New Reactions of

2-Methyleneaziridines

by

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for the degree of Doctor of Philosophy in Chemistry

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# Table of Contents

Acknowledgements ........................................................................... 4

Declaration ......................................................................................... 5

Abstract ........................................................................................... 6

Abbreviations ..................................................................................... 7

Chapter 1: Introduction to Methyleneaziridines ........................................ 10

1.1 Introduction ................................................................................ 11

1.2 Synthesis of Methyleneaziridines .................................................. 11

1.2.1 Dehydrohalogenation of 2-bromo-allylamines ............................ 11

1.2.2 Mechanism for the dehydrohalogenation of 2-bromo-allylamines .... 14

1.2.3 Dehydrohalogenation of aziridines ......................................... 18

1.2.4 Nitrene addition to allenes ...................................................... 18

1.2.5 Olefination of $\alpha$-lactams ................................................... 20

1.3 Reactions of Methyleneaziridines ................................................... 20

1.3.1 Protonations ........................................................................... 20

1.3.2 Ring-openings ......................................................................... 21

1.3.3 Thermal rearrangements ....................................................... 25

1.3.4 Ring functionalisations ......................................................... 26

1.3.5 Ring expansion ....................................................................... 28

1.3.6 Intramolecular radical rearrangements .................................... 29

1.3.7 Reactions of the exocyclic double bond .................................. 31

1.3.8 Multi-component reactions involving methyleneaziridines ........ 35

1.4 Conclusion ................................................................................... 36
5.2.2 Stereocontrol in Pictet-Spengler cyclisations..........................100
5.2.3 Intramolecular allylic alkylation ...........................................104
5.2.4 Synthesis of 1,1-disubstituted tetrahydro-β-carbolines.............104
5.3 Attempted 3-CR to 1,1-Disubstituted β-Carbolines .....................106
5.3.1 Synthesis of indole tethered methyleneaziridines ....................106
5.3.2 Initial model reactions .....................................................108
5.4 Synthesis of 1,1-Disubstituted β-Carbolines .............................115
5.4.1 Scope and limitations .....................................................121
5.5 Attempted Synthesis of Tetrahydroisoquinolines .......................125
5.6 Conclusions .....................................................................127

Chapter 6: Experimental ..........................................................128
References .............................................................................175
Appendix .................................................................................190
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Last, but by no means least, to my family, especially Mum, Dad and Liz for their support and encouragement throughout my life so far. I love you and thank you.
Declaration

I declare that the material described that is not original has been identified and referenced. Any contribution made by myself to work based on collaborative research has been indicated. I certify that no material within this thesis has been submitted for a prior degree or a degree at another university.

Signed __________________________

Date __________________________
Abstract

Chapter One reviews the synthesis, properties and reactions of 2-methyleneaziridines, the subject of this thesis.

Chapter Two describes the use of these heterocycles in the development of a new four-component synthesis of biologically important α-aminophosphonates. This new chemistry proceeds in moderate to good yield via a “one-pot” process that involves the sequential formation of three new intermolecular bonds and a quaternary carbon centre. This reaction is tolerant to a range of functionalities incorporated in the various components. Deprotection of one of these α-aminophosphonates to the corresponding α-aminophosphonic acid is achieved via a two-step process in very good yield.

Chapter Three discusses efforts made towards the development of a multi-component imino Diels-Alder reaction for the generation of 2,3-dihydro-4-pyridones. Initial work suggests acyclic ketimine intermediates are unsuitable for this process.

Chapter Four reports unsuccessful attempts made to generate methyleneaziridines bearing electron-withdrawing substituents via in situ N-derivatisation.

In Chapter Five, the synthesis of 1,1-disubstituted tetrahydro-β-carbolines from methyleneaziridines is described. The reaction is shown to proceed in moderate to very good yields and a range of β-carbolines were successfully synthesised. High levels of diastereocontrol are demonstrated using a substrate containing a pre-existing stereocentre.

Chapter Six details the experimental procedures and characterisation data for the novel compounds produced.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Ad</td>
<td>Adamantyl</td>
</tr>
<tr>
<td>AIBN</td>
<td><em>azo-bis</em>-Isobutyronitrile</td>
</tr>
<tr>
<td>Anal.</td>
<td>Analysis</td>
</tr>
<tr>
<td>atm</td>
<td>Atmosphere</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td><em>tert</em>-Butyloxy carbonyl</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>Bus</td>
<td><em>tert</em>-Butylsulfonyl</td>
</tr>
<tr>
<td>c</td>
<td>Cyclo</td>
</tr>
<tr>
<td>c.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>ca.</td>
<td>Circa</td>
</tr>
<tr>
<td>Calcd</td>
<td>Calculated</td>
</tr>
<tr>
<td>cat.</td>
<td>Catalytic</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carbobenzyloxy</td>
</tr>
<tr>
<td>cf.</td>
<td>Confer</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentadienyl</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylidene acetone</td>
</tr>
<tr>
<td>(+)-DDB</td>
<td>(S,S)-(+)1,4-bis(dimethylamino)-2,3-dimethoxybutane</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DPPBA</td>
<td>Diphenylphosphino benzoic acid</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>E</td>
<td>Electrophile</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>ES</td>
<td>Electrospray</td>
</tr>
<tr>
<td>equiv.</td>
<td>Molar equivalents</td>
</tr>
<tr>
<td>er</td>
<td>Enantiomeric ratio</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron-withdrawing group</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectroscopy</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons</td>
</tr>
<tr>
<td>i</td>
<td>Iso</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>L</td>
<td>Ligand</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>lit.</td>
<td>Literature value</td>
</tr>
<tr>
<td>LSIMS</td>
<td>Liquid secondary ion mass spectrometry</td>
</tr>
<tr>
<td>µ</td>
<td>micro</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>M</td>
<td>Metal</td>
</tr>
<tr>
<td>m-CPBA</td>
<td><em>meta</em>-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MCR</td>
<td>Multi-component reaction</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>Napth</td>
<td>Naphthyl</td>
</tr>
<tr>
<td>NMO</td>
<td><em>N</em>-Methylmorpholine-<em>N</em>-oxide</td>
</tr>
</tbody>
</table>
Nu  Nucleophile
NMR  Nuclear magnetic resonance
p-  para-
ppm  Parts per million
py  Pyridine
R_f  Retention factor
s  sec-
S_N2  Bimolecular nucleophilic substitution
t  tert-
t_1/2  Half-life
TBDMS  tert-Butyldimethylsilyl
TCNE  Tetracyanoethylene
Temp.  Temperature
Tf  Triflate
TFA  Trifluoroacetic acid
THBC  Tetrahydro-β-carboline
THF  Tetrahydrofuran
THP  Tetrahydropyran
THQ  Tetrahydroisoquinoline
TM  Target molecule
TMEDA  Tetramethylethylenediamine
TMS  Trimethylsilyl
Tol  Tolyl
Ts  Tosyl
w/v  Weight per unit volume
Chapter 1:

Introduction to

Methyleneaziridines
1.1 Introduction

This thesis will discuss new developments in the application of methyleneaziridines in organic synthesis. As such it is appropriate to begin with an introduction to this compound class. This chapter describes the synthesis and reactivity of these fascinating heterocycles.

2-Methyleneaziridines are a class of highly strained heterocycles, based on aziridine and featuring an exocyclic alkene group (Figure 1.1). The combination of functional groups within these molecules, along with their high ring strain energy,\(^1\) grants them great potential in a variety of synthetic processes.

![2-Methyleneaziridine](image)

Figure 1.1. 2-Methyleneaziridine.

1.2 Synthesis of Methyleneaziridines

1.2.1 Dehydrohalogenation of 2-bromo-allylamines

Methyleneaziridines 1 were first synthesised, accidentally, in 1951 by Pollard and Parcell whilst attempting the dehydrohalogenation of \(N\)-(2-bromoallyl)-alkylamines 2 to propargylamines 3 with sodium amide in liquid ammonia.\(^2\) Their results were however inconsistent with their previous work on the preparation of propargylamines from the corresponding tertiary amines.\(^3\) The presence of a strong signal at 1770 cm\(^{-1}\) in the infrared spectrum, and absence of the expected N–H or triple bond stretching frequencies, led Pollard and Parcell to propose \(N\)-allylidene-alkylamine 4 as the product. The
reaction was believed to proceed via allene intermediate 5 which would isomerise to give the more stable conjugated product 4 (Scheme 1.1).

Scheme 1.1. Proposed formation of \( N \)-allylidene-alkylamines.

In 1956, Ettlinger and Kennedy noted that the stretching frequency of 1770 cm\(^{-1}\) was similar to that of the exocyclic alkene bond in methylenecyclopropane and thus proposed the methyleneaziridine structure 1.\(^4\) This structure was confirmed by Bottini and Roberts through nuclear magnetic resonance (NMR) spectroscopy and chemical degradation studies.\(^5\)

The cyclisation is very tolerant of a wide range of functional groups;\(^6\) \( N \)-substituents include double bonds and aryl selenides,\(^7\) benzyl and silyl ethers,\(^8\) alcohols and acetals,\(^9\) and non-racemic, chiral derivatives.\(^10,11\) Substitution patterns on the exocyclic double bond include \textit{gem}-di-methyl\(^{12}\) and cyclohexyl substituents.\(^13\)
Chapter 1

In 1973, Quast and Risler, using the conditions of Pollard and Parcell, were able to synthesise methyleneaziridines 6 featuring substitution on the exocyclic double bond. In this process, disubstituted vinyl bromides 7 were synthesised from the high temperature reaction of 1,1-dibromo-2,2-dimethyl-cyclopropane (8) with primary amines according to Sandler’s procedure. Ring-closure of the 3-bromo-2-butenes 7 with sodium amide in liquid ammonia yielded the corresponding disubstituted methyleneaziridines 6 (Scheme 1.2).

![Scheme 1.2. Synthesis of disubstituted methyleneaziridines.](image)

Steinberg et al. developed an alternative route to disubstituted methyleneaziridines 6. Their strategy involved ring-closing using n-butyl lithium in THF and hexanes at low temperatures. They also developed an alternate strategy to disubstituted vinyl bromides 7 as the conditions of Sandler involve high temperatures, long reaction times and can be low yielding when thermally labile or sterically encumbered amines were used. Despite an increase in the number of chemical steps, this process is reported to proceed in acceptable overall yields (16 - 49% over 4 steps) (Scheme 1.3).
Chapter 1

Scheme 1.3. Alternative route to disubstituted methyleneaziridines.

1.2.2 Mechanism for the dehydrohalogenation of 2-bromo-allylamines

Bottini and Olsen conducted a study into the mechanism of the formation of methyleneaziridines by the ring closure process described above. They proposed four possible reaction mechanisms for the formation of methyleneaziridines; (i) displacement of the bromide ion by internal S_N_2 attack (path a); (ii) an addition-elimination process (path b); (iii) elimination-addition via an allenic intermediate (path c); or (iv) analogous elimination-addition reaction of a propargylamine (path d) (Scheme 1.4). Pathway d was however immediately discounted due to Pollard and Parcell’s high yielding synthesis of propargylamines from N-(2-chloroallyl)-alkylamines under similar conditions.
Scheme 1.4. Proposed mechanisms for the formation of methyleneaziridines.

It was considered that conducting the ring-closure of vinyl bromide 9 with sodium amide in tritium labelled ammonia would lead to an insight into the reaction pathway. The product, 10, was found to possess the specific radioactivity corresponding to the abstraction of a single hydrogen atom from the solvent. From this observation it was concluded that the reaction mechanism did not follow cyclisation pathways a and b. Degradation studies of the product indicated tritium incorporation into the ring methylene group.

To examine whether proton exchange occurs during this process 11 was treated with sodium amide in tritium labelled ammonia and 10 treated with sodium amide in unlabelled ammonia. In neither case was there a change in the recorded
radioactivity of these materials, indicating that the ring methylene protons did not exchange with those of the solvent under the reaction conditions. These observations led to the proposal of an elimination-addition mechanism via allene intermediate 12 (Scheme 1.5).

\[\begin{align*}
\text{Br} & \quad \text{NaNH}_2 \quad \text{NH}_3, \text{Br} \\
\text{Pr} & \\
\text{NH} & \quad \text{NH}_3, \text{Pr} \\
9 & \quad 12 \\
\end{align*}\]

**Scheme 1.5.** Proposed elimination-addition mechanism.

Recently however, the elimination-addition pathway described above has been challenged by Shipman and co-workers.\(^{17}\) In the synthesis of ethyleneaziridines 13 and 14, it was observed that the reaction proceeded with net stereochemical inversion from vinyl bromide starting materials 15 and 16 (Scheme 1.6).

\[\begin{align*}
\text{NH} & \quad \text{NH}_3 (l), -78 \, ^\circ\text{C}, 1 \, \text{h} \\
\text{Pr} & \quad \text{NH} \\
\text{Br} & \quad \text{NaNH}_2 \\
\text{R} & \\
15 & \quad 13 \\
\text{NH} & \quad \text{NH}_3 (l), -78 \, ^\circ\text{C}, 1 \, \text{h} \\
\text{Pr} & \quad \text{NH} \\
\text{Br} & \quad \text{NaNH}_2 \\
\text{R} & \\
16 & \quad 14
\end{align*}\]

\(R = \text{Bn, S-CH(Me)Ph}\)

**Scheme 1.6.** Synthesis of ethyleneaziridines.
The stereochemical inversion observed appeared to rule out an elimination-addition mechanism as both 15 and 16 would be expected to yield the same allene intermediate, thus leading to convergence of stereochemistry. To investigate the mechanism of the ring-closure, deuterated methyleneaziridine 17 was formed from the ring-closure of deuterated vinyl bromide 18 with sodium amide, generated in situ from sodium (Scheme 1.7). This result meant that the mechanism cannot proceed via a C–3 anion intermediate. Furthermore, treatment of 18 with excess sodium amide under extended reaction times yielded aziridine 19, featuring no detectable amounts of deuterium. Aziridine 17 was also re-subjected to the reaction conditions, yielding clean conversion to nondeuterated 19. These observations indicated that 19, formed quickly under the reaction conditions ($t_{1/2} \approx 10$ s at $-78^\circ$C, 2.5 equiv. NaNH$_2$), underwent a slow reversible exchange with the solvent by deprotonation at C–3. It was postulated that this exchange was not detected by Bottini and Olsen due to their use of a sub-stoichiometric quantity of commercial sodium amide. It was found that sodium amide generated in situ is more active than that bought from a commercial source.$^{18}$

Scheme 1.7. Deuterium labelled cyclisation studies.
Chapter 1

The observed stereochemical inversion in the preparation of ethyleneaziridines, along with the studies with deuterium labelled substrates led to the proposal that the ring-closure proceeds via substitution with inversion by in-plane $\sigma$-attack from the backside of the C-Br bond (Path a, Scheme 1.4).

1.2.3 Dehydrohalogenation of aziridines

De Kimpe et al. reported the synthesis of methyleneaziridines 20 from 2-(bromomethyl)aziridines 21 via a based-induced, exocyclic $\beta$-elimination reaction. $^{19}$ 21 was synthesised in three chemical steps from the corresponding aldehyde 22. However, the reaction also yielded an equimolar quantity of tert-butyl ether 23, inseparable from methyleneaziridine 20 (Scheme 1.8).

![Scheme 1.8. Dehydrohalogenation of aziridines.](image)

1.2.4 Nitrene addition to allenes

Bleiholder and Schecter postulated that methyleneaziridines could be synthesised by reaction of allenes with singlet nitrenes. $^{20}$ They expected that insertion of an azide into tetramethylallene (24) would give methyleneaziridine
25 via decomposition of methyltriazoline 26, or by direct addition of the nitrene onto the allene (Scheme 1.9). However, in the majority of systems studied, thermolysis of triazoline 26 only gave rise to conjugated imine 27 being isolated.

![Scheme 1.9. Postulated nitrene addition to an allene.](image)

Bingham and Gilbert also investigated the use of nitrenes for the synthesis of methyleneaziridines. They treated N-(p-nitrobenzenesulphonyloxy)urethane (28) with triethylamine to generate ethoxycarbonylnitrene in situ, which was then reacted with allenes 29 to give the corresponding methyleneaziridines 30 in low yields (Scheme 1.10). In the case of 29a, a second regioisomer 31 was anticipated but not detected. This observation led to the hypothesis that the nitrene attacked the least sterically hindered terminal double bond. However, due to the low yields of the reaction, no definitive conclusions could be made.

![Scheme 1.10. Methyleneaziridine synthesis via nitrene addition to allenes.](image)
1.2.5 Olefination of α-lactams

De Kimpe et al. reported the synthesis of methyleneaziridine \(32\) from 1,3-di-tert-butyl-2-aziridinone \(33\) using dimethyltitanocene (Scheme 1.11).\(^{22}\)

However, many other α-lactams were found to be unstable to the temperatures required for this transformation. Moreover, the products could not be purified, limiting the scope of this method.

\[
\begin{array}{c}
\begin{aligned}
{^t\text{Bu}} & \text{N} & \text{O} \\
\text{Cp}_2\text{TiMe}_2 & \text{C}_6\text{H}_5\text{CH}_3, 80 \degree\text{C}, 6\text{ h} & 56\% \text{ crude}
\end{aligned}
\end{array}
\]

Scheme 1.11. Dimethyltitanocene mediated olefination of α-lactams.

1.3 Reactions of Methyleneaziridines

1.3.1 Protonations

Jongejan et al. have shown that \(N\)-protonation of 1-alkyl-2-methyleneaziridines \(1\) can occur with \(\text{FSO}_3\text{H}/\text{SbF}_5\) in sulphur dioxide at \(-78\) \degree\text{C} to generate the corresponding methyleneaziridinium fluorosulfate \(34\) without ring-opening or attack of the exocyclic double bond (Scheme 1.12).\(^{23}\) Under similar conditions, it was shown that \(1\) could be \(N\)-methylated with \([(\text{Me})_2\text{Cl}]^+[\text{SbF}_5\text{Cl}]^-\) to yield \(35\). Both \(34\) and \(35\) showed surprising thermal stability, no decomposition of either cation being observed by \(^1\text{H}\) NMR spectroscopy, even when warmed to 50 \degree\text{C}. Methyleneaziridinium cations \(34\) and \(35\) were shown to undergo thermally induced isomerisation upon further heating.\(^{24}\)
1.3.2 Ring-opening

Bottini and Roberts observed the formation of chloroacetate 36, along with ethylamine when 1-ethyl-2-methyleneaziridine (37) was treated with hydrochloric acid. This reaction most likely proceeds by ring-opening of the protonated methyleneaziridine, followed by hydrolysis of enamine intermediate 38 (Scheme 1.13).\(^5\)

\[
\begin{align*}
\text{Et} & \quad \text{HCl} \quad \left[\begin{array}{c}
\text{Et} \\
\text{N} \\
\text{\_\_\_}
\end{array}\right] \\
\text{37} & \quad \text{38} \quad \text{36}
\end{align*}
\]

Scheme 1.13. Chloride ring-opening of methyleneaziridines.

Crandall \textit{et al.} demonstrated that 1-isopropyl-2-methyleneaziridine (39) undergoes reaction with excess phenol to generate acetal 40.\(^{25,26}\) It was envisioned that the reaction proceeds \textit{via} initial Markovnikov addition of the first equivalent of the phenol across the exocyclic double bond, followed by ring-opening of the aziridine intermediate by the second equivalent of phenol (Scheme 1.14).
Vélez and Quast, during their investigations into the alkylation of methyleneaziridines at C-3 via lithiation with sec-butylithium, reported the dimerisation of tert-butyl-2-methyleneaziridine (41) (Scheme 1.15).\textsuperscript{27} Formation of dimer 42 was proposed to proceed by nucleophilic ring-opening of 41 by lithiated methyleneaziridine 43.

Shipman et al. have demonstrated methyleneaziridines can undergo ring-opening by chloroformates to give carbamates 44 (Scheme 1.16).\textsuperscript{28} This reaction proceeds well with a variety of \(N\)-substituents on the methyleneaziridine, however, the sterically crowded trityl-derivative (\(R = \text{CPh}_3\)) failed to react. Ring-opening in this fashion was also possible using acid chlorides (acetyl chloride, \(p\)-nitrobenzoyl chloride) to give the corresponding...
tertiary amide 45. However, the reaction proved to be less tolerant to more electron-rich acid chlorides such as benzoyl chloride and \( p \)-anisoyl chloride.

\[
\begin{align*}
\text{N} & \quad \text{R} \quad \text{O} \\
\text{Cl} & \quad \text{CH}_2 & \text{Cl}_2 & \quad 24 \text{ h, rt} & \quad \text{R}^2 \text{COCl} \\
\text{45} & \quad \text{R} & \quad \text{Cl} & \quad \text{N} & \quad \text{OR} \\
\text{44} & \quad \text{R}^1 & \quad \text{Cl} & \quad \text{N} & \quad \text{OR}^1
\end{align*}
\]

\( R = \text{Bn, CH(Me)Ph, }^{\text{t}}\text{Hex, CH(CH}_2\text{OBn)}\text{CH(Me)}_2 \)

\( R^1 = \text{Me, Bn} \)

\( R^2 = \text{Me, 4-N}O_2\text{C}_6\text{H}_4 \)

**Scheme 1.16.** Ring-opening with acid chlorides and chloroformates.

Studies of the reaction of deuterated methyleneaziridine 46 with methyl chloroformate established that attack of the chloride anion occurred solely at C-3 of the methyleneaziridinium ion (Scheme 1.17).\(^9\)

\[
\begin{align*}
\text{N} & \quad \text{Cl} \\
\text{Ph} & \quad \text{D} & \quad \text{MeO} & \quad \text{Cl} \\
\text{46} & \quad \text{Ph} & \quad \text{D} & \quad \text{MeO} & \quad \text{Cl} \\
\text{Ph} & \quad \text{D} & \quad \text{MeO} & \quad \text{Cl} & \quad \text{D}
\end{align*}
\]

**Scheme 1.17.** Deuterium labelled ring-opening with chloroformates.

Shipman and co-workers have demonstrated that methyleneaziridines could be ring-opened with carbon-based nucleophiles in the presence of a Lewis acid.\(^{29}\)

Treatment of methyleneaziridine 1 with Gilman cuprates or Grignard reagents afforded methyl ketone 47 after acidic hydrolysis (Scheme 1.18). This reaction has been further exploited to give rise to a variety of multi-component reactions from methyleneaziridines and these will be discussed later (Section 1.3.8).
Recently, Oh et al. reported the palladium catalysed synthesis of \( \alpha \)-amido-ketone \( 48 \) from the reaction of methyleneaziridine \( 1 \) with carboxylic acids.\(^{30} \) Through catalyst screening they established that treating methyleneaziridine \( 1 \) with carboxylic acids in the presence of \( \text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3 \) (5 mol\%) and \( \text{PPh}_3 \) (10 mol\%) yielded the corresponding \( \alpha \)-amido-ketone \( 48 \) (Scheme 1.19).

The synthesis of \( \alpha \)-amido-ketones was proposed to proceed via the catalytic cycle below (Scheme 1.20). It is thought that oxidative addition of palladium (0) into the carboxylic acid O–H bond is followed by hydropalladation of the exocyclic double bond. Reductive elimination of palladium (0) yields \( N,O \)-acetal \( 49 \), which further rearranges to give the \( \alpha \)-amido-ketone \( 48 \).
Scheme 1.20. Proposed catalytic cycle for the synthesis of α-amido-ketones.

Deuterium labelling studies supported the catalytic cycle proposed by Oh and co-workers. Deuterated acetic acid (98% D) was reacted with 1-benzyl-2-methyleneaziridine (50), giving rise to the corresponding deuterated α-amido-ketone 51 with 93% deuterium incorporation in the α-position (Scheme 1.21).

Scheme 1.21. Deuterium labelling studies for the synthesis of α-amido-ketones.

1.3.3 Thermal rearrangements

Quast and Risler reported that substituted and unsubstituted methyleneaziridines 52 undergo thermal decomposition, slowly above 120 °C and rapidly above 190 °C, to the corresponding olefin 53 and isonitrile 54 in quantitative yield (Scheme 1.22). These observed products were rationalised by an initial
Chapter 1

rearrangement to cyclopropanimine intermediate 55 or the structural isomer 56. Both of these intermediates were detected via NMR spectroscopy.

![Diagram of thermal decomposition of methyleneaziridines]

**Scheme 1.22.** Thermal decomposition of methyleneaziridines.

1.3.4 Ring functionalisations

In their studies using tert-butyl-2-methyleneaziridine (41), Vélez and Quast reported that methyleneaziridines can be lithiated at C-3 with sec-butyllithium and tetramethylethylenediamine at −78 °C.\(^{27}\) Treatment of lithiated species 43 with various electrophiles gave rise to the corresponding ring substituted methyleneaziridine 57 (Scheme 1.23).

![Diagram of alkylation via lithiation of methyleneaziridines]

**Scheme 1.23.** Alkylation via lithiation of methyleneaziridines.

The lithiation/alkylation sequence above was used to form enantiopure methyleneaziridine 58 via lithiation of 1-methyl-2-methyleneaziridine (59) in
the presence of chiral auxiliary \((S,S)-(\ (+)\)-1,4-bis(dimethylamino)-2,3-dimethoxybutane \((\ (+)\)-DDB\)), followed by anion quenching with trimethylsilyl chloride (Scheme 1.24). However, \textbf{58} was isolated in moderate yield with a poor level of stereocontrol (12\% ee).\textsuperscript{31}

\[
\begin{array}{c}
\text{N} \\
\text{59} \\
\xrightarrow{1) \text{\textsuperscript{6}BuLi, C}_5\text{H}_{12}, (+)-\text{DDB, } -125 \, \text{°C}} \\
2) \text{TMSCl, } -125 \, \text{°C} \rightarrow -20 \, \text{°C} \\
\xrightarrow{36-48\%} \text{N} \\
\text{58}
\end{array}
\]

\textbf{Scheme 1.24.} Stereocontrol in the lithiation/alkylation of methyleneaziridines.

Shipman \textit{et al.} achieved much higher levels of stereocontrol using methyleneaziridines bearing chiral \(N\)-substituents.\textsuperscript{11} Methyleneaziridines, \textbf{19} and \textbf{60}, with a \((S)-\alpha\)-methylbenzyl \(N\)-substituent gave high levels of diastereoselectivity in the corresponding products \textbf{61}, when reacted with a range of electrophiles. The highest levels of diastereoselectivity were obtained from \textbf{60}, bearing \textit{gem}-dimethyl substitution on the exocyclic double bond. Only moderate induction was recorded in the absence of this substitution (Scheme 1.25). A comprehensive study on this lithiation/alkylation of methyleneaziridines was carried out with a range of electrophiles. Benzophenone, benzaldehyde, trialkysilyl chlorides and several alkyl halides can all be used as can a variety of methyleneaziridines bearing different \(N\)-substitution or levels of functionalisation of the double bond.\textsuperscript{32} However, a second lithiation/alkylation sequence at C-3 was found not to be possible.
1.3.5 Ring expansions

Alpher and Hamel demonstrated that methyleneaziridines can undergo palladium-catalysed carbonylation reactions to give α-methylene-β-lactams. Various N-substituted methyleneaziridines were reacted with carbon monoxide in the presence of palladium (0) or palladium (II) and triphenylphosphine catalysts to produce the corresponding methyleneazetidones as single regioisomers (Scheme 1.26).

Yamamoto et al. expanded the use of palladium catalysis in ring expansion reactions of methyleneaziridines to produce pyrrole derivatives. Palladium catalysed reaction of with o-acetylpyridines gave α-pyridinylpyrroles whilst reaction of with 1,3-diketones led to 1,2,3,4-tetrasubstituted pyroles (Scheme 1.27).
1.3.6 Intramolecular radical rearrangements

Prévost and Shipman successfully subjected methyleneaziridines 65 bearing a phenylselenide group to tin hydride radical conditions to give 3-methylenepiperidines 66. The reaction is proposed to proceed through 3-(2-methyleneaziridin-1-yl)propyl radical 67 which undergoes 5-exo-trig cyclisation to give the corresponding aziridinylcarbinyl radical 68. Further C–N bond fission leads to 66 (Scheme 1.28).\textsuperscript{7,36}
Chapter 1

Using the above methodology, Shipman and Prévost achieved a tandem radical process to form indolizidine 69 from methyleneaziridine 70. Intermediate 71 features an additional radical acceptor, allowing a further 5-\textit{exo-trig} cyclisation leading to octahydroindolizine 69 (Scheme 1.29).

Scheme 1.28. Radical rearrangement to 3-methylenepiperidines.

Scheme 1.29. Tandem radical cyclisation to an octahydroindolizine.
1.3.7 Reactions of the exocyclic double bond

Cookson and co-workers demonstrated that 1-ethyl-2-methyleneaziridine (37) can undergo [2π+2π] cycloaddition reactions with electron deficient alkenes.\(^\text{37}\)

Treatment of 37 with tetracyanoethylene (TCNE) was shown to give the corresponding spiroadduct 72 (Scheme 1.30).

![Scheme 1.30. [2π+2π] Cycloaddition reactions with electron deficient alkenes.](image1)

Shipman et al. demonstrated that stereocontrolled [2π+2π] cycloadditions are possible from methyleneaziridines bearing chiral N-substituents to give the corresponding spirocycloadducts.\(^\text{38}\) Methyleneaziridines 73 were heated with TCNE to give 5-azaspiro[3.2]hexanes 74 and 75 with modest diastereoccontrol (Scheme 1.31).

![Scheme 1.31. Stereocontrolled [2π+2π] cycloadditions.](image2)

Crandall et al. attempted to react 1-isopropyl-2-methyleneaziridine (39) with organic azides to give 1,4-diazospiropentanes 76 (Scheme 1.32).\(^\text{25}\) However, with phenylazide, reaction with 39 generated triazole 77 as the major product.
This triazole was believed to have arisen from isomerisation of the initial triazoline product 78, driven by relief of ring-strain. β-Lactamimide 79 was also isolated from the reaction, presumably from 78 opening to betaine 80, followed by elimination of $N_2$. The reaction was reported to generate a 65:35 mixture of 77 and 79.

