New Reactions of

2-Methyleneaziridines

by

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To my friends in London, thanks for keeping me grounded and in the real world. It's been a while, see you shortly.

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.

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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

Ac	Acetyl
Ad	Adamantyl
AIBN	*azo-bis*-Isobutyronitrile
Anal.	Analysis
atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
Bus	*tert*-Butylsulfonyl
c	Cyclo
c.	Concentrated
ca.	*Circa*
Calcd	Calculated
cat.	Catalytic
Cbz	Carbobenzyloxy
cf.	*Confer*
Cp	Cyclopentadienyl
δ	Chemical shift
dba	Dibenzylidene acetone
(+)-DDB	(*S*,*S*)-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane
de	Diastereomeric excess
DPPBA	Diphenylphosphino benzoic acid
dr	Diastereomeric ratio

E	Electrophile
EI	Electron impact
ee	Enantiomeric excess
ES	Electrospray
equiv.	Molar equivalents
er	Enantiomeric ratio
EWG	Electron-withdrawing group
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectroscopy
HWE	Horner-Wadsworth-Emmons
i	Iso
IR	Infrared
L	Ligand
LA	Lewis acid
LDA	Lithium diisopropylamide
lit.	Literature value
LSIMS	Liquid secondary ion mass spectrometry
μ	micro
m.p.	Melting point
M	Metal
m-CPBA	*meta*-Chloroperoxybenzoic acid
MCR	Multi-component reaction
MS	Mass spectrometry
Napth	Naphthyl
NMO	*N*-Methylmorpholine-*N*-oxide

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*-
$t_{½}$	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.

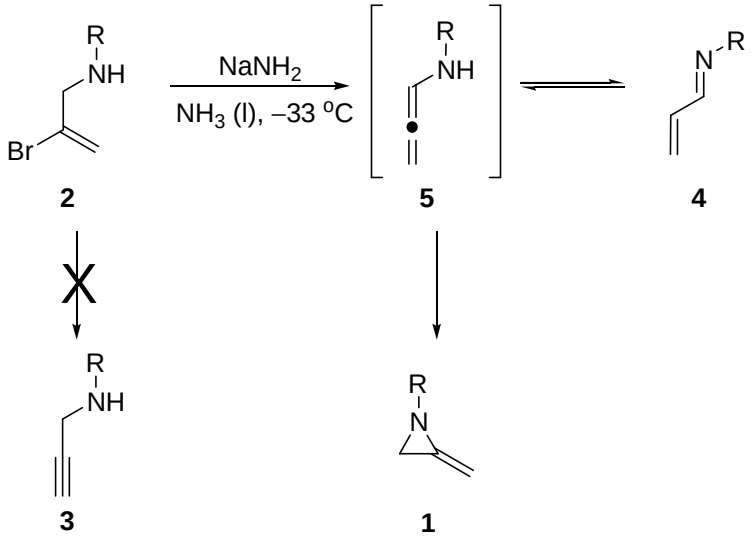
Figure 1.1. 2-Methyleneaziridine.

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).

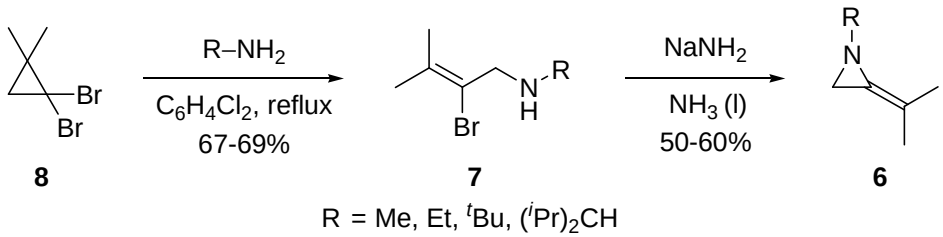


Scheme 1.1. Proposed formation of *N*-allylidene-alkylamines.

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]

