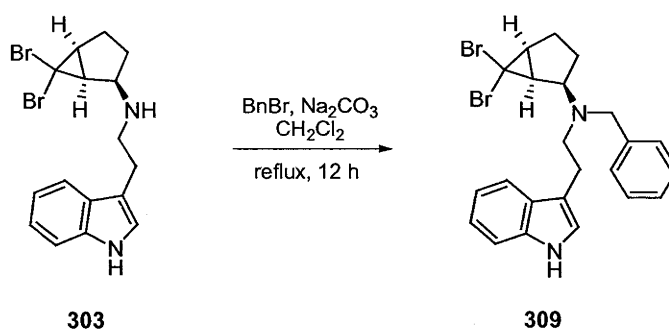
$^{13}\text{C NMR}$ (75 MHz) δ 171.7 (C), 136.1 (C), 127.1 (C), 122.4 (CH), 122.1 (CH), 119.5 (CH), 118.4 (CH), 112.2 (C), 111.4 (CH), 59.2 (CH_2), 47.1 (CH), 40.8 (CH), 35.8 (C), 35.2 (CH), 26.8 (CH_2), 25.6 (CH_2), 21.0 (CH_2), 14.1 (CH_3).

IR (CH_2Cl_2) ν_{max} 3254, 3054, 2925, 2855, 1615, 1420, 1356, 1297, 1264, 1230, 1179, 1101, 1037, 1013, 797, 742 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 442, 440 and 438 [M^+ , 1, 2 and 1%], 360 and 358 [($\text{M}-\text{HBr}$) $^+$, 2 and 1], 270, 268 and 266 (2, 5 and 2), 143 (84), 130 (41), 117 (17).

HRMS Found M^+ , 437.9944. Calculated for $\text{C}_{18}\text{H}_{20}^{79}\text{Br}_2\text{N}_2\text{O}$ M^+ , 437.9942.

(1*SR*,2*RS*,5*SR*)- *N*-[2-(Indol-3-yl)-ethyl]-*N*-benzyl-6,6-dibromobicyclo[3.1.0]hexan-2-amine (309)



A magnetically stirred mixture of amine **303** (500 mg, 1.26 mmol) and sodium carbonate (1.3 mL of a 2 M aqueous solution) in dichloromethane (12.6 mL) maintained at 18 °C under a nitrogen atmosphere was treated with benzyl bromide (150 μ L, 0.21 mg, 1.26 mmol). The resulting orange solution was then heated at reflux for 12 hours. The cooled and now orange reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were washed with brine (1 x 100 mL), before being dried (MgSO_4), filtered and concentrated under reduced pressure to provide an orange oil. Subjection of this material to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions ($R_f = 0.4$), the *title amine 309* (60 mg, 98%) as a pale-orange oil.

$^1\text{H NMR}$ (300 MHz) δ 7.89 (broad s, 1H), 7.50 (d, $J = 7.5$ Hz, 2H), 7.39-7.27 (complex m, 5H), 7.16 (dt, $J = 7.5$ and 1.2 Hz, 1H), 7.05 (dq, $J = 7.5$ and 1.2 Hz, 1H), 6.94 (s, 1H), 4.01 (s, 2H), 3.91-3.82 (complex m, 1H), 3.22-3.05 (complex m, 4H), 2.51 (dd, $J = 5.7$ and 1.8 Hz, 1H), 2.41-2.34 (complex m, 1H), 2.22-2.15 (complex m, 2H), 2.11-1.98 (complex m, 2H).

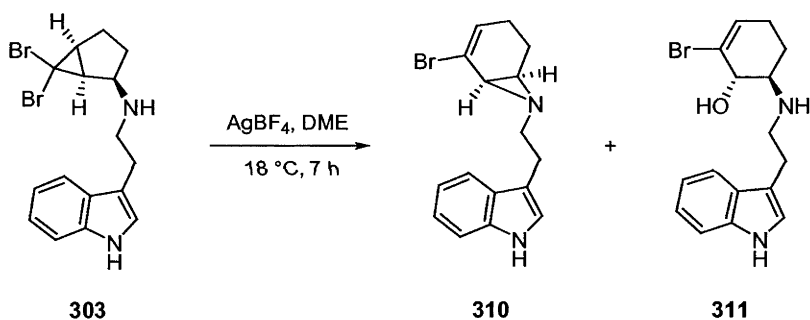
$^{13}\text{C NMR}$ (75 MHz) δ 135.9 (2 x C, overlapping), 128.6 (2 x CH), 128.3 (2 x CH), 128.1 (CH), 127.2 (C), 121.5 (CH), 118.9 (CH), 118.8 (CH), 118.6 (CH), 113.8 (C), 111.0 (CH), 67.3 (CH), 57.4 (CH_2), 55.2 (CH_2), 53.0 (CH_2), 40.7 (CH), 37.7 (CH), 32.3 (C), 27.2 (CH_2), 21.4 (CH_2).

IR (neat) ν_{\max} 3422, 3282, 3058, 3028, 2930, 2855, 2804, 2246, 1884, 1721, 1709, 1619, 1602, 1553, 1493, 1455, 1419, 1339, 1228, 1149, 1117, 1091, 1074, 1042, 1027, 1013, 982, 909, 883, 810, 740, 699 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 490, 488 and 486 [M^+ , all <1%], 408 and 406 [(M-HBr) $^+$, both 9], 358 (38), 327 (20), 278 (8), 250 (5), 219 (14), 159 (12), 144 (13), 130 (14), 120 (15), 91 (100), 77 (29), 65 (8).

HRMS Found (M-HBr) $^+$, 406.1049. Calculated for $C_{23}H_{23}^{79}\text{BrN}_2$ (M-HBr) $^+$, 406.1045.

**3-{2-[(1*RS*,6*RS*)-2-Bromo-7-aza-bicyclo[4.1.0]hept-2-en-7-yl]ethyl}-indole (310)
and (6*RS*)-6-[2-(Indol-3-yl)ethylamino]-2-bromocyclohex-2-enol (311)**



A magnetically stirred solution of dibromocyclopropane **303** (100 mg, 0.25 mmol) in anhydrous dimethoxyethane (6.3 mL) was treated, in one portion, with silver tetrafluoroborate (200 mg, 1.0 mmol). The ensuing mixture was protected from light and stirred at ambient temperature for 7 hours then poured into water (10 mL) and extracted with ethyl acetate (15 mL). NH_4OH (4 mL of a 25% v/v aqueous solution) was then added to the separated aqueous phase to dissolve the silver precipitate. The aqueous phase was extracted with additional ethyl acetate (2 x 20 mL) before being washed with brine (1 x 50 mL), dried (MgSO_4), filtered and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to flash column chromatography (silica, 2:3 v/v acetone/hexane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f = 0.6$) afforded *aziridine 310* (40 mg, 52%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 8.00 (broad s, 1H), 7.60 (dt, $J = 7.8$ and 0.9 Hz, 1H), 7.36 (dt, $J = 7.8$ and 0.9 Hz, 1H), 7.19 (dt, $J = 6.9$ and 0.9 Hz, 1H), 7.11 (dt, $J = 6.9$ and 0.9 Hz, 1H), 7.03 (d, $J = 2.1$ Hz, 1H), 6.00 (m, 1H), 3.04 (dt, $J = 7.8$ and 0.9 Hz, 2H), 2.84-2.76 (complex m, 1H), 2.54 (m, 1H), 2.07-1.92 (complex m, 4H), 1.72-1.59 (complex m, 1H), 1.46-1.33 (complex m, 1H).

$^{13}\text{C NMR}$ (125 MHz) δ 136.2 (C), 128.2 (CH), 127.4 (C), 121.9 (CH), 121.8 (CH), 119.2 (CH), 118.8 (CH), 118.4 (C), 114.0 (C), 111.1 (CH), 60.6 (CH₂), 44.4 (CH), 41.9 (CH), 25.6 (CH₂), 23.6 (CH₂), 19.4 (CH₂).

IR (CH₂Cl₂) ν_{max} 3745, 3402, 3209, 3055, 2925, 2851, 1595, 1456, 1432, 1354, 1230, 1099, 982, 854, 802, 740 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 318 and 316 [M^+ , 14 and 14%], 237 [(M-Br)⁺, 14], 190 (18), 144 (41), 130 (100), 117 (9), 105 (6), 91 (9), 77 (21).

HRMS Found M^+ , 316.0576. Calculated for C₁₆H₁₇⁷⁹BrN₂ M^+ , 316.0575.