![Chemical structures](image)

**Scheme 1.32.** Attempted synthesis of 1,4-diazospiropentanes.

Busch *et al.* developed a nickel-catalysed cyclo-oligomerisation of 1-isopropyl-2-methyleneaziridine (39) with excess butadiene. The reaction gave a mixture of six products, the composition of which depends upon the ligand used and nickel/ligand ratio (Scheme 1.33). Use of triphenyl phosphine ($L^1$) gave a fairly even distribution of products 81 to 86, whereas, when ligand $L^2$ was deployed, 81 and 82 were observed to be the major products. When no ligand was used, 85 and 86 were favoured.
Ando et al. showed that 1-tert-butyl-2-adamantylideneaziridine (87), when subjected to photooxygenation, underwent oxidative cleavage with singlet oxygen (Scheme 1.34). The reaction initially forms dioxetane 88, characterised by low temperature NMR spectroscopy. However, above –78 °C 88 rapidly decomposed to adamantanone (89) and α-lactam 90. α-Lactam 90 was characterised by conversion to oxaziridine 91 via in situ oxidation with m-CPBA in the presence of sodium carbonate.

Scheme 1.33. Nickel-catalysed cyclo-oligomerisation.
Shipman and co-workers showed that a range of polycyclic systems featuring seven membered rings were accessible via the Lewis acids catalysed [4+3] cycloadditions of methyleneaziridines. It was shown that the Lewis acid activated ring cleavage of a suitably C-3 functionalised methyleneaziridine led to the formation of a 2-aminoallyl cation which underwent [4+3] cycloaddition.

For example, reaction of furan-tethered methyleneaziridine with BF$_3$·Et$_2$O yielded tricyclic ketone in good yield as a single stereoisomer after acidic work-up (Scheme 1.35).

**Scheme 1.34.** Photooxygenation of methyleneaziridines.

**Scheme 1.35.** Lewis acid catalysed [4+3] cycloadditions of methyleneaziridines.
1.3.8 Multi-component reactions involving methyleneaziridines

Ivar Ugi defined multi-component reactions (MCRs) as “reactions in which more than two starting compounds react to form a product in such a way that the majority of the atoms of the starting materials can be found in the product”.

Famous examples of MCRs include the Strecker,43 Biginelli,44 Mannich,45 Passerini,46 Ugi47 and Pauson-Khand48 reactions. MCRs have emerged as powerful tools in the rapid synthesis of a wide range of molecular arrays. These processes provide practical, economical and environmental advantages over traditional, linear approaches to molecular construction. The most recent developments in this area are described in various monographs49 and reviews.42,50

Shipman and co-workers have developed a variety of multi-component reactions from methyleneaziridines 1.6,51,52 These multi-component processes all involve the ring-opening of 1 with Grignard reagents to generate enamine intermediates 94. Further in situ C-alkylation with an electrophile leads to ketimines 95 via the sequential formation of two new C–C bonds. By effecting different known reactions of ketimines, this chemistry has been used to rapidly synthesise 1,3-disubstituted propanones 96,29 achiral53 and homochiral amines 97,54 natural products,29b,55 heterocycles,51,52,53,55 α-amino nitriles 98,53 hydantoins51 99 and β-lactams52 100 (Scheme 1.36). The multi-component synthesis of 1,3-disubstituted propanones was also shown to be possible on solid supports.56 These sequential multi-component processes have been shown to be tolerant to a wide range of functionalities in all constituents.
Chapter 1

Scheme 1.36. Multi-component reactions of methyleneaziridines.

1.4 Conclusion

Despite being first reported over sixty years ago, the chemistry of methyleneaziridines is still relatively undeveloped. The basis of the work presented in this thesis is to establish new methodologies using this heterocyclic ring system that would provide rapid routes to a variety of important compound classes including those of medicinal relevance.
Chapter 2:
A Four Component Synthesis
of α-Aminophosphonates
2.1 α-Aminophosphonates and Phosphonic Acids

Due to their obvious structural similarities to α-amino acids, α-aminophosphonic acids constitute important motifs in medicinal chemistry (Figure 2.1). Many natural and unnatural aminophosphonic acids and their ester and peptide derivatives display a wide range of biological activities. A considerable part of the biological activity of these compounds arises from the ability of the tetrahedral phosphonic moiety to mimic the tetrahedral intermediate of reactions involving nucleophilic substitution on the carbonyl. Therefore they serve as inhibitors of enzymes such as proteases and peptide ligases. As such, aminophosphonic acids are known to act as peptide mimics, herbicides, enzyme inhibitors and pharmacological, antibacterial, antiviral, and antitumor agents.

![Chemical structures](image)

**Figure 2.1. Similarities between α-aminophosphonic acids and α-amino acids.**

The most common route to α-aminophosphonic acids is via chemical manipulation of the corresponding α-aminophosphonates (Scheme 2.1). As such, α-aminophosphonates have become key targets in the synthesis of this compound class. The most common route to α-aminophosphonates, the Kabachnik-Fields reaction is discussed in detail in the following section.
2.1.1 Synthesis of α-aminophosphonates

The most common route to α-aminophosphonates remains the hydrophosphonylation of imines (Scheme 2.2).\textsuperscript{70} This is achieved by one of two pathways: (i) in a two-component fashion known as the Pudovik reaction\textsuperscript{71,72} or (ii) by the Kabachnik-Fields reaction,\textsuperscript{69} which combines \textit{in situ} imine formation by condensation of an amine with an aldehyde or ketone, with the hydrophosphonylation step. This three-component synthesis of α-aminophosphonates was discovered independently by Kabachnik and Fields in 1952.\textsuperscript{73} In fact, Pudovik and Kabachnik both published these groundbreaking observations in the same volume of \textit{Doklady Chemistry} in 1952.

The reaction mechanism for the formation of α-aminophosphonates \textit{via} the processes outlined above is complicated by the fact that a wide range of catalysts and activators have been deployed. The first consideration is the reactive state of the hydrophosphoryl component. Dialkyl phosphites are known to exist in equilibrium between two forms, the phosphite \textsuperscript{104} and phosphonate \textsuperscript{105} forms with the equilibrium lying to the side of the phosphonate under neutral conditions (Scheme 2.3). However, it is known that the phosphite and
not the phosphonate form is the nucleophilic species. It has been demonstrated that the presence of a base can influence the balance of the equilibrium, allowing for the phosphite form to become more prevalent.

![Scheme 2.3. Tautomeric forms of diethyl phosphite.](image)

In the Pudovik reaction, the reaction is considered to go via direct insertion of the phosphite into the imine through a five-membered cyclic transition state (Scheme 2.4). Protic and Lewis acidic activators are envisioned to activate the imine to nucleophilic attack.

![Scheme 2.4. Pudovik reaction via a five-membered cyclic transition state.](image)

The mechanism for the three-component Kabachnik-Fields reaction is however more complicated, especially as many different types of activators have been shown to be beneficial. As a multi-component process, the carbonyl, amine and hydrophosphoryl species could react via different intermediates to liberate the final $\alpha$-aminophosphonate. Since its discovery there have been numerous insights into this reaction mechanism, and it has been shown that the nature of the aldehyde, the activator, the solvent and the $pK_a$ of the amine all have an effect. However, it is most commonly considered that the reaction...
proceeds via in situ generation of the imine from condensation of the carbonyl compound with the amine, followed by subsequent nucleophilic attack of the hydrophosphoryl component in a Pudovik style process (Scheme 2.5).

Scheme 2.5. The mechanism of the Kabachnik-Fields reaction.

The initial reports published in 1952 on the Pudovik\textsuperscript{71} and Kabachnik-Fields\textsuperscript{73} reactions have received over 500 citations, revealing substantial interest in these processes. Recent developments relating to these reactions are surveyed below.

Beers et al., during their investigations on phosphatase inhibitors, synthesised a range of benzylaminophosphonic acids via the corresponding \(\alpha\)-aminophosphonates.\textsuperscript{81} Aryl aldehydes 22 were reacted with primary amines to generate aldimine intermediates 107. Addition of dialkyl phosphites to 107 at high temperatures was found to produce \(\alpha\)-aminophosphonates 108 in poor to very good yield (Scheme 2.6). 108 was then deprotected with TMSBr in propylene oxide to yield the phosphonic acid.
Wieczorek and co-workers have described the synthesis of α-aminophosphonates from ketimines under solvent-free conditions. The reaction of a pre-formed imine 109 with a dialkyl phosphite at 70 °C was shown to give the corresponding α-aminophosphonate in moderate to very good yields (Scheme 2.7). Many reports have described the use of Lewis acid catalysts including TiCl₄, AlCl₃, InCl₃, In(OTf)₃, Me₂AlCl, ZrCl₄, BF₃ in the synthesis of α-aminophosphonates. A few recent illustrative examples are given herein.

Kabachnik et al. reported the use of cadmium iodide as a Lewis acid catalyst in their synthesis of α-aminophosphonates. From screening a range of metal halides they showed that CdI₂ (2 mol%) greatly improved the rate of reaction.
between imines (aldimines and ketimines) \( \text{109} \) and diethyl phosphite (Scheme 2.8).

\[
\begin{array}{cccc}
\text{R}^2 & \text{R} & \text{H}^+ & \text{P(O)(OEt)}_2 \\
\text{109} & \text{CdI}_2, \text{H(O)P(OEt)}_2 & \text{C}_6\text{H}_6, 45^\circ\text{C}, 1.5 \text{ h} & \text{R}^2\text{R} \text{P(O)(OEt)}_2 \\
\end{array}
\]

\( R = \text{H, } \text{^6Hex} \)
\( R^1 = \text{Et, } \text{^6Pr, } \text{^7Pr, } \text{^6Pen, } \text{^6Hex, 3-py, Ph} \)
\( R^2 = \text{Me, } \text{^6Bu, } \text{^6Hex, Ph, Bn} \)

**Scheme 2.8.** Synthesis of \( \alpha \)-aminophosphonates using cadmium iodide.

Lithium perchlorate has been shown to be a very effective Lewis acid for the generation of \( \alpha \)-aminophosphonates.\(^{91}\) As an example, \( \alpha \)-aminophosphonate \( \text{110} \) was generated in 98% yield from the reaction of benzaldehyde with aniline and trimethyl phosphite in the presence of TMSCl in a 5 M ethereal solution of LiClO\(_4\) (Scheme 2.9).

\[
\begin{array}{ccc}
\text{C}_6\text{H}_5\text{CHO} & + & \text{PhNH}_2 \\
& + & \text{P(O)(OMe)}_3 \\
& & \text{LiClO}_4, \text{TMSCl} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{PhCH} = \text{NH}^+ \\
\text{P(O)(OMe)}_2 \\
\text{Et}_2\text{O, rt, 30 min} \\
98\% \\
\end{array}
\]

**Scheme 2.9.** Kabachnik-Fields reaction using lithium perchlorate.

Matveeva *et al.* developed an aluminium based tetra-\textit{tert}-butyl-substituted phthalocyanine \( \text{111} \) Lewis acid for the production of \( \alpha \)-aminophosphonates from ketones.\(^{92}\) For example, the reaction of 3-methylcyclohexanone with benzylamine and diethyl phosphite in the presence of \( \text{111} \) was found to give \( \alpha \)-aminophosphonate \( \text{112} \) in 98% yield (Scheme 2.10). Notably, this reaction appeared to tolerate sterically bulky ketones such as camphor and norbonanone, although the yields reported were low in these cases (20-30%).
Bhagat et al. reported that magnesium perchlorate was found to be a highly efficient catalyst in the Kabachnik-Fields reaction under solvent-free conditions.\textsuperscript{93} Having screened a wide range of metal perchlorates under various reaction conditions, they found that the reaction between aldehydes or ketones, primary or secondary amines and dialkyl phosphites in the presence of Mg(ClO$_4$)$_2$ under solvent free conditions gave the corresponding $\alpha$-aminophosphonates 113 in good yields (Scheme 2.11).

\begin{align*}
  \text{R}^1\text{O} + \text{R}^2\text{R}^3\text{N} + \text{H(O)P(OR)}_2 &\xrightarrow{\text{Mg(ClO}_4)_2 (5 \text{ mol{\%}}), \text{rt or 80 }^\circ\text{C, 6 h}} \text{R}^2\text{N}^\text{R}^3\text{P(OR)}_2 \\
  &\text{75-98\%}
\end{align*}

\begin{footnotesize}
R = Alkyl, Aryl \\
R' = H, Alkyl \\
R^2 = Alkyl, Aryl \\
R^3 = H, Alkyl \\
R^4 = Me, Et
\end{footnotesize}

\textbf{Scheme 2.11.} Kabachnik-Fields reaction using magnesium perchlorate.
Recently, Ambica et al. reported the use of antimony trichloride adsorbed on alumina as an efficient and recyclable catalyst in a Kabachnik-Fields reaction. They reported that the reaction between aldehydes, amines and dialkyl phosphites led to the corresponding $\alpha$-aminophosphonates in high yields in the presence of $\text{SbCl}_3/\text{Al}_2\text{O}_3$ (Scheme 2.12).

\[
\text{RCHO} + \text{R}^1\text{NH}_2 + \text{H}(\text{O})\text{P(O)}(\text{OR}_2)_2 \xrightarrow{\text{SbCl}_3/\text{Al}_2\text{O}_3 \ (5 \text{ mol\%}) \ \text{CH}_3\text{CN, rt, 7 h}} \text{NHR}^1\text{P(O)(OR}_2)_2 \quad 65-92\%
\]

$R = \text{Alkyl, Aryl}$

$R^1 = \text{Alkyl, Aryl}$

$R^2 = \text{Me, Et}$

**Scheme 2.12.** Kabachnik-Fields reaction using $\text{SbCl}_3/\text{Al}_2\text{O}_3$.

Protic acids have also been shown to promote the nucleophilic addition of phosphites into imines. Interestingly, Rabasso and co-workers synthesised a range of cyclic $\alpha$-aminophosphonates using acetic acid as activator. Sequential reaction of cyclic ketones with benzylic amines in the presence of acetic acid and magnesium sulfate was found to lead to the *in situ* generation of the iminium intermediate. Addition of triethyl phosphate was found to give the resultant cyclic product in moderate to good yields (Scheme 2.13).

\[
\text{R}^-\text{NH}_2, \text{AcOH, MgSO}_4 \xrightarrow{\text{EtOH, 55 °C, 4 h}} \text{NHR}^1\text{P(O)(OEt)}_2 \quad 46-92\%
\]

$n = 0, 1, 2$

$X = \text{CH}_2, \text{NMe}, \text{O}, \text{S}$

$R = \text{Bn, 4-MeOBn, CH(Me)Ph, CH(CH}_2\text{OH)Ph}$

**Scheme 2.13.** Kabachnik-Fields reaction for cyclic $\alpha$-aminophosphonates.
Chapter 2

Amberlyst-15, containing a sulfonic acid functionality, has been shown to be a highly efficient and recyclable acidic promoter in the Kabachnik-Fields reaction. Tajbakhsh et al. showed that α-aminophosphonates 117 could be generated from the reaction of aldehydes, amines and trimethyl phosphite in the presence of Amberlyst-15 (Scheme 2.14).

\[
\begin{align*}
R\text{H}O & \quad + \quad R^1\text{NH}_2 & + & \quad \text{P(O)(OMe)}_3 \\
\text{Amberlyst-15} & \quad \text{CH}_3\text{CN, rt, 1 h} & \quad \rightarrow & \quad \text{R}\text{P(OMe)}_2
\end{align*}
\]

\[\text{R} = \text{Alkyl, Aryl} \]
\[\text{R}^1 = \text{Alkyl, Aryl} \]

**Scheme 2.14.** Kabachnik-Fields reaction using Amberlyst-15.

Bases have also been used as activators for the nucleophilic addition of a phosphite into an imine. For example, Klepacz et al. deployed sodium hydride in their synthesis of N-Boc-1-amoalkylphosphonates (Scheme 2.15). Sodium hydride was used to induce elimination of \(p\)-toluene sulfonic acid from α-amidoalkyl-\(p\)-tolyl sulfones 118 to generate \(N\)-Boc imines 119 *in situ*. Addition of *in situ* generated sodium diethyl phosphite afforded \(N\)-Boc-1-amoalkylphosphonates 120 in good yields.

\[
\begin{align*}
\text{Boc} & \quad \text{NH} & \quad \text{NaH, H(O)(OEt)}_2 \\
\text{R} & \quad \text{Ts} & \quad \text{THF, rt, 2 h} & \quad \rightarrow & \quad \text{Boc} & \quad \text{NaP(O)(OEt)}_2
\end{align*}
\]

\[\text{R} = \text{H, Me, Et, }^7\text{Pr, }^9\text{Pr, }^9\text{Bu, }^9\text{Bu, Ph, 4-MeOC}_6\text{H}_4 \]

**Scheme 2.15.** Synthesis of α-aminophosphonates under basic conditions.
2.1.2 Asymmetric synthesis of $\alpha$-aminophosphonates

As $\alpha$-aminophosphonates contain an asymmetric carbon centre there have been many reports on developing asymmetric routes to these systems. As such, the development of enantiocontrolled routes to $\alpha$-aminophosphonates has received a great deal of attention. Several reviews on this topic have recently been published,\textsuperscript{99} and some highlights are described herein.

Yager \textit{et al.} used amines with a chiral directing group to induce stereochemistry into $\alpha$-aminophosphonates in a two step process.\textsuperscript{100} Reaction of an enantiopure amine with an aldehyde generated chiral imine \textbf{121}. Treatment of \textbf{121} with lithium diethyl phosphite was found to give the corresponding $\alpha$-aminophosphonate \textbf{122} in moderate to good yields with high levels of diastereomeric excess. Hydrogenolysis of the chiral directing group afforded the corresponding amino ester \textbf{123} in good yields and very high levels of enantiomeric purity (Scheme 2.16). The stereocontrol achieved in transition state \textbf{124} was proposed to derive from the methoxymethyl ether and nitrogen-lone pair chelating the lithium ion, allowing for directed attack of the phosphite anion into the \textit{Re} face of the imine.
Chapter 2

Scheme 2.16. Asymmetric synthesis of α-aminophosphonates.

Davis and co-workers used sulfinimines in their asymmetric synthesis of quaternary α-aminophosphonates. They demonstrated that the reaction of enantiopure ketosulfinimines with lithium diethyl phosphite afforded the corresponding N-sulfinyl α-aminophosphonates in good yields with high levels of diastereomeric excess (Scheme 2.17).

Scheme 2.17. Asymmetric synthesis of N-sulfinyl α-aminophosphonates.

As with the example of Yager, above, the asymmetric induction was believed to have originated from chelation of the lithium cation. In this case, the cation was chelated to the sulfinyl and phosphite oxygens in a seven-membered twisted
Chapter 2

chair-like transition state 127. For the major (S<sub>S</sub>,R) diastereomer pictured, the bulky aryl and p-tolyl groups adopt energetically favourable equatorial positions leading to the observed stereochemical outcome (Scheme 2.18).

![Scheme 2.18. Rational for the stereocontrol of N-sulfinyl α-aminophosphonates.](image)

Pettersen et al. demonstrated that good enantioselectivities could be obtained in the nucleophilic attack on aldimines by diethyl phosphite using an organocatalytic approach. Using cinchona alkaloid derivative 128 as catalyst, they were able to show that reaction between N-Boc imines 119 with phosphite 104 proceeded to 129 in good yields and high levels of enantioselectivity could be obtained (Scheme 2.19).

![Scheme 2.19. Stereocontrol using organocatalysis.](image)
It was proposed that the hydroxyl group and the free nitrogen-lone pair on 128 activated the imine and phosphite via hydrogen bonding as shown in transition state 130. This activation would arise in a stereoselective fashion due to the donor and acceptor positions in the catalyst, giving rise to the observed stereochemical outcome.

Katsuki and co-workers developed an optically active Al(salalen) complex 131 for the enantioselective hydrophosphonylation of aldímínnes. They showed that 131 catalysed the reaction between aliphatic and aromatic aldímínnes 107 and dimethyl phosphite to give 132 in very good yield with modest to high levels of enantioselectivity (Scheme 2.20).

![Scheme 2.20. Asymmetric Pudovik reaction with an organometallic catalyst.](image-url)
Recently, Cheng et al. developed a direct catalytic asymmetric three-component Kabachnik-Fields reaction. They found that chiral phosphonic acid catalysed the reaction between aryl substituted aldehydes, \( p \)-anisidine and di(3-pentyl)phosphate to in good yields and high dia- and enantioselectivity (Scheme 2.21). Impressively, they were able to generate one C–N bond, one C–P bond and two asymmetric centres in a single vessel from achiral starting materials.

\[
\begin{align*}
\text{R}_1 \text{C}=\text{O} + \text{C}_{\text{Ar}} \text{H}_2 + \text{HPO(O)P(O)H} & \quad \text{Catalyst 133 (10 mol\%)} \\
\qquad \text{Hex, 50 °C, 7 days} & \quad \text{dr = 3:2-28:1} \\
& \quad \text{er = 51:49-97:3}
\end{align*}
\]

\( \text{R} = \text{Me, Et, \text{^6}Pr, \text{^6}Pen, \text{^6}Hex} \)

\( \text{R}_1 = \text{Ar} \text{yl or 2-thienyl} \)

\[
\text{Scheme 2.21. An asymmetric Kabachnik-Fields reaction.}
\]
2.2 α-Aminophosphonates from Methyleneaziridines

2.2.1 Approach

This thesis is concerned with the development of new synthetic methods from methyleneaziridines. Herein is described our development of a new four-component synthesis of α-aminophosphonates from methyleneaziridines.

The most common approach to α-aminophosphonates is via nucleophilic addition of an alkyl phosphite into an imine. Therefore, it was envisioned that the multi-component reaction of methyleneaziridines (Section 1.3.8) could be adapted to generate α-aminophosphonates. Reaction of methyleneaziridines 1 with a Grignard reagent followed by an electrophile is known to lead to the in situ generation of ketimines 95. Subsequent addition of a dialkyl phosphite under Lewis acidic catalysis should lead to the formation of α-aminophosphonates 138 in a new sequential four-component reaction (Scheme 2.22). By this process, two new C–C bonds, a new C–P bond and a quaternary carbon centre would be generated in ‘one-pot’. As the multi-component chemistry of methyleneaziridines is known to be tolerant to a good range of functionality, it is expected that this approach would hold true value for rapid generation of a wide variety of α-aminophosphonates.
2.2.2 Initial model reactions

Before attempting to execute the sequence depicted above, we decided to explore the hydrophosphonylation of preformed ketimines using simple activators. Initially, it was decided to examine whether CdI$_2$, as described by Kabachnik, was a suitable activator. To examine this proposal, the Pudovik reaction of an alkyl derived ketimine with diethyl phosphite was examined. $N$-Benzyl-4-heptanimine$^{18}$ (139) was viewed as a suitable test substrate. 4-Heptanone (140) and benzylamine in toluene were heated under reflux with azeotroping removal of water for 48 h. After work-up and purification by distillation, imine 139 was isolated in good yield (Scheme 2.23).

Under the reaction conditions described by Kabachnik, imine 139 (1 equiv.) was dissolved in benzene and treated with CdI$_2$ (5 mol%) and diethyl phosphite (1 equiv.). After heating at 45 °C for 1.5 h, α-aminophosphonate 141 was
obtained in good yield after work-up and purification on silica gel. Encouragingly, repeating the reaction in tetrahydrofuran to test the compatibility of this reaction with the solvent needed for the MCR yielded \( \text{141} \) in comparable yield (Scheme 2.24).

![Scheme 2.24. Synthesis of an \( \alpha \)-aminophosphonate from a preformed ketimine.](image)

As copper (I) iodide would be present in a MCR involving the ring-opening of methyleneaziridines, we decided to ascertain if this metal salt could be used instead of cadmium iodide. To this end, imine \( \text{139} \) was treated with diethyl phosphite and copper iodide (5 mol\%) in tetrahydrofuran under the conditions described above. However, after work-up and purification, \( \text{141} \) was isolated in a somewhat reduced yield (Scheme 2.25).

![Scheme 2.24. CuI in the synthesis of an \( \alpha \)-aminophosphonate.](image)

Next, we sought to establish whether the Pudovik conditions identified above could be used in a MCR involving methyleneaziridines. In preparation for the MCR studies, methyleneaziridines \( \text{19, 50} \) and \( \text{142} \) were synthesised in two steps from the parent amine according to standard procedures.\(^6\) Amines \( \text{143-145} \) were alkylated with 2,3-dibromopropene in tetrahydrofuran in the presence of
K₂CO₃ to generate the corresponding vinyl bromides 146-148. Ring-closure with sodium amide, generated in situ from sodium and ammonia in the presence of Fe(NO₃)₃·9H₂O, in liquid ammonia gave methyleneaziridines 19, 50 and 142 in good overall yields (Scheme 2.26).

\[
\begin{align*}
\text{R-} &\text{NH}_2 \xrightarrow{\text{THF, rt, 18 h}} \text{H}_2\text{C}=\text{C(Br)CH}_2\text{Br}, \; \text{K}_2\text{CO}_3 \quad \xrightarrow{-78 \text{ or } -33 \text{ °C, 1 or 3 h}} \quad \text{R} &\text{N} \\
143: \text{R} = \text{S-CH(Me)Ph} &\quad 146: \text{91\% (lit. 100\%)}^{18} &\quad 19: \text{91\% (lit. 91\%)}^{18} \\
144: \text{R} = \text{Bn} &\quad 147: \text{99\% (lit. 98\%)}^{18} &\quad 50: \text{68\% (lit. 78\%)}^{18} \\
145: \text{R} = \text{cHex} &\quad 148: \text{70\% (lit. 86\%)}^{9} &\quad 142: \text{63\% (lit. 76\%)}^{10} \\
\end{align*}
\]


Thus, 1-benzyl-2-methyleneaziridine (50) (1 equiv.) was ring-opened with ethylmagnesium chloride (3 equiv.) and CuI (20 mol%) in tetrahydrofuran. The mixture was then cooled to 0 °C and treated with benzyl bromide (1.5 equiv.) and heated to 45 °C with stirring for 3 h. The resulting mixture was treated with CdI₂ (5 mol%) and diethyl phosphite (1 equiv.) and stirred for 1.5 h at 45 °C. Pleasingly, after work-up and purification on silica gel, α-aminophosphonate 149a was isolated in 58% yield (Scheme 2.27). This initial finding showed that α-aminophosphonates could be generated in a four component process. α-Aminophosphonate 149a displayed a distinctive signal at 30.6 ppm in the ³¹P NMR spectrum and a doublet at 59.7 in the ¹³C NMR spectrum with characteristic splitting of 135.7 Hz. These signals are indicative of a phosphorous bonded to a quaternary carbon centre and gave us confidence, in conjunction with other data, in the structural assignment of the product.
Scheme 2.27. Synthesis of an α-aminophosphonate from a methyleneaziridine.

A further control reaction performed in the absence of CdI$_2$ produced 149a in 59% yield. This finding suggests that the Cu and Mg salts present in the MCR are sufficient to promote the hydrophosphonylation step. In the $^{31}$P NMR spectrum of the crude product, an unexpected peak was observed at 26.6 ppm. This extra peak suggested that a phosphine oxide (Figure 2.2) had been generated from reaction of excess Grignard reagent with diethyl phosphite.$^{105}$

![Figure 2.2. Postulated phosphine oxide.](image)

As such, it was a concern that the presence of another phosphorus nucleophile in the reaction could take part in a competitive nucleophilic addition into the ketimine species generated from the methyleneaziridine. Thus, it was investigated whether reducing the equivalents of ethylmagnesium chloride and increasing the equivalents of diethyl phosphite would have a bearing on the reaction. Thus, methyleneaziridine 50 (1 equiv.) was treated with ethylmagnesium chloride (2.5 equiv.), CuI (20 mol%) and benzyl bromide (1.5 equiv.) under the conditions described. After addition of diethyl phosphite (2.5 equiv.) the reaction mixture was stirred at 45 °C overnight. Gratifyingly,
149a was isolated in an improved 65% yield after work-up and purification (Scheme 2.28). Importantly, the excess phosphite in the reaction was readily removed by washing the crude reaction mixture with 50% w/v aqueous sodium hydroxide prior to column chromatography.

Scheme 2.28. Improved four-component synthesis of an α-aminophosphonate.

2.2.3 Four-component synthesis of α-aminophosphonates

Having established conditions for the formation of α-aminophosphonates 149a from methyleneaziridines 50, a range of Grignard reagents and electrophiles were examined in order to evaluate the scope and limitations of the reaction. These reactions were performed under the reaction conditions described above (Scheme 2.29), and the results summarised in Table 2.1.

Scheme 2.29. Multi-component synthesis of α-aminophosphonates.
Pleasingly, we were able to readily synthesise a range of α-aminophosphonates in “one-pot” following a single general method. The yields ranged from a moderate 42% (Entry 10) to a very good 65% (Entry 1). The efficiency with respect to each new bond formed is excellent, up to 87%. It was gratifying to see that this multi-component reaction was tolerant to a good range of functionality including ethers, alkenes, alkynes, aromatic rings and halides.

The use of cyclohexylmagnesium chloride gave a lower yield (Entry 10), although this may be due to the fact that this Grignard reagent was in a diethyl ether solution rather than tetrahydrofuran. It is known that the multi-component
chemistry of methyleneaziridines is very sensitive to the nature of the solvent with tetrahydrofuran preferred.\textsuperscript{13}

Cyclohexene oxide and iodomethane, which had previously been successfully used in similar MCRs,\textsuperscript{11,29b} unfortunately met with failure in the above process. The use of iodomethane led to a complex mixture of inseparable phosphonate containing products as judged by \textsuperscript{1}H and \textsuperscript{31}P NMR spectroscopy. The high volatility of this reagent may account for the problems observed in this MCR, as it may have evaporated during heating at 45\textdegree{}C.