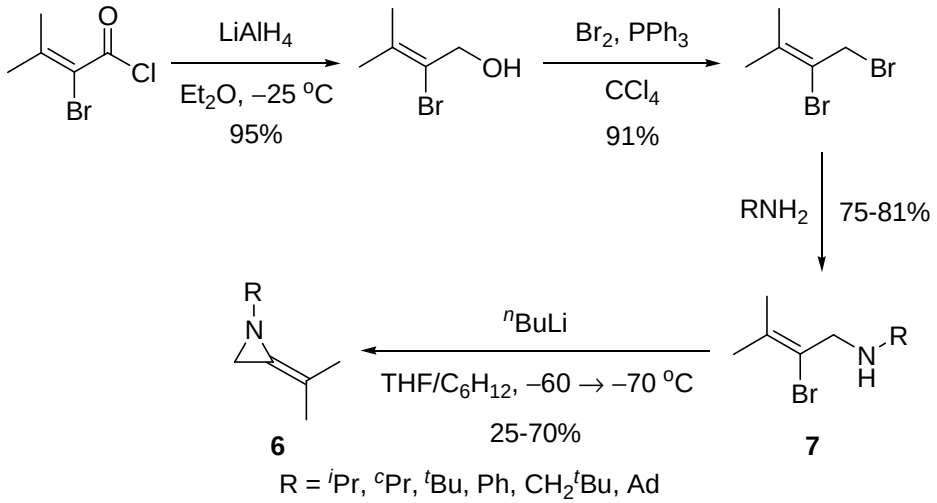
The cyclisation is very tolerant of a wide range of functional groups;[6] *N*-substituents include double bonds and aryl selenides,[7] benzyl and silyl ethers,[8] alcohols and acetals,[9] and non-racemic, chiral derivatives.[10,11] Substitution patterns on the exocyclic double bond include *gem*-di-methyl[12]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

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.[12] 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.[14] 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.

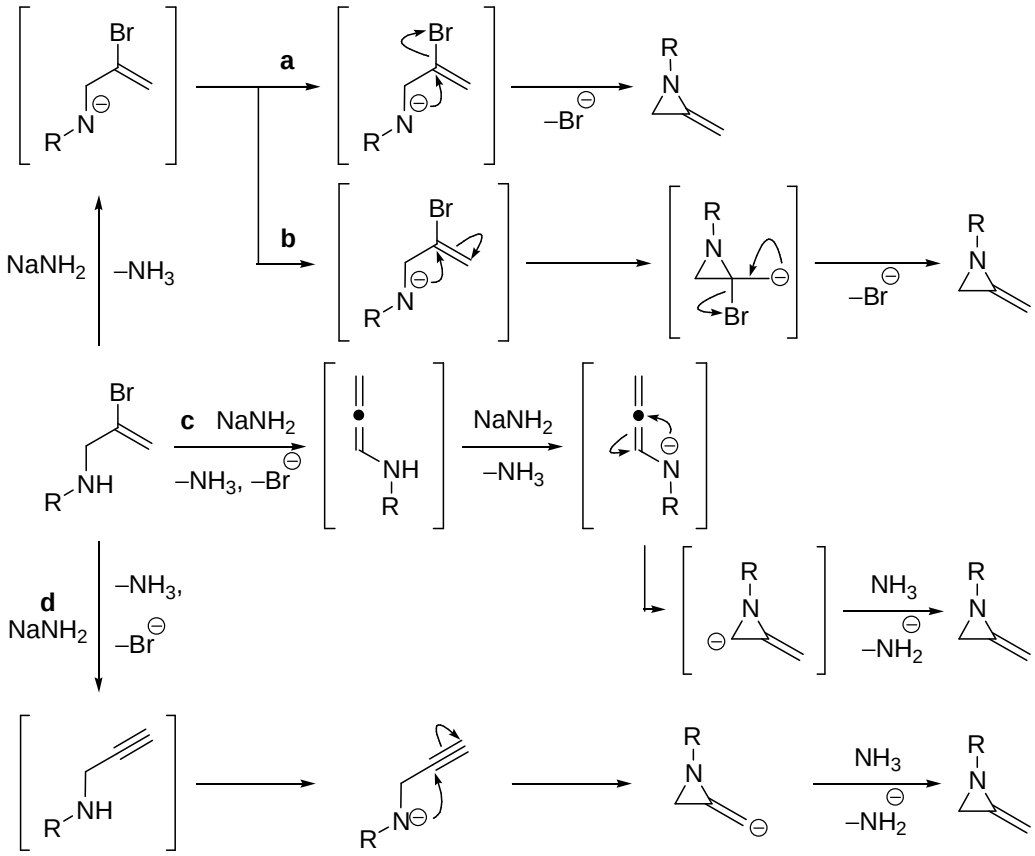
Steinberg *et al*. developed an alternative route to disubstituted methyleneaziridines **6**.[15] Their strategy involved ring-closing using *n*-butyl lithium in THF and hexanes at low temperatures. They also developed an alternate strategy to disubstituted vinyl bromides **7** as the conditions of Sandler[14] 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).