Concentration of fraction B ($R_f = 0.1$) afforded *alcohol 311* (20 mg, 29%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 8.12 (broad s, 1H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.21 (dt, $J = 7.5$ and 1.2 Hz, 1H), 7.13 (dt, $J = 7.5$ and 1.2 Hz, 1H), 7.07 (d, $J = 2.4$ Hz, 1H), 6.41 (s, 1H), 4.95 (t, $J = 3.0$ Hz, 1H), 4.78 (t, $J = 3.0$ Hz, 1H), 3.05 (m, 2H), 2.44 (m, 2H), 2.23-1.83 (complex m, 4H).

$^{13}\text{C NMR}$ (125 MHz) δ 138.0 (C), 136.3 (C), 127.2 (C), 125.4 (CH), 122.1 (CH), 119.4 (CH), 118.7 (CH), 114.5 (CH), 113.1 (C), 111.2 (CH), 87.4 (CH), 70.6 (CH₂), 56.2 (CH), 46.2 (CH₂), 29.7 (CH₂), 26.5 (CH₂).

IR (CH_2Cl_2) ν_{max} 3274, 2925, 2854, 1641, 1457, 1364, 1230, 1101, 977, 744 cm^{-1} .

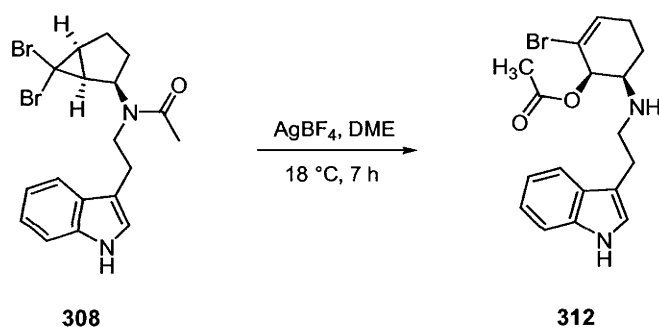
Mass Spectrum (EI, 70 eV) m/z 336 and 334 [M^+ , both 2%], 318 and 316 [$(\text{M}-\text{H}_2\text{O})^+$, both 6], 208 and 206 (both 11), 179 and 177 (both 12), 143 (14), 131 (100), 97 (47), 83 (24), 69 (24), 57 (42), 43 (33).

HRMS Found M^+ , 336.0664. Calculated for $\text{C}_{16}\text{H}_{19}^{81}\text{BrN}_2\text{O}$ M^+ , 336.0660.

Found M^+ , 334.0672. Calculated for $\text{C}_{16}\text{H}_{19}^{79}\text{BrN}_2\text{O}$ M^+ , 334.0688.

Found $(\text{M}-\text{H}_2\text{O})^+$, 316.0579. Calculated for $\text{C}_{16}\text{H}_{17}^{79}\text{BrN}_2$ $(\text{M}-\text{H}_2\text{O})^+$, 316.0575.

[(1*RS*,6*RS*)-6-(2-Indol-3-yl)ethylamino]-2-bromocyclohex-2-enyl acetate (312)



Silver tetrafluoroborate (180 mg, 0.92 mmol) was added, in one portion, to a magnetically stirred solution of acetamide **308** (100 mg, 0.22 mmol) in anhydrous dimethoxyethane (5.6 mL). The resulting mixture was protected from light and stirred at 18 °C for 7 hours then poured into water (10 mL) and extracted with ethyl acetate (20 mL). NH_4OH (3 mL of a 25% v/v aqueous solution) was subsequently added to the separated aqueous phase to dissolve the resultant silver precipitate. The aqueous phase was then extracted with additional ethyl acetate (2 x 20 mL) before the combined organic fractions were washed with brine (1 x 50 mL), then dried (MgSO_4) and filtered to provide, after concentration under reduced pressure, a yellow oil. This material was subjected to flash column chromatography (silica, 2:3 v/v acetone/hexane elution) to afford, after concentration of the appropriate fractions ($R_f = 0.4$), *compound 312* (70 mg, 85%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 8.05 (broad s, 1H), 7.61 (d, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.20 (dt, $J = 6.9$ and 1.2 Hz, 1H), 7.13 (dt, $J = 6.9$ and 1.2 Hz, 1H), 7.07 (d, $J = 2.4$ Hz, 1H), 6.28 (q, $J = 2.7$ Hz, 1H), 5.67 (d, $J = 3.3$ Hz, 1H), 3.07-2.88 (complex m, 4H), 2.22-2.03 (complex m, 3H), 1.83 (s, 3H), 1.80-1.70 (complex m, 1H), 1.67-1.50 (complex m, 1H).

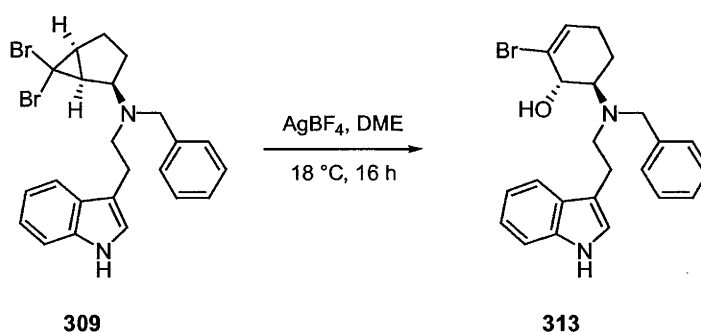
$^{13}\text{C NMR}$ (75 MHz) δ 170.1 (C), 136.2 (C), 134.8 (CH), 127.2 (C), 122.0 (CH), 121.9 (CH), 119.2 (CH), 118.9 (CH), 118.5 (C), 113.5 (C), 111.0 (CH), 71.2 (CH), 57.4 (CH), 47.0 (CH₂), 27.0 (CH₂), 25.9 (CH₂), 23.5 (CH₂), 20.6 (CH₃).

IR (CH₂Cl₂) ν_{max} 3410, 3168, 3054, 2925, 1736, 1646, 1619, 1456, 1429, 1370, 1341, 1229, 1112, 1095, 1043, 1013, 969, 932, 921, 763, 741, 620, 605 537 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 378 and 376 [M^+ , both 5%], 248 and 246 (both 51), 188 and 186 (30 and 31), 159 and 157 (19 and 18), 144 (38), 131 (100), 106 (14), 77 (24).

HRMS Found M^+ , 376.0787. Calculated for C₁₈H₂₁⁷⁹BrN₂O₂ M^+ , 376.0786.

(6*RS*)-6-{*N*-[2-(1-3-yl)ethyl]-*N*-benzylamino}-2-bromocyclohex-2-enol (313)



Silver tetrafluoroborate (270 mg, 1.39 mmol) was added, in one portion, to a magnetically stirred solution of compound **309** (170 g, 0.35 mmol) in anhydrous dimethoxyethane (8.7 mL). The resulting mixture was protected from light and stirred at 18 °C for 16 hours then poured into water (20 mL) and extracted with ethyl acetate (40 mL). NH₄OH (5 mL of a 25%

v/v aqueous solution) was subsequently added to the separated aqueous phase to dissolve the resultant silver precipitate. The aqueous phase was extracted with additional ethyl acetate (2 x 40 mL) and the combined organic phases washed with brine (1 x 80 mL), then dried (MgSO₄), filtered and concentrated under reduced pressure to provide a yellow oil. This residue was subjected to flash column chromatography (silica, 2:3 v/v acetone/hexane elution) to deliver, after concentration of the relevant fractions ($R_f = 0.4$), *compound 313* (120 mg, 79%) as a pale-yellow oil.

¹H NMR (300 MHz) δ 7.95 (broad s, 1H), 7.42 (d, $J = 7.2$ Hz, 1H), 7.35-7.32 (complex m, 5H), 7.29 (d, $J = 7.2$ Hz, 1H), 7.17 (dt, $J = 7.2$ and 1.2 Hz, 1H), 7.07 (dt, $J = 7.2$ and 1.2 Hz, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 6.16 (m, 1H), 4.02 (m, 3H), 3.53-3.47 (complex m, 1H), 3.38-3.31 (complex m, 2H), 3.18-3.08 (complex m, 2H), 2.93 (broad s, 1H, OH), 2.89-2.70 (complex m, 2H), 2.17-2.05 (complex m, 2H).

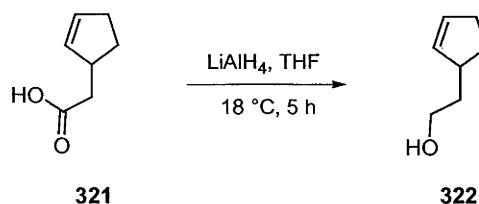
¹³C NMR (75 MHz) δ 140.8 (C), 136.3 (C), 133.5 (CH), 129.0 (2 x CH, overlapping), 128.5 (2 x CH, overlapping), 127.3 (C), 127.2 (CH), 122.7 (C), 122.0 (CH), 121.7 (CH), 119.2 (CH), 118.8 (CH), 114.0 (C), 111.2 (CH), 70.4 (CH), 70.2 (CH), 56.7 (CH₂), 53.3 (CH₂), 28.0 (CH₂), 26.7 (CH₂), 25.7 (CH₂).