When cyclohexanone was used in the reaction of methyleneaziridine 50 with ethyl magnesium chloride and diethyl phosphite under the conditions above, \(\alpha\)-aminophosphonate 150 was isolated in 52\%. It is known that the hydrogens in the \(\alpha\) position of cyclohexanone are relatively acidic,\textsuperscript{106} as such it could be imagined that protonation of enamine species 151 is occurring rather than alkylation (Scheme 2.30).

\begin{center}
\textbf{Scheme 2.30.} Reaction involving cyclohexanone.
\end{center}
\(\alpha\)-Aminophosphonate 150 was initially identified by a doublet at 1.32 ppm \((J = 16.4 \text{ Hz})\) integrating for 3 protons in the \(^1\text{H} \text{NMR} \) spectrum and an absence of cyclohexane-type ring hydrogens in the isolated product. This CH\(_3\) was found not to couple to any other proton signal by COSY correlation, leading us to believe that the splitting observed derived from \(^1\text{H}–^{31}\text{P} \) coupling. As such, it was thought that this CH\(_3\) was bonded directly to the quaternary carbon centre. Mass spectroscopy \((m/z = 314)\) gave us further confidence in the structure of 150.

### 2.2.4 Attempted asymmetric induction

Since asymmetric induction is possible in the synthesis of \(\alpha\)-aminophosphonates (Section 2.1.2), we next decided to explore if any stereocontrol could be exerted over the quaternary carbon centre formed in our four-component process. It was envisioned that chiral methyleneaziridine 19 might be a suitable substrate to induce such stereocontrol as some success had been realised in earlier MCRs using this substrate.\(^{54}\) Initially, 19 (1 equiv.) was treated with ethylmagnesium chloride (2.5 equiv.), CuI (20 mol%), benzyl bromide (1.5 equiv.) and diethyl phosphite (2.5 equiv.) to afford phosphonate 152 in 54\% (Scheme 2.31). Unfortunately, 152 was found to be a 1:1 mixture of diastereomers as judged by \(^1\text{H} \text{NMR} \) spectroscopy with two triplets for the terminal CH\(_3\) of the propyl chain at 0.88 and 0.62 ppm.

![Scheme 2.31. Attempted asymmetric induction with a chiral methyleneaziridine.](image-url)
Whilst disappointing, the lack of facial selectivity in the synthesis of 152 was not surprising due to the similar steric size of the propyl and ethyl phenyl chains around the newly formed quaternary carbon centre. This observation is in agreement with the report of Hayes et al. who demonstrated that little selectivity was achieved in the synthesis of amine 153a from methyleneaziridine 19. They proposed that this was due to little facial selectivity in the reduction due to the near equal steric size of the ethyl and propyl groups. However, from gem-dimethyl-methyleneaziridine 60 excellent levels of diastereocontrol could be obtained in amine 153b due to the increased steric bulk of the tert-butyl group compared to the propyl chain (Scheme 2.32).

Scheme 2.32. Steric dependent diastereocontrol in a MCR for amine formation.

It was thought that the use of a substrate with significant size difference in the alkyl chains off the ketimine might allow for better stereocontrol. Thus, a stock sample of chiral gem-dimethyl-methyleneaziridine29b 60 was reacted with ethylmagnesium chloride (2.5 equiv.), CuI (20 mol%), iodomethane (2 equiv.) and diethyl phosphite (2.5 equiv.). However, none of the expected α-aminophosphonate 154 was observed. Instead imine107 155 was detected as the major product by 1H and 13C NMR spectroscopy (Scheme 2.33). The lack of any signal in the 31P NMR spectrum and a signal of 175.1 in the 13C spectrum led us to believe that imine 155 and not α-aminophosphonate 154 had been
formed in this reaction. Unfortunately, attempted purification of 155, for full characterisation, on silica gel led to decomposition of the product.

Scheme 2.33. Undesired imine formation.

In contrast to earlier successful hydride reduction (Scheme 2.32), the large diethyl phosphite nucleophile was too large to attack sterically hindered imine 155. As such no Pudovik type reaction occurred between the components and only imine 155 was observed after work-up.

It was considered that addition of a chiral phosphorous nucleophile into the ketimine intermediate might impart stereocontrol over the reaction. To test this idea, methyleneaziridine 50 was treated with ethylmagnesium chloride (2.5 equiv.), CuI (20 mol%), benzyl bromide (1.5 equiv.) and freshly distilled racemic ethyl phenylphosphinate (2.5 equiv.). Phosphonate 156 was isolated in 64% yield, however, 156 was judged to be a 1:1 mixture of diastereomers as judged by $^1$H and $^{31}$P NMR spectroscopy (Scheme 2.34).

Scheme 2.34. Attempted stereocontrol with a racemic hydrophosphoryl.
2.2.5 Four-component synthesis of a heterocyclic α-aminophosphonate

It is known that piperidine based systems are accessible from the multi-component chemistry of methyleneaziridines by deploying 1,3-diiodopropane as the electrophile. As such it was considered that piperidine derived α-aminophosphonates could be accessed in a similar manner. Initially, 50 (1 equiv.) was ring-opened with ethylmagnesium chloride (2.5 equiv.), CuI (20 mol%) in tetrahydrofuran. The mixture was then cooled to 0 °C and treated with 1,3-diiodopropane (2.5 equiv.) and heated to 45 °C with stirring for 3 h. The reaction mixture was treated with diethyl phosphite (2.5 equiv.) and stirred overnight at 45 °C. However after work-up and purification, piperidine product 157 was only isolated in a rather poor 10% yield (Scheme 2.35). Phosphonate 150 (Scheme 2.30) was also observed in the crude reaction mixture, leading to the belief that alkylation by with 1,3-diiodopropane was not complete in the 3 h reaction time.

Cyclic iminium ion 158 is believed to be a key intermediate in the synthesis of piperidine derivatives by this route. It was thought that an anionic hydrophosphoryl component would be more suitable for attack on this iminium
A longer reaction time before the addition of the hydrophosphoryl nucleophile would also ensure complete alkylation by 1,3-diiodopropane. To this end, 50 was ring-opened with ethylmagnesium chloride, CuI in tetrahydrofuran. The mixture was then cooled to 0 °C and treated with 1,3-diiodopropane and heated to 45 °C with stirring overnight. In a separate flask, lithium diethyl phosphite was prepared according to the procedure of Yager. Lithium diethyl phosphite was then added via cannula to the reaction vessel at room temperature. The reaction mixture was then heated to 45 °C and stirred overnight. Upon cooling to room temperature, and after work-up and purification cyclic α-aminophosphonate 157 was isolated in a much improved 49% yield.

In their multi-component synthesis of (S)-coniine, Hayes et al. showed that hydride could be added into iminium species such as 158 in a diastereoselective fashion by employment of a chiral auxiliary. Inspired by this report, we sought to examine if diastereocontrol could be realised in the synthesis of piperidine derived α-aminophosphonates. Chiral methyleneaziridine 19 was reacted with ethylmagnesium chloride, CuI, 1,3-diiodopropane and lithium diethyl phosphite in tetrahydrofuran under the conditions described above. Disappointingly, none of the expected α-aminophosphonate 159 was detected by 1H NMR, 31P NMR or mass spectroscopy (Scheme 2.36).

Scheme 2.36. Failed selective synthesis of a heterocyclic α-aminophosphonate.
The failure of this reaction can be rationalised by analysis of the reaction pathway presented by Hayes.\textsuperscript{55} They assumed that the iminium cation \textbf{160} would adopt a twisted conformation where the allylic 1,3-strain is minimised, allowing for hydride addition to the least hindered \textit{Re}-face (Scheme 2.37). The presence of the extra methyl group on the chiral auxiliary increases the steric bulk around iminium cation \textbf{160} compared to iminium cation \textbf{158}. Diethyl phosphite anion is a much larger nucleophile than hydride and the extra steric bulk around iminium \textbf{158} would crowd out this large phosphite anion leading to failure of the reaction.

![Scheme 2.37](image)

\textbf{Scheme 2.37.} Comparison of cation reactivity.

\subsection*{2.2.6 Deprotection to $\alpha$-aminophosphonic acids}

As stated earlier (Section 2.1) the most common route to $\alpha$-aminophosphonic acids is via chemical manipulation of the corresponding $\alpha$-aminophosphonates. Having demonstrated a general four-component synthesis of $\alpha$-aminophosphonates, it was expected that $\alpha$-aminophosphonic acids could be readily accessed from these materials, especially in the case of \textbf{149a} and \textbf{149c-k} bearing an $N$-benzyl group.
Initially, hydrolysis of the phosphonate ester was attempted using TMSBr and propylene oxide under the conditions described by, amongst others, Hubert et al.$^{108}$ α-Aminophosphonate 149a was dissolved in dichloromethane, treated with excess TMSBr and stirred at room temperature. After 16 h, the solvent was removed \textit{in vacuo} and the residue redissolved in methanol. Diethyl ether and excess propylene oxide were added and the mixture stirred for 1 h at room temperature. The solvent was removed \textit{in vacuo} and the crude material examined by $^1$H, $^{13}$C and $^{31}$P NMR spectroscopy. $^1$H NMR spectroscopy indicated the loss of the two ethyl chains, however, the characteristic benzylic signal was also absent. $^{13}$C NMR spectroscopy indicated the lost of the two ethyl chains, although surprisingly the characteristic quaternary carbon at approximately 60 ppm was absent and a new signal at 210 ppm was detected, indicating carbonyl formation. Further, no phosphorous signal was detected by $^{31}$P NMR spectroscopy. Purification of the crude material on silica gel yielded ketone$^{109}$ 161 as the product of this reaction in effectively quantitative yield (Scheme 2.38). Phosphonic acid 162 was completely undetected.

![Scheme 2.38. Unexpected ketone formation.](image)

We postulated that this observation arose from activation of the phosphite group by TMS followed by E2 elimination via the removal of the amine hydrogen by the bromide anion. Resultant imine 163 would be readily hydrolysed to ketone 161 by hydrolysis with hydrogen bromide (Scheme 2.39).
Chapter 2

### Scheme 2.38. Postulated rationalisation of ketone formation.

It was believed that the \( N \)-benzyl group could be readily removed by catalytic hydrogenation. Phosphonate 149a was dissolved in methanol, water and aqueous hydrogen chloride, subjected to a hydrogen atmosphere in the presence of palladium on activated carbon and stirred at room temperature overnight. After filtration and purification on silica gel in the presence of triethylamine, amino ester 164 was isolated in essentially quantitative yield (Scheme 2.40). Phosphonate 164 was easily identified by the loss of the benzylic signals and reduction in the integrals of the aromatic signals of the \(^1\)H NMR spectra.

### Scheme 2.40. Benzyl removal via hydrogenation.

After some optimisation, an effective protocol was developed for hydrolysis of phosphonate 164 using the procedure reported by Davis and co-workers.\(^{101} A\)
solution of \textbf{164} in concentrated aqueous hydrogen chloride was heated to reflux overnight. After cooling to room temperature and removal of the solvent \textit{in vacuo} the residue was redissolved in ethanol, treated with excess propylene oxide and stirred at room temperature for 3 h. \(\alpha\)-Aminophosphonic acid \textbf{165} was then collected as a white solid in 91\% yield (Scheme 2.41). Phosphonic acid \textbf{165} was readily identified by \(^1\)H and \(^{31}\)P NMR spectroscopy, along with IR spectroscopy. \(^1\)H NMR spectroscopy revealed the loss of the two ethyl chains from the phosphonate ester. \(^{31}\)P NMR spectroscopy revealed that the phosphorous signal had moved up field from 31.1 ppm to 17.1 ppm, indicative of a phosphonic acid. Infrared spectroscopy revealed bands at 2872 and 1525 cm\(^{-1}\) which were assigned to the unmasked phosphonic acid moiety.

![Scheme 2.41](image)

**Scheme 2.41.** Synthesis of an \(\alpha\)-aminophosphonic acid.

Due to time constrains, the deprotection sequence outlined above was only conducted with phosphonate \textbf{149a}. However, it is believed that this sequence would be readily applicable to \(\alpha\)-aminophosphonates \textbf{149c-k} and \textbf{157}.
2.3 Alternative MCR to $\alpha$-aminophosphonates from nitriles

Recently, Montagne et al. demonstrated that hydantoins could be synthesised in a modified Bucherer-Bergs reaction from nitriles.\textsuperscript{110} They showed that reaction between a nitrile and an organometallic reagent generates ketimine intermediate 166 which can be subjected \textit{in situ} to a Bucherer-Bergs reaction to give hydantoin 167 (Scheme 2.42).

\textbf{Scheme 2.42.} A modified Bucherer-Bergs reaction.

We reasoned that $\alpha$-aminophosphonates could be generated in an analogous fashion from nitriles \textit{via} a modified Pudovik reaction (Scheme 2.43). This chemistry would be complementary to that described above, allowing access to aryl substituted $\alpha$-aminophosphonates.

\textbf{Scheme 2.43.} Proposed synthesis of $\alpha$-aminophosphonates from nitriles.

To test these ideas, $n$-butyl lithium (1.2 equiv.) was cooled to 0 °C in tetrahydrofuran then reacted with $n$-hexane nitrile (168) (1 equiv.). The reaction mixture was stirred at 0 °C for 30 min then cadmium iodide (10 mol%) and diethyl phosphite (1.2 equiv.) were added. The mixture was rapidly heated to 75 °C in a pre-heated oil bath and stirred overnight. Upon cooling to room
temperature and after work-up and purification, α-aminophosphonate 169 was isolated in an encouraging 37% yield (Scheme 2.44). A further control reaction performed in the absence of CdI$_2$ failed to yield any of 169.

**Scheme 2.44.** Synthesis of an α-aminophosphonate from a nitrile.

The analogous reaction with a Grignard organometallic reagent was also attempted. A solution of $n$-hexane nitrile (168) in tetrahydrofuran was reacted with ethylmagnesium chloride (1.2 equiv.) in the presence of copper (I) iodide (5 mol%). The mixture was rapidly heated to 75 °C in a pre-heated oil bath and stirred overnight. Upon cooling to room temperature diethyl phosphite was added and the mixture heated at 75 °C overnight. However, upon cooling to room temperature and after work-up, none of α-aminophosphonate 170 could be detected by $^1$H, $^{31}$P NMR or mass spectroscopy (Scheme 2.45). A repeat reaction in the presence of cadmium iodide (10 mol%) was equally unsuccessful.

**Scheme 2.45.** Unsuccessful use of a Grignard reagent.
2.4 Conclusion

In summary, a new sequential four-component modified Pudovik reaction has been developed for the synthesis of α-aminophosphonates from methyleneaziridines. Reaction between a methyleneaziridine, a Grignard reagent, an electrophile and a dialkyl phosphite affords the corresponding α-aminophosphonate in good yield with high chemical efficiency per new bond formed. It has been demonstrated that this reaction tolerates a range of functionality and variation in all four components (Scheme 2.29 and Table 2.1). This work has recently been published.\textsuperscript{111}

The scope of this reaction was further broadened by its application to the synthesis of a heterocyclic α-aminophosphonate (Scheme 2.35).

Unfortunately, all attempts to induce diastereoccontrol into the newly formed quaternary carbon centre were unsuccessful. In the synthesis of α-aminophosphonates derived from acyclic ketimines no stereocontrol was observed when using either chiral methyleneaziridine \textsuperscript{19} or a racemic phosphorous based nucleophile (Schemes 2.31 and 2.34). Failure to induce stereocontrol in the synthesis of heterocyclic α-aminophosphonates can be rationalised in terms of the steric size of the incoming phosphorous nucleophile (Scheme 2.37).

An α-aminophosphonate formed in the 4-CRs was successfully deprotected in two steps to the corresponding α-aminophosphonic acid (Schemes 2.40 and 2.41). Thanks to the high yields for this two step deprotection, a wide range of
\(\alpha\)-aminophosphonic acids could conceivably be formed quickly and efficiently from methyleneaziridines in three operations.

Finally, a simple three-component synthesis of \(\alpha\)-aminophosphonates from nitriles has been discovered (Scheme 2.44). Although only proceeding in moderate yields, this process merits further optimisation, a realistic objective in view of the wide range of published conditions for nucleophilic attack of phosphites onto imines. This MCR would be complementary to our approach based on methyleneaziridines. This chemistry should allow for the synthesis of aryl and alkyl substituted \(\alpha\)-aminophosphonates. As such, further research into this methodology may be warranted.
Chapter 3:

Attempted MCR to

2,3-Dihydro-4-pyridones
3.1 Introduction to Imino-Diels-Alder Reactions

The imino Diels-Alder reaction is a common method for the construction of functionalised heterocyclic rings.\textsuperscript{112} High levels of regio-\textsuperscript{113}, diastereo-\textsuperscript{114} and enantio-selectivity\textsuperscript{115,116} can be achieved. There are essentially three different types of imino Diels-Alder reaction as depicted in Scheme 3.1. These involve reaction of an imine with an electron-rich diene (path 1), and reaction of dienophiles with 1-azadienes\textsuperscript{117} (path 2), or 2-azadienes (path 3).\textsuperscript{118}

\begin{center}
\textbf{Scheme 3.1.} Imino Diels-Alder reactions.
\end{center}

Of particular interest to us was the imino Diels-Alder reaction of imines \textsuperscript{109} acting as the dienophiles (path 1) towards electron-rich dienes such as Danishefsky’s diene\textsuperscript{119} (171) to give 2,3-dihydro-4-pyridones 172 (Scheme 3.2). We anticipated that such systems could be constructed by a novel 4-CR (see Section 1.3.8).

\begin{center}
\textbf{Scheme 3.2.} Synthesis of 2,3-dihydro-4-pyridones.
\end{center}
2,3-Dihydro-4-pyridones have been used widely in the synthesis of alkaloids and other biologically active compounds and are valuable intermediates en route to many compound classes.\textsuperscript{120}

For example, Comins et al. synthesised polyhydroxy piperidine alkaloid (-)-deoxynojirimycin (173) via chiral pyridone 174.\textsuperscript{121} Cbz protection of 174, followed by stereoselective acetoxylation provided trans-3-acetoxy-2,3-dihydropyridone 175. Ester hydrolysis of 175 followed by regio- and stereoselective reduction gave dihydroxy tetrahydropyridine 176. Subsequent dihydroxylation followed by deprotection afforded enantiopure (-)-deoxynojirimycin (173) in 26% overall yield in seven steps from 174 (Scheme 3.3).

\begin{equation}
\begin{align*}
1) \text{BuLi} \\
2) \text{CbzCl} \\
3) \text{Pb(OAc)}_4 \\
&77\% \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
1) \text{HCl, EtOH} \\
2) (\text{Me})_4\text{NBH(OAc)}_3 \\
&62\% \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
1) \text{OsO}_4, \text{NMO} \\
2) \text{Pd(OH)}_2, \text{H}_2, \text{HCl} \\
&55\% \\
\end{align*}
\end{equation}

\textbf{Scheme 3.3.} Synthesis of (-)-deoxynojirimycin from a chiral pyridone.

As a prelude to our work, a brief overview of the synthesis of 2,3-dihydro-4-pyridones via imino Diels-Alder reactions is presented.
Much of the research into the imino Diels-Alder reaction has focused on the use of Lewis acid activators. A number of metal triflates have been successfully deployed in the reaction of imine 177 with Danishefsky’s diene (171) to give pyridone 178 (Scheme 3.4). Examples include In(OTf)$_3^{122}$, Yb(OTf)$_3$ and Sc(OTf)$_3^{123}$ under various reaction conditions.

Scheme 3.4. Lewis acid catalysed imino Diels-Alder reactions.

Akiyama et al. have shown that Brønsted acids can also be used as activators in imino Diels-Alder reactions.$^{124}$ Tetrafluoroboric acid was shown to catalyse the cycloaddition of imines 107 with diene 171 in good yields in methanol to pyridones 179 (Scheme 3.5).

Scheme 3.5. Tetrafluoroboric acid catalysed imino Diels-Alder reactions.

Stereoselectivity in the imino Diels-Alder reaction can be achieved in a number of ways. Badorrey et al. showed that stereo-induction can arise from using imines derived from chiral aldehydes.$^{125}$ For example, pyridone 180 was
isolated in good yield and selectivity from the reaction of $N$-benzyl imine 181 with Danishefsky’s diene (171) in the presence of ZnI$_2$ (Scheme 3.6).

Scheme 3.6. Example of the use of imines derived from chiral aldehydes.

Imines derived from chiral amines have also been shown to impart stereoselectivity under Lewis acid catalysis.$^{126,127}$ In particular imines derived from aldehydes and $\alpha$-phenylethylamine were shown to give pyridones in high selectivities, although in only moderate yields. Several Lewis acids were screened, including BF$_3$·Et$_2$O, TiCl$_2$(i-OPr)$_2$, B(OPh)$_3$ and ZnCl$_2$, with the latter reagent giving the best results in terms of selectivity and yield. For example, reaction of imine 182 with Danishefsky’s diene (171) in the presence of ZnCl$_2$ was shown to give pyridone 183 in good yield and selectivity (Scheme 3.7).$^{128}$

Scheme 3.7. Example of the use of imines derived from chiral amines.

Chiral Lewis acids have also been used to induce selectivity in imino Diels-Alder reactions.$^{129,130}$ Kobayashi et al. showed that chiral Lewis acid 184 imparted good enantioselectivities in the reaction of aldmines 185 with
Danishefsky-type dienes 186 to give pyridones 187 in good yields (Scheme 3.8).\textsuperscript{131}

\begin{equation}
\begin{array}{c}
\text{185} \\
\text{+} \\
\text{186} \\
\text{184 (5 mol\%)} \\
\text{61-93\%} \\
\text{83-94\% ee}
\end{array}
\end{equation}

\begin{itemize}
\item $R^1 = \text{o-Hex, Ph, 4-MeC}_6\text{H}_4, \text{Napth, 2-thiophene}$
\item $R^1 = H, \text{Me}$
\end{itemize}

Scheme 3.8. Use of a chiral Lewis acid in an imino Diels-Alder reaction.

Of concern to us at the outset of this study, there appear to be few examples of imino Diels-Alder reactions yielding pyridones from imines derived from ketones.

Huang \textit{et al.} have reported that unactivated imines derived from cyclic ketones undergo cycloaddition with Danishefsky’s diene in the presence of Zn(OTf)$_3$.\textsuperscript{132} Reaction of cyclohexanones 188 with amines and diene 171 produced the corresponding spiro-adducts 189 in poor to good yields. With 3- and 4-substituted cyclohexanones, a single stereoisomer was produced. The reaction was very sensitive to steric effects. Small $N$-substituents ($R = \text{Me or } n\text{-Bu}$) gave
good yields, however with larger groups (R = Bn or tert-Bu), only moderate yields were obtained at best (Scheme 3.9). Moreover, no reaction was observed with 2-substituted ketones.

\[
\begin{align*}
\text{188} & \xrightarrow{\text{Zn(OTf)}_2, \text{R-NH}_2, 171} \text{189} \\
\text{CH}_2\text{Cl}_2, \text{rt, 18 h} & \quad 7\text{-}84\% \\
R & = \text{Me, } \text{ } \text{ } \text{Bu, Bn} \\
R^1 & = \text{H, Me} \\
R^2 & = \text{H, } \text{ } \text{ } \text{Bu} \\
R^1 = R^2 & = -\text{OCH}_2\text{CH}_2\text{-}
\end{align*}
\]

**Scheme 3.9.** Synthesis of pyridones from cyclohexanones.

### 3.2 Pyridone Synthesis Attempt via Methyleneaziridine MCRs

Since it has been shown that pyridones can be accessed from the imino Diels-Alder reaction of ketimines with an electron-rich diene,\(^\text{132}\) it was thought that these systems could be reached from methyleneaziridines \(1\) via a one-pot process. The ketimine \(95\) produced in a typical MCR might be expected to undergo cycloaddition with electron rich dienes under Lewis acid catalysis to give a variety of pyridone based systems \(190\) (Scheme 3.10). Clearly, the sensitivity of these reactions to steric effects was of some concern but we were optimistic that suitable conditions for the imino Diels-Alder reaction could be found.

\[
\begin{align*}
\text{1} & \xrightarrow{1) \text{Nu}^\ominus} \text{95} \\
\xrightarrow{2) \text{E}^\ominus} & \text{cycloaddition} \xrightarrow{} \text{190}
\end{align*}
\]

**Scheme 3.10.** Proposed approach to pyridones via an imino Diels-Alder MCR.
Many of the reports of imino Diels-Alder reactions employ Danishefsky’s diene (171) and so this material was selected for our studies. This diene can be readily made using published methods.\textsuperscript{119,133,134} Thus, treatment of trans-4-methoxy-but-3-en-2-one 191 with lithium bromide and chlorotrimethylsilane followed by triethylamine gave diene 171 in 61\% yield after careful work-up and distillation (Scheme 3.11).

\begin{center}
\includegraphics[width=\textwidth]{reaction_11}
\end{center}

\textbf{Scheme 3.11.} Synthesis of Danishefsky’s diene.

To develop a methyleneaziridine based MCR approach to pyridones, the first challenge was to explore if an imino Diels-Alder reaction could be effected in tetrahydrofuran. To this end, zinc triflate catalysed reaction of cyclohexanone derived imines with diene 171 was repeated according to Huang’s method\textsuperscript{132} in tetrahydrofuran (Scheme 3.12). Cyclohexanone (192) in tetrahydrofuran was treated with Zn(OTf)\textsubscript{2} (0.5 equiv.), methylamine (4 equiv.) and Danishefsky’s diene (171) (2 equiv.) and stirred at room temperature overnight. Gratifyingly, after work-up and purification, 193 was isolated in comparable yield to that reported in dichloromethane (64\%).\textsuperscript{132}

\begin{center}
\includegraphics[width=\textwidth]{reaction_12}
\end{center}

\textbf{Scheme 3.12.} Solvent compatibility test reaction.
In agreement with Huang,\textsuperscript{132} it was observed that reaction of cyclohexanone (192) with more hindered (±)-1-phenylethylamine under comparable conditions gave none of the expected pyridone. Rather, conjugated enamine\textsuperscript{135} 194 was isolated as the major product (Scheme 3.13). This result suggested that methyleneaziridines bearing no branching at the \(\alpha\)-carbon would be needed to realise the proposed new MCR (Scheme 3.11).

\[ \text{O} \quad \text{Zn(OTf)}_2, \text{Ph(Me)CHNH}_2, 171 \quad \text{THF, rt, 18 h} \quad 63\% \]

**Scheme 3.13. Probing N-substituent size.**

Next, we sought to establish if acyclic ketimines could be used in this imino Diels-Alder reaction. Such materials were expected from our MCR methodology. To this end, 4-heptanone (140) was reacted with Zn(OTf)_2, methylamine and 171 under the conditions described previously. However, none of the desired pyridone 195 was detected by \(^1\text{H} \) NMR or mass spectroscopy (Scheme 3.14).

\[ \text{O} \quad \text{Zn(OTf)}_2, \text{CH}_3\text{NH}_2, 171 \quad \text{THF, rt, 18 h} \]

**Scheme 3.14. Unsuccessful use of 4-heptanone.**

Using 2-heptanone (196) under the same conditions, pyridone 197 was isolated in a modest 29% yield (Scheme 3.15).
Chapter 3

![Scheme 3.15. Synthesis of a pyridone from 2-heptanone.](image)

The low yields of the above reactions may be due to the reduced reactivity of these ketones compared to cyclohexanone in imine formation, or alternatively due to a lack of reactivity of the imine itself. To differentiate between these possibilities, we decided to explore the use of a preformed imine in these reactions.

To this end, ketimine 139 (made from 4-heptanone and benzylamine, Scheme 2.23) was dissolved in tetrahydrofuran and reacted with Zn(OTf)$_2$ (0.5 equiv.) and Danishefsky’s diene (171) (2 equiv.) at room temperature. Unfortunately, after work-up none of the desired pyridone 198 was detected by $^1$H NMR or mass spectroscopy (Scheme 3.16).

![Scheme 3.16. Attempted synthesis of pyridones from ketimines.](image)

This finding suggests that acyclic ketimines are rather poor substrates for imino Diels-Alder reactions with electron-rich dienes. The small quantities of product derived from 2-heptanone, cf. 4-heptanone, suggest steric factors play a role.
Using a model similar to that proposed by Huang\textsuperscript{132} it is apparent that an appreciable amount of steric clashing between the $N$-benzyl and the $n$-propyl chains is likely to arise (Figure 3.1). Less steric clashing would be expected using cyclohexanone derived imines as the substrates would be ‘tied back’. Based on these observations, it appears unlikely that a general route to pyridones from ketimines could be realised using a methyleneaziridine MCR.

![Figure 3.1. Steric clashing in the synthesis of pyridones from ketimines.](image)

### 3.3 Conclusion

Experiments to ascertain if a MCR route to pyridones \textit{via} an imino Diels-Alder reaction from methyleneaziridines have met with failure. Model studies indicated that acyclic ketimines that would be used as intermediates in these reactions are poor substrates for imino Diels-Alder reactions. Although the steric clashing could be reduced with the use of small $N$-substituents (e.g. Me group), this would lead to $N$-methyl pyridones of limited synthetic value. In light of these findings, this chemistry was not pursued further.
Chapter 4:
Towards *in situ* 

\textit{N}-Functionalisation of 

Methyleneaziridines
4.1 Introduction

Methyleneaziridines have been shown to be useful building blocks for a range of chemical transformations (Section 1.3). To date, studies have been limited by the fact that electron withdrawing substituents on the methyleneaziridine nitrogen atom cannot be obtained.\textsuperscript{10} The presence of an electron withdrawing group would lower the basicity of methyleneaziridine nitrogen and increase the polarisation of the C–N bond when compared to traditional $N$-alkyl derivatives. It could be envisioned that the changes in physical properties would lead to greater reactivity of these strained heterocycles. For example, compound 199 might allow: (i) dialkylation at the C-3 position; (ii) ring-opening without Lewis acid activation; and (iii) new palladium catalysed chemistry leading to heterocycles and carbocycles via $\pi$-allyl palladium intermediates (Scheme 4.1).