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.[16] They proposed four possible reaction mechanisms for the formation of methyleneaziridines; (i) displacement of the bromide ion by internal S_N2 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.[3]

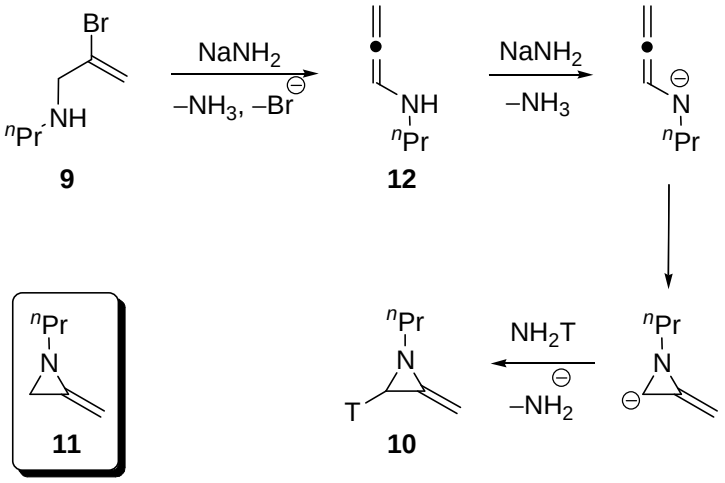


Scheme 1.4. Proposed mechanisms for the formation of methyleneaziridines.

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.

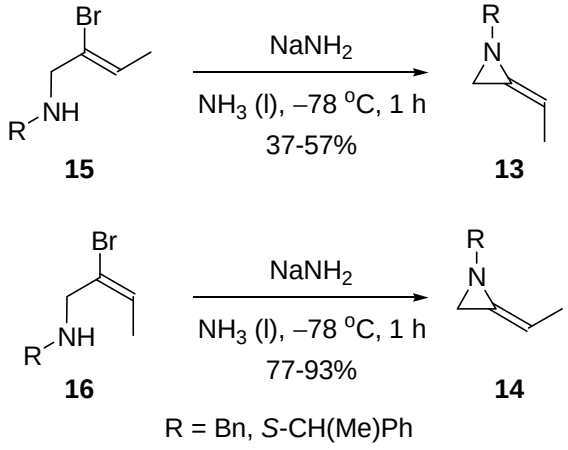
To examine whether proton exchange occurs during this process **11** was treated with sodium amide in tritium labelled ammonia and **10** treated with sodium amide in unlabelled ammonia. In neither case was there a change in the recorded

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).



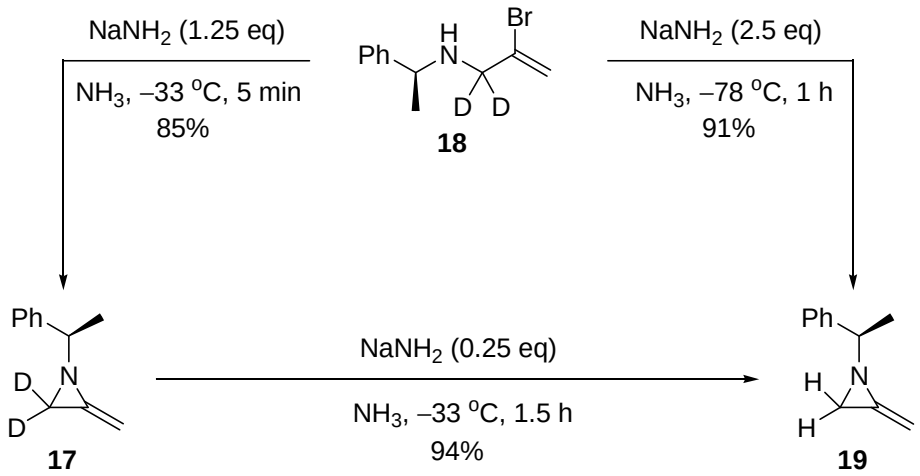
Scheme 1.5. Proposed elimination-addition mechanism.

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).



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 ($t_{½}$ ~ 10 s at –78 ^{o}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]