IR (neat) ν_{\max} 3295, 3056, 2925, 2853, 1734, 1456, 1354, 1246, 1092, 821, 742, 699 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 426 and 424 [M^+ , both <1%], 408 and 406 [($M-H_2O$)⁺, both <1], 296 and 294 (both 68), 144 (9), 130 (34), 120 (32), 91 (100), 77 (6).

HRMS Found ($M-H_2O$)⁺, 408.1026. Calculated for C₂₃H₂₃⁸¹BrN₂ ($M-H_2O$)⁺, 408.1024.

Found ($M-H_2O$)⁺, 406.1039. Calculated for C₂₃H₂₃⁷⁹BrN₂ ($M-H_2O$)⁺, 406.1045.

2-Cyclopentene-1-ethanol (322)

Following a procedure reported by Banwell and co-workers,²⁶ lithium aluminium hydride (63 mL of a 1 M solution in THF, 63.0 mmol) was added to a solution of cyclopentene-1-acetic acid (**321**) (9.6 mL, 10.0 g, 79.0 mmol) in anhydrous THF (26 mL) at such a rate so as to maintain gentle reflux. The resulting solution was allowed to cool to room temperature and stirring continued for 5 hours. The reaction was then quenched, at 0 °C, through the dropwise addition of ethyl acetate (10 mL) then sodium hydroxide (10 mL of a 15% w/v aqueous solution) and water (25 mL). The ensuing suspension was stirred at 0 °C for a further 2 hours before being filtered through a sintered-glass funnel. The retained solid was then washed with diethyl ether (1 x 200 mL) and the combined filtrates concentrated under reduced pressure. The residue was cooled to 0 °C and treated with HCl (1 x 300 mL of a 2 M aqueous solution) and the ensuing mixture extracted with diethyl ether (4 x 300 mL). The combined organic fractions were then washed with brine (1 x 600 mL), before being dried (MgSO₄), filtered and concentrated under reduced pressure to provide a pungent yellow liquid. Subjection of this material to flash column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.3$) then afforded the title compound **322**²⁷ (8.6 g, 97%) as a clear, colourless oil.

¹H NMR (300 MHz) δ 5.69-5.66 (complex m, 1H), 5.64-5.60 (complex m, 1H), 3.61 (dt, $J = 6.9$ and 2.1 Hz, 2H), 2.69 (m, 1H), 2.31-2.20 (complex m, 2H), 2.06-1.95 (complex m, 1H), 1.73-1.56 (complex m, 1H), 1.55-1.41 (m, 1H), 1.40-1.31 (m, 1H).

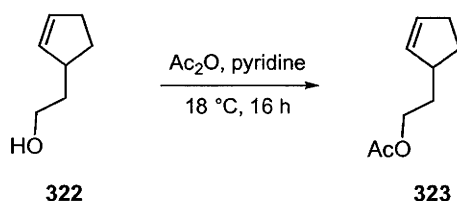
¹³C NMR (75 MHz) δ 134.6 (CH), 130.4 (CH), 61.3 (CH₂), 42.0 (CH), 38.7 (CH₂), 31.8 (CH₂), 29.7 (CH₂).

IR (neat) ν_{\max} 3338, 3052, 2930, 2852, 1613, 1457, 1432, 1359, 1260, 1240, 1059, 1010, 910, 719 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 112 [M^+ , 13%], 95 [$(\text{M}-\text{HO})^+$, 12], 94 [$(\text{M}-\text{H}_2\text{O})^+$, 65], 88 (10), 81 (22), 79 (86), 67 (100), 61 (13), 53 (22).

HRMS Found M^+ , 112.0886. Calculated for $\text{C}_7\text{H}_{12}\text{O}$ M^+ , 112.0888.

2-Cyclopentene-1-ethanol acetate (**323**)



A magnetically stirred solution of alcohol **322** (8.2 g, 73 mmol) in pyridine (14.2 mL, 15.3 g, 0.15 mol) maintained under a nitrogen atmosphere was treated with acetic anhydride (11.8 mL, 11.6 g, 0.15 mol). The resultant solution was then stirred at 18 °C for a further 16 hours. After this time, excess acetic anhydride was destroyed by the addition of methanol (5 mL) to the ice-cooled solution. After a further 2 hours the methanol was removed under reduced pressure and the residue partitioned between water (100 mL) and diethyl ether (300 mL). The separated aqueous phase was extracted with additional diethyl ether (2 x 300 mL) and the combined ethereal fractions were then washed with HCl (2 x 100 mL of a 1 M aqueous solution), water (1 x 300 mL) and brine (1 x 500 mL). Subsequent drying (MgSO_4) and filtration yielded, after concentration under reduced pressure, a yellow oil. This material was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions ($R_f = 0.5$), the desired product **323**²⁸ (11.2 g, 99%) as a clear, colourless oil.

$^1\text{H NMR}$ (300 MHz) δ 5.76-5.72 (m, 1H), 5.67-5.63 (m, 1H), 4.16-4.03 (m, 2H), 2.77-2.68 (m, 1H), 2.40-2.21 (m, 2H), 2.12-2.04 (m, 1H), 2.04 (s, 3H, CH_3), 1.80-1.67 (m, 1H), 1.6-1.54 (m, 1H), 1.48-1.36 (m, 1H).

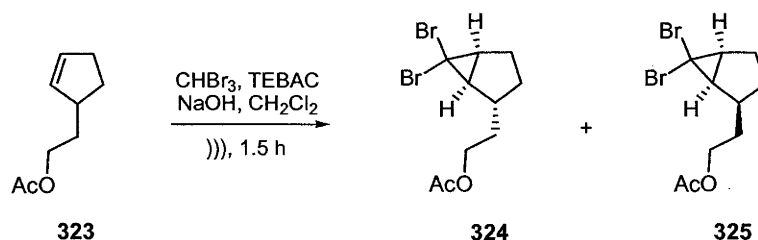
$^{13}\text{C NMR}$ (75 MHz) δ 171.0 (C), 134.0 (CH), 130.8 (CH), 63.4 (CH_2), 42.2 (CH), 34.5 (CH_2), 31.8 (CH_2), 29.6 (CH_2), 20.9 (CH_3).

IR (neat) ν_{max} 3052, 2952, 2852, 1742, 1459, 1387, 1366, 1240, 1046, 721, 606 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 111 (5%), 94 [$(\text{M}-\text{CH}_3\text{COOH})^+$], 72], 79 (100), 67 (47), 43 (39).

HRMS Found $(\text{M}-\text{CH}_3\text{COOH})^+$, 94.0787. C_7H_{10} requires $(\text{M}-\text{CH}_3\text{COOH})^+$, 94.0783.

[1*SR*,2*SR*,5*SR*]-6,6-Dibromo-2-(2'-hydroxyethyl)bicyclo[3.1.0]hexane acetate (324) and [1*SR*,2*RS*,5*SR*]-6,6-Dibromo-2-(2'-hydroxyethyl)bicyclo[3.1.0]hexane Acetate (325)



Benzyltriethylammonium chloride (320 mg, 1.40 mmol), powdered sodium hydroxide (17.1 g, 0.43 mol), and bromoform (12.5 mL, 36.1 g, 0.14 mol) were added to a magnetically stirred solution of acetate **323** (11.0 g, 71.0 mmol) in CH_2Cl_2 (43 mL). The flask containing the ensuing mixture was then equipped with a reflux condenser and subjected to sonication without external temperature control for 1.5 hours. Upon completion of the reaction a small amount of CeliteTM was added into the reaction flask and the entire mixture filtered through a 1 cm plug of CeliteTM which was washed with CH_2Cl_2 (400 mL). The combined filtrates were

concentrated under reduced pressure and the ensuing brown oil subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). Concentration of the appropriate fractions ($R_f = 0.4$) delivered a *ca.* 3:1 mixture of compounds (\pm)-**324** and (\pm)-**325**²⁸ (17.8 g, 77%) as a pale-yellow oil.

¹H NMR (300 MHz) δ [(\pm)-**324**] 4.11 (dt, $J = 6.6$ and 2.4 Hz, 2H), 2.29-2.19 (complex m, 2H), 2.15-1.79 (complex m, 5H), 2.07 (s, 3H, CH₃), 1.75-1.62 (complex m, 1H), 1.52-1.42 (complex m, 1H); δ [(\pm)-**325**] 4.21 (m, 2H), 2.53 (broad m, 1H), 2.15-1.59 (complex m, 7H), 2.09 (s, 3H, CH₃), 1.55-1.45 (complex m, 1H).