As such they would greatly increase the potential of methyleneaziridines in chemical synthesis.

![Scheme 4.1. Synthetic potential of electron withdrawing $N$-substituents.](image-url)
Previously, Shipman and co-workers attempted to generate methyleneaziridines featuring electron withdrawing N-substituents via the ring closure of the corresponding 2-bromoallylamines using standard methodology. When the ring-closure of N-tosyl \textbf{200a} and N-Boc \textbf{200b} derivatives was attempted with sodium amide (1.1 equiv.), starting amines were recovered unchanged. Using excess sodium amide (2.1 to 15 equiv.) led to clean conversion to the corresponding acetylenes \textbf{201} (Scheme 4.2).

![Scheme 4.2. Undesired generation of acetylenes.](image)

The increased acidity of the NH within \textbf{200} means that these vinyl bromides would become irreversibly deprotonated to generate the corresponding sodium anions \textbf{202} rather than ring-close to methyleneaziridines \textbf{203}. Further competitive E2 elimination accounts for the formation of acetylenes which would be of lower nucleophilicity than the corresponding anions when R = alkyl. From these results, it can be concluded that the use of Pollard and Parcell’s methodology to methyleneaziridines\textsuperscript{2} is not suitable for the direct synthesis of methyleneaziridines possessing electron-withdrawing groups on nitrogen.

Recently, Shipman and Cariou explored an alternative approach based upon a Horner-Wadsworth-Emmons\textsuperscript{136} type strategy.\textsuperscript{137} Aziridine \textbf{204} (made in three
steps from the corresponding vinyl phosphonate) when treated with potassium hydride and benzaldehyde yielded the corresponding methyleneaziridine 205 in a modest yield as a single geometric isomer (Scheme 4.3). The structure of this derivative has been confirmed by X-ray crystallography. Whilst these results are encouraging, the length of this sequence, and low yields led us to consider alternate strategies.

Scheme 4.3. Attempted synthesis of methyleneaziridines via a HWE protocol.

A new strategy to methyleneaziridines possessing N-substitution with electron withdrawing groups was imagined in which 2-methyleneaziridine (206) or its isomer 2-methylazirine (207) might be N-acylated or sulfonated (Scheme 4.4).

Scheme 4.4. Proposed in situ alkylation to N-substituted methyleneaziridines

Goumans et al., during their studies into the endo/ exo preferences for double bonds in three-membered rings, calculated using Gaussian 98 that azirine 207 would be more stable than methyleneaziridine 206 by 8.6 kcal mol\(^{-1}\).\(^{138}\) They showed that the preference for exo- vs. endocyclic unsaturation in three-membered heterocycles is dependant on the heteroatom in the ring. Relative ring-strain and the nature of the substituent enabling tautomerisation
were shown to be the two major factors that determine whether substituted three-membered rings prefer \textit{exo}- or \textit{endo}-cyclic unsaturation.

Hassner \textit{et al.} reported the synthesis of 2-methylazirine (207) from $\alpha$-halo ketoximes via oxazaphospholes.\textsuperscript{139} They showed that 207 could be accessed in four chemical steps from chloroacetone 36. This ketone was converted to oxime phosphonium salt 208, which was cyclised to oxazaphosphole 209. Subsequent pyrolysis was found to give azirine 207 (Scheme 4.5).

Scheme 4.5. Synthesis of 2-methylazirine.

2-Methylazirine (207) was reported to be unstable and underwent rapid decomposition on standing at room temperature. Moreover, the length of this route made it somewhat unattractive for the synthesis of methyleneaziridines bearing electron-withdrawing $N$-substituents.
4.2 Attempted in situ functionalisation to 2-methyleneaziridines

As an alternative, we considered generating N-functionalised methyleneaziridines in situ from 2-methyleneaziridine (206). It was thought that 206 could be accessed from the ring-closure of N-(2-bromoallyl)-amine (210) upon treatment with sodium amide in liquid ammonia (Scheme 4.6).

\[
\begin{array}{c}
\text{Br} & \text{NH}_2 \\
210 & \rightarrow \\
\text{NaNH}_2 & \text{EWG} \\
\text{H} & \text{N} \\
206 & \leftrightarrow \\
\text{N} & \text{EWG-X} \\
207 & \\
199
\end{array}
\]


In order to explore the approach outlined above it was required to synthesise vinyl bromide 210. This was achieved according to the procedure first described by Bottini et al.\(^{140}\) Reaction of 2,3-dibromopropene 211 with hexamethylenetetramine under reflux led to quaternary ammonium salt 212 which was subjected to acid hydrolysis to give 210 after distillation (Scheme 4.7).

\[
\begin{array}{c}
\text{Br} & \text{Br} & \text{NH}_2 \\
210 & \rightarrow \\
\text{C}_6\text{H}_{12}\text{N}_4 & \text{CHCl}_3, \text{reflux}, 4 \text{ h} \\
211 & \rightarrow \\
\text{HCl, H}_2\text{O} & \text{EtOH, rt, } 48 \text{ h} \\
63\% (\text{lit. } 72\%^{140}) \\
212 & \rightarrow \\
210
\end{array}
\]

Scheme 4.7. Synthesis of N-(2-bromoallyl)-amine.

Next, we investigated whether 2-methyleneaziridine (206) could be generated from the ring-closure of 210. To this end, 210 was reacted with sodium amide in liquid ammonia and the reaction quenched with deuterium oxide so the products
of the reaction could be observed directly by NMR spectroscopy (Scheme 4.8). It was thought that 206 could be water soluble and would possess a low boiling point (ca. 2-methylazirine 42 °C at 1 atm) making isolation potentially difficult. The organic soluble extract was also obtained by partitioning between D$_2$O/CDCl$_3$. Through a series of experiments, the molar equivalents of NaNH$_2$, the time and temperature of the reaction were varied. The reactions were followed by $^1$H NMR spectroscopy and the results summarised in Table 4.1.


<table>
<thead>
<tr>
<th>Entry</th>
<th>Na (equiv.)</th>
<th>Time (min)</th>
<th>Temperature (°C)</th>
<th>Product Ratio$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D$_2$O</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>210</td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
<td>10</td>
<td>–33</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>60</td>
<td>–33</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>60</td>
<td>–78</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>120</td>
<td>–33</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>360</td>
<td>–33</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>60</td>
<td>–33</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>60</td>
<td>–33</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>120</td>
<td>–33</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>60</td>
<td>–33</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Product ratios calculated via $^1$H NMR spectroscopy.

Table 4.1
At low molar quantities of sodium amide, only unconsumed \(N\)-(2-bromoallyl)-amine (210) or acetylene\(^{141}\) 213 were observed (Entries 1, 2, 4 to 6). However, running the reaction at –78 °C (Entry 3) a new product 214 was observed in a low ratio compared to acetylene 213. Using a five-fold excess of sodium amide for an hour, product 214 was again observed (Entry 7). Increasing the reaction time to two hours led to full consumption of 210 with just 213 and 214 detected by \(^1\)H NMR spectroscopy (Entry 8). Using a six-fold excess of sodium amide for one hour led again to full consumption of 210 with the product ratio favouring 214 over 213 as judged by \(^1\)H NMR spectroscopy (Entry 9).

In order to determine the structure of 214, the possible products of the reaction of \(N\)-(2-bromoallyl)-amine (210) with sodium amide were considered. The reaction (Scheme 4.8) was designed to lead to either methyleneaziridine 206 or azirine 204. However, comparison of the signals observed by \(^1\)H and \(^{13}\)C NMR spectroscopy did not match those reported for 207 or for methyleneaziridine 50, (Table 4.2) and we can conclude that neither 206 nor 207 had been generated.
Alternatively, 206 or 207 may have been generated then reacted with the ammonia or deuterium oxide used to quench the reaction. Azirines are well known to undergo reactions with nucleophiles at the highly electrophilic $sp^2$ hybridised carbon to generate aziridines. Consequently, aziridines formed in this process could be susceptible to further ring-opening reactions. Hence, 2-methylazirine (207) could undergo nucleophilic addition with NH$_3$ or D$_2$O to aziridine 215. Subsequent ring-opening would lead to the corresponding imine 216 or ketone. Ketone-like products were ruled out due to the absence of signals around 200 ppm in the $^{13}$C NMR spectra. It was thought that the observed signal of 167.5 ppm was more indicative of an imine than a ketone. It was also

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Structure</th>
<th>$\delta_H$ (CDCl$_3$)</th>
<th>$\delta_C$ (CDCl$_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>214</td>
<td>-</td>
<td>3.99 (2H), 2.00 (3H)</td>
<td>167.5 (C/CH$_2$), 52.1 (C/CH$_2$), 24.3 (CH/CH$_3$)</td>
</tr>
<tr>
<td>2</td>
<td>207</td>
<td>$^\text{N}$</td>
<td>2.50 (3H), 1.35 (2H)$^{139}$</td>
<td>-$^a$ 137.0 (C),</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>$^\text{Bn}$</td>
<td>4.72 (2H), 2.06 (2H)$^9$</td>
<td>83.5 (=CH$_2$), 30.6 (ring CH$_2$)$^9$</td>
</tr>
<tr>
<td>4</td>
<td>219</td>
<td>$^\text{N}$</td>
<td>3.35 (4H), 2.15 (6H)$^{142}$</td>
<td>45.8 (CH$_2$), 24.0 (CH$_3$)$^{142}$</td>
</tr>
</tbody>
</table>

$^{13}$C NMR data for 207 was not reported.$^{139}$

Table 4.2
postulated that imine 216 could be accessed via ring-opening of methyleneaziridine 206 to enamine 217 and subsequent tautomerisation. Imine 216 was also considered to be able to dimerise to form cyclic diimine 218 via loss of ammonia (Scheme 4.9). As such cyclic diimine 219 (Table 4.2) was considered to be a suitable reference structure for 218. Azirine tautomer 220 was also considered, however, this structure was considered not to fit with the NMR data obtained. Azirine products of type 220 were also discounted as the $^{13}$C NMR spectrum does not appear to fit this type of structure.$^{146}$

![Scheme 4.9. Postulated reaction pathways for imine formation.](image)

Whilst structures 216 and 218 bear reasonable resemblance to 214, there are still considerable discrepancies on comparing the observed data to known analogues (Table 4.2). As such, it is difficult to determine the identity of 214, although the
presence of a peak at 167.5 ppm in the $^{13}$C NMR spectra seems to indicate an imine-type system is present. Therefore, it is tentatively concluded that attempted ring-closure of $N$-(2-bromoallyl)-amine (210) led to the generation of either imine 216 or cyclic diimine 218 (Figure 4.1).

![Figure 4.1. Tentatively proposed imine products.](image)

To try and confirm the product structure of 214, vinyl bromide 210 was again subjected to ring-closure with sodium amide (6 equiv.) in liquid ammonia. After one hour, the mixture was quenched with deuterium oxide and CDCl$_3$ was added. $p$-Toluenesulfonyl chloride (1.1 equiv.) and pyridine (1.1 equiv.) were added to the reaction mixture and stirred for 48 hours. However, only sulphonamide$^{147}$ 201a and tosic acid could be identified via $^1$H NMR spectroscopy in both the organic and aqueous phases (Scheme 4.10).

![Scheme 4.10. Attempted in situ tosylation.](image)

In a second experiment benzyl bromide was used. Again 210 was treated with sodium amide (6 equiv.) in liquid ammonia. After one hour diethyl ether was added and the ammonia left to evaporate. The reaction mixture was re-dissolved in THF and benzyl bromide (6 equiv.) added. Unfortunately, no identifiable
products could be deduced *via* $^1$H NMR or mass spectroscopy after aqueous work-up.

4.3 Conclusion

Attempts to form methyleneaziridines *via* the *in situ* functionalisation of 2-methyleneaziridine have proven fruitless. Ring-closure of $N$-(2-bromoallyl)-amine (210) led to acetylene 213 and a second product tentatively assigned to being either imine 216 or diimine 218. However, further experiments to derivatise this product for identification were unsuccessful.

Despite the failure of forming methyleneaziridines by this approach, further work aimed at making derivatives bearing electron-withdrawing groups is merited.
Chapter 5:

Synthesis of 1,1-Disubstituted Tetrahydro-β-carbolines
5.1 Introduction to Tetrahydro-β-carbolines

The tetrahydro-β-carboline (THBC) nucleus is an important motif in many biologically active natural alkaloids.\(^{148}\) Examples such as harmicine \(^{221}\)\(^{149}\) fumitremorgin C\(^ {150}\) \(^{222}\) and haploscleridamine\(^ {151}\) \(^{223}\) (Figure 5.1) have been shown to possess anti-leishmania, cytostatic and enzyme inhibitory activities respectively. It is well understood that THBCs have strong neurological effects within the mammalian brain, especially as a competitive binder for dopamine receptors.\(^ {152}\) Studies have also reported the \textit{in vitro} and \textit{in vivo} formation of THBCs within brain and other tissue cells.\(^ {153}\)

![Figure 5.1. Selected β-carboline containing natural products.](image)

Consequently, THBCs are also important structures in drug discovery,\(^ {154}\) and this heterocycle appears in approved drugs such as Tadalafil,\(^ {155}\) which is prescribed in the treatment of male erectile dysfunction (Figure 5.2). β-Carbolines have been found in many foods, and it has been postulated that they are important in the prevention of diseases associated with oxidative damage.\(^ {156}\)
5.2 Synthesis of Tetrahydro-β-carbolines

5.2.1 The Pictet-Spengler cyclisation

Due to their substantial biological activity and natural occurrence, THBCs are important targets for chemical synthesis. The most common approach to this tricyclic core is by way of the Pictet-Spengler reaction. This reaction has been the subject of a number of reviews and as such only highlights are discussed herein.

The Pictet-Spengler cyclisation involves the condensation of an aldehyde or ketone with a β-arylethylamine, typically under Brönsted or Lewis acid catalysis, to give an electrophilic iminium ion, which undergoes electrophilic aromatic substitution. This reaction was first reported in 1911 by Pictet and Spengler in their synthesis of tetrahydroisoquinolines from phenethylamine and aldehydes under acidic conditions. (Scheme 5.1).158

\[
\begin{align*}
  \text{Scheme 5.1. Pictet and Spengler’s synthesis of tetrahydroisoquinolines.}
\end{align*}
\]
In 1928, Tatsui adopted this methodology in the first reported synthesis of tetrahydro-β-carboline 226, from the acid catalysed condensation of tryptamine (227a) and acetaldehyde (Scheme 5.2).\textsuperscript{159}

![Scheme 5.2. Tatsui’s synthesis of tetrahydro-β-carbolines.](image)

The precise mechanism of the synthesis of THBCs has yet to be fully defined, although it is widely accepted that it proceeds through a spirol-indolenine intermediate 228,\textsuperscript{160} which collapses to form the carboline (Scheme 5.3). However, direct attack at C-2 of the indole by reactive electrophiles has been reported\textsuperscript{161} and the rearrangement from 228 to 229 has been calculated to be energetically unfavourable.\textsuperscript{162}

![Scheme 5.3. Accepted mechanism of the Pictet-Spengler cyclisation.](image)

Bailey obtained evidence for the spirol-indolenine intermediate through deuterium labelling studies (Scheme 5.4).\textsuperscript{163} It was found via NMR and mass
spectroscopy studies that reaction of indolic hydrazine 230 with isotopically enriched formaldehyde gave a roughly equal mixture of 231, 232, 233, and 234. This statistical mixing is consistent with an equilibrium between a spiro intermediate and reversible imine formation/hydrolysis. The cyclisation to the 2,3-dimethyl-1,2,3,4-tetrahydro-3-aza-β-carboline was shown to be slow compared with these processes.

Scheme 5.4. Mechanistic study into the Pictet-Spengler cyclisation.

5.2.2 Stereocontrol in Pictet-Spengler cyclisations

In 1981, Ungemach et al. reported the stereospecific synthesis of trans-1,3-disubstituted THBCs.\textsuperscript{164} \textit{N}-BenzyItryptophan methyl ester (235) was condensed with aldehydes in a stereospecific fashion. Catalytic hydrogenation of \textit{N}-benzyl derivatives 236 gave \textit{trans}-β-carbolines 237 in good yields and high selectivities (Scheme 5.5).
The stereochemical preference in this cyclisation was rationalised by examination of the likely transition states. When the 1- and 3-substituents lie cis there would be appreciable 1,3-interactions between the R and ester groups in transition state cis-238. However, when the substituents adopt the low energy trans transition state, trans-238, the 1,3-interactions are greatly reduced, giving rise to a faster rate of reaction (Scheme 5.6).

Further, Ungemach and co-workers considered whether attack of the iminium occurred from C-2 or C-3 of the indole double bond. Attack through C-3 was
postulated to proceed through spiroindolenine intermediate 239. Attack of the
top face of the iminium double bond in *trans*-238 would result in
spiroindolenine 239a with the substituents ecoming eclipsed and hence more
crowded. Attack of the bottom face would proceed via 239b which would result
in far less steric crowding, favouring the formation of *trans*-236.

![Figure 5.3. Consideration of attack from C-3 of indole double bond.](image)

When considering direct electrophilic attack from C-2 of the indole double bond
of the top face of the iminium double bond in *trans*-238, Ungemach postulated
that carbocation 240a would result. This carbocation would feature equatorial
C-1 and C-3 substituents but also a disfavoured axial N-2 substituent. Moreover,
240a would suffer from unfavourable A\textsubscript{1,2} strain between the equatorial C-1
substituent and the indole NH. Carbocation 240b, resulting from attack of the
bottom face of the iminium double bond, would have the N-2 substituent occupy
a favoured equatorial position. Further, an axial C-1 substituent would result in
reduced A\textsubscript{1,2} strain, thus 240b would be the more stable cation intermediate.

![Figure 5.4. Consideration of attack from C-2 of indole double bond.](image)
Bailey et al. also reported complete stereochemical control in Pictet-Spengler cyclisations to 1,3-disubstituted THBCs.\textsuperscript{165} For example, in the acid catalysed condensation of tryptophan methyl ester (241) with benzaldehyde they showed that solvent and temperature effects have a profound effect on the stereochemical course of the reaction. In benzene under reflux, the \textit{trans}-isomer of 242 is formed preferentially, whereas in dichloromethane at 0 °C, the \textit{cis}-isomer is favoured (Scheme 5.7).

\textbf{Scheme 5.7.} Stereochemical control in the Pictet-Spengler cyclisation.

Bailey et al. have provided an explanation for these observations.\textsuperscript{160b} At high temperatures the reaction is reversible and a slight preference for the \textit{trans} isomer is noted. However, at low temperatures the reaction can be considered to be under kinetic control, with the C-1 and C-3 substituents adopting equatorial orientations to minimise 1,3-diaxial interactions in the transition state (Figure 5.5).

\textbf{Figure 5.5.} Preference for \textit{cis} configuration under kinetic control.
5.2.3 Intramolecular allylic alkylation

In 2005, Bandini et al. reported the first enantioselective metallo-catalysed synthesis of THBCs 238 and tetrahydro-γ-carbolines (Scheme 5.8).\textsuperscript{166} This was achieved by palladium-catalysed intramolecular allylic alkylation of indolyl carbonates 239 with DPPBA-based Trost’s\textsuperscript{167} ligand 240.

\[ \text{R} = \text{H, Me, OMe, Cl, pyrrole} \]
\[ \text{R}^1 = \text{H, Me} \]
\[ \text{R}^2 = \text{H, Me} \]

Scheme 5.8. Bandini’s metallo-catalysed synthesis of THBCs.

5.2.4 Synthesis of 1,1-disubstituted tetrahydro-β-carbolines

The Pictet-Spengler reaction works well with aldehydes and activated ketones but is slow and low yielding with simple ketones. In the latter case, it is assumed that steric and electronic factors slow the rate of iminium ion formation, and make it less reactive towards further cyclisation. As such, the synthesis of THBCs from tryptamines by this approach is generally inefficient and examples in the literature are sparse. For example, Hester reported the synthesis of THBC 246 in a two step synthesis from tryptamine (227a) and acetone under acidic conditions (Scheme 5.9).\textsuperscript{168} However, this process is rather inefficient.
The first significant advance came in 2003, when Horiguchi et al. reported the use of titanium (IV) isopropoxide as iminating agent for the generation of indole functionalised ketimines. Further cyclisation promoted by TFA led to simple 1,1-disubstituted THBCs (Scheme 5.10).

Very recently, Lingam et al. showed that molecular iodine in ethanol can act as an effective catalyst for the formation of 1,1-disubstituted THBCs from simple, unactivated ketones (Scheme 5.11).

**Scheme 5.9.** Synthesis of 1,1-disubstituted THBCs with POCl₃.

**Scheme 5.10.** Horiguchi’s synthesis of simple 1,1-disubstituted THBCs.

**Scheme 5.11.** Lingam’s conditions utilising I₂.
5.3 Attempted 3-CR to 1,1-Disubstituted β-Carbolines

As one of the key intermediates in the synthesis of THBCs is an imine, it was imagined that methyleneaziridine MCR methodology (Section 1.3.8) could be used to produce 1,1-disubstituted THBCs. Nucleophilic ring-opening of an indole functionalised methyleneaziridine 249a, followed by quenching with an electrophile would give indole imine 250. Subsequent electrophilic cyclisation would be expected to yield 1,1-disubstituted THBC 251 (Scheme 5.12). As well as providing a route to a diverse set of THBCs in ‘one-pot’, a key advantage of this strategy is that it circumvents the need to make the ketimine in a traditional condensation, a process believed to be difficult (Section 5.2.4).

Scheme 5.12. Proposed formation of THBCs via a 3-CR.

5.3.1 Synthesis of indole tethered methyleneaziridines

To explore this idea, a range of indole substituted methyleneaziridines were required. Previous research within the group by Jason Shiers had established that indole functionalised methyleneaziridine 249a could be prepared in two steps from tryptamine (227a) via vinyl bromide 252a. This sequence was readily reproduced in my hands with comparable yields. Alkylation of tryptamine (227a) with 2,3-dibromopropene (2 equiv.) gave vinyl bromide 252a in 93% yield. Ring closure using sodium amide (3.5 equiv.) in liquid ammonia at –33 °C afforded known methyleneaziridine 249a in 88% yield after
Chapter 5

bulb-to-bulb distillation. Three novel derivatives were made using the same general approach. Thus, methoxy-derivative \(249b\) was prepared from 5-methoxytryptamine (\(227b\)) in 85% overall yield using the same sequence. Similarly, \(249c\) was made in 62% overall yield from \(N\)-2-(1-methyl-1\(H\)-indol-3-yl)ethylamine\(^{171}\) (\(227c\)) and \(249d\) was synthesised from (±)-\(\alpha\)-methyl-tryptamine (\(227d\)) in 92% overall yield (Scheme 5.13).

\[
\begin{align*}
\text{X} & \quad \text{R}^1 \\
\text{227a-d} & \\
\text{CH}_2\text{C(\(\text{Br}\))CH}_2\text{Br, K}_2\text{CO}_3 & \quad \text{THF, rt, 48 h} \\
\text{252a} & : 93\% \quad \text{(lit. 94\%)} \\
\text{252b} & : 98\% \\
\text{252c} & : 88\% \\
\text{252d} & : 98\% \\
\end{align*}
\]

\[
\begin{align*}
\text{249a} & : 88\% \quad \text{(lit. 87\%)} \\
\text{249b} & : 87\% \\
\text{249c} & : 70\% \\
\text{249d} & : 94\% \\
\end{align*}
\]

\(\text{a R} = \text{H, R}^1 = \text{H, X} = \text{H}; \quad \text{b R} = \text{H, R}^1 = \text{H, X} = \text{OMe} \)

\(\text{c R} = \text{Me, R}^1 = \text{H, X} = \text{H}; \quad \text{d R} = \text{H, R}^1 = \text{Me, X} = \text{H} \)

**Scheme 5.13.** Synthesis of indole tethered methyleneaziridines.

It is known that primary amines can be converted to methyleneaziridines bearing a \textit{gem}-dimethyl substituent on the exocyclic double bond.\(^{32}\) Thus, we attempted to construct an indole tethered substrate of this type. Dibromocyclopropane \(8\) was synthesised according to known methods from isobutylene (\(253\)) in 71% yield.\(^{172}\) This cyclopropane was converted to vinyl bromide \(254\) by reaction with tryptamine (\(227a\)) and K\(_2\)CO\(_3\) in 1,2-dichlorobenzene at 170 °C for 48 hours. After work-up and purification, \(254\) was isolated in 59% yield. Unfortunately,
attempted aziridination of 254 under the standard conditions failed to furnish 255 (Scheme 5.14).

![Diagram of Scheme 5.14]

**Scheme 5.14.** Attempted synthesis of gem-di-methyl methyleneaziridine.

### 5.3.2 Initial model reactions

Methyleneaziridine 249a has been shown to be a suitable substrate for the formation of 1,3-disubstituted propanone 256 (Scheme 5.15).

![Diagram of Scheme 5.15]

**Scheme 5.15.** Successful formation of 1,3-disubstituted propanones.

However, the use of 249a in a modified MCR failed to yield any of the desired 1,1-disubstituted THBC 257 using trifluoroacetic acid 169 to induce the final cyclisation (Scheme 5.16).
Initially, it was thought that the free indole nitrogen might undergo deprotonation/alkylation under the reaction conditions, giving a more hindered indole which might be unable to cyclise. To test this idea, methyleneaziridine 249a was N-Boc protected to give derivative 258. Unfortunately, the use of 258 in a simple amine forming MCR failed to produce 259 (Scheme 5.17).\textsuperscript{18}

Of course the tert-butyl carbamate protecting group might be unstable to the acidic conditions, leading to deprotection of the indole nitrogen. As such, a different protecting strategy was sought. \textit{N}-Methyl derivative 249c was chosen.

Initially we needed to establish whether methyleneaziridine 249c was a suitable substrate for MCRs. To this, 249c was reacted with \textit{n}-butylmagnesium chloride (2.5 equiv.), benzyl chloride (1.5 equiv.) and sodium borohydride (3 equiv.). After work-up and purification, 260 was obtained in 69\% yield (Scheme 5.18).
Having established that methyleneaziridine 249c could be used in MCRs, we next sought appropriate conditions for Pictet-Spengler cyclisation. As stated earlier, there are a wide range of conditions available for the synthesis of THBCs. However a large majority of cyclisations are conducted using trifluoroacetic acid, in a non-polar solvent such as dichloromethane.\(^{173}\) However, all earlier attempts at using these types of conditions in our chemistry in the presence of tetrahydrofuran had failed. It is a requirement of our MCR methodology that these reactions are performed in tetrahydrofuran.

In order to test new conditions, imine 261 was made as a substrate for model cyclisations. Hester had synthesised indole functionalised imines by the condensation reaction of acetone and tryptamine (227a) in refluxing benzene in the presence of \( p \)-toluenesulfonic acid, to give 3-(2-isopropylideneaminoethyl)indole (261).\(^{168}\) In our hands, using toluene as solvent, this chemistry provided 261 in 45\% yield (lit. 64\%\(^{168}\) in benzene) (Scheme 2.19).

\[ \text{Scheme 5.18. Amine formation from indole functionalised aziridine.} \]

\[ \text{Scheme 5.19. Synthesis of indole tethered ketimines.} \]
We also attempted to synthesise imine 262, as it would more closely resemble the imines resulting from the MCR. Tryptamine (227a), 4-heptanone and catalytic $p$-TSA were refluxed in toluene with azeotropic distillation of water. Surprisingly, this reaction failed to yield the expected product. The poor solubility of 4-heptanone in toluene may explain this outcome (Scheme 5.20).

**Scheme 5.20.** Attempted synthesis of an indole functionalised imine.

Imine 261 was subjected to various literature cyclisation conditions $^{168,170,174,175,176}$ for the formation of carboline 246. The reactions were performed in the presence of tetrahydrofuran to see which conditions would be most suitable for our chemistry (Scheme 5.21). The results of these experiments are summarised in Table 5.1.
Scheme 5.21. Pictet-Spengler cyclisation of 261.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activator</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>POCl\textsubscript{3}\textsuperscript{168}</td>
<td>THF</td>
<td>Reflux</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Sc(OTf)\textsubscript{3}\textsuperscript{174}</td>
<td>THF</td>
<td>Reflux</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>B(Bu)\textsubscript{3}\textsuperscript{175}</td>
<td>THF</td>
<td>–78 °C</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>c. H\textsubscript{2}SO\textsubscript{4}\textsuperscript{176}</td>
<td>MeOH/THF</td>
<td>0 °C</td>
<td>91%</td>
</tr>
<tr>
<td>5</td>
<td>I\textsubscript{2}\textsuperscript{170}</td>
<td>EtOH/THF</td>
<td>Rt</td>
<td>56%</td>
</tr>
</tbody>
</table>

Table 5.1.

The most suitable conditions were identified as I\textsubscript{2} in ethanol/tetrahydrofuran (Entry 5) and concentrated sulphuric acid in methanol/tetrahydrofuran (Entry 4), with the latter conditions being very high yielding. Knowing that ketimine Pictet-Spengler cyclisations could be achieved, and that methyleneaziridine 249c was a suitable substrate for MCRs, we now set about combining these ideas to effect a MCR approach to THBCs.

As an initial test, Lingam’s\textsuperscript{170} cyclisation conditions of I\textsubscript{2} in EtOH were applied to the MCR. These conditions were chosen initially as they were considered to be milder than concentrated sulphuric acid in methanol.\textsuperscript{176} Methyleneaziridine 249c in tetrahydrofuran was ring-opened with ethylmagnesium chloride in the presence of copper (I) iodide (20 mol%) at –30 °C using standard conditions. After subsequent metalloenamine alkylation with benzyl bromide, the reaction
mixture was treated with I$_2$ in ethanol (final THF/EtOH = 1:1) and stirred at room temperature overnight. However, after work-up, 263 not was identified in the crude reaction mixture by $^1$H NMR or mass spectroscopy (Scheme 5.22).