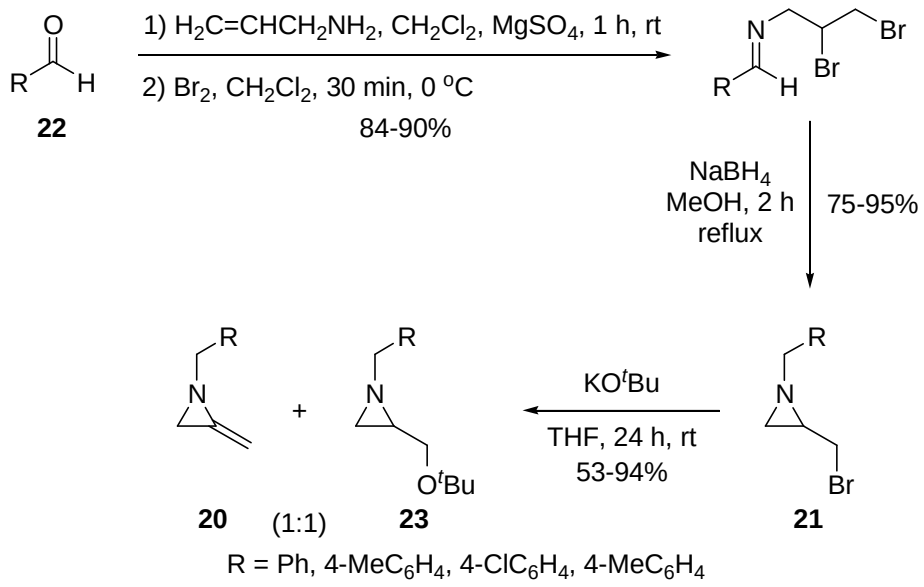


Scheme 1.7. Deuterium labelled cyclisation studies.

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 σ-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 β-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).

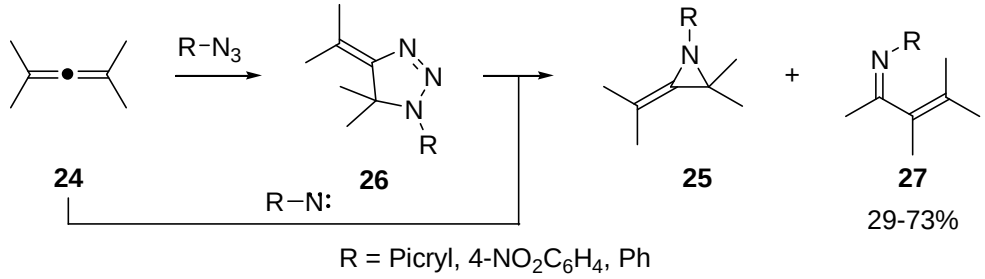


Scheme 1.8. Dehydrohalogenation of aziridines.

1.2.4 Nitrene addition to allenes

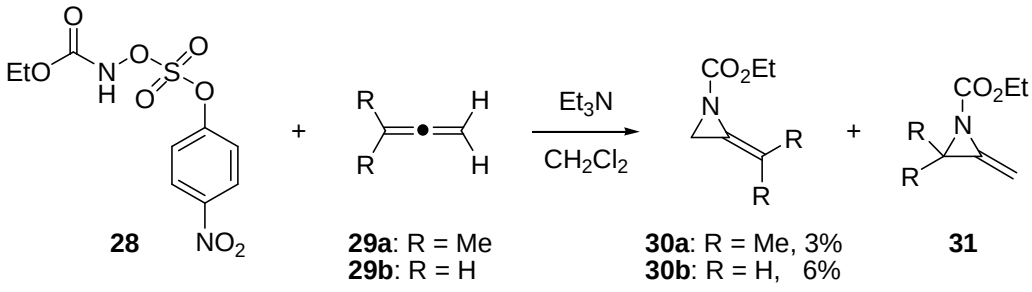
Bleiholder and Schecter postulated that methyleneaziridines could be synthesised by reaction of allenes with singlet nitrenes.[20] They expected that insertion of an azide into tetramethylallene (**24**) would give methyleneaziridine

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.

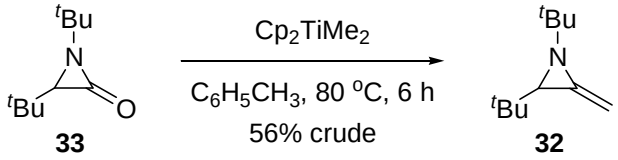
Bingham and Gilbert also investigated the use of nitrenes for the synthesis of methyleneaziridines.[21] They treated *N*-(*p*-nitrobenzenesulphonyloxy)urethane (**28**) with triethylamine to generate ethoxycarbonylnitrene *in situ*, which was then reacted with allenes **29** to give the corresponding 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.

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.

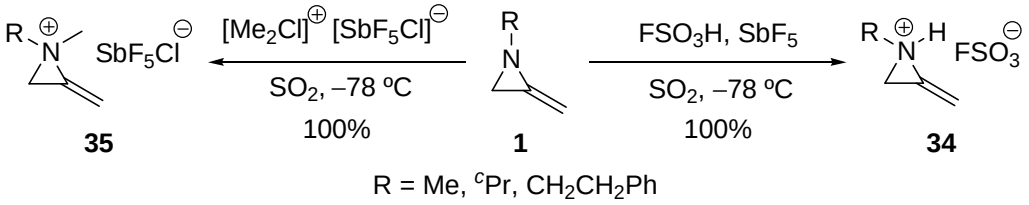


Scheme 1.11. Dimethyltitanocene mediated olefination of α-lactams.

1.3 Reactions of Methyleneaziridines

1.3.1 Protonations