¹³C NMR (75 MHz) δ [(\pm)-**324**] 171.0 (C), 62.7 (CH₂), 44.1 (CH), 39.7 (CH), 39.3 (CH), 38.5 (C), 34.4 (CH₂), 32.9 (CH₂), 28.3 (CH₂), 20.9 (CH₃); δ [(\pm)-**325**] 171.2 (C), 63.8 (CH₂), 41.8 (CH), 41.3 (CH), 36.2 (C), 29.4 (CH₂), 29.3 (CH), 28.9 (CH₂), 28.7 (CH₂), 21.0 (CH₃).

IR (neat) ν_{\max} 3460, 3023, 2954, 2932, 2865, 1740, 1460, 1442, 1387, 1366, 1240, 1101, 1044, 970, 873, 743, 605 cm⁻¹.

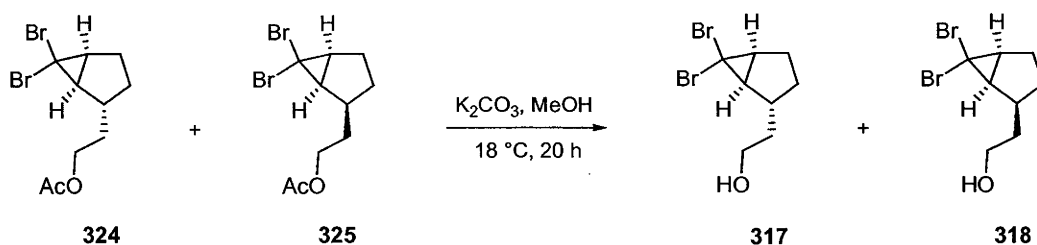
Mass Spectrum (EI, 70 eV) m/z 328, 326 and 324 [M^+ , all <1%], 268, 266 and 264 [(M-CH₃COOH)⁺, 2, 4 and 2], 187 and 185 (both 77), 159 and 157 (22 and 21), 105 (92), 91 (40), 77 (53), 43 (100).

HRMS Found (M-CH₃COOH)⁺, 267.9109. C₈H₁₀⁸¹Br₂ requires (M-CH₃COOH)⁺, 267.9108.

Found (M-CH₃COOH)⁺, 265.9132. C₈H₁₀⁷⁹Br⁸¹Br requires (M-CH₃COOH)⁺, 265.9129.

Found (M-CH₃COOH)⁺, 263.9153. C₈H₁₀⁷⁹Br₂ requires (M-CH₃COOH)⁺, 263.9149.

[1*SR*,2*SR*,5*SR*]-6,6-Dibromo-2-(2'-hydroxyethyl)bicyclo[3.1.0]hexane (317) and [1*SR*,2*RS*,5*SR*]-6,6-Dibromo-2-(2'-hydroxyethyl)bicyclo[3.1.0]hexane (318)



Hydrolysis of the 3:1 mixture of acetates (\pm)-**324** and **325** (16.5 g, 49.0 mmol) was carried out by treatment with potassium carbonate (13.5 g, 98.0 mmol) in methanol (49 mL). This suspension was stirred at room temperature for 20 hours after which time the reaction mixture was poured into brine (150 mL) and extracted with CH_2Cl_2 (5 x 250 mL). The combined organic fractions were then washed with water (1 x 800 mL) and brine (1 x 800 mL) before being dried (MgSO_4), filtered and concentrated under reduced pressure to provide a dark-yellow oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.2$) afforded a *ca.* 3:1 mixture of alcohols (\pm)-**317** and (\pm)-**318**²⁸ (13.2 g, 95%) as a clear, colourless oil.

¹H NMR (300 MHz) δ [(\pm)-**317**] 3.67 (dt, $J = 6.6$ and 2.7 Hz, 2H), 3.19 (broad s, 1H, OH), 2.24 (m, 2H), 2.12-1.98 (complex m, 2H), 1.95-1.86 (complex m, 1H), 1.83-1.72 (complex m, 2H), 1.60 (pentet, $J = 6.6$ Hz, 1H), 1.48 – 1.38 (complex m, 1H); δ [(\pm)-**318**] 3.72 (m, 2H), 2.58 (broad m, 1H, OH), 2.24 (m, 2H), 2.12-1.72 (complex m, 6H), 1.60 (m, 1H).

¹³C NMR (75 MHz) δ [(\pm)-**317**] 61.0 (CH_2), 44.1 (CH), 39.7 (CH and C, 2 signals overlapping), 39.2 (CH), 38.4 (CH_2), 32.9 (CH_2), 28.2 (CH_2); δ [(\pm)-**318**] 62.0 (CH_2), 41.9 (CH), 40.6 (CH), 38.4 (CH), 36.5 (C), 33.2 (CH_2), 29.5 (CH_2), 28.7 (CH_2).

IR (neat) ν_{max} 3338, 3028, 2929, 1718, 1638, 1463, 1442, 1356, 1288, 1238, 1190, 1056, 910, 885, 743, 655, 535 cm^{-1} .

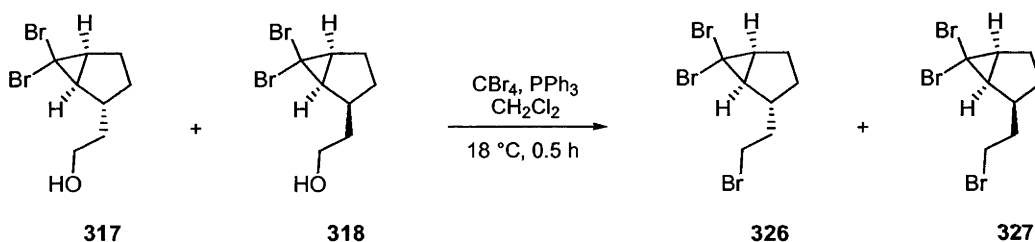
Mass Spectrum (EI, 70 eV) m/z 286, 284 and 282 [M^+ , all <1%], 268, 266 and 264 [($M-H_2O$) $^+$, 5, 10 and 6], 240, 238 and 236 (9, 20 and 10), 214, 212 and 210 (3, 6 and 3), 200, 198 and 196 (5, 9 and 5), 187 and 185 (57 and 58), 159 and 157 (28 and 27), 105 (84), 93 (42), 91 (42), 79 (49), 77 (43), 67 (33), 51 (21), 43 (100).

HRMS Found ($M-H_2O$) $^+$, 267.9109. $C_8H_{10}^{81}Br_2$ requires ($M-H_2O$) $^+$, 267.9108.

Found ($M-H_2O$) $^+$, 265.9129. $C_8H_{10}^{79}Br^{81}Br$ requires ($M-H_2O$) $^+$, 265.9129.

Found ($M-H_2O$) $^+$, 263.9152. $C_8H_{10}^{79}Br_2$ requires ($M-H_2O$) $^+$, 263.9149.

[1*SR*,2*SR*,5*SR*]-6,6-Dibromo-2-(2'-bromoethyl)bicyclo[3.1.0]hexane (326) and [1*SR*,2*RS*,5*SR*]-6,6-Dibromo-2-(2'-bromoethyl)bicyclo[3.1.0]hexane (327)



Carbon tetrabromide (21.9 g, 66.0 mmol) was added, in one portion, to a magnetically stirred solution of alcohols **317** and **318** (9.4 g, 33.0 mmol) and triphenylphosphine (34.6 g, 0.13 mol) in anhydrous CH_2Cl_2 (330 mL) which was maintained under a nitrogen atmosphere at *ca.* 18 °C. Conversion of the resultant brown mixture to a dark-green solution was observed upon reaction and after 0.5 hours TLC analysis indicated complete consumption of starting materials. Consequently, the reaction mixture was washed with water (3 x 300 mL) and brine (1 x 500 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a brown solid. Subjection of this material to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) afforded, after concentration of the appropriate fractions ($R_f = 0.6$), a 3:1 mixture of the *title compounds* **326** and **327** (9.4 g, 82%) as a yellow oil.

¹H NMR (300 MHz) δ [(±)-**326**] 3.61-3.48 (m, 2H), 2.36-2.22 (complex m, 2H), 2.14-1.90 (m, 4H), 1.89-1.75 (complex m, 2H), 1.48-1.38 (m, 1H); δ [(±)-**327**] 3.70-3.54 (m, 2H), 2.38-2.22 (complex m, 2H), 2.14-1.90 (m, 4H), 1.89-1.75 (complex m, 2H), 1.48-1.38 (m, 1H).