![Scheme 5.22. Attempted MCR utilising I$_2$.](image)

Using the conditions of Rodríguez,$^{176}$ methyleneaziridine 249c was reacted with $n$-butylmagnesium chloride, copper (I) iodide (20 mol%) and benzyl chloride as described above. Treatment with methanol and concentrated sulphuric acid at 0 °C with subsequent warming to room temperature, again after work-up, failed to produce β-carboline 264 (Scheme 2.53).

![Scheme 5.23. Unsuccessful acid activated Pictet-Spengler MCR.](image)

The Pictet-Spengler step (3) was repeated at reflux, however, no product 264 was detected. We reasoned that imine 265 formed in this MCR may be too sterically hindered to undergo the electrophilic cyclisation. Thus, a simplified two-component sequence was attempted. Methyleneaziridine 249c was reacted
with $n$-butylmagnesium chloride and copper (I) iodide (20 mol%), under the conditions described above. Direct treatment with methanol and concentrated sulfuric acid again failed to produce β-carboline 266a (R = Bu) (Scheme 5.24). Fearing that even the butyl chain may give rise to an imine which would still possess too much hindrance, a smaller Grignard reagent was used. Thus, methylmagnesium chloride was employed under the same conditions. However, only a trace amount of THBC 266b (R = Me) was identified in the crude reaction mixture by $^1$H NMR and mass spectroscopy.

**Scheme 5.24.** Attempted 2 component Pictet-Spengler reactions.

These reactions may have failed for a number of reasons. Firstly it is known that Pictet-Spengler reactions involving ketimines are hard to perform due to the increased steric hindrance around the imine. Also, tetrahydrofuran is not an ideal solvent due to its slight basicity. This could lead to the acid promoters reacting with the solvent in preference to the substrates. Other complicating issues include the presence of magnesium and copper salts in the reaction mixture, which may have a detrimental effect upon the cyclisation. These salts have been shown to be unfavourable in other multi-component reactions.
5.4 Synthesis of 1,1-Disubstituted β-Carbolines

It is known that BF$_3$:OEt$_2$ promotes nucleophilic attack at C-3 of the methyleneaziridine ring.$^{29a}$ The Shipman group has recently developed a synthetic procedure for opening methyleneaziridines with hetero-nucleophiles in the presence of BF$_3$:OEt$_2$ in dichloromethane.$^{178}$ It was postulated that ring-opening of methyleneaziridine 249a bearing an indole nucleus by a hetero-nucleophile (NuH = ROH, RSH, etc.) in presence of BF$_3$ could lead to iminium ion 267, which may undergo further cyclisation to 1,1-disubstituted THBCs 268 (Scheme 5.25)

![Scheme 5.25. Re-evaluated approach to THBCs.]

To test this idea, methyleneaziridine 249a was dissolved in dichloromethane, cooled to $-30$ °C and treated with BF$_3$:Et$_2$O (2 equiv.), followed by benzyl alcohol (3 equiv.). The reaction mixture was allowed to warm to room temperature and stirred overnight. After work-up and purification, we were delighted to isolate THBC 269a in 62% yield (Scheme 5.26).
Scheme 5.26. Successful synthesis of THBCs from methyleneaziridines.

Having successfully established the viability of forming THBCs from methyleneaziridines, we sought to optimise the reaction conditions. To this end, a series of reactions were performed using an equimolar quantity of BF$_3$-OEt$_2$ with variation in the amount of nucleophile (benzyl alcohol) used (Scheme 5.27). The results are summarised in Table 5.2, the yields presented are after work-up and purification.

From these results, we ascertained that using an equimolar quantity of BF$_3$-OEt$_2$, and 2 equivalents of benzyl alcohol were optimal. Using less benzyl alcohol (Entries 1 and 2), a side product 270, was isolated.
β-Carbol ine 269a was identified by a distinct quaternary carbon at 53.4 ppm in the $^{13}$C NMR spectrum and the presence of two AB systems (4.54, 4.50, 3.55 and 3.51 ppm) in the $^1$H NMR spectrum. These AB systems were readily assigned as the benzylic CH$_2$ and the CH$_2$ bonded to the quaternary carbon. An $m/z$ of 307 in the mass spectrum is consistent with the MH$^+$ ion of 269a. By-product 270 was assigned in a similar manner. $^{13}$C NMR spectroscopy revealed the distinct quaternary carbon at 53.4 ppm. $^1$H NMR spectroscopy showed a multiplet at 3.54-3.45 ppm for the two CH$_2$ groups either side of the oxygen, and an MH$^+$ ion ($m/z = 245$) in the mass spectrum.

We speculate that carbol ine 270 is formed by ring-opening of 249a, co-ordinated to a boron trifluoride anion, by ethanol and subsequent electrophilic cyclisation, the ethanol nucleophile being derived from BF$_3$:OEt$_2$. A plausible mechanism is that activated by the BF$_3$, the diethyl ether undergoes a transelecterification reaction, liberating ethanol and producing benzyl ethyl ether as by-product (Scheme 5.28).
Next, we examined whether solvent effects would further improve the reaction. A range of non-coordinating solvents were selected. All the reactions were conducted with an equimolar quantity of BF$_3$·OEt$_2$ and 2 equivalents of benzyl alcohol (Scheme 5.29). The results are summarised in Table 5.3.
Scheme 5.29. Solvent optimisation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield 269a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅CH₃</td>
<td>38%</td>
</tr>
<tr>
<td>3</td>
<td>ClCH₂CH₂Cl</td>
<td>44%</td>
</tr>
<tr>
<td>4</td>
<td>CHCl₃</td>
<td>32%</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>52%</td>
</tr>
</tbody>
</table>

Table 5.3.

Dichloromethane was established to be the ideal solvent for the reaction, the product 269a being isolated in 73% yield (Entry 1). The final optimisation experiments involved a brief screen of other acid activators, both Lewis and Brönsted, to gauge their effectiveness. The Brönsted acids chosen possessed non-nucleophilic counter-ions, to counter potential problems with them directly opening the methyleneaziridine. The reactions were all conducted in dichloromethane with an equimolar quantity of activator, and 2 molar equivalents of benzyl alcohol (Scheme 5.30). The results of these studies are described in Table 5.4.
Scheme 5.30. Screening of Lewis/Brönsted acids.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activator</th>
<th>Yield 269a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_3$-OEt$_2$</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>BF$_3$-THF</td>
<td>41%</td>
</tr>
<tr>
<td>3</td>
<td>BF$_3$-SMe$_2$</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Sc(OTf)$_3$</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>AlMe$_3$</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>TFA</td>
<td>28%</td>
</tr>
<tr>
<td>7</td>
<td>TCA</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>H$_2$SO$_4$</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>AcOH</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>CH$_3$SO$_3$H</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5.4.

Clearly, BF$_3$-OEt$_2$ was the best activator for the cyclisation (Entry 1). Lower conversions were observed with BF$_3$-THF and TFA (Entries 2 and 6). None of the other activators produced any of the desired product by $^1$H NMR or mass spectroscopy.

To summarise, the best conditions involved the use of equimolar amounts of methyleneaziridine and BF$_3$-OEt$_2$, with a two fold excess of the alcohol nucleophile in dichloromethane.
5.4.1 Scope and limitations

A range of alcohol nucleophiles and methyleneaziridine substitution patterns were examined. These were all performed under the optimised reaction conditions developed above (Scheme 5.31). The results are summarised in Table 5.5.

![Scheme 5.31. Synthesis of 1,1-disubstituted tetrahydro-β-carbolines.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aziridine</th>
<th>R</th>
<th>X</th>
<th>R¹OH</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>249a</td>
<td>H</td>
<td>H</td>
<td>BnOH</td>
<td>269a</td>
<td>73%</td>
</tr>
<tr>
<td>2</td>
<td>249a</td>
<td>H</td>
<td>H</td>
<td>nPrOH</td>
<td>269b</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>249a</td>
<td>H</td>
<td>H</td>
<td>'HexOH</td>
<td>269c</td>
<td>63%</td>
</tr>
<tr>
<td>4</td>
<td>249a</td>
<td>H</td>
<td>H</td>
<td>'BuOH</td>
<td>269d</td>
<td>58%</td>
</tr>
<tr>
<td>5</td>
<td>249a</td>
<td>H</td>
<td>H</td>
<td>H₂C=CHCH₂OH</td>
<td>269e</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>249a</td>
<td>H</td>
<td>H</td>
<td>HC=CH₂OH</td>
<td>269f</td>
<td>71%</td>
</tr>
<tr>
<td>7</td>
<td>249b</td>
<td>H</td>
<td>OMe</td>
<td>BnOH</td>
<td>269g</td>
<td>66%</td>
</tr>
<tr>
<td>8</td>
<td>249c</td>
<td>Me</td>
<td>H</td>
<td>BnOH</td>
<td>269h</td>
<td>43%</td>
</tr>
<tr>
<td>9</td>
<td>249c</td>
<td>Me</td>
<td>H</td>
<td>H₂C=CHCH₂OH</td>
<td>269i</td>
<td>37%</td>
</tr>
</tbody>
</table>

Table 5.5.

These reactions proceeded well in most cases (Entries 1 to 7), and yielded the desired THBC in moderate to very good yields. Substitution of the indole nitrogen leads to lower product yields (Entry 8 cf. Entry1). This observation is consistent with Kuo’s findings that increased steric congestion suppresses
Pictet-Spengler cyclisations. These results also indicate that the reaction is tolerant to additional functionalities contained within the alcohol or indole nucleus.

Sulfur based nucleophiles were also briefly investigated, however, reaction of thiophenol with methyleneaziridine 244a under the reactions conditions yielded none of THBC 266 (Scheme 5.32).

\[
\text{Scheme 5.32. Attempted use of sulfur based nucleophiles.}
\]

Since a new quaternary asymmetric centre is generated in the reaction, it was interesting to examine if any asymmetric induction could be achieved. Bailey et al. have shown that asymmetric induction is possible in the synthesis of 1,3-disubstituted THBCs from tryptophan methyl ester derivatives. Thus, we thought that the presence of a “chiral handle” in the 3-position of the cyclised ring might lead to some diastereoccontrol.

Gratifyingly, reaction of methyleneaziridine 229d with benzyl alcohol (2 equiv.) in the presence of BF₃·OEt₂ (1 equiv.) under the conditions previously described led to the isolation of 272 in 63% yield as a single diastereomer (Scheme 5.33).
Scheme 5.33. Stereoselective cyclisation to a 1,1,3-trisubstituted-β-carboline.

A further diastereomer was tentatively assigned (dr = 8:1) by analysis of the crude reaction mixture by $^1$H NMR spectroscopy. However, this second component could not be isolated. The relative stereochemistry of 272 was deduced by NOESY experiments. These showed a strong enhancement between the $CH_2OBn$ hydrogens and the methyl group at C-3, as well as between the methyl group at C-1 and H-3 (Figure 5.6).

Figure 5.6. Depiction of NOESY correlations.

These data are consistent with the formation of the cis-(1$R^*$,3$R^*$)-diastereomer depicted. The origin of this stereochemical outcome is difficult to rationalise. Bailey$^{160b}$ rationalised their observations concerning the reaction of tryptophan methyl ester derivatives with aldehydes, by suggesting that the cyclisation is under kinetic control with the alkyl substituents adopting the lower energy equatorial orientations, leading to the cis product (Section 5.2.2).
In the formation of 272, there is little difference in size between the C-1 substituents CH₃ and CH₂OBn. Thus, rationalising the preference for the CH₃ to be axial and the CH₂OBn to be equatorial is difficult, even if the reaction is considered to be under kinetic control (Figure 5.7).

**Figure 5.7.** Depiction of *cis* and *trans* conformations.

With an unknown rate determining step, it is difficult to explain the stereochemical outcome of the reaction. That said, the observation of the surprisingly high diastereomeric ratio was very gratifying.

At this juncture, it seemed sensible to re-evaluate our planned MCR approach to THBCs (Scheme 5.12). Having proven successful in the formation of THBCs from methyleneaziridines, BF₃·OEt₂ was used as an activator, given its known compatibility with tetrahydrofuran.²⁹a Methyleneaziridine 249c was reacted with ethylmagnesium bromide (3 equiv.), benzyl bromide (1.5 equiv.) and copper (I) iodide (20 mol%) under the conditions described earlier (Section 5.3.2). The reaction mixture was then cooled to −30 °C and a dichloromethane solution of BF₃·OEt₂ (1 equiv.) added (Scheme 5.34). Unfortunately, after work-up none of the desired product 263 was identified by ¹H NMR or mass spectroscopy.
Scheme 5.34. Attempted Pictet-Spengler MCR with BF$_3$-OEt$_2$ activation.

The reaction was repeated, as described above, but with the tetrahydrofuran removed and the residue re-dissolved in dichloromethane before addition of BF$_3$-OEt$_2$. Again, 263 was not observed.

These reactions probably failed due to steric hindrance around the ketimine centre$^{177}$ and the detrimental effects of the copper and magnesium salts present in the reaction.$^{18}$ Moreover, methyleneaziridine 249c has already been shown to be a poor substrate for the formation of THBCs as demonstrated with alcohol based nucleophiles (Table 5.5).

5.5 Attempted Synthesis of Tetrahydroisoquinolines

The Pictet-Spengler reaction was originally developed as a route to tetrahydroisoquinolines (THQs).$^{158}$ Thus, it was postulated that similar chemistry to that developed in Section 5.4.1 could be used to make THQs 268 by way of opening a suitable methyleneaziridine 269 with a nucleophile and Lewis acidic activation (Scheme 5.35).
In order to explore this idea, an appropriate methyleneaziridine, bearing an electron rich aromatic ring was required. Previous work by Jason Shiers had shown that methyleneaziridine 275 was available from commercially available 3,4-dimethoxyphenethylamine. Unfortunately, reaction of an existing sample of 275 with BF$_3$-OEt$_2$ (1 equiv.) and benzyl alcohol (2 equiv.) under the conditions used to prepare THBCs failed to yield any of the desired isoquinoline 276 (Scheme 5.36). Time constraints prevented us from further explaining the origin of this failure.

**Scheme 5.35.** Approach to tetrahydroisoquinolines from methyleneaziridines.

**Scheme 5.36.** Attempted synthesis of tetrahydroisoquinolines.
5.6 Conclusions

In summary, a new approach to 1,1-disubstituted tetrahydro-β-carbolines has been devised based on the Lewis acid promoted nucleophilic ring-opening of indole substituted methyleneaziridines, and subsequent in situ Pictet-Spengler cyclisation. This reaction was shown to be tolerant to functionalisation in the indole nucleus as well as the alcohol nucleophile (Scheme 5.31 and Table 5.5). Using this methodology, a surprisingly high degree of diastereocontrol can be achieved as demonstrated by the synthesis of 272 (Scheme 5.33). This work has recently been published.\textsuperscript{179}

Attempts to affect more general MCRs of indole substituted methyleneaziridines met with failure. The problems met during the development of this chemistry seem to arise primarily from the mismatch between reagents and solvents.

Methyleneaziridines bearing an indole functionality were required for these studies. It was gratifying to observe that the indole nucleus was tolerant to the harshly basic cyclisation conditions, and that the desired methyleneaziridines could be isolated in good yields (Scheme 5.15).

Attempts to broaden the methodology to the formation of tetrahydroisoquinolines was however unsuccessful. Methyleneaziridine 275 failed to yield the expected product under the reaction conditions developed for the Pictet-Spengler cyclisation.
Chapter 6:

Experimental
General Information

Anhydrous solvents were purchased in Sure/Seal™ bottles from Sigma-Aldrich. All other solvents and reagents were used as received or purified by standard protocols. Petroleum ether refers to the fraction of petroleum ether having a boiling point between 40-60 °C. All experiments were performed under an inert atmosphere and moisture sensitive reactions were performed in flame-dried or oven-dried glassware. Copper (I) iodide was re-purified prior to use.

Column chromatography was carried out using Matrex silica 60 unless otherwise stated. Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and were visualised using UV light and stained with potassium permanganate followed by heating.

Melting points were recorded on a Gallenkamp MPD350 apparatus and are reported uncorrected.

Infrared spectra were recorded on an Avatar 320 FT-IR or PerkinElmer Spectrum One FT-IR spectrometer with internal calibration.

$^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded at 300 MHz, 75 MHz and 121 MHz respectively on a Bruker DPX-300; at 400 MHz, 100 MHz and 161 MHz respectively on a Bruker DPX-400. Signals in the $^1$H and $^{13}$C NMR spectra are reported as singlets (s), doublets (d), triplets (t), etc, which refer to the observed spin-spin coupling patterns. Chemical shifts are quoted in ppm, downfield from TMS, with the residual solvent as internal standard. Coupling constants ($J$) are...
Chapter 6

reported in Hertz, as observed, not averaged. Ambiguous signals were assigned using COSY, HMQC and NOESY correlative spectra.

Low resolution mass spectra were recorded on an Esquire 2000 platform with electrospray ionisation. High resolution mass spectra were obtained using a Bruker MicroTOF instrument or from the EPSRC National Mass Spectrometry Service Centre, Swansea.

Microanalyses were performed by Warwick Analytical Services Ltd or MEDAC Ltd.
Diethyl [4-(benzylamino)heptan-4-yl]phosphonate (141)

To a stirred solution of 139 (500 mg, 2.46 mmol) in THF (1 mL) was added cadmium (II) iodide (45 mg, 0.12 mmol) and the mixture was stirred at room temperature. After 10 minutes diethyl phosphite (320 µL, 2.46 mmol) was added dropwise and the reaction mixture was heated to 45 °C for 1.5 h. After cooling to room temperature the solvent was removed in vacuo. Purification on silica gel (50% ethyl acetate in petroleum ether pre-treated with Et₃N) afforded 141 (705 mg, 84%) as a pale yellow oil. Rₜ = 0.36 (50% ethyl acetate in petroleum ether); vₘₐₓ (film) 2960, 1711, 1454, 1226, 1022 cm⁻¹; δₜ (400 MHz, CDCl₃) 7.37-7.21 (5H, m, Ar), 4.16 (4H, dt, J = 7.2, 14.7 Hz, 2 x OCH₂), 3.87 (2H, d, J = 2.6 Hz, NCH₂), 1.79-1.61 (4H, m, CH₂CCH₂), 1.55-1.39 (4H, m, 2 x CH₂CH₃), 1.34 (6H, t, J = 7.0 Hz, 2 x OCH₂CH₃), 0.92 (6H, t, J = 7.2 Hz, 2 x CH₂CH₃) ppm; δＣ NMR (100 MHz, CDCl₃) 141.3 (C, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 126.8 (CH, Ar), 61.9 (OCH₂, d, Jₜp = 7.6 Hz), 59.7 (C, d, Jₜp = 134.8 Hz), 47.3 (NCH₂, d, Jₜp = 2.9 Hz), 35.9 (CH₂, d, Jₜp = 4.2 Hz), 16.7 (CH₃, d, Jₜp = 5.6 Hz), 16.4 (CH₂, d, Jₜp = 5.6 Hz), 14.8 (CH₃) ppm; δp NMR (161 MHz, CDCl₃) 31.2 ppm; MS (ES⁺) m/z = 341.1 [MH⁺]; HRMS (ES⁺) m/z calcd for C₁₈H₃₂NNaO₃P [MNa⁺]: 364.2012; found: 364.2015.
Synthesis of $\alpha$-aminophosphonates from methyleneaziridines

**General Method 1:**

\[ \text{R}^1 \quad \text{N} \quad \text{R}^2 \quad \text{P(O)(OR)}_2 \quad \text{HN} \quad \text{R}^1 \quad \text{R}^2 \]

Re-purified Copper (I) iodide (20 mol%) in a round-bottomed flask was flame dried under vacuum and then purged with nitrogen (three cycles performed). THF (2 mL) was added and the mixture cooled to –30 °C, whereupon the Grignard reagent (2.5 equiv.) was added. After 10 min, methyleneaziridine 19, 50, or 142 (1 equiv.) in THF (1 mL) was added and the reaction mixture stirred at room temperature for 3 h. Upon cooling to 0 °C, the electrophile (1.5 equiv.) was added dropwise, and the mixture heated at 45 °C. After 3 h, the phosphite (2.5 equiv.) was added dropwise and heating continued at 45 °C overnight. Upon cooling to room temperature, the mixture was diluted with Et$_2$O (20 mL) and washed with a saturated aqueous solution of NH$_4$Cl (2 x 20 mL), 50% NaOH solution (2 x 20 mL) and brine (2 x 20 mL). The organic phase was dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification of the $\alpha$-aminophosphonate was achieved by column chromatography with silica pre-treated with Et$_3$N.
Diethyl [3-(benzylamino)-1-phenylhexan-3-yl]phosphonate (149a).

Methyleneaziridine 50 (102 mg, 0.70 mmol) was reacted with CuI (26 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 880 µL, 1.76 mmol), benzyl bromide (130 µL, 1.09 mmol) and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149a (185 mg, 65%) as a pale yellow oil. Rf = 0.37 (50% ethyl acetate in petroleum ether); νmax (film) 2958, 1603, 1453, 1230, 1049 cm⁻¹; δH (400 MHz, CDCl₃) 7.44-7.23 (10H, m, Ar), 4.24 (4H, dt, J = 7.6, 14.6 Hz, 2 x OCH₂), 3.97 (2H, s, NCH₂), 2.91-2.76 (2H, m, CH₂Ar), 2.13-1.99 (2H, m, CCH₂), 1.93-1.75 (2H, m, CCH₂), 1.62-1.55 (3H, m, CH₂ + NH), 1.41 (6H, t, J = 6.9 Hz, 2 x OCH₂CH₃), 1.01 (3H, t, J = 7.3 Hz, CH₂CH₃) ppm; δC (100 MHz, CDCl₃) 142.6 (C, Ar), 141.1 (C, Ar), 128.43 (CH, Ar), 128.41 (CH, Ar), 128.40 (CH, Ar), 128.2 (CH, Ar), 126.9 (CH, Ar), 125.8 (CH, Ar), 61.7 (OCH₂, d, JCP = 7.6 Hz), 59.7 (C, d, JCP = 135.7 Hz), 47.6 (NCH₂, d, JCP = 2.8 Hz), 35.9 (CH₂, d, JCP = 4.0 Hz), 35.8 (CH₂, d, JCP = 4.4 Hz), 29.7 (CH₂, d, JCP = 5.4 Hz), 16.7 (CH₃, d, JCP = 5.6 Hz), 16.5 (CH₂, d, JCP = 7.6 Hz), 14.7 (CH₃) ppm; δP (161 MHz, CDCl₃) 30.6 ppm; MS (ES⁺) m/z 404 [MH⁺]; HRMS (ES⁺) calcd for C₂₃H₃₅NO₃P [MH⁺]: 404.2349; found: 404.2345.
Diethyl [3-(cyclohexylamino)-1-phenylhexan-3-yl]phosphonate (149b).

Methyleneaziridine 142 (104 mg, 0.76 mmol) was reacted with CuI (29 mg, 0.15 mmol), ethylmagnesium chloride (2M in THF, 950 µL, 1.90 mmol), benzyl bromide (140 µL, 1.18 mmol) and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149b (171 mg, 57%) as a pale yellow oil. Rf = 0.47 (50% ethyl acetate in petroleum ether); v_max (film) 2972, 1602, 1449, 1230, 1021 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.30-7.16 (5H, m, Ar), 4.14 (4H, dt, J = 7.2, 14.4 Hz, 2 x OCH₂), 2.91-2.67 (3H, m, CH₂Ar + CH), 2.05-1.46 (12H, m, 5 x CH₂ + NH + CHH), 1.33 (6H, t, J = 7.1 Hz, 2 x OCH₂CH₃), 1.28-1.05 (5H, m, 2 x CH₂ + CHH), 0.94 (3H, t, J = 7.2 Hz, CH₂CH₃) ppm; δ_C (100 MHz, CDCl₃) 142.8 (C, Ar), 128.41 (CH, Ar), 128.38 (CH, Ar), 125.7 (CH, Ar), 61.7 (OCH₂, d, J_Cp = 7.8 Hz), 61.6 (OCH₂, d, J_Cp = 7.6 Hz), 60.3 (C, d, J_Cp = 135.8 Hz), 50.8 (CH), 36.81 (CH₂), 36.76 (CH₂), 36.7 (CH₂, d, J_Cp = 4.8 Hz), 29.9 (CH₂Ar, d, J_Cp = 5.4 Hz), 25.8 (CH₂), 25.7 (CH₂), 16.7 (CH₂), 16.7 (CH₃, d, J_Cp = 5.2 Hz), 14.8 (CH₃) ppm; δ_P (161 MHz, CDCl₃) 31.6 ppm; MS (ES⁺) m/z 396 [MH⁺]; HRMS (ES⁺) calcd for C₂₂H₃₉NO₃P [MH⁺]: 396.2662; found: 396.2677.
Chapter 6


Methyleneaziridine 50 (106 mg, 0.73 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 920 µL, 1.84 mmol), 2-(3-bromopropoxy)-tetrahydro-2H-pyran (250 mg, 1.12 mmol) and diethyl phosphite (240 µL, 1.86 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149c (201 mg, 60%) as a pale yellow oil. Rf = 0.29 (50% ethyl acetate in petroleum ether); νmax (film) 2938, 1453, 1231, 1119, 1021 cm⁻¹; δH (400 MHz, CDCl₃) 7.37-7.21 (5H, m, Ar), 4.58 (1H, s, OCH), 4.16 (4H, dt, J = 7.2, 14.6 Hz, 2 x OCH₂), 3.87 (3H, m, NCH₂ + OCH), 3.78-3.73 (1H, m, OCHH), 3.51-3.48 (1H, m, OCHH), 3.43-3.37 (1H, m, OCHH), 1.85-1.41 (17H, m, 8 x CH₂ + NH), 1.34 (6H, t, J = 7.0 Hz, 2 x OCH₂CH₃), 0.92 (3H, t, J = 7.2 Hz, CH₃CH₃) ppm; δC (100 MHz, CDCl₃) 141.3 (C, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 126.8 (CH, Ar), 98.8 (OCH, d, JCP = 3.9 Hz), 67.3 (OCH₂, d, JCP = 5.8 Hz), 62.3 (OCH₂), 61.6 (OCH₂, d, JCP = 7.7 Hz), 59.7 (C, d, JCP = 135.8 Hz), 47.4 (NCH₂, d, JCP = 2.9 Hz), 35.9 (CH₂, d, JCP = 3.7 Hz), 33.3 (CH₂, d, JCP = 4.3 Hz), 30.8 (CH₂), 30.4 (CH₂), 25.5 (CH₂), 19.7 (CH₂), 19.6 (CH₂), 16.7 (CH₃, d, JCP = 5.6 Hz), 16.4 (CH₂, d, JCP = 3.7 Hz), 14.8 (CH₃) ppm; δP (161 MHz, CDCl₃) 31.1 ppm; MS (ES⁺) m/z 456 [MH⁺]; HRMS (ES⁺) calcd for C₂₄H₄₃NO₅P [MH⁺]: 456.2873; found: 456.2894.
Diethyl [5-(benzylamino)oct-1-en-5-yl]phosphonate (149d).

Methyleneaziridine 50 (104 mg, 0.72 mmol) was reacted with CuI (26 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 900 µL, 1.80 mmol), allyl bromide (93 µL, 1.08 mmol) and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149d (155 mg, 61%) as a pale yellow oil. Rf = 0.33 (50% ethyl acetate in petroleum ether); v_{max} (film) 2959, 1603, 1453, 1231, 1049 cm\(^{-1}\); δ_H (400 MHz, CDCl\(_3\)) 7.37-7.22 (5H, m, Ar), 5.86-5.78 (1H, m, CH=) 5.04 (1H, d, J = 17.2 Hz, =CH\(\text{H}\)), 4.95 (1H, d, J = 9.4 Hz, =CH\(\text{H}\)), 4.17 (4H, dt, J = 7.2, 14.3 Hz, 2 x OCH\(_2\)), 3.87 (2H, s, NCH\(_2\)), 2.31-2.14 (2H, m, CH\(_2\)CH), 1.89-1.62 (4H, m, 2 x CH\(_2\)), 1.56-1.41 (2H, m, CH\(_2\)), 1.34 (6H, t, J = 7.2 Hz, 2 x OCH\(_2\)CH\(_3\)), 0.93 (3H, t, J = 7.4 Hz, CH\(_2\)CH\(_3\)) ppm; δ_C (100 MHz, CDCl\(_3\)) 141.2 (C, Ar), 136.7 (CH=), 128.3 (CH, Ar), 128.2 (CH, Ar), 126.9 (CH, Ar), 114.5 (=CH\(_2\)), 61.7 (OCH\(_2\), d, J_\text{CP} = 7.7 Hz), 59.5 (C, d, J_\text{CP} = 136.1 Hz), 47.3 (NCH\(_2\), d, J_\text{CP} = 2.9 Hz), 35.8 (CH\(_2\), d, J_\text{CP} = 4.3 Hz), 32.7 (CH\(_2\), d, J_\text{CP} = 4.3 Hz), 27.4 (CH\(_2\), d, J_\text{CP} = 5.7 Hz), 16.7 (CH\(_3\), d, J_\text{CP} = 5.3 Hz), 16.4 (CH\(_2\), d, J_\text{CP} = 5.3 Hz), 14.9 (CH\(_3\)) ppm; δ_P (161 MHz, CDCl\(_3\)) 30.8 ppm; MS (ES\(^{+}\)) m/z 354 [MH\(^{+}\)]; HRMS (ES\(^{+}\)) calcd for C\(_{19}\)H\(_{33}\)NO\(_3\)P [MH\(^{+}\)]: 354.2193; found: 354.2202.
Diethyl [3-(benzylamino)-1-(4-methoxyphenyl)hexan-3-yl]phosphonate (149e).

Methyleneaziridine 50 (105 mg, 0.72 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 910 µL, 1.82 mmol), 4-methoxybenzyl bromide (160 µL, 1.14 mmol) and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149e (195 mg, 62%) as a pale yellow oil. Rf = 0.30 (50% ethyl acetate in petroleum ether); \( \nu_{\text{max}} \) (film) 2955, 1611, 1511, 1453, 1231 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.39-7.22 (5H, m, Ar), 7.11 (2H, d, \( J = 7.8 \) Hz, Ar), 6.82 (2H, d, \( J = 8.2 \) Hz, Ar), 4.19 (4H, dt, \( J = 7.4 \) Hz, 14.7 Hz, 2 x OCH\(_2\)), 3.91 (2H, s, NCH\(_2\)), 3.78 (3H, s, OCH\(_3\)), 2.80-2.65 (2H, m, CH\(_2\)Ar), 2.08-1.97 (2H, m, CH\(_2\)H\(_2\)), 1.84-1.68 (2H, m, CH\(_2\)), 1.58-1.49 (3H, m, CH\(_2\) + NH), 1.35 (6H, t, \( J = 7.0 \) Hz, 2 x OCH\(_2\)CH\(_3\)), 0.95 (3H, t, \( J = 7.2 \) Hz, CH\(_2\)CH\(_3\)) ppm; \( \delta_C \) (100 MHz, CDCl\(_3\)) 157.8 (CO, Ar), 141.2 (C, Ar), 129.3 (CH, Ar), 128.4 (CH, Ar), 128.2 (CH, Ar), 126.9 (CH, Ar), 113.9 (CH, Ar), 61.7 (OCH\(_2\), d, \( J_{CP} = 7.8 \) Hz), 59.7 (C, d, \( J_{CP} = 135.6 \) Hz), 55.3 (OCH\(_3\)), 47.4 (NCH\(_2\), d, \( J_{CP} = 3.0 \) Hz), 36.1 (CH\(_2\), d, \( J_{CP} = 4.4 \) Hz), 35.9 (CH\(_2\), d, \( J_{CP} = 4.4 \) Hz), 28.7 (CH\(_2\)Ar, d, \( J_{CP} = 6.1 \) Hz), 16.7 (CH\(_3\), d, \( J_{CP} = 5.7 \) Hz), 16.5 (CH\(_2\), d, \( J_{CP} = 5.7 \) Hz), 14.7 (CH\(_3\)) ppm; \( \delta_P \) (161 MHz, CDCl\(_3\)) 30.9 ppm; MS (ES\(^+\)) \( m/z \) 434 [MH\(^+\)]; HRMS (ES\(^+\)) calcd for C\(_{24}\)H\(_{37}\)NO\(_4\)P [MH\(^+\)]: 434.2455; found: 434.2463.
Diethyl [6-(benzylamino)non-2-yn-6-yl]phosphonate (149f).

Methyleneaziridine 50 (103 mg, 0.71 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 890 µL, 1.78 mmol), 1-bromo-2-butyne (100 µL, 1.14 mmol) and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149f (147 mg, 57%) as a pale yellow oil. Rf = 0.35 (50% ethyl acetate in petroleum ether); \( \nu_{\text{max}} \) 2960, 1603, 1452, 1230, 1019 cm\(^{-1}\);
\( \delta_{\text{H}} \) (400 MHz, CDCl\(_3\)) 7.36-7.21 (5H, m, Ar), 4.20-4.12 (4H, m, 2 x OCH\(_2\)), 3.87 (2H, d, \( J = 2.0 \) Hz, NCH\(_2\)), 2.41-2.24 (2H, m, CH\(_2\)), 2.05-1.89 (2H, m, CH\(_2\)), 1.75 (3H, t, \( J = 2.6 \) Hz, CCH\(_3\)) 1.73-1.61 (2H, m, CH\(_2\)), 1.55-1.42 (3H, m, CH\(_2\) + NH), 1.34 (6H, t, \( J = 7.2 \) Hz, 2 x OCH\(_2\)CH\(_3\)), 0.92 (3H, t, \( J = 7.2 \) Hz, CH\(_2\)CH\(_3\)) ppm; \( \delta_{\text{C}} \) (100 MHz, CDCl\(_3\)) 141.0 (C, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 126.9 (CH, Ar), 79.2 (C=), 75.6 (C=), 61.8 (OCH\(_2\)), d, \( J_{CP} = 10.6 \) Hz), 61.7 (OCH\(_2\)), d, \( J_{CP} = 11.1 \) Hz), 59.2 (C, d, \( J_{CP} = 137.3 \) Hz), 47.2 (NCH\(_2\), d, \( J_{CP} = 2.9 \) Hz), 35.6 (CH\(_2\)), d, \( J_{CP} = 3.4 \) Hz), 33.1 (CH\(_2\)), d, \( J_{CP} = 4.3 \) Hz), 16.7 (CH\(_3\)), d, \( J_{CP} = 3.9 \) Hz), 16.5 (CH\(_2\)), d, \( J_{CP} = 8.3 \) Hz), 14.7 (CH\(_3\)), 13.0 (CH\(_2\)C=, d, \( J_{CP} = 6.7 \) Hz), 3.5 (CCH\(_3\)) ppm; \( \delta_{\text{P}} \) (161 MHz, CDCl\(_3\)) 30.1 ppm; HRMS (ES\(^+\)) calcd for C\(_{20}\)H\(_{33}\)NO\(_3\)P [MH\(^+\)]: 336.2193; found: 336.2206.
Diethyl [3-(benzylamino)-1-(4-bromophenyl)hexan-3-yl]phosphonate (149g).

![Chemical Structure](image)

Methyleneaziridine 50 (101 mg, 0.70 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 880 µL, 1.76 mmol), 4-bromobenzyl bromide (260 mg, 1.04 mmol) in THF (30 µL), and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149g (177 mg, 52%) as a pale yellow oil. 

$R_f = 0.31$ (50% ethyl acetate in petroleum ether); $\nu_{\text{max}}$ 2959, 1487, 1453, 1229, 1048 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 7.39-7.23 (7H, m, Ar), 7.05 (2H, d, $J = 7.8$ Hz, Ar), 4.19 (4H, dt, $J = 7.2$, 14.3 Hz, 2 x OCH$_2$), 3.89 (2H, s, NCH$_2$), 2.81-2.65 (2H, m, CH$_2$Ar), 2.07-1.97 (2H, m), 1.89-1.68 (2H, m), 1.58-1.46 (3H, m, CH$_2$ + NH), 1.35 (6H, t, $J = 7.0$ Hz, 2 x OCH$_2$CH$_3$), 0.96 (3H, t, $J = 7.3$ Hz, CH$_2$CH$_3$) ppm; $\delta_C$ (100 MHz, CDCl$_3$) 141.6 (C, Ar), 141.0 (C, Ar), 131.5 (CH, Ar), 130.2 (CH, Ar), 128.4 (CH, Ar), 128.2 (CH, Ar), 126.9 (CH, Ar), 119.6 (CBr), 61.8 (OCH$_2$, d, $J_{CP} = 8.1$ Hz), 59.6 (C, d, $J_{CP} = 135.3$ Hz), 47.5 (NCH$_2$, d, $J_{CP} = 2.6$ Hz), 35.8 (CH$_2$, d, $J_{CP} = 5.3$ Hz), 35.75 (CH$_2$, d, $J_{CP} = 5.0$ Hz), 29.1 (CH$_2$Ar, d, $J_{CP} = 6.0$ Hz), 16.7 (CH$_3$, d, $J_{CP} = 5.5$ Hz), 16.5 (CH$_2$, d, $J_{CP} = 5.3$ Hz), 14.7 (CH$_3$) ppm; $\delta_P$ (161 MHz, CDCl$_3$) 30.4 ppm; MS (ES$^+$) $m/z$ 482 [MH$^+$, $^{79}$Br], 484 [MH$^+$, $^{81}$Br]; HRMS (ES$^+$) calcd for C$_{23}$H$_{34}$$^{81}$BrNO$_3$P [MH$^+$]: 484.1437; found: 484.1453.
Diethyl [3-(benzylamino)-6-methyl-1-phenylheptan-3-yl]phosphonate (149h).

\[
\begin{array}{c}
\text{HN} \\
\text{Ph} \\
\text{P(O)(OEt)}_2
\end{array}
\]

Methyleneaziridine 50 (104 mg, 0.72 mmol) was reacted with CuI (27 mg, 0.14 mmol), isobutylmagnesium chloride (2M in THF, 900 µL, 1.80 mmol), benzyl bromide (130 µL, 1.09 mmol) and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149h (197 mg, 63%) as a pale yellow oil. \( R_f = 0.40 \) (50% ethyl acetate in petroleum ether); \( \nu_{\text{max}} \) (film) 2953, 1603, 1453, 1228, 1020 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.39-7.16 (10H, m, Ar), 4.20 (4H, dt, \( J = 6.9, 13.8 \) Hz, 2 x OCH\(_2\)), 3.92 (2H, s, NCH\(_2\)), 2.86-2.70 (2H, m CH\(_2\)Ar), 2.11-1.93 (2H, m, CH\(_2\)), 1.89-1.72 (2H, m, CH\(_2\)), 1.55-1.46 (2H, m, CH\(_2\)), 1.43-1.40 (1H, m, CH), 1.36 (6H, t, \( J = 7.0 \) Hz, 2 x OCH\(_2\)CH\(_3\)), 0.93 (6H, d, \( J = 6.4 \) Hz, 2 x CH\(_2\)CH\(_3\)) ppm; \( \delta_C \) (100 MHz, CDCl\(_3\)) 142.6 (C, Ar), 141.1 (C, Ar), 128.5 (CH, Ar), 128.3 (CH, Ar), 126.9 (CH, Ar), 125.8 (CH, Ar), 61.8 (OCH\(_2\), d, \( J_{CP} = 7.6 \) Hz), 61.7 (OCH\(_2\), d, \( J_{CP} = 7.6 \) Hz), 59.6 (C, d, \( J_{CP} = 136.1 \) Hz), 47.4 (NCH\(_2\), d, \( J_{CP} = 2.4 \) Hz), 35.8 (CH\(_2\), d, \( J_{CP} = 4.0 \) Hz), 31.8 (CH\(_2\), d, \( J_{CP} = 5.2 \) Hz), 31.2 (CH\(_2\), d, \( J_{CP} = 3.6 \) Hz), 29.7 (CH\(_2\)Ar, d, \( J_{CP} = 5.6 \) Hz), 28.8 (CH), 22.7 (CH\(_3\)), 16.7 (CH\(_3\), d, \( J_{CP} = 5.2 \) Hz) ppm; \( \delta_P \) (161 MHz, CDCl\(_3\)) 30.7 ppm; MS (ES\(^+\)) \( m/z \) 432 [MH\(^+\)]; HRMS (ES\(^+\)) calcd for C\(_{25}\)H\(_{39}\)NO\(_3\)P [MH\(^+\)]: 432.2662; found: 432.2665.
Diethyl [3-(benzylamino)-1,5-diphenylpentan-3-yl]phosphonate (149i).

Methyleneaziridine 50 (103 mg, 0.71 mmol) was reacted with CuI (26 mg, 0.14 mmol), benzylmagnesium chloride (2M in THF, 890 µL, 1.78 mmol), benzyl bromide (130 µL, 1.09 mmol) and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149i (205 mg, 62%) as a white solid. m.p. 69-70 °C (from ethyl acetate/petroleum ether); Rf = 0.32 (50% ethyl acetate in petroleum ether); υmax (film) 2923, 1601, 1451, 1221, 1022 cm⁻¹; δH (400 MHz, CDCl₃) 7.41-7.17 (15H, m, Ar), 4.22 (4H, dt, J = 7.3, 14.5 Hz, 2 x OCH₂), 3.96 (2H, s, NCH₂), 2.92-2.76 (4H, m, 2 x CH₂Ar), 2.21-2.03 (4H, m, 2 x CH₂), 1.70 (1H, br s, NH), 1.37 (6H, t, J = 7.1 Hz, 2 x OCH₂CH₃) ppm; δC (100 MHz, CDCl₃) 142.5 (C, Ar), 141.0 (C, Ar), 128.6 (CH, Ar), 128.5 (CH, Ar) 128.3 (CH, Ar), 127.1 (CH, Ar), 126.0 (CH, Ar), 62.0 (OCH₂, d, JCP = 7.4 Hz), 59.7 (C, d, JCP = 136.4 Hz), 47.4 (NCH₂, d, JCP = 3.2 Hz), 35.9 (CH₂, d, JCP = 4.6 Hz), 29.8 (CH₂Ar, d, JCP = 5.4 Hz), 16.8 (CH₃, d, JCP = 8.6 Hz) ppm; δp (161 MHz, CDCl₃) 30.2 ppm; MS (ES⁺) m/z 466 [MH⁺]; HRMS (ES⁺) calcd for C₂₈H₃₇NO₃P [MH⁺]: 466.2506; found: 466.2519. Anal. Calcd for C₂₈H₃₆NO₃P: C, 72.23; H, 7.79; N, 3.01%. Found: C, 72.56; H, 7.78; N, 2.95%.
Diethyl [2-(benzylamino)-1-cyclohexyl-4-phenylbutan-2-yl]phosphonate (149j).

Methyleneaziridine 50 (103 mg, 0.71 mmol) was reacted with CuI (26 mg, 0.14 mmol), cyclohexylmagnesium chloride (2M in diethyl ether, 890 µL, 1.78 mmol), benzyl bromide (130 µL, 1.09 mmol) and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149j (137 mg, 42%) as a pale yellow oil. Rf = 0.30 (50% ethyl acetate in petroleum ether); νmax (film) 2921, 1602, 1450, 1225, 1021 cm⁻¹; δH (400 MHz, CDCl₃) 7.39-7.16 (10H, m, Ar), 4.19 (4H, dt, J = 7.2, 14.4 Hz, OCH₂), 3.93 (2H, d, J = 1.9 Hz, NCH₂), 2.86-2.73 (2H, m, CH₂Ar), 2.11-2.03 (2H, m, CH₂), 1.94 (1H, d, J = 12.2 Hz, CH), 1.84-1.52 (8H, m, 4 x CH₂), 1.36 (6H, t, J = 7.0 Hz, 2 x OCH₂CH₃), 1.29-1.05 (5H, m 2 x CH₂ + NH) ppm; δC (100 MHz, CDCl₃) 142.6 (C, Ar), 141.2 (C, Ar), 128.44 (CH, Ar), 128.41 (CH, Ar), 128.38 (CH, Ar), 128.1 (CH, Ar), 126.9 (CH, Ar), 125.8 (CH, Ar), 61.8 (OCH₂, d, JCP = 8.0 Hz), 61.7 (OCH₂, d, JCP = 7.8 Hz), 60.7 (C, d, JCP = 134.6 Hz), 47.5 (NCH₂, d, JCP = 2.8 Hz), 40.5 (CH₂, d, JCP = 3.8 Hz), 36.4 (CH₂, d, JCP = 4.4 Hz), 35.8 (CH₂), 35.6 (CH₂), 32.6 (CH, d, JCP = 7.4 Hz), 30.1 (CH₂, d, JCP = 5.0 Hz), 26.6 (CH₂), 26.3 (CH₂), 16.7 (CH₃, d, JCP = 5.4 Hz) ppm; δP (161 MHz, CDCl₃) 30.5 ppm; MS (ES⁺) m/z 458 [MH⁺]; HRMS (ES⁺) calcd for C₂₇H₄₁NO₃P [MH⁺]: 458.2819; found: 458.2814.
Diethyl [3-(benzylamino)-1-phenylhept-6-en-3-yl]phosphonate (149k).

Methyleneaziridine 50 (102 mg, 0.70 mmol) was reacted with CuI (26 mg, 0.14 mmol), allylmagnesium chloride (2M in THF, 880 µL, 1.76 mmol), benzyl bromide (130 µL, 1.09 mmol) and diethyl phosphite (230 µL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 149k (178 mg, 61%) as a pale yellow oil. R<sub>f</sub> = 0.34 (50% ethyl acetate in petroleum ether); <sup>υ</sup>max (film) 2976, 1602, 1452, 1232, 1020 cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.43-7.21 (10H, m, Ar), 5.94-5.84 (1H, m, CH), 5.10 (1H, d, <sup>J</sup>= 17.0 Hz, CH<sub>H</sub>), 5.02 (1H, d, <sup>J</sup>= 10.2 Hz, CH<sub>H</sub>), 4.24 (4H, dt, <sup>J</sup> = 7.2, 14.4 Hz, 2 x OCH<sub>2</sub>), 3.96 (2H, s, NCH<sub>2</sub>), 2.91-2.76 (2H, m, CH<sub>2</sub>Ar), 2.41-2.25 (2H, m, CH<sub>2</sub>), 2.17-2.03 (2H, m, CH<sub>2</sub>), 2.01-1.86 (2H, m, CH<sub>2</sub>), 1.65 (1H, br s, NH), 1.40 (6H, t, <sup>J</sup>= 7.0 Hz, 2 x OCH<sub>2</sub>CH<sub>3</sub>) ppm; δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 142.5 (C, Ar), 141.0 (C, Ar), 138.5 (CH=), 128.5 (CH, Ar), 128.4 (CH, Ar), 127.0 (CH, Ar), 125.9 (CH, Ar), 114.7 (=CH<sub>2</sub>), 61.9 (OCH<sub>2</sub>, d, <sup>J</sup><sub>CP</sub> = 7.7 Hz), 59.5 (C, d, <sup>J</sup><sub>CP</sub> = 136.0 Hz), 47.3 (NCH<sub>2</sub>, d, <sup>J</sup><sub>CP</sub> = 2.9 Hz), 35.8 (CH<sub>2</sub>, d, <sup>J</sup><sub>CP</sub> = 3.8 Hz), 32.7 (CH<sub>2</sub>, d, <sup>J</sup><sub>CP</sub> = 4.8 Hz), 29.7 (CH<sub>2</sub>, d, <sup>J</sup><sub>CP</sub> = 5.3 Hz), 27.6 (CH<sub>2</sub>, d, <sup>J</sup><sub>CP</sub> = 5.8 Hz), 16.7 (CH<sub>3</sub>, d, <sup>J</sup><sub>CP</sub> = 5.3 Hz) ppm; δ<sub>P</sub> (121 MHz, CDCl<sub>3</sub>) 29.6 ppm; MS (ES<sup>+</sup>) m/z 416 [MH<sup>+</sup>]; HRMS (ES<sup>+</sup>) calcd for C<sub>24</sub>H<sub>35</sub>NO<sub>3</sub>P [MH<sup>+</sup>]: 416.2349; found: 416.2356.
Diethyl [2-(benzylamino)pentan-2-yl]phosphonate (150).

Methyleneaziridine 50 (107 mg, 0.74 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 920 µL, 1.84 mmol), cyclohexanone (110 µL, 1.06 mmol) and diethyl phosphite (240 µL, 1.87 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 150 (121 mg, 52%) as a pale yellow oil. Rf = 0.23 (50% ethyl acetate in petroleum ether); νmax (film) 2959, 1604, 1453, 1225, 1021 cm⁻¹; δH (400 MHz, CDCl3) 7.37-7.21 (5H, m, Ar), 4.22-4.13 (4H, m, 2 x OCH₂), 3.93 (1H, dd, J = 2.0, 12.7 Hz, NCH₂H), 3.85 (1H, dd, J = 1.74, 12.7 Hz, NC₃H), 1.82-1.39 (5H, m, CH₂CH₂ + NH), 1.34 (6H, t, J = 7.0 Hz, 2 x OCH₂CH₃), 1.32 (3H, d, J = 16.4 Hz, CCH₃), 0.94 (3H, t, J = 7.2 Hz, CH₂CH₃) ppm; δC (100 MHz, CDCl3) 141.2 (C, Ar), 128.3 (CH, Ar), 128.2 (CH), 126.8 (CH), 62.0 (OCH₂, d, JCP = 7.2 Hz), 61.7 (OCH₂, d, JCP = 7.9 Hz), 56.5 (C, d, JCP = 140.9 Hz), 47.5 (NCH₂, d, JCP = 3.6 Hz), 36.9 (CH₂, d, JCP = 4.3 Hz), 20.8 (CCH₃, d, JCP = 2.3 Hz), 16.7 (OCH₂CH₃, d, JCP = 2.2 Hz), 16.6 (OCH₂CH₃, d, JCP = 2.1 Hz), 15.8 (CH₃, d, JCP = 8.4 Hz), 14.6 (CH₂CH₃) ppm; δP (161 MHz, CDCl3) 31.1 ppm; MS (ES⁺) m/z = 314.0 [MH⁺]; HRMS (ES⁺) m/z caleed for C₁₆H₂₈NNaO₃P [MNa⁺]: 336.1699; found: 336.1713.
Chapter 6

**Diethyl [3-(1-phenylethylamino)-1-phenylhexan-3-yl]phosphonate (152).**

Methyleneaziridine 19 (102 mg, 0.64 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 800 µL, 1.60 mmol), benzyl bromide (110 µL, 0.93 mmol) and diethyl phosphite (210 µL, 1.63 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded 152 (143 mg, 54%) as a pale yellow oil as ca 1:1 mixture of diastereomers as judged by $^1$H NMR spectroscopy. $R_f = 0.33$ (50% ethyl acetate in petroleum ether); $\nu_{\text{max}}$ (film) 2960, 1602, 1452, 1229, 1020 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 7.41-7.07 (9H, m, Ar), 6.77 (1H, d, $J = 7.0$ Hz, Ar), 4.36-4.30 (1H, m, NCH), 4.21-4.09 (4H, m, 2 x OCH$_2$), 2.90-2.83 (0.5H, m, ¼ x CH$_2$Ar), 2.63-2.41 (1.5H, m, ¼ x CH$_2$Ar), 1.99-1.48 (6H, m, 3 x CH$_2$), 1.37-1.32 (10H, m, 2 x OCH$_2$CH$_3$ + CHCH$_3$ + NH), 0.88 (1.5H, t, $J = 6.9$ Hz, ½ x CH$_2$CH$_3$), 0.62 (1.5H, t, $J = 6.9$ Hz, ½ x CH$_2$CH$_3$) ppm; $\delta_C$ (100 MHz, CDCl$_3$) 149.1 (C, Ar), 149.0 (C, Ar), 142.7 (C, Ar), 142.4 (C, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.22 (CH, Ar), 128.19 (CH, Ar), 128.12 (CH, Ar), 126.5 (CH, Ar), 126.4 (CH, Ar), 126.34 (CH, Ar), 126.31 (CH, Ar), 126.2 (CH, Ar), 125.7 (CH, Ar), 125.5 (CH, Ar), 62.0 (OCH$_2$, d, $J_{CP} = 8.0$ Hz), 61.9 (OCH$_2$, d, $J_{CP} = 8.0$ Hz), 61.3 (OCH$_2$, d, $J_{CP} = 8.0$ Hz), 61.0 (C, d, $J_{CP} = 134.4$ Hz), 52.4 (NCH, d, $J_{CP} = 3.6$ Hz), 37.8 (CH$_2$, d, $J_{CP} = 3.6$ Hz), 37.2 (CH$_2$, d, $J_{CP} = 4.0$ Hz), 34.8 (CH$_2$, d, $J_{CP} = 4.8$ Hz), 34.5 (CH$_2$, d, $J_{CP} = 6.0$ Hz), 29.6 (CH$_2$Ar, d, $J_{CP} = 4.0$ Hz), 27.3 (CH$_3$, d, $J_{CP} = 4.4$ Hz), 16.8 (CH$_2$), 16.7 (CH$_3$, d, $J_{CP} = 4.8$ Hz), 16.7 (CH$_3$, d, $J_{CP} = 6.0$ Hz) 14.8 (CH$_3$), 14.7 (CH$_3$) ppm; $\delta_P$ (161 MHz, CDCl$_3$)
31.2, 31.1 ppm; MS (ES\(^+\)) \(m/z\) 418 [MH\(^+\)]; HRMS (ES\(^+\)) calcd for C\(_{24}\)H\(_{37}\)NO\(_3\)P [MH\(^+\)]: 418.2506; found: 418.2521.

Ethyl [3-(benzylamino)-1-phenylhexan-3-yl](phenyl)phosphinate (156).

Methyleneaziridine 50 (104 mg, 0.72 mmol) was reacted with CuI (26 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 900 \(\mu\)L, 1.80 mmol), benzyl bromide (130 \(\mu\)L, 1.09 mmol) and freshly distilled ethyl phenylphosphinate (270 \(\mu\)L, 1.79 mmol) as described in General Method 1. Purification on silica gel (25% ethyl acetate in petroleum ether) afforded 156 (202 mg, 64%) as a yellow oil as ca 1:1 mixture of diastereomers as judged by \(^1\)H and \(^{31}\)P NMR spectroscopy. \(R_f\) = 0.29 (50% ethyl acetate in petroleum ether); \(\nu_{\text{max}}\) (film) 2957, 2362, 1602, 1453, 1210, 1023 cm\(^{-1}\); \(\delta_H\) (400 MHz, C\(_6\)D\(_6\)) 8.14-8.08 (2H, m, Ar), 7.54 (2H, d, \(J = 7.8\) Hz, Ar), 7.36-7.17 (11H, m, Ar), 4.21 (2H, m, NCH\(_2\)), 4.15-4.04 (1H, m, OCH\(_2\)), 3.80-3.69 (1H, m, OCHH), 3.14-2.89 (2H, m, CH\(_2\)Ar), 2.37-2.12 (2H, m, CH\(_2\)), 2.06-1.55 (5H, m, 2 x CH\(_2\) + NH), 1.12 (3H, t, \(J = 7.0\) Hz, OCH\(_2\)CH\(_3\)), 0.98 (1.5H, t, \(J = 7.4\) Hz, ½ x CH\(_2\)CH\(_3\)), 0.97 (1.5H, t, \(J = 7.0\) Hz, ½ x CH\(_2\)CH\(_3\)) ppm; \(\delta_C\) (75 MHz, CDCl\(_3\)) 142.0 (C, Ar), 141.9 (C, Ar), 140.5 (C, Ar), 132.4 (CH, Ar), 132.3 (CH, Ar), 131.6 (CH, Ar, d, \(J_{CP} = 2.2\) Hz), 130.0 (C, Ar, d, \(J_{CP} = 6.2\) Hz), 128.6 (CH, Ar, d, \(J_{CP} = 6.2\) Hz), 127.9 (CH, Ar), 127.8 (CH, Ar), 127.79 (CH, Ar), 127.6 (CH, Ar), 126.4 (CH, Ar), 125.3 (CH, Ar, d, \(J_{CP} = 1.8\) Hz), 60.17 (OCH\(_2\), d, \(J_{CP} = 7.8\) Hz), 60.16 (OCH\(_2\), d, \(J_{CP} = 8.0\) Hz), 59.8 (C, d, \(J_{CP} = 98.3\) Hz), 59.7 (C, d, \(J_{CP} = 97.8\) Hz), 46.5 (NCH\(_2\)), 34.2 (CH\(_2\),...
d, $J_{CP} = 5.3$ Hz), 34.1 (CH$_2$, d, $J_{CP} = 6.7$ Hz), 29.1 (CH$_2$Ar, d, $J_{CP} = 4.9$ Hz), 16.2 (CH$_3$, d, $J_{CP} = 5.7$ Hz), 15.9 (CH$_2$, d, $J_{CP} = 4.7$ Hz), 14.2 (CH$_3$, d, $J_{CP} = 3.5$ Hz) ppm; $\delta_P$ (161 MHz, C$_6$D$_6$) 58.8, 58.7 ppm; MS (ES$^+$) $m/z$ 436 [MH$^+$]; HRMS (ES$^+$) calcd for C$_{27}$H$_{34}$NNaO$_2$P [MNa$^+$]: 458.2219; found: 458.2228.

**Diethyl (1-benzyl-2-propylpiperidiny-2-yl)-2-phosphonate (157).**

Copper (I) iodide (26 mg, 0.14 mmol) in a round-bottomed flask was flame dried under vacuum and then purged with nitrogen (three cycles performed). THF (2 mL) was added and the mixture cooled to –30 °C, whereupon ethylmagnesium chloride (2M in THF, 900 $\mu$L, 1.80 mmol) was added. After 10 min, methyleneaziridine 50 (104 mg, 0.72 mmol) in THF (1 mL) was added and the mixture stirred at room temperature for 3 h. Upon cooling to 0 °C, 1,3-diodopropane (210 $\mu$L, 1.83 mmol) was added dropwise, then the mixture heated at 45 °C overnight. In a separate flask, n-butyllithium (1.6 M in hexanes, 1.12 mL, 1.79 mmol) was added dropwise to a solution of diethyl phosphite (230 $\mu$L, 1.79 mmol) in THF (1 mL) at 0 °C. After 30 min, this mixture was allowed to warm to room temperature then added *via* cannula to the first flask stirred at room temperature. The mixture was heated overnight at 45 °C. Upon cooling to room temperature, the mixture was diluted with Et$_2$O (20 mL) then washed with saturated aqueous NH$_4$Cl solution (2 x 20 mL), 50% NaOH solution (2 x 20 mL) and brine (2 x 20 mL). The organic phase was separated, dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification on silica gel
(30% ethyl acetate in petroleum ether) afforded 157 (124 mg, 49%) as a pale orange oil. \( R_f = 0.31 \) (50% ethyl acetate in petroleum ether); \( \nu_{\text{max}} \) (film) 2959, 1654, 1450, 1230, 1017 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl\(_3\)) 7.35-7.18 (5H, m, Ar), 4.23 (5H, m, 2 x OCH\(_2\) + NCH\(\text{H} \)), 3.60 (1H, dd, \( J = 4.8 \), 15 Hz, NCH\(\text{H} \)), 2.93-2.85 (1H, m, ring NCH\(\text{H} \)), 2.55-2.52 (1H, m, ring NCH\(\text{H} \)), 2.04-1.93 (2H, m, CH\(_2\)), 1.87-1.45 (9H, m, 4 x CH\(_2\) + NH), 1.37 (3H, t, \( J = 7.0 \) Hz, OCH\(_2\)CH\(_3\)), 1.35 (3H, t, \( J = 7.0 \) Hz, OCH\(_2\)CH\(_3\)), 0.89 (3H, t, \( J = 7.0 \) Hz, CH\(_2\)CH\(_3\)) ppm; \( \delta_C \) (100 MHz, CDCl\(_3\)) 141.0 (C, Ar), 128.2 (CH, Ar), 127.8 (CH, Ar), 126.4 (CH, Ar), 61.8 (C, d, \( J_{\text{CP}} = 122.3 \) Hz), 61.4 (OCH\(_2\), d, \( J_{\text{CP}} = 8.0 \) Hz), 60.6 (OCH\(_2\), d, \( J_{\text{CP}} = 8.0 \) Hz), 54.9 (CH\(_2\)), 46.7 (NCH\(_2\)), 36.6 (CH\(_2\), d, \( J_{\text{CP}} = 6.3 \) Hz), 31.2 (CH\(_2\)), 25.9 (CH\(_2\)), 21.1 (CH\(_2\), d, \( J_{\text{CP}} = 2.6 \) Hz), 16.8 (CH\(_3\), d, \( J_{\text{CP}} = 6.0 \) Hz), 16.7 (CH\(_3\), d, \( J_{\text{CP}} = 6.3 \) Hz), 15.7 (CH\(_2\), d, \( J_{\text{CP}} = 6.7 \) Hz), 14.8 (CH\(_3\)) ppm; \( \delta_P \) (161 MHz, CDCl\(_3\)) 32.5 ppm; MS (ES\(^+\)) m/z 354 [MH\(^+\)]; HRMS (ES\(^+\)) calcd for C\(_{19}\)H\(_{33}\)NO\(_3\)P [MH\(^+\)]: 354.2193; found: 354.2200.