¹³C NMR (75 MHz) δ [(±)-**326**] 43.8 (CH₂), 42.8 (CH), 40.6 (CH), 39.2 (CH), 39.1 (C), 38.5 (CH₂), 32.5 (CH₂), 28.2 (CH₂); δ [(±)-**327**] 44.4 (CH₂), 41.3 (CH), 40.1 (CH), 37.4 (CH), 36.0 (C), 35.8 (CH₂), 33.0 (CH₂), 28.8 (CH₂).

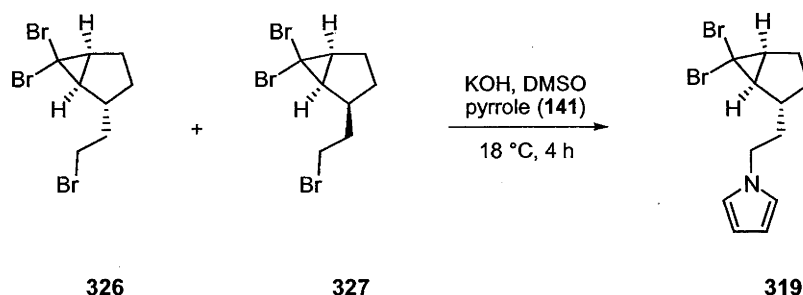
IR (neat) ν_{\max} 3356, 2930, 2863, 1633, 1444, 1315, 1288, 1189, 1048, 861, 741, 655 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 350, 348, 346 and 344 [M⁺, 1, 3, 3 and 1%], 269, 267 and 265 [(M-Br)⁺, 13, 27 and 13], 239, 237 and 235 (5, 10 and 6), 201, 199 and 197 (10, 20 and 11), 187 and 185 (14 and 15), 159 and 157 (14 and 13), 105 (100), 91 (13), 77 (40).

HRMS Found M⁺, 347.8371. C₈H₁₁⁷⁹Br⁸¹Br₂ requires M⁺, 347.8370.

Found M⁺, 345.8387. C₈H₁₁⁷⁹Br₂⁸¹Br requires M⁺, 345.8390.

1-[2-(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl)-ethyl]pyrrole (**319**)



A magnetically stirred suspension of powdered potassium hydroxide (1.3 g, 0.02 mol) in DMSO (11.5 mL) was allowed to stir for 5 minutes under a nitrogen atmosphere then treated with pyrrole (**141**) (0.4 mL, 390 mg, 5.80 mmol). After 1 hour a 3:1 mixture of bromides **326** and **327** (2.0 g, 5.80 mmol) was added and the ensuing yellow reaction mixture immediately turned dark-brown. TLC analysis indicated that all of the starting materials had been

consumed after 3 hours and so the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 150 mL). Between each extraction the obtained organic phase was washed with additional water (1 x 100 mL) to remove all DMSO. The combined organic fractions were subsequently washed with brine (1 x 400 mL) before being dried (MgSO_4), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions ($R_f = 0.3$), the *title compound 319* (1.3 g, 65%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 6.67 (t, $J = 2.1$ Hz, 2H), 6.16 (t, $J = 2.1$ Hz, 2H), 3.93 (dt, $J = 7.2$ and 2.1 Hz, 2H), 2.28 (dt, $J = 7.2$ and 2.1 Hz, 1H), 2.17-2.07 (complex m, 2H), 2.04-1.90 (complex m, 2H), 1.87-1.77 (complex m, 2H), 1.57-1.44 (complex m, 2H).

$^{13}\text{C NMR}$ (75 MHz) δ 120.3 (2 x CH), 108.1 (2 x CH), 48.0 (CH_2), 43.9 (CH), 40.7 (CH), 39.4 (C), 39.3 (CH), 37.6 (CH_2), 33.0 (CH_2), 28.3 (CH_2).

IR (neat) ν_{max} 3099, 2926, 2854, 1499, 1458, 1442, 1365, 1282, 1188, 1158, 1088, 1061, 989, 967, 916, 861, 818, 723, 617 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 335, 333 and 331 [M^+ , 5, 9 and 5%], 254 and 252 [$(\text{M}-\text{Br})^+$, 51 and 51], 172 (23), 160 (18), 145 (9), 132 (17), 120 (39), 105 (33), 97 (26), 80 (100), 66 (29).

HRMS Found M^+ , 332.9551. $\text{C}_{12}\text{H}_{15}\text{N}^{79}\text{Br}^{81}\text{Br}$ requires M^+ , 332.9551.

10-Bromo-5,6,6a,7,8,10a-hexahydro-pyrrolo[2,1-a]isoquinoline (328)

Silver tetrafluoroborate (880 mg, 4.50 mmol) was added, in one portion, to a magnetically stirred solution of pyrrole **319** (250 mg, 0.75 mmol) in anhydrous DME (19 mL) maintained under a nitrogen atmosphere. The resulting suspension was then protected from light and stirred at 18 °C for 6.5 hours. After this time the reaction mixture was filtered through a plug of Celite™ that was washed with ethyl acetate (150 mL). Concentration of the combined filtrates under reduced pressure afforded a dark-purple syrup. This material was then subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) to provide, after concentration of the appropriate fractions ($R_f = 0.3$), *compound 328* (100 mg, 76%) as a clear, colourless oil.

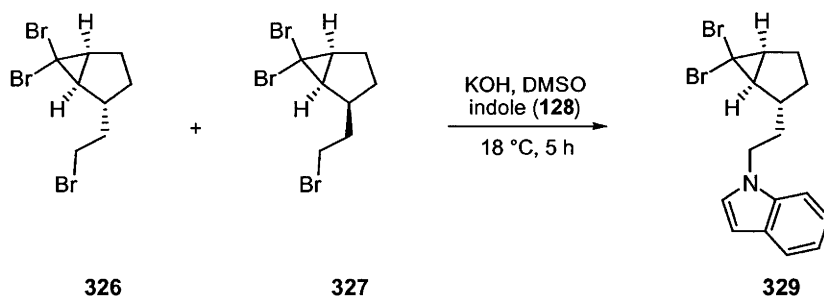
$^1\text{H NMR}$ (300 MHz) δ 6.41 (m, 1H), 6.25 (m, 1H), 6.23-6.16 (complex m, 1H), 6.10 (m, 1H), 3.92-3.76 (complex m, 2H), 3.74-3.66 (complex m, 1H), 2.34-2.21 (complex m, 1H), 2.18-2.10 (complex m, 2H), 2.09-1.82 (complex m, 4H).

$^{13}\text{C NMR}$ (75 MHz) δ 132.7 (C), 129.3 (CH), 123.8 (CH), 120.2 (C), 115.0 (CH), 105.8 (CH), 53.8 (CH₂), 43.0 (CH), 41.6 (CH), 33.4 (CH₂), 27.4 (CH₂), 26.7 (CH₂).

IR (neat) ν_{max} 2955, 2924, 2854, 1739, 1641, 1465, 1377, 1260, 1081, 909, 805, 721 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 253 and 251 [M^+ , both <1%], 97 (14), 84 (82), 69 (15), 55 (21), 49 (100), 43 (27).

HRMS Found M^+ , 251.0310. $\text{C}_{12}\text{H}_{14}^{79}\text{BrN}$ requires M^+ , 251.0314.

1-{2-[(1*RS*,2*RS*,5*SR*)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]ethyl}-indole (**329**)

A magnetically stirred solution of finely-ground potassium hydroxide (1.3 g, 20.0 mmol) in DMSO (11.5 mL) was stirred under a nitrogen atmosphere at ambient temperature for 5 minutes. One equivalent of indole (**128**) (680 mg, 5.80 mmol) was then added to the resulting white suspension and stirring continued for a further hour, during which time the reaction mixture turned pale-pink. A 3:1 mixture of tribromides **326** and **327** (2.0 g, 5.80 mmol) was subsequently added in one portion and stirring continued for a further 4 hours. After this time TLC analysis indicated that the reaction had reached completion. Consequently the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 150 mL). Between each extraction the obtained organic phase was washed with additional water (1 x 100 mL) to remove all DMSO. The combined organic phases were washed with brine (1 x 400 mL), then dried (MgSO_4), filtered and concentrated under reduced pressure. Subjection of the ensuing yellow oil to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.4$) then delivered the *title indole* **329** (1.5 g, 67%) as a pale-yellow oil.

$^1\text{H NMR}$ (300 MHz) δ 7.65 (dt, $J = 7.8$ and 0.6 Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.23 (dt, $J = 7.8$ and 0.9 Hz, 1H), 7.14-7.09 (complex m, 2H), 6.52 (dd, $J = 3.0$ and 0.9 Hz, 1H), 4.18 (dt, $J = 7.8$ and 0.9 Hz, 2H), 2.28 (dt, $J = 7.8$ and 0.9 Hz, 1H), 2.17-1.95 (complex m, 4H), 1.93-1.79 (complex m, 3H), 1.54-1.46 (complex m, 1H).