**Diethyl (3-amino-1-phenylhexan-3-yl)phosphonate (164).**

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P(O)(OEt)_2
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Palladium, 10 wt.% on activated carbon (52 mg) was added to \( \alpha \)-aminophosphonate 149a (346 mg, 0.86 mmol) in methanol (10 mL), water (10 mL) and conc. hydrochloric acid (5 mL). The resulting mixture was stirred at room temperature under a hydrogen atmosphere for 14 h. After filtration through Celite\(^\circledR\), the mixture was concentrated in vacuo. Purification on silica gel (10% methanol in dichloromethane) afforded 164 (267 mg, 99%) as a clear colourless oil. \( R_f = 0.39 \) (10% methanol in dichloromethane); \( \nu_{\text{max}} \) (film) 2959,
Chapter 6

1603, 1454, 1224, 1020 cm$^{-1}$; $\delta_H$ (400 MHz, d$_4$-MeOD) 7.31-7.16 (5H, m, Ar), 4.21 (4H, dt, $J = 7.3, 14.6$ Hz, 2 x OCH$_2$), 2.82-2.69 (2H, m, CH$_2$Ar), 2.00-1.84 (2H, m, CH$_2$), 1.80-1.62 (2H, m, CH$_2$), 1.60-1.46 (2H, m, OCH$_2$), 1.39 (6H, t, $J = 7.1$ Hz, 2 x OCH$_2$CH$_3$), 0.99 (3H, t, $J = 7.3$ Hz, CH$_3$CH$_3$) ppm; $\delta_C$ (100 MHz, d$_4$-MeOD) 143.6 (C, Ar), 129.5 (CH, Ar), 129.3 (CH, Ar), 127.0 (CH, Ar), 64.0 (OCH$_2$, d, $J_{CP} = 7.8$ Hz), 63.9 (OCH$_2$, d, $J_{CP} = 8.0$ Hz), 56.1 (C, d, $J_{CP} = 145.7$ Hz), 39.3 (CH$_2$, d, $J_{CP} = 3.1$ Hz), 39.1 (CH$_2$, d, $J_{CP} = 2.6$ Hz), 30.8 (CH$_2$Ar, d, $J_{CP} = 5.2$ Hz), 17.6 (CH$_2$, d, $J_{CP} = 5.4$ Hz), 16.9 (CH$_3$, d, $J_{CP} = 5.4$ Hz), 15.1 (CH$_3$) ppm; $\delta_P$ (161 MHz, d$_4$-MeOD) 31.1 ppm; MS (ES$^+$) m/z 314 [MH$^+$]; HRMS (ES$^+$) calcd for C$_{16}$H$_{29}$NO$_3$P [MH$^+$]: 314.1880; found: 314.1890.

(3-Amino-1-phenylhexan-3-yl)phosphonic acid (165).

$\alpha$-Aminophosphonate 164 (0.203 mg, 0.65 mmol) in conc. hydrochloric acid (20 mL) was refluxed for 14 h. On cooling to room temperature, the solvent was removed in vacuo. The residue was dissolved in the minimum amount of hot ethanol (ca 1 mL), cooled to room temperature and excess propylene oxide (20 mL) added. After stirring for 3 h, the precipitated phosphonic acid 165 (152 mg, 91%) was isolated by filtration as a white solid. m.p. 204-206 °C (from ethanol propylene oxide); $\nu_{\text{max}}$ (film) 2961, 2872, 1603, 1525, 1496, 1454, 1147 cm$^{-1}$; $\delta_H$ (400 MHz, d$_4$-AcOD) 7.32-7.19 (5H, m, Ar), 2.91-2.77 (2H, m, CH$_2$Ar), 2.36-1.99 (4H, m, 2 x CH$_2$), 1.67-1.52 (2H, m, CH$_2$), 1.00 (3H, t, $J = 7.1$ Hz, CH$_3$) ppm; $\delta_C$ (100 MHz, d$_4$-AcOD) 141.1 (C, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 126.0 (CH, Ar), 58.5 (C, d, $J_{CP} = 145.0$ Hz), 35.1 (CH$_2$), 34.8
5-(Ethoxy(ethylperoxy)phosphino)decan-5-amine (169).

A round-bottomed flask was flame dried under vacuum and then purged with nitrogen (three cycles performed). Upon cooling to room temperature, THF (1 mL) and n-butyl lithium (1.6 M in hexanes, 620 µL, 0.99 mmol) were added and the mixture cooled to 0 °C, whereupon hexanenitrile (100 µL, 0.84 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was allowed to warm to room temperature. Then, cadmium iodide (31 mg, 0.08 mmol) and diethyl phosphate (130 µL, 1.01 mmol) were added and the mixture heated to 75 °C (preheated bath). After 24 h the mixture was cooled to room temperature and poured into H₂O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (3 x 20 mL), dried over MgSO₄, filtered and the solvent removed in vacuo. Purification on silica gel (2% methanol in dichloromethane) afforded 169 (90 mg, 37%) as a pale yellow oil. Rₐ = 0.58 (10% methanol in dichloromethane); νmax (film) 2954, 1607, 1458, 1229, 1022 cm⁻¹; δH (400 MHz, CDCl₃) 4.17-4.10 (4H, m, OCH₂), 1.67-1.19 (22H, m, 7 x CH₂ + 2 x CH₃ + NH₂), 0.94-0.88 (6H, m, 2 x CH₃) ppm; δC (100 MHz, CDCl₃) 62.0 (OCH₂, d, JCP = 7.6 Hz), 54.8 (C, d, JCP = 143.3 Hz), 54.7 (C, d, JCP = 143.0 Hz), 35.3 (CH₂, d, JCP = 3.4 Hz), 35.0 (CH₂, d, JCP = 3.4 Hz), 32.4 (CH₂), 24.2 (CH₃, d, JCP = 5.6 Hz), 23.3 (CH₂), 22.6 (CH₂, d, JCP = 5.6 Hz), 22.5 (CH₂), 16.5 (OCH₂CH₃, d, JCP = 5.6 Hz), 14.0
2,3-Dihydro-1,2-dimethyl-2-pentylpyridin-4(1H)-one (197).

To a stirred solution of 2-heptanone (70 µL, 0.52 mmol) in CH₂Cl₂ (1 mL) were added Zn(OTf)₂ (93 mg, 0.26 mmol), methyl amine (2.0M in THF, 1.0 mL, 2.1 mmol), and Danishefsky’s diene (171) (200 µL, 1.0 mmol). After stirring at room temperature for 16 h, the reaction mixture was diluted with CH₂Cl₂ (5 mL) and a saturated solution of NH₄Cl (5 mL) added. The reaction mixture was stirred for 2 h and the organic layer separated and the aqueous layer extracted with CH₂Cl₂ (2 x 5 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and the solvent removed in vacuo. Purification on silica gel (ethyl acetate) afforded 197 (30 mg, 29%, contaminated with small amounts of unknown impurities) as a pale yellow oil. Rᵣ = 0.12 (ethyl acetate); δH (400 MHz, CDCl₃) 6.80 (1H, d, J = 7.4 Hz, =CHN), 4.84 (1H, d, J = 7.5 Hz, =CH), 2.86 (3H, s, NCH₃), 2.50 (1H, d, J = 16.2 Hz, COCHH), 2.20 (1H, d, J = 16.0 Hz, COCHH), 1.25-1.19 (8H, m, 4 x CH₂), 1.16 (3H, s, CCH₃), 0.82 (3H, t, J = 6.7 Hz, CH₂CH₃) ppm; MS (ES⁺) m/z = 196.1 [MH⁺].
Preparation of $N$-(2-bromo-2-propenyl)-alkylamines

**General Method 2:**

![Chemical Structure](image)

To a stirred suspension of amine (2 equiv.) and K$_2$CO$_3$ (1 equiv.) in THF (100 mL) was added 2,3-dibromopropene (1 equiv.) dropwise. The reaction mixture was stirred at room temperature for 48 h, then diluted with Et$_2$O (200 mL) and 10% NaOH (200 mL), and the phases separated. The organic phase was washed with 10% NaOH (200 mL) and brine (200 mL). The organic phase was dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification of the $N$-(2-bromo-2-propenyl)-alkylamine was achieved by column chromatography with silica pre-treated with Et$_3$N.

3-[2-(2-Methyleneaziridin-1-yl)ethyl]indole (252a).$^{1,8}$

Tryptamine (227a) (10.5 g, 65.5 mmol) was reacted with potassium carbonate (4.79 g, 34.7 mmol) and 2,3-dibromopropene (3.40 mL, 32.9 mmol) as described in General Method 2. Purification on silica gel (ethyl acetate) afforded 252a (8.31 g, 93%) as a brown oil. $R_f = 0.20$ (ethyl acetate); $\nu_{\text{max}}$ (film) 3413, 3168, 2917, 2844, 1627, 1455 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 8.16 (1H, br s, indole NH), 7.61 (1H, $d$, $J = 7.9$ Hz, Ar), 7.31 (1H, $d$, $J = 7.9$ Hz, Ar), 7.18 (1H, m, Ar), 7.11 (1H, m, Ar), 7.09 (2H, $s$, NCH$_2$CBr), 5.71 (1H, $d$, $J = 1.8$ Hz, $=\text{CHH}$), 5.50 (1H, $d$, $J = 1.8$ Hz, $=\text{CHH}$), 3.47 (2H, $s$, NCH$_2$CBr), 3.00-2.88 (4H, m, CH$_2$CH$_2$), 1.57 (1H, br s, NH) ppm; $\delta_C$ (100 MHz, CDCl$_3$) 136.4 (C,
2-Bromo-N-[2-(5-methoxy-1H-indol-3-yl)ethyl]prop-2-en-1-amine (252b).

5-Methoxy-tryptamine (227b) (2.50 g, 13.1 mmol) was reacted with potassium carbonate (0.91 g, 6.6 mmol) and 2,3-dibromopropene (0.68 mL, 6.6 mmol) as described in General Method 2. Purification on silica gel (ethyl acetate) afforded 252b (1.99 g, 98%) as a brown oil. Rf = 0.23 (ethyl acetate); υmax (film) 3176, 2910, 1624, 1484, 1456, 1438 cm⁻¹; δH (400 MHz, CDCl₃) 8.01 (1H, br s, indole NH), 7.23 (1H, d, J = 8.8 Hz, Ar), 7.05 (1H, d, J = 2.4 Hz, Ar), 7.02 (1H, d, J = 2.3 Hz, Ar), 6.85 (1H, dd, J = 2.4, 8.8 Hz, Ar), 5.73 (1H, d, J = 1.5 Hz, =CHH), 5.52 (1H, d, J = 1.5 Hz, =CHH), 3.86 (3H, s, CH₃), 3.48 (2H, s, NCH₂CBr), 2.97-2.88 (4H, m, CH₂CH₂), 1.71 (1H, br s, NH) ppm; δC (100 MHz, CDCl₃) 153.9 (CO), 133.5 (CBr), 131.5 (C, Ar), 127.8 (C, Ar), 122.7 (CH, Ar), 117.5 (=CH₂), 113.5 (C, Ar), 112.3 (CH, Ar), 111.9 (CH, Ar), 100.7 (CH, Ar), 57.4 (NCH₂), 55.9 (CH₃O), 47.9 (NCH₂), 25.8 (ArCH₂) ppm; MS (ES⁺) m/z 309 [MH⁺, ⁷⁹Br], 311 [MH⁺, ⁸¹Br]; HRMS (ES⁺) calcd for C₁₄H₁₈BrN₂O [MH⁺, ⁷⁹Br]:

Ar), 133.5 (CBr), 127.5 (C, Ar), 122.1 (CH, Ar), 122.0 (CH, Ar), 119.3 (CH, Ar), 118.9 (CH, Ar), 117.5 (=CH₂), 113.8 (C, Ar), 111.2 (CH, Ar), 57.5 (NCH₂), 48.1 (NCH₂), 25.8 (ArCH₂) ppm; MS (ES⁺) m/z 281 [MH⁺, ⁸¹Br], 279 [MH⁺, ⁷⁹Br]; HRMS (ES⁺) calcd for C₁₃H₁₆BrN₂ [MH⁺, ⁷⁹Br]: 279.0491; found: 279.0489. Anal. calcd for C₁₃H₁₅BrN₂: C, 55.93; H, 5.42; N, 10.03%. Found: C, 55.56; H, 5.32; N, 9.72%.
309.0597; found: 309.0596. Anal. calcd for C_{14}H_{17}BrN_{2}O: C, 54.38; H, 5.54; N, 9.06%. Found: C, 54.12; H, 5.35; N, 8.94%.

2-Bromo-N-[2-(1-methyl-1H-indol-3-yl)ethyl]prop-2-en-1-amine (252c).

\[
\begin{align*}
\text{N-2-(1-Methyl-1H-indol-3-yl)ethylamine}^{171} & \quad (227c) \quad (1.62 \text{ g, 9.31 mmol}) \quad \text{was} \\
& \quad \text{reacted with potassium carbonate (0.64 g, 4.65 mmol) and 2,3-dibromopropene} \\
& \quad (0.48 \text{ mL, 4.65 mmol) as described in General Method 2. Purification on silica} \\
& \quad \text{gel (ethyl acetate) afforded 252c (1.19 g, 88%) as a brown oil. R} \_f = 0.22 \quad \text{(ethyl} \\
& \quad \text{acetate); } \nu_{\text{max}} \quad \text{(film) 3054, 2911, 2824, 1625, 1472 cm}^{-1}; \quad \delta_H \quad \text{(400 MHz, CDCl}_3) \\
& \quad 7.60 \quad (1\text{H, d, } J = 7.6 \text{ Hz, Ar}), 7.28 \quad (1\text{H, d, } J = 8.2 \text{ Hz, Ar}), 7.22 \quad (1\text{H, ddd, } J = 1.1, \\
& \quad 6.9, 8.0 \text{ Hz, Ar}), 7.10 \quad (1\text{H, ddd, } J = 1.0, 6.8, 7.9 \text{ Hz, Ar}), 6.91 \quad (1\text{H, s, Ar}), 5.73 \\
& \quad (1\text{H, d, } J = 1.4 \text{ Hz, } =\text{CH})H, 5.51 \quad (1\text{H, d, } J = 1.4 \text{ Hz, } =\text{CH})H, 3.74 \quad (3\text{H, s, CH}_3), \\
& \quad 3.47 \quad (2\text{H, s, NCH}_2\text{CBr}), 2.99-2.88 \quad (4\text{H, m, CH}_2\text{CH}_2), 1.63 \quad (1\text{H, br s, NH}) \text{ ppm;} \\
& \delta_C \quad (100 \text{ MHz, CDCl}_3) \quad 137.1 \quad (\text{C, Ar}), 133.4 \quad (\text{CBr}), 127.8 \quad (\text{C, Ar}), 126.7 \quad (\text{CH,} \\
& \quad \text{Ar}), 121.6 \quad (\text{CH, Ar}), 119.0 \quad (\text{CH, Ar}), 118.7 \quad (\text{CH, Ar}), 117.4 \quad (=\text{CH}_2), 112.2 \quad (\text{C,} \\
& \quad \text{Ar}), 109.2 \quad (\text{CH, Ar}), 57.4 \quad (\text{NCH}_2), 48.2 \quad (\text{NCH}_2), 32.6 \quad (\text{NCH}_3) \quad 25.7 \quad (\text{ArCH}_2) \\
& \text{ppm; MS (EI\textsuperscript{+}) } m/z \quad 292 \quad [\text{MH}^+,\textsuperscript{79}\text{Br}], 294 \quad [\text{MH}^+,\textsuperscript{81}\text{Br}]; \quad \text{HRMS (EI\textsuperscript{+}) calcd for} \\
& \text{C}_{14}\text{H}_{17}\text{BrN}_2; \quad [\text{MH}^+,\textsuperscript{79}\text{Br}] \quad 292.0575; \quad \text{found: 292.0575.} \quad \text{Anal. calcd for} \\
& \text{C}_{14}\text{H}_{17}\text{BrN}_2; \quad \text{C, 57.35; H, 5.84; N, 9.55\%. Found: C, 57.57; H, 5.85; N, 9.42\%.} \\
\end{align*}
\]
Chapter 6

*N-[1-(1H-Indol-3-yl)propan-2-yl]-2-bromoprop-2-en-1-amine (252d).*

(±)-α-Methyl-tryptamine (227d) (3.00 g, 17.2 mmol) was reacted with potassium carbonate (1.19 g, 8.6 mmol) and 2,3-dibromopropene (0.89 mL, 8.6 mmol) as described in General Method 2. Purification on silica gel (ethyl acetate) afforded 252d (2.48 g, 98%) as a brown oil. R<sub>f</sub> = 0.39 (ethyl acetate); \( \nu_{\text{max}} \) (film) 2961, 2907, 1625, 1455, 1355 cm\(^{-1}\); \( \delta_H \) (400 MHz, CDCl<sub>3</sub>) 8.09 (1H, br s, indole NH), 7.61 (1H, d, \( J = 7.9 \) Hz, Ar), 7.35 (1H, d, \( J = 8.0 \) Hz, Ar), 7.19 (1H, t, \( J = 7.3 \) Hz, Ar), 7.11 (1H, t, \( J = 7.3 \) Hz, Ar), 7.05 (1H, d, \( J = 2.2 \) Hz, Ar), 5.65 (1H, d, \( J = 1.2 \) Hz, =CHH), 5.47 (1H, d, \( J = 1.2 \) Hz, =CHH), 3.47 (2H, s, NCH<sub>2</sub>CBr), 3.10-3.02 (1H, m, CH), 2.88-2.79 (2H, m, CH<sub>2</sub>CH), 1.78 (1H, br s, NH), 1.11 (3H, d, \( J = 6.6 \) Hz, CH<sub>3</sub>) ppm; \( \delta_C \) (100 MHz, CDCl<sub>3</sub>) 136.3 (C, Ar), 133.7 (CBr), 127.7 (C, Ar), 122.5 (CH, Ar), 122.0 (CH, Ar), 119.3 (CH, Ar), 119.0 (CH, Ar), 117.3 (=CH<sub>2</sub>), 113.2 (C, Ar), 111.1 (CH, Ar), 54.8 (NCH<sub>2</sub>), 50.9 (NCH), 33.2 (CH<sub>3</sub>), 20.2 (ArCH<sub>2</sub>) ppm; MS (ES<sup>+</sup>) \( m/z \) 293 [MH<sup>+</sup>,<sup>79</sup>Br], 295 [MH<sup>+</sup>,<sup>81</sup>Br]; HRMS (ES<sup>+</sup>) calcd for C<sub>14</sub>H<sub>17</sub>BrN<sub>2</sub> [MH<sup>+</sup>,<sup>79</sup>Br]: 293.0648; found: 293.0650. Anal. calcd for C<sub>14</sub>H<sub>17</sub>BrN<sub>2</sub>: C, 57.35; H, 5.84; N, 9.55%. Found: C, 57.20; H, 5.73; N, 9.40%.
Chapter 6

*N-(2-(1H-Indol-3-yl)ethyl)-2-bromo-3-methylbut-2-en-1-amine (254).*

To a stirred solution of 1,1-dibromo-2,2-dimethyl-cyclopropane\(^{172}\) (8) (10.0 g, 43.9 mmol) in 1,2-dichlorobenzene (80 mL) was added tryptamine (227a) (15.5 g, 96.5 mmol) and potassium carbonate (6.67 g, 48.3 mmol). The mixture was then heated at 170 °C for 48 h. On cooling to room temperature, the mixture was diluted with diethyl ether (50 mL), and separated with 10% aqueous sodium hydroxide (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over MgSO\(_4\), filtered and concentrated in vacuo. The 1,2-dichlorobenzene was removed by distillation (60 °C/15 mmHg) prior to purification on silica gel, pre-treated with Et\(_3\)N (ethyl acetate), which afforded 254 (7.95 g, 59 %) as a brown solid. m.p. 97-98 °C (from ethyl acetate); R\(_f\) = 0.19 (ethyl acetate); \(v_{\text{max}}\) (film) 2921, 2839, 1618, 1448, 1109, 742 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 8.07 (1H, br s, indole NH), 7.62 (1H, d, \(J = 8.0\) Hz, Ar), 7.35 (1H, d, \(J = 8.2\) Hz, Ar), 7.21-7.17 (1H, m, Ar), 7.13-7.09 (1H, m, Ar), 7.05 (1H, d, \(J = 2.0\) Hz, Ar), 3.59 (2H, s, NCH\(_2\)CBr), 3.01-2.97 (2H, m, NCH\(_2\)), 2.90-2.87 (2H, m, ArCH\(_2\)), 1.97 (1H, br s, NH), 1.87 (3H, s, CH\(_3\)), 1.80 (3H, s, CH\(_3\)) ppm; \(\delta_C\) (100 MHz, CDCl\(_3\)) 136.4 (C, Ar), 133.4 (CBr), 127.5 (C, Ar), 122.0 (CH, Ar), 121.8 (CH, Ar), 121.4 (C, Ar), 119.3 (CH, Ar), 118.9 (CH, Ar), 114.0 (=C), 111.1 (CH, Ar), 53.4 (NCH\(_2\)), 48.0 (NCH\(_2\)), 25.9 (ArCH\(_2\)), 25.5 (CH\(_3\)), 20.7 (CH\(_3\)) ppm; MS (ES\(^+\)) \(m/\varepsilon\) 309 [MH\(^+\), \(^{81}\)Br], 307 [MH\(^+\), \(^{79}\)Br]; HRMS (ES\(^+\)) calcd for C\(_{15}\)H\(_{19}\)BrN\(_2\) [MH\(^+\), \(^{79}\)Br]:
307.0804; found 307.0803. Anal. calcd for C\textsubscript{13}H\textsubscript{19}BrN\textsubscript{2}: C, 58.64; H, 6.23; N, 9.11%. Found: C, 58.76; H, 6.25; N, 9.06%.

**Preparation of 2-Methyleneaziridines**

**General Method 3:**

An oven-dried 3-neck flask was fitted with an oven-dried cold-finger condenser and gas inlet. Iron (III) nitrate nonahydrate (0.10 mol%) was added and the system flushed with anhydrous ammonia. Ammonia was then condensed into the flask by the addition of dry-ice to the condenser. Sodium metal (3.5 equiv.) was added to the solution in small pieces, a blue colour was initially observed, which faded to grey as the suspension of sodium amide was formed. Upon cooling to –33 °C a solution of vinyl bromide 252 in Et\textsubscript{2}O (1:1 w/v) was added and the solution stirred for 10 min. The mixture was diluted with Et\textsubscript{2}O (20 mL) and quenched by the dropwise addition of water (20 mL) (CAUTION). Once the ammonia had evaporated, Et\textsubscript{2}O (50 mL) was added and the organic phase separated, washed with 10% NaOH solution (3 x 50 mL) and brine (3 x 50 mL). The organic phase was dried over MgSO\textsubscript{4}, filtered and concentrated *in vacuo*. Purification of the 2-methyleneaziridine was achieved by bulb-to-bulb distillation unless otherwise stated.
**3-[2-(2-Methyleneaziridin-1-yl)ethyl]indole (244a)**.\(^\text{18}\)

![Chemical Structure](image)

Sodium amide, generated from sodium (1.08 g, 47.1 mmol) and iron (III) nitrate nonahydrate (2.0 mg, 5.0 µmol) in ammonia (100 mL), was reacted with vinyl bromide 252a (3.76 g, 13.5 mmol) as described in General Method 3. Purification by bulb-to-bulb distillation (175 °C, 0.1 Torr) afforded 249a (2.36 g, 88%) as a clear colourless oil. \(\nu_{\text{max}}\) (film) 3412, 1766, 1619, 1455, 1339 cm\(^{-1}\); \(\delta_\text{H}\) (400 MHz, CDCl\(_3\)) 8.06 (1H, br s, indole NH), 7.60 (1H, d, \(J = 6.8\) Hz, Ar), 7.32 (1H, d, \(J = 8.1\) Hz, Ar), 7.18 (1H, t, \(J = 7.5\) Hz, Ar), 7.11 (1H, t, \(J = 7.5\) Hz, Ar), 7.00 (1H, s, Ar), 4.71 (1H, s, =CHH), 4.69 (1H, s, =CHH), 3.10 (2H, t, \(J = 7.5\) Hz, NCH\(_2\)), 2.84 (2H, t, \(J = 7.5\) Hz, ArCH\(_2\)), 2.06 (2H, s, ring CH\(_2\)) ppm; \(\delta_\text{C}\) (100 MHz, CDCl\(_3\)) 137.4 (C, Ar), 136.3 (C=), 127.5 (C, Ar), 122.0 (CH, Ar), 121.9 (CH, Ar), 119.3 (CH, Ar), 118.8 (CH, Ar), 113.6 (C, Ar), 111.2 (CH, Ar), 83.2 (=CH\(_2\)), 60.0 (NCH\(_2\)), 30.9 (ring CH\(_2\)), 25.9 (ArCH\(_2\)) ppm; MS (ES\(^+\)) \(m/\text{z}\) 199 [MH\(^+\)]; HRMS (ES\(^+\)) calcd for C\(_{13}\)H\(_{15}\)N\(_2\) [MH\(^+\)]: 199.1230; found 199.1231.
Chapter 6

5-Methoxy-3-[2-(2-methyleneaziridin-1-yl)ethyl]-1H-indole (249b).

Sodium amide, generated from sodium (585 mg, 25.4 mmol) and iron (III) nitrate nonahydrate (12.0 mg 29.7 µmol) in ammonia (50 mL), was reacted with vinyl bromide 252b (2.25 g, 7.27 mmol) as described in General Method 3. 249b (1.44 g, 87%) was isolated as a brown oil which was characterised and used without further purification. $\nu_{\text{max}}$ (film) 2938, 1766, 1623, 1583, 1484 cm$^{-1}$; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.98 (1H, br s, indole NH), 7.22 (1H, d, $J = 8.8$ Hz, Ar), 7.04 (1H, d, $J = 2.1$ Hz, Ar), 7.01 (1H, m, Ar), 6.85 (1H, dd, $J = 2.4$, 8.8 Hz, Ar), 4.71 (1H, d, $J = 1.3$ Hz, –CHH), 4.69 (1H, s, –CHH), 3.86 (3H, s, OCH$_3$), 3.06 (2H, t, $J = 7.5$ Hz, NCH$_2$), 2.82 (2H, t, $J = 7.5$ Hz, ArCH$_2$), 2.07 (2H, s, ring CH$_2$) ppm; $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 153.9 (CO, Ar)), 137.4 (C, Ar), 131.5 (=C), 127.8 (C, Ar), 122.7 (CH, Ar), 113.4 (C, Ar), 112.1 (CH, Ar), 111.9 (CH, Ar), 100.8 (CH, Ar), 83.1 (=CH$_2$), 59.9 (NCH$_2$), 55.9 (CH$_3$), 30.9 (ring CH$_2$), 25.9 (ArCH$_2$) ppm; MS (ES$^+$) $m/z$ 229 [MH$^+$]; HRMS (ES$^+$) calcd for C$_{14}$H$_{17}$N$_2$O [MH$^+$]: 229.1335; found 229.1333.
1-Methyl-3-[2-(2-methyleneaziridin-1-yl)ethyl]-1H-indole (249c).

Sodium amide, generated from sodium (403 mg, 17.5 mmol) and iron (III) nitrate nonahydrate (12.0 mg, 29.7 µmol) in ammonia (50 mL), was reacted with vinyl bromide 252c (1.47 g, 5.0 mmol) as described in General Method 3. Purification by bulb-to-bulb distillation (185 °C, 0.1 Torr) gave 249c (741 mg, 70%) as a yellow oil. $\nu_{\text{max}}$ (film) 3051, 1765, 1615, 1472, 1173 cm$^{-1}$; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.59 (1H, d, $J = 7.9$ Hz, Ar), 7.29 (1H, d, $J = 8.4$ Hz, Ar), 7.24-7.19 (1H, m, Ar), 7.12-7.08 (1H, m, Ar), 6.91 (1H, s, Ar), 4.72-4.71 (1H, m, =CH$_2$), 4.68 (1H, s, =CHH), 3.74 (3H, s, NCH$_3$), 3.08 (2H, t, $J = 7.6$ Hz, NCH$_2$), 2.82 (2H, t, $J = 7.6$ Hz, ArCH$_2$), 2.07 (2H, s, ring CH$_2$) ppm; $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 136.4 (C, Ar), 135.9 (C), 127.8 (C, Ar), 125.6 (CH), 120.5 (CH, Ar), 117.8 (CH, Ar), 117.7 (CH, Ar), 111.1 (C, Ar), 108.2 (CH, Ar), 81.9 (C), 59.2 (NCH$_2$), 31.5 (CH$_3$), 29.8 (ring CH$_2$), 24.7 (Ar CH$_2$) ppm; MS (EI$^+$) $m/z$ 212 [M$^+$], 211 [M–H$^+$]; HRMS (EI$^+$) calcd for C$_{14}$H$_{15}$N$_2$ [M–H$^+$]: 211.1235; found 211.1243. Anal. calcd for C$_{14}$H$_{16}$N$_2$: C, 79.21; H, 7.60; N, 13.20%. Found: C, 79.25; H, 7.70; N, 13.11%.
3-[2-(2-Methyleneaziridin-1-yl)propyl]-1H-indole (249d).

Sodium amide, generated from sodium (1.17 g, 50.9 mmol) and iron (III) nitrate nonahydrate (12.0 mg, 29.7 µmol) in ammonia (100 mL), was reacted with vinyl bromide 252d (4.28 g, 14.54 mmol) as described in General Method 3. 249d (2.92 g, 94%) was isolated as a brown oil which was characterised and used without further purification. $\nu_{\text{max}}$ (film) 2967, 1771, 1454, 1162, 1089 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 8.11 (1H, br s, indole NH), 7.58 (1H, d, $J$ = 7.6 Hz, Ar), 7.35 (1H, d, $J$ = 8.0 Hz, Ar), 7.21-7.17 (1H, m, Ar), 7.13-7.09 (1H, m, Ar), 7.02 (1H, d, $J$ = 2.0 Hz, Ar), 4.73 (1H, m, =CHH), 4.67 (1H, s, =CHH), 3.16 (1H, dd, $J$ = 5.1, 14.1 Hz, ArCHH), 2.91 (1H, dd, $J$ = 8.0, 14.1 Hz, ArCHH), 2.27-2.18 (1H, m, CH), 2.06 (1H, s, ring CHH), 2.00 (1H, s, ring CHH), 1.20 (3H, d, $J$ = 6.6 Hz, CH$_3$) ppm; $\delta_C$ (100 MHz, CDCl$_3$) 135.8 (C, Ar), 135.2 (=C), 126.7 (C, Ar), 121.6 (CH, Ar), 120.8 (CH, Ar), 118.2 (CH, Ar), 117.9 (CH, Ar), 112.0 (C, Ar), 110.1 (CH, Ar), 81.9 (=CH$_2$) 63.6 (CH), 31.8 (ArCH$_2$), 28.7 (ring CH$_2$), 18.8 (CH$_3$) ppm; MS (ES$^+$) $m/z$ 213 [MH$^+$]; HRMS (ES$^+$) calcd for C$_{14}$H$_{17}$N$_2$ [MH$^+$] 213.1386, found 213.1386.
N-(2-(1-methyl-1H-indol-3-yl)ethyl)-1-phenyloctan-3-amine (260).

Re-purified Copper (I) iodide (36 mg, 0.19 mmol) in a round-bottomed flask was flame dried under vacuum and then purged with nitrogen (three cycles performed). THF (4 mL) was added and the mixture cooled to –30 °C, whereupon n-butylmagnesium chloride (2M in THF, 1.06 mL, 2.12 mmol) was added. After 10 min, methyleneaziridine 249c (200 mg, 0.94 mmol) in THF (2 mL) was added and the reaction mixture stirred at room temperature for 16 h. Upon cooling to 0 °C, benzyl chloride (0.16 mL, 1.39 mmol) was added dropwise, and the mixture heated at 40 °C for 20 h. Upon cooling to room temperature, the reaction mixture was added via cannula to a stirred solution of sodium borohydride (140 mg, 3.70 mmol) in glacial acetic acid (2.5 mL) at 10 °C. After 2 h, water (2 mL) was added slowly, followed by 10% NaOH (2 mL) and EtOAc (4 mL). Stirring was continued for 10 min, then the mixture was extracted with EtOAc (3 x 20 mL) and the combined organic phases were washed with saturated NH₄Cl solution (3 x 20 mL), saturated NaHCO₃ solution (3 x 20 mL) and brine (3 x 30 mL). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. Purification on silica gel (5% methanol in dichloromethane) afforded 260 (228 mg, 69%) as a brown oil. Rₓ = 0.23 (5% methanol in dichloromethane); νₓ max (film) 2927, 1585, 1454, 1327, 698 cm⁻¹; δₓH (400 MHz, CDCl₃) 7.53 (1H, d, J = 7.8 Hz, Ar), 7.19-6.98 (8H, m, Ar), 6.80 (1H, s, Ar), 3.62 (3H, s, NCH₃), 2.94-2.84 (4H, m, CH₂CH₂NH), 2.51-2.45 (3H, m, CH₂Ar + CH), 1.68-1.62 (2H, m, CHCH₂), 1.37 (1H, br s, NH), 1.18-1.22 (8H, m, 4 x CH₂), 0.76 (3H, t, J = 6.9 Hz, CH₃) ppm; δₓC (100 MHz, CDCl₃)
142.4 (C, Ar), 137.2 (C, Ar), 128.4 (CH, Ar), 127.9 (CH, Ar), 126.9 (C, Ar), 125.7 (CH, Ar), 121.7 (CH, Ar), 119.1 (CH, Ar), 118.8 (CH, Ar), 112.2 (C, Ar), 109.3 (CH, Ar), 57.1 (CH), 47.0 (NCH$_2$), 35.3 (CH$_2$), 33.5 (CH$_2$), 32.6 (NCH$_3$), 32.1 (CH$_2$), 32.0 (CH$_2$), 25.6 (CH$_2$), 25.4 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$) ppm; MS (ES$^+$) m/z 363 [MH$^+$]; HRMS (ES$^+$) calcd for C$_{25}$H$_{34}$N$_2$ [MH$^+$]: 363.2722; found 363.2752.

**Synthesis of 1,1 disubstituted tetrahydro-β-carbolines.**

**General Method 4:**

![Chemical Structure](image)

To a stirred solution of methyleneaziridine 249 (1 equiv.) in CH$_2$Cl$_2$ (2 mL) at −30 °C was added BF$_3$·Et$_2$O (1 equiv.) dropwise. After 5 minutes, the alcohol (2 equiv.) was added dropwise and the solution was allowed to warm to room temperature and stirred for 16 hours. The mixture was poured into 10% NaOH (20 mL), at which point a colour change from red to yellow was observed. The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO$_4$, filtered through a pad of decolourising charcoal and concentrated *in vacuo*. Purification of the tetrahydro-β-carboline was achieved by column chromatography with silica pre-treated with Et$_3$N.
Chapter 6

1-[(Benzyloxy)methyl]-2,3,4,9-tetrahydro-1-methyl-1H-pyrido[3,4-b]indole (269a).

Methyleneaziridine 249a (200 mg, 1.01 mmol) was reacted with BF$_3$·Et$_2$O (130 µL, 1.03 mmol) and benzyl alcohol (210 µL, 2.03 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded 269a (226 mg, 73%) as a brown oil. R$_f$ = 0.22 (5% methanol in dichloromethane); $\nu_{\text{max}}$ (film) 2853, 1724, 1452, 1297, 1092 cm$^{-1}$; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 8.22 (1H, br s, indole NH), 7.48 (1H, d, $J = 7.5$ Hz, Ar), 7.36-7.24 (6H, m, Ar), 7.15-7.05 (2H, m, Ar), 4.54 (1H, d, $J = 11.9$ Hz, OCHH), 4.50 (1H, d, $J = 11.9$ Hz, OCHH), 3.52 (1H, d, $J = 8.5$ Hz, OCHH), 3.21-3.10 (2H, m, NCH$_2$), 2.70 (2H, t, $J = 5.8$ Hz, ArCH$_2$), 1.70 (1H, br s, NH), 1.48 (3H, s, CH$_3$) ppm; $\delta_{\text{C}}$ (100 MHz, CDCl$_3$) 138.4 (C, Ar), 138.1 (C, Ar), 135.7 (C, Ar), 128.6 (CH, Ar), 128.0 (CH, Ar), 127.9 (CH, Ar), 127.2 (C, Ar), 121.6 (CH, Ar), 119.2 (CH, Ar), 118.3 (CH, Ar), 110.9 (CH, Ar), 108.2 (C, Ar), 77.8 (OCH$_2$), 73.8 (CH$_2$O), 53.4 (C), 39.9 (CH$_2$CH$_2$), 25.5 (CH$_3$), 22.9 (CH$_2$CH$_2$) ppm; MS (ES$^+$) $m/z$ 307 [MH$^+$]; HRMS (ES$^+$) for C$_{20}$H$_{23}$N$_2$O [MH$^+$]: 307.1805; found 307.1802.
1-(Ethoxymethyl)-2,3,4,9-tetrahydro-1-methyl-1H-pyrido[3,4-b]indole (270).

Methyleneaziridine 249a (200 mg, 1.01 mmol) was reacted with BF₃·Et₂O (130 µL, 1.03 mmol) and benzyl alcohol (110 µL, 1.11 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded 269a (169 mg, 54%) as a brown oil, with the data described above. Further elution afforded 270 (33 mg, 14%) as a brown oil. Rᵣ = 0.21 (5% methanol in dichloromethane); νₓ max (film) 2971, 2869, 1451, 1296, 1104 cm⁻¹; δₓH (400 MHz, CDCl₃) 8.37 (1H, br s, indole NH), 7.48 (1H, d, J = 7.4 Hz, Ar), 7.29 (1H, d, J = 8.1 Hz, Ar), 7.15-7.11 (1H, m, Ar), 7.09-7.05 (1H, m, Ar), 3.54-3.45 (4H, m, CH₂OCH₂), 3.22-3.11 (2H, m, NCH₂), 2.70 (2H, t, J = 5.6 Hz, ArCH₂), 2.06 (1H, br s, NH), 1.47 (3H, s, CCH₃), 1.21 (3H, t, J = 6.9 Hz, CH₂CH₃) ppm; δₓC (100 MHz, CDCl₃) 138.6 (C, Ar), 135.7 (C, Ar), 127.2 (C, Ar), 121.5 (CH, Ar), 119.2 (CH, Ar), 118.2 (CH, Ar), 111.0 (CH, Ar), 108.0 (C, Ar), 78.0 (OCH₂), 67.1 (OCH₂), 53.4 (C), 39.8 (NCH₂), 25.4 (CCH₃), 22.9 (ArCH₂), 15.3 (CH₂CH₃) ppm; MS (LSIMS⁺) m/z 245.1 [MH⁺]; HRMS (LSIMS⁺) calculated for C₁₅H₂₀DN₂O [MD⁺]: 246.1711; found 246.1714.
1-Methyl-1-(propoxymethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (269b).

Methyleneaziridine 249a (200 mg, 1.01 mmol) was reacted with BF$_3$.Et$_2$O (130 µL, 1.03 mmol) and propan-1-ol (150 µL, 2.01 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded 269b (217 mg, 83%) as a brown oil. R$_f$ = 0.22 (5% methanol in dichloromethane); $\nu_{\text{max}}$ (film) 2962, 2919, 2850, 1452, 1297 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 8.31 (1H, br s, indole NH), 7.48 (1H, d, $J = 7.9$ Hz, Ar), 7.30 (1H, d, $J = 7.9$ Hz, Ar), 7.16-7.11 (1H, m, Ar), 7.10-7.05 (1H, m, Ar), 3.51-3.37 (4H, m, CH$_2$OCH$_2$), 3.24-3.12 (2H, m, NCH$_2$), 2.71 (2H, t, $J = 5.7$ Hz, ArCH$_2$), 1.68-1.59 (3H, br m, NH and CH$_2$C$_3$H$_7$), 1.49 (3H, s, CCH$_3$), 0.95 (3H, t, $J = 7.3$ Hz, CH$_2$CH$_3$) ppm; $\delta_C$ (100 MHz, CDCl$_3$) 138.7 (C, Ar), 135.7 (C, Ar), 127.2 (C, Ar), 121.5 (CH, Ar), 119.1 (CH, Ar), 118.2 (CH, Ar), 110.9 (CH, Ar), 108.0 (C, Ar), 78.5 (OCH$_2$), 73.4 (OCH$_2$), 53.5 (C), 39.9 (NCH$_2$), 25.5 (CCH$_3$), 22.95 (CH$_2$CH$_3$), 22.90 (ArCH$_2$), 10.8 (CH$_2$CH$_3$) ppm; MS (LSIMS$^+$) m/z 259 [MH$^+$]; HRMS (LSIMS$^+$) calculated for C$_{16}$H$_{23}$N$_2$O [MH$^+$]: 259.1810; found 259.1820.
1-(Cyclohexyloxymethyl)-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (269c).

Methyleneaziridine 249a (200 mg, 1.01 mmol) was reacted with BF$_3$·Et$_2$O (130 µL, 1.03 mmol) and cyclohexanol (210 µL, 1.99 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded 269c (191 mg, 63%) as a brown oil. $R_f = 0.20$ (5% methanol in dichloromethane); $\nu_{\text{max}}$ (film) 2928, 2853, 1449, 1297, 1093 cm$^{-1}$; $\delta$H (400 MHz, CDCl$_3$) 8.45 (1H, br s, indole NH), 7.54 (1H, d, $J = 7.8$ Hz, Ar), 7.37 (1H, d, $J = 8.2$ Hz, Ar), 7.22-7.18 (1H, m, Ar), 7.16-7.11 (1H, m, Ar), 3.59 (1H, d, $J = 8.2$ Hz, OCH$_2$H), 3.55 (1H, d, $J = 8.2$ Hz, OCHH), 3.38-3.20 (3H, m, OCH + NCH$_2$), 2.79 (2H, t, $J = 5.7$ Hz, ArCH$_2$), 1.98-1.29 (11H, m, 5 x CH$_2$ + NH), 1.57 (3H, s, CH$_3$) ppm; $\delta$C (100 MHz, CDCl$_3$) 138.9 (C, Ar), 135.6 (C, Ar), 127.1 (C, Ar), 121.4 (CH, Ar), 119.1 (CH, Ar), 118.2 (CH, Ar), 110.9 (CH, Ar), 107.8 (C, Ar), 78.2 (OCH), 75.9 (OCH$_2$), 53.4 (C), 39.9 (NCH$_2$), 32.3 (CH$_2$), 31.9 (CH$_2$), 25.8 (CH$_2$), 25.6 (CH$_3$), 23.9 (CH$_2$), 22.9 (ArCH$_2$) ppm; MS (ES$^+$) $m/z$ 299 [MH$^+$]; HRMS (ES$^+$) calcd for C$_{19}$H$_{27}$N$_2$O [MH$^+$]: 299.2118; found 299.2121.
1-(tert-Butoxymethyl)-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (269d).

Methyleneaziridine 249a (200 mg, 1.01 mmol) was reacted with BF$_3$.Et$_2$O (130 µL, 1.03 mmol) and 2-methyl-propanol (190 µL, 1.99 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded 269d (160 mg, 58%) as a brown oil. R$_f$ = 0.28 (5% methanol in dichloromethane); $\nu_{\text{max}}$ (film) 2848, 1431, 1363, 1192, 1093 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 8.38 (1H, br s, indole NH), 7.48 (1H, d, $J = 7.9$ Hz, Ar), 7.31 (1H, d, $J = 7.9$ Hz, Ar), 7.16-7.11 (1H, m, Ar), 7.10-7.05 (1H, m, Ar), 3.45 (1H, d, $J = 7.8$ Hz, OCH$_3$), 3.39 (1H, d, $J = 7.8$ Hz, OCH$_2$), 3.26-3.14 (2H, m, NCH$_2$), 2.72 (2H, t, $J = 5.6$ Hz, ArCH$_2$), 1.77 (1H, br s, NH), 1.48 (3H, s, CH$_3$), 1.21 (9H, s, (CH$_3$)$_3$) ppm; $\delta_C$ (100 MHz, CDCl$_3$) 139.2 (C, Ar), 135.6 (C, Ar), 127.2 (C, Ar), 121.4 (CH, Ar), 119.1 (CH, Ar), 118.2 (CH, Ar), 110.9 (CH, Ar), 107.8 (C, Ar), 73.5 (OCH$_2$), 69.8 (C(CH$_3$)$_3$), 53.2 (C), 40.0 (NCH$_2$), 27.6 (C(CH$_3$)$_3$), 25.6 (CCH$_3$), 22.9 (ArCH$_2$) ppm; MS (LSIMS$^+$) $m/z$ 273 [MH$^+$]; HRMS (LSIMS$^+$) calcd for C$_{17}$H$_{25}$N$_2$O [MH$^+$]: 273.1967; found 273.1973.
1-(Allyloxymethyl)-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (269e).

Methyleneaziridine 249a (200 mg, 1.01 mmol) was reacted with BF$_3$·Et$_2$O (130 µL, 1.03 mmol) and allyl alcohol (140 µL, 2.06 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded 269e (206 mg, 80%) as a brown oil. $R_f = 0.22$ (5% methanol in dichloromethane); $\nu_{\text{max}}$ (film) 2972, 2901, 1451, 1297, 1075 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 8.27 (1H, br s, indole NH), 7.48 (1H, d, $J = 7.8$ Hz, Ar), 7.29 (1H, d, $J = 7.8$ Hz, Ar), 7.16-7.12 (1H, m, Ar), 7.09-7.05 (1H, m, Ar), 5.95-5.85 (1H, m, =CHCH$_2$), 5.33-5.23 (1H, m, =CHH), 5.19-5.09 (1H, m, =CHH), 4.05-3.96 (2H, m, OCH$_2$), 3.52 (1H, d, $J = 8.6$ Hz, OCHH), 3.49 (1H, d, $J = 8.6$ Hz, OCHH), 3.24-3.12 (2H, m, NCH$_2$), 2.71 (2H, t, $J = 5.7$ Hz, ArCH$_2$), 1.69 (1H, br s, NH), 1.49 (3H, s, CH$_3$) ppm; $\delta_C$ (100 MHz, CDCl$_3$) 138.4 (C, Ar), 135.7 (C, Ar), 134.6 (=CH), 127.2 (C, Ar), 121.5 (CH, Ar), 119.2 (CH, Ar), 118.3 (CH, Ar), 117.4 (=CH$_2$), 110.9 (CH, Ar), 108.2 (C, Ar), 77.8 (OCH$_2$), 72.6 (OCH$_2$), 53.3 (C), 39.9 (NCH$_2$), 25.5 (CH$_3$), 22.9 (ArCH$_2$) ppm; MS (ES$^+$) $m/z$ 257 [MH$^+$]; HRMS (ES$^+$) calcd for C$_{16}$H$_{21}$N$_2$O [MH$^+$]: 257.1648; found 257.1648.
1-Methyl-1-[(pent-4-ynyloxy)methyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (269f).

Methyleneaziridine 249a (200 mg, 1.01 mmol) was reacted with BF$_3$·Et$_2$O (130 µL, 1.03 mmol) and 4-pentyn-1-ol (190 µL, 2.04 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded 269f (201 mg, 71%) as a brown oil. R$_f$ = 0.22 (5% methanol in dichloromethane); $\nu_{\text{max}}$ (film) 3287, 2862, 1620, 1452, 1297 cm$^{-1}$; $\delta$$_H$ (400 MHz, CDCl$_3$) 8.33 (1H, br s, indole NH), 7.49 (1H, d, $J$ = 8.4 Hz, Ar), 7.33 (1H, d, $J$ = 8.4 Hz, Ar), 7.17-7.13 (1H, m, Ar), 7.10-7.06 (1H, m, Ar), 3.59 (2H, t, $J$ = 6.0 Hz, OCH$_2$), 3.54 (1H, d, $J$ = 8.4 Hz, OCHH), 3.48 (1H, d, $J$ = 8.4 Hz, OCHH), 3.26-3.14 (2H, m, NCH$_2$), 2.73 (2H, t, $J$ = 5.7 Hz, ArCH$_2$), 2.39-2.25 (2H, m, CH$_2$CH$_2$CH$_2$), 2.01 (1H, t, $J$ = 2.8 Hz, =CH), 1.88-1.80 (2H, m, CH$_2$C=CH), 1.65 (1H, br s, NH), 1.51 (3H, s, CH$_3$) ppm; $\delta$$_C$ (100 MHz, CDCl$_3$) 138.4 (C, Ar), 135.7 (C, Ar), 127.1 (C, Ar), 121.5 (CH, Ar), 119.2 (CH, Ar), 118.2 (CH, Ar), 111.0 (CH, Ar), 108.1 (C, Ar), 84.0 (C=), 78.5 (OCH$_2$), 70.2 (OCH$_2$), 69.0 ($=CH$), 53.4 (C), 39.9 (NCH$_2$), 28.3 (CH$_2$C=CH), 25.4 (CH$_3$), 22.9 (ArCH$_2$), 15.5 (CH$_2$CH$_2$CH$_2$) ppm; MS (LSIMS$^+$) $m/z$ 283 [MH$^+$]; HRMS (LSIMS$^+$) calcd for C$_{18}$H$_{23}$N$_2$O [MH$^+$]: 283.1806; found 283.1810.
1-(Benzyloxymethyl)-6-methoxy-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4 indole (269g).

Methyleneaziridine 249b (412 mg, 1.80 mmol) was reacted with BF₃·Et₂O (230 µL, 1.81 mmol) and benzyl alcohol (370 µL, 3.58 mmol) as described in General Method 4. Purification on silica gel (3% methanol in dichloromethane) afforded 269g (401 mg, 66%) as a brown oil. Rₐ = 0.21 (5% methanol in dichloromethane); ν_max (film) 2935, 1705, 1625, 1590, 1453 cm⁻¹; δ_H (400 MHz, CDCl₃) 8.14 (1H, br s, indole NH), 7.37-7.28 (5H, m, Ar), 7.15 (1H, d, J = 8.7 Hz, Ar), 6.95 (1H, d, J = 2.4 Hz, Ar), 6.79 (1H, dd, J = 2.4, 8.7 Hz, Ar), 4.57 (1H, d, J = 12.2 Hz, OCHH), 4.51 (1H, d, J = 12.2 Hz, OCHH), 3.84 (3H, s, OCH₃), 3.56 (1H, d, J = 8.4 Hz, OCHH), 3.53 (1H, d, J = 8.4 Hz, OCHH), 3.23-3.11 (2H, m, NCH₂), 2.69 (2H, t, J = 5.7 Hz, ArCH₂), 1.92 (1H, br s, NH), 1.49 (3H, s, CH₃) ppm; δ_C (100 MHz, CDCl₃) 153.9 (C, Ar), 139.1 (C, Ar), 137.9 (C, Ar), 130.8 (C, Ar), 128.5 (CH, Ar), 127.9 (CH, Ar), 127.8 (CH, Ar), 127.4 (C, Ar), 111.5 (CH, Ar), 111.4 (CH, Ar), 107.9 (C, Ar), 100.6 (C, Ar), 77.7 (OCH₂), 73.7 (OCH₂), 56.1 (OCH₃), 53.5 (C), 39.8 (NCH₂), 25.4 (CH₃), 22.8 (ArCH₂) ppm; MS (ES⁺) m/z 337 [MH⁺]; HRMS (ES⁺) calcd for C₂₁H₂₅N₂O₂ [MH⁺]: 337.1911; found 337.1911.
Methyleneaziridine 249c (200 mg, 0.94 mmol) was reacted with BF₃·Et₂O (120 µL, 0.95 mmol) and benzyl alcohol (195 µL, 1.89 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded 269h (130 mg, 43%) as a brown oil. Rᵣ = 0.25 (5% MeOH in CH₂Cl₂); νₑₑₓₑ (film) 2928, 1705, 1469, 1453, 1091 cm⁻¹; δₑₑ (400 MHz, CDCl₃) 7.48 (1H, d, J = 7.8 Hz, Ar), 7.33-7.23 (6H, m, Ar), 7.21-7.17 (1H, m, Ar), 7.10-7.06 (1H, m, Ar), 4.56 (1H, d, J = 12.3 Hz, OCH₂), 4.49 (1H, d, J = 12.3 Hz, OCH₂), 3.87 (1H, d, J = 9.7 Hz, OCH₂), 3.63 (3H, s, NCH₃), 3.58 (1H, d, J = 9.7 Hz, OCH₂), 3.22-3.07 (2H, m, NCH₂), 2.77 (2H, t, J = 5.7 Hz, ArCH₂), 1.93 (1H, br s, NH), 1.49 (3H, s, CH₃) ppm; δₑ (100 MHz, CDCl₃) 138.0 (C, Ar), 137.8 (C, Ar), 137.4 (C, Ar), 128.4 (CH, Ar), 127.8 (CH, Ar), 127.7 (CH, Ar), 126.7 (C, Ar), 121.4 (CH, Ar), 118.9 (CH, Ar), 118.2 (CH, Ar), 110.0 (C, Ar), 108.7 (CH, Ar), 74.7 (OCH₂), 73.3 (OCH₂), 55.0 (C), 39.4 (NCH₂), 31.6 (NCH₃), 23.9 (CH₃), 23.3 (ArCH₂) ppm; MS (ES⁺) m/z 321 [MH⁺]; HRMS (ES⁺) calcd for C₂₁H₂₅N₂O [MH⁺]: 321.1961; found 321.1962.
1-(Allyloxy)methyl)-1,9-dimethyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (269i).

Methyleneaziridine 249c (200 mg, 0.94 mmol) was reacted with BF₃·Et₂O (120 µL, 0.95 mmol) and allyl alcohol (130 µL, 1.91 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) gave 269i (94 mg, 37%) as a brown oil. R₆ = 0.23 (5% methanol in dichloromethane); νₘₐₓ (film) 2930, 1647, 1470, 1364, 1237 cm⁻¹; δₕ (400 MHz, CDCl₃) 7.48 (1H, d, J = 8.0 Hz, Ar), 7.27 (1H, d, J = 8.7 Hz, Ar), 7.23-7.18 (1H, m, Ar), 7.11-7.06 (1H, m, Ar), 5.91-5.81 (1H, m, =CHCH₂), 5.25-5.15 (2H, m, =CH₂), 3.99 (2H, d, J = 5.8 Hz, OCH₂), 3.89 (1H, d, J = 9.6 Hz, OCHH), 3.78 (3H, s, NCH₃), 3.59 (1H, d, J = 9.6 Hz, OCHH), 3.25-3.09 (2H, m, NCH₂), 2.77 (2H, t, J = 5.7 Hz, ArCH₂), 1.95 (1H, br s, NH), 1.51 (3H, s, CH₃) ppm; δc (100 MHz, CDCl₃) 137.8 (C, Ar), 137.4 (C, Ar), 134.6 (CH, Ar), 126.7 (C, Ar), 121.5 (CH, Ar), 118.9 (CH, Ar), 118.2 (CH, Ar), 117.4 (=CH₂), 110.0 (C, Ar), 108.7 (CH, Ar), 74.9 (OCH₂), 72.4 (OCH₂), 55.0 (C), 39.3 (NCH₂), 31.8 (NCH₃), 23.9 (CH₃), 23.3 (ArCH₂), ppm; MS (ES⁺) m/z 271 [MH⁺]; HRMS (ES⁺) calcd for C₁₇H₂₃N₂O [MH⁺]: 271.1805; found 271.1802.
(1R*,3R*)-1-[(Benzyloxy)methyl]-2,3,4,9-tetrahydro-1,3-dimethyl-1H-pyrido[3,4-b]indole (272).

Methyleneaziridine 249d (200 mg, 0.94 mmol) was reacted with BF₃·Et₂O (120 µL, 0.94 mmol) and benzyl alcohol (195 µL, 1.88 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded (1R*,3R*)-272 (190 mg, 63%) as a light brown oil. Rf = 0.25 (5% methanol in dichloromethane); νmax (film) 2862, 1707, 1453, 1307, 1092 cm⁻¹; δH (400 MHz, CDCl₃) 8.45 (1H, br s, indole NH), 7.46 (1H, d, J = 7.8 Hz, Ar), 7.41-7.33 (5H, m, Ar), 7.27 (1H, d, J = 8.0 Hz, Ar), 7.18-7.14 (1H, m, Ar), 7.11-7.07 (1H, m, Ar), 4.64 (1H, d, J = 11.6 Hz, OCHH), 4.58 (1H, d, J = 11.6 Hz, OCHH), 4.00-3.88 (2H, m, OCH₂), 3.63-3.53 (1H, m, NCH), 2.92 (1H, dd, J = 4.1, 15.7 Hz, ArCH₂H), 2.76-2.73 (1H, m, ArCH₃H), 1.74 (3H, s, CCH₃), 1.55 (3H, d, J = 6.3 Hz, CHCH₃), 1.25 (1H, br s, NH) ppm; δC (100 MHz, CDCl₃) 138.3 (C, Ar), 137.9 (C, Ar), 135.9 (C, Ar), 128.6 (CH, Ar), 128.0 (CH, Ar), 127.9 (CH, Ar), 126.9 (C, Ar), 121.5 (CH, Ar), 119.2 (CH, Ar), 118.2 (CH, Ar), 110.9 (CH, Ar), 108.3 (C, Ar), 78.6 (OCH₂), 73.7 (OCH₂), 55.5 (C), 45.1 (CH), 30.6 (CCH₃), 25.1 (ArCH₂), 22.6 (CHCH₃) ppm; MS (ES⁺) m/z 321 [MH⁺]; HRMS (ES⁺) calcd for C₂₁H₂₅N₂O [MH⁺] 321.1961, found 321.1960.
References


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Appendix
Appendix

$^1$H NMR spectra (400 MHz) of 155

$^{13}$C NMR spectra (100 MHz) of 155
Appendix

${}^{31}$P NMR spectra (161 MHz) of 155
Appendix

$^1$H NMR spectra (400 MHz) of 244d

$^{13}$C NMR spectra (100 MHz) of 244d
Appendix

$^1$H NMR spectra (400 MHz) of 267

$^{13}$C NMR spectra (100 MHz) of 267
Appendix

NOSEY correlation (400 MHz) of 267