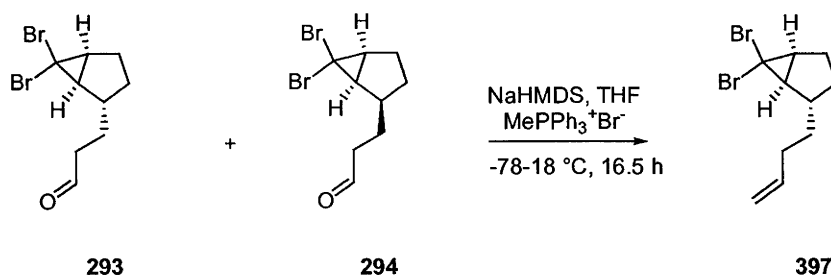
$^{13}\text{C NMR}$ (75 MHz) δ 135.7 (C), 128.6 (C), 127.6 (CH), 121.5 (CH), 121.1 (CH), 119.3 (CH), 109.2 (CH), 101.3 (CH), 44.9 (CH_2), 44.0 (CH), 40.9 (CH), 39.4 (C), 36.1 (CH), 33.4 (CH_2), 29.7 (CH_2), 28.4 (CH_2).

IR (neat) ν_{\max} 3392, 2927, 1732, 1611, 1511, 1462, 1315, 1193, 1058, 739, 562 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 385, 383 and 381 [M^+ ; 17, 34 and 17%], 304 and 302 [($\text{M}-\text{Br}\cdot$)⁺, 61 and 63], 222 (12), 184 (5), 170 (27), 143 (10), 130 (100), 117 (29), 103 (25), 77 (46).

HRMS Found M^+ , 382.9726. $\text{C}_{16}\text{H}_{17}^{79}\text{Br}^{81}\text{BrN}$ requires M^+ , 382.9707.

7.5 Experimental Section for Chapter Five

(1*RS*,2*SR*,5*SR*)-6,6-Dibromo-2-(but-3-enyl)bicyclo[3.1.0]hexane (397)

Sodium hexamethyldisilazide (3.75 mL of a 1 M solution in THF, 3.75 mmol) was added, dropwise, to a magnetically stirred solution of methyl triphenylphosphonium bromide (1.3 g, 3.75 mmol) in anhydrous THF (10 mL) which was maintained under a nitrogen atmosphere at $-78\text{ }^{\circ}\text{C}$ (dry ice/acetone cooling bath). After 30 minutes a solution of a 4:1 mixture of aldehydes **293** and **294** (740 mg, 2.50 mmol) in THF (2 mL) was added in one portion. The resulting mixture was allowed to warm to room temperature, stirred for 16 hours, then concentrated under reduced pressure to give a yellow oil. A solution of this material in hexane (10 mL) was filtered through a plug of CeliteTM and washed with additional hexane (40 mL). The combined filtrates were concentrated under reduced pressure to give a pale-yellow oil that was subjected to gravity column chromatography (silica, hexane elution). Concentration of the appropriate fractions ($R_f = 0.6$) then delivered the *title alkene* **397** (580 mg, 79%) as a clear, colourless oil.

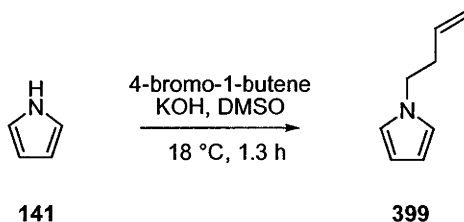
¹H NMR (300 MHz) δ 5.82 (m, 1H), 5.07-4.95 (complex m, 2H), 2.25 (dt, $J = 6.0$ and 1.2 Hz, 1H), 2.20-2.01 (complex m, 5H), 1.98-1.73 (complex m, 2H), 1.64-1.39 (complex m, 3H).

¹³C NMR (75 MHz) δ 138.2 (CH), 114.8 (CH₂), 44.4 (CH), 42.8 (CH), 40.1 (C), 39.4 (CH), 35.2 (CH₂), 32.9 (CH₂), 32.0 (CH₂), 28.4 (CH₂).

IR (neat) ν_{max} 3077, 2926, 2854, 1641, 1452, 1415, 1288, 1259, 1188, 1050, 992, 912, 744 cm^{-1} .

Mass Spectrum (GC-MS) m/z 296, 294 and 292 [M^+ , all <1%], 214, 212 and 210 (8, 15 and 8), 201, 199 and 197 (10, 20 and 10), 173 and 171 (both 21), 159 and 157 (both 12), 147 and 145 (both 11), 133 (57), 121 (19), 105 (23), 91 (100), 79 (64), 67 (38), 51 (18).

1-(But-3-enyl)-pyrrole (399)



Following a literature procedure²⁹ utilised to synthesise the lower homologue of the title compound, powdered potassium hydroxide (1.7 g, 0.03 mol) was added to a round-bottom flask containing DMSO (15 mL). The resulting white suspension was stirred for 5 minutes before pyrrole (**141**) (0.5 mL, 500 mg, 7.45 mmol) was in one portion. After stirring for a further 45 minutes 4-bromo-1-butene (1.0 mL, 1.3 g, 9.69 mmol) was then added to the reaction mixture and stirring continued for a further 0.5 hours. After this time TLC analysis indicated that all of the starting materials had been consumed so the reaction mixture was poured into water (30 mL) and extracted with diethyl ether (3 x 50 mL). Each organic extract was also washed with additional water (1 x 50 mL) between extractions. The combined organic fractions were then washed with brine (1 x 150 mL), before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjecting of this material to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions ($R_f = 0.4$) then provided the title alkene **399**³⁰ (590 mg, 65%) as a clear, colourless oil.

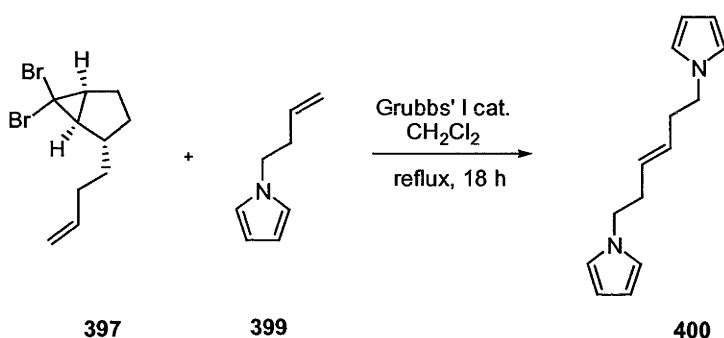
¹H NMR (300 MHz) δ 6.67 (t, $J = 2.1$ Hz, 2H), 6.15 (t, $J = 2.1$ Hz, 2H), 5.78 (ddt, $J = 17.1$, 10.2 and 6.9 Hz, 1H), 5.13-5.05 (complex m, 2H), 3.95 (t, $J = 7.2$ Hz, 2H), 2.53 (ddt, $J = 7.2$, 6.9 and 1.5 Hz, 2H).

^{13}C NMR (75 MHz) δ 134.6 (CH), 120.4 (2 x CH), 117.2 (CH₂), 107.9 (2 x CH), 49.1 (CH₂), 35.9 (CH₂).

IR (neat) ν_{max} 3352, 2958, 2925, 2855, 1641, 1457, 1261, 1089, 801, 720 cm^{-1} .

Mass Spectrum (GCMS) m/z 121 [M^+ , 61%], 106 [($\text{M}-\text{CH}_3$)⁺, 8], 93 (10), 80 (100), 67 (5), 53 (21).

1-[(*E*)-6-(Pyrrol-1-yl)hex-3-enyl]-pyrrole (400)



Grubbs' I catalyst (11 mg, 0.01 mmol) was added, in one portion, to a deoxygenated solution of cyclopropane **397** (80 mg, 0.27 mmol) and 1-(but-3-enyl)-pyrrole (**399**) (33 mg, 0.27 mmol) in anhydrous CH_2Cl_2 (5 mL). The resulting magenta-coloured solution was then heated at reflux for 18 hours. The cooled reaction mixture was treated, in one portion, with DMSO (0.1 mL, 110 mg, 1.36 mmol) and stirring continued for a further 18 hours before the solvent was removed under reduced pressure. The residue so-obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/hexane elution) and thus affording two fractions, A and B, were afforded.

Concentration of fraction A ($R_f = 0.6$ in hexane elution) furnished the starting cyclopropane **397** (75 mg, 94% recovery) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample.

Concentration of fraction B ($R_f = 0.4$) afforded the *title compound 400* (25 mg, 88%).

$^1\text{H NMR}$ (300 MHz) δ 6.62 (t, $J = 2.1$ Hz, 4H), 6.13 (t, $J = 2.1$ Hz, 4H), 5.45-5.38 (complex m, 2H), 3.86 (t, $J = 6.9$ Hz, 2H), 3.77 (t, $J = 6.9$ Hz, 2H), 2.46-2.34 (complex m, 4H).

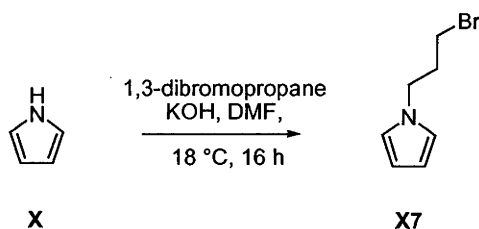
$^{13}\text{C NMR}$ (75 MHz) δ 128.2 (2 x CH), 120.4 (4 x CH), 108.0 (4 x CH), 49.2 (2 x CH₂), 34.8 (2 x CH₂).

IR (neat) ν_{max} 3370, 3099, 2928, 2854, 1499, 1448, 1360, 1282, 1089, 1068, 971, 723, 618 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 214 [M^+ , 70%], 148 (58), 134 (79), 120 (71), 107 (61), 93 (56), 80 (100), 67 (65), 53 (84), 41 (78).

HRMS Found M^+ , 214.1475. $\text{C}_{14}\text{H}_{18}\text{N}_2$ requires M^+ , 214.1470.

1-(3-Bromopropyl)-pyrrole (403)



Pyrrole (141) (0.5 mL, 500 mg, 7.50 mmol) and powdered potassium hydroxide (420 g, 7.50 mmol) were added to a magnetically stirred solution of 1,3-dibromopropane (2.3 mL, 4.5 g, 22.00 mmol) in anhydrous DMF (32 mL) maintained under a nitrogen atmosphere. Stirring continued at 18 °C for 16 hours then water (60 mL) was added to the reaction mixture which was subsequently extracted with diethyl ether (3 x 30 mL). The combined ethereal extracts were washed with water (1 x 100 mL) and brine (1 x 150 mL) before being dried (MgSO_4), filtered and concentrated to provide a yellow oil. Subjection of this material to flash column

chromatography (silica, hexane \rightarrow 1:9 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions ($R_f = 0.5$ in 1:9 v/v ethyl acetate/hexane) under reduced pressure then afforded compound **403**³¹ (960 mg, 68%) as a pale-yellow oil.

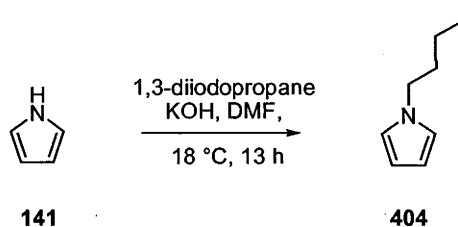
¹H NMR (300 MHz) δ 6.71 (t, $J = 2.1$ Hz, 2H), 6.20 (t, $J = 2.1$ Hz, 2H), 4.11 (t, $J = 6.3$ Hz, 2H), 3.34 (t, $J = 6.3$ Hz, 2H), 2.28 (pentet, $J = 6.3$ Hz, 2H).

¹³C NMR (75 MHz) δ 120.4 (2 x CH), 108.2 (2 x CH), 46.8 (CH₂), 34.0 (CH₂), 30.1 (CH₂).

IR (neat) ν_{\max} 3100, 2933, 1499, 1436, 1362, 1270, 1242, 1089, 968, 724 cm⁻¹.

Mass Spectrum (ESI) m/z 189 and 187 [M^+ , both 100%], 95 (63).

1-(3-Iodopropyl)-pyrrole (**404**)



Following a similar procedure to that utilised in the synthesis of 1-(3-bromo-propyl)-pyrrole (**403**) finely-ground potassium hydroxide (2.1 g, 38.0 mmol) was added to a magnetically stirred solution of pyrrole (**141**) (2.6 mL, 2.5 g, 38.0 mmol) and 1,3-diiodopropane (17 mL, 33.3 g, 113.0 mmol) in anhydrous DMF (75 mL). The resulting suspension was protected from light and stirring continued for 13 hours. After this time TLC analysis indicated that the reaction had reached completion and therefore the reaction mixture was poured into water (150 mL) and extracted with diethyl ether (3 x 75 mL). The combined organic phases were subsequently washed with water (3 x 150 mL) and brine (1 x 350 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash column chromatography (silica, hexane elution) and concentration of the

appropriate fractions ($R_f = 0.4$ in 1:9 v/v ethyl acetate/hexane elution) afforded the title compound **404**³² (6.5 g, 73%) as a pale-yellow brown oil.

¹H NMR (300 MHz) δ 6.70 (t, $J = 2.1$ Hz, 2H), 6.18 (t, $J = 2.1$ Hz, 2H), 4.03 (t, $J = 6.3$ Hz, 2H), 3.09 (t, $J = 6.3$ Hz, 2H), 2.22 (pentet, $J = 6.3$ Hz, 2H).

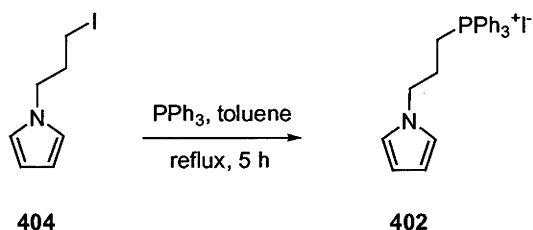
¹³C NMR (75 MHz) δ 120.6 (2 x CH), 108.3 (2 x CH), 49.0 (CH₂), 34.7 (CH₂), 3.0 (CH₂).

IR (neat) ν_{\max} 3391, 3099, 2931, 1498, 1445, 1427, 1359, 1285, 1263, 1214, 1173, 1089, 1066, 917, 725, 616 cm⁻¹.

Mass Spectrum (EI, 70 eV) m/z 235 [(M⁺, 36%), 108 [(M-I)⁺, 62], 93 (20), 80 (100), 67 (23).

HRMS Found M⁺, 234.9860. Calculated for C₇H₁₀NI, M⁺, 234.9858.

3-(1-Pyrrolyl)-1-triphenylphosphonium iodide (**402**)



A magnetically stirred solution of 1-(3-iodopropyl)pyrrole (**404**) (1.3 g, 5.53 mmol) in anhydrous toluene (14 mL) was treated, in one portion, with triphenylphosphine (1.5 g, 5.53 mmol). The resulting suspension was heated at reflux for 5 hours during which time a coral-coloured precipitate formed. The solvent was then removed from the cooled reaction mixture and the solid so-obtained recrystallised (diethyl ether/hexane) to give *title compound* **402** (2.6 g, 94%) as a pale-brown powdery solid.

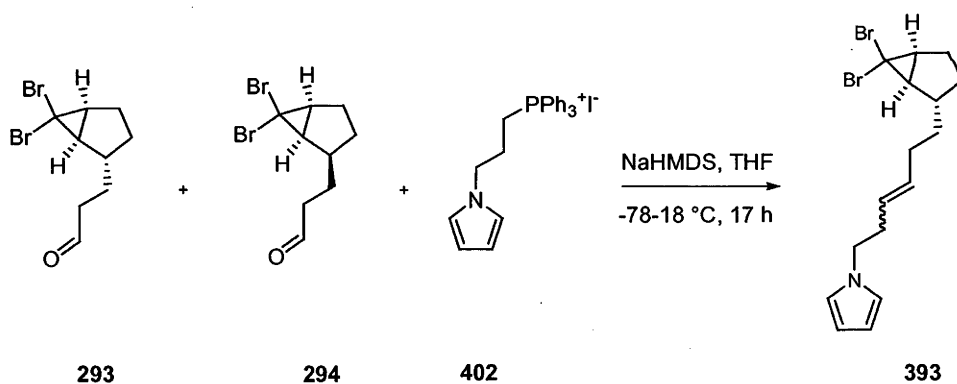
$^1\text{H NMR}$ (300 MHz) δ 7.81-7.64 (complex m, 15H), 6.75 (t, $J = 2.1$ Hz, 2H), 6.14 (t, $J = 2.1$ Hz, 2H), 4.35 (t, $J = 5.1$ Hz, 2H), 3.75 (m, 2H), 2.07 (m, 2H).

$^{13}\text{C NMR}$ (75 MHz) δ 135.0 (3 x C), 133.4 (6 x CH), 130.4 (6 x CH), 126.9 (3 x CH), 120.9 (2 x CH), 108.4 (2 x CH), 48.3 (CH_2), 25.1 (CH_2), 19.9 (CH_2).

IR (CH_2Cl_2) ν_{max} 3370, 3082, 2931, 2863, 2798, 1586, 1500, 1483, 1435, 1339, 1280, 1187, 1109, 1089, 1063, 995, 740, 722, 688, 530, 511 cm^{-1} .

Elemental Analysis Found: C, 60.22; H, 5.02; N, 2.68; I, 25.48; $\text{C}_{25}\text{H}_{25}\text{INP}$ requires C, 60.37; H, 5.07; N, 2.82; I, 25.52%.

1-{(E)-6-[(1R,2S,5S)-6,6-Dibromobicyclo[3.1.0]hexan-2-yl]hex-3-enyl}-pyrrole (393)



A magnetically stirred solution of phosphonium salt **402** (400 mg, 0.81 mmol) in anhydrous THF (4 mL) was maintained under an atmosphere of nitrogen, cooled to -78 $^\circ\text{C}$ (dry ice/acetone cooling bath) and treated with sodium hexamethyldisilazide (0.8 mL of a 0.95 M solution in THF, 0.78 mmol). The resulting yellow-brown suspension was stirred for a further 30 minutes before a solution of a 4:1 mixture of aldehydes **293** and **294** (230 mg, 0.78 mmol) in THF (0.5 mL) was added in one portion. The reaction mixture was maintained at -78 $^\circ\text{C}$ for a further 5 minutes then warmed to and maintained at 0 $^\circ\text{C}$ (ice/water bath). After 25

minutes the ensuing mixture was allowed to warm to room temperature and stirring continued overnight. After this time the solvent was removed under reduced pressure and the tan residue treated with ethyl acetate/hexane (1:19 v/v mixture). The resulting suspension was then filtered through a plug of Celite™ which was washed with ethyl acetate/hexane (1:19 v/v mixture). The combined filtrates were concentrated under reduced pressure and the resulting yellow oil subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution). Concentration of the relevant fractions ($R_f = 0.3$) then gave the *title compound 393* (230 mg, 76%) as a pale-yellow oil.

^1H NMR (300 MHz) δ 6.67 (t, $J = 2.1$ Hz, 2H), 6.14 (t, $J = 2.1$ Hz, 2H), 5.42 (m, 2H), 3.92 (t, $J = 7.2$ Hz, 2H), 2.51 (q, $J = 7.2$ Hz, 2H), 2.25 (t, $J = 7.2$ Hz, 1H), 2.14-1.68 (complex m, 8H), 1.51-1.29 (complex m, 2H).

^{13}C NMR (75 MHz) δ 131.9 (CH), 125.7 (CH), 120.4 (2 x CH), 107.9 (2 x CH), 49.3 (CH₂), 44.3 (CH), 42.8 (CH), 40.1 (C), 39.3 (CH), 35.5 (CH₂), 32.9 (CH₂), 29.7 (CH₂), 28.4 (CH₂), 25.4 (CH₂).

IR (neat) ν_{max} 2961, 2925, 2853, 1605, 1499, 1450, 1283, 1261, 1088, 1020, 869, 799, 721, 618 cm^{-1} .

Mass Spectrum (EI, 70 eV) m/z 389, 387 and 385 [M^+ , 1, 2 and 1%], 308 and 306 [(M-Br) $^+$, both 17], 226 (3), 149 (16), 120 (17), 106 (13).

HRMS Found (M-Br) $^+$, 306.0862. Calculated for C₁₆H₂₁⁷⁹BrN, (M-Br) $^+$, 306.0857.

7.6 References

- ¹ Xu, L., Brinker, U.H.; in *Synthetic Organic Sonochemistry*, Luche, J.L. (Ed.), Plenum Press: New York, **1998**, pp. 344-345.
- ² Sonnenberg, J., Winstein, S.; *J. Org. Chem.*, **1962**, *27*, 748-751.
- ³ Routier, S., Sauge, L., Ayerbe, N., Coudert, G., Merour, J-Y.; *Tetrahedron Lett.*, **2002**, *43*, 589-591.
- ⁴ Flynn, D.L., Zelle, R.E., Grieco, P.A.; *J. Org. Chem.*, **1983**, *48*, 2424-2426.
- ⁵ Deiter, R.K., Sharma, R.R.; *J. Org. Chem.*, **1996**, *61*, 4180-4184.
- ⁶ Mori, M., Washioka, Y., Urayama, T., Yoshiura, K., Chiba, K., Ban, Y.; *J. Org. Chem.*, **1983**, *48*, 4058-4067.
- ⁷ Stille, J.K., Becker, Y.; *J. Org. Chem.*, **1980**, *45*, 2139-2145.
- ⁸ Dreyfuss, M.P.; *J. Org. Chem.*, **1963**, *28*, 3269-3272.
- ⁹ Rieke, R.D., Daruwala, K.P., Forkner, M.W.; *Organometallics*, **1991**, *10*, 2946-2955.
- ¹⁰ Wallace, T.W., Wardell, I., Li, K-D., Leeming, P., Redhouse, A.D., Challand, S.R.; *J. Chem. Soc. Perkin Trans. 1*, **1995**, *18*, 2293-2308.
- ¹¹ Crotti, P., Ferretti, M., Macchia, F., Stoppioni, A.; *J. Org. Chem.*, **1984**, *49*, 4706-4711.
- ¹² Boldt, P., Schulz, L., Etzemüller.; *Chem. Ber.*, **1967**, *100*, 1281-1288.
- ¹³ Boldt, P., Schulz, L., Klinsmann, U., Köster, H., Thielecke, W.; *Tetrahedron*, **1970**, *26*, 3591-3615.
- ¹⁴ Boldt, P., Schulz, L., Etzemüller.; *Chem. Ber.*, **1967**, *100*, 1281-1288.
- ¹⁵ Oster, T.A., Harris, T.M.; *Tetrahedron. Lett.*, **1983**, *24*, 1851-1854.
- ¹⁶ Petasis, N.A., Bzowej, E.I.; *J. Am. Chem. Soc.*, **1990**, *112*, 6392-6394.
- ¹⁷ Claus, K., Bestian, H.; *Justus Liebigs Ann. Chem.*, **1962**, *654*, 8-19.
- ¹⁸ Baran, P.S., Richter, J.M.; *J. Am. Chem. Soc.*, **2004**, *126*, 7450-7451.
- ¹⁹ Washburn, W.N., Zahker, R., Chen, I.; *J. Am. Chem. Soc.*, **1978**, *100*, 5863-5874.
- ²⁰ Alder, K., Flock, F.H.; *Chem. Berichte*, **1956**, *89*, 1732-1737.
- ²¹ Hansson, S., Heumann, A., Rein, T., Akermark, B.; *J. Org. Chem.*, **1990**, *55*, 975-984.
- ²² Banwell, M.G., Wu, A.; *J. Chem. Soc. Perkin Trans. 1.*, **1994**, *19*, 2671-2672.
- ²³ Washburn, W.N., Zahker, R., Chen, I.; *J. Am. Chem. Soc.*, **1978**, *100*, 5863-5874.

- ²⁴ Dondas, H.A., Grigg, R., Thibault, S.; *Tetrahedron*, **2001**, *57*, 7035-7045.
- ²⁵ Julia, M., Goffic, F.L., *Compt. Rend.*, **1962**, *255*, 714-716.
- ²⁶ Banwell, M.G., Harvey, J.E., Hockless, D.C.R., Wu, A.W.; *J. Org. Chem.*, **2000**, *65*, 4241-4250.
- ²⁷ Balme, G., Bouyssi, D., Faure, R., Gore, J., van Hemelryck, B.; *Tetrahedron*, **1992**, *48*, 3891-3902.
- ²⁸ Banwell, M.G., Harvey, J.E., Hockless, D.C.R., Wu, A.W.; *J. Org. Chem.*, **2000**, *65*, 4241-4250.
- ²⁹ Lazzaroni, R., Settambolo, R., Caiazzo, A., Pontorno, L.; *J. Organomet. Chem.*, **2000**, *601*, 320-323.
- ³⁰ Banwell, M.G., Beck, D.A.S., Smith, J.A.; *Org. and Biomol. Chem.*, **2004**, *2*, 157-159.
- ³¹ Coche, L., Ehui, B., Limosin, D., Moutet, J.C.; *J. Org. Chem.*, **1990**, *55*, 5905-5910.
- ³² Ozaki, S., Mitoh, S., Ohmori, H.; *Chem. Pharm. Bull.*, **1996**, *44*, 2020-2024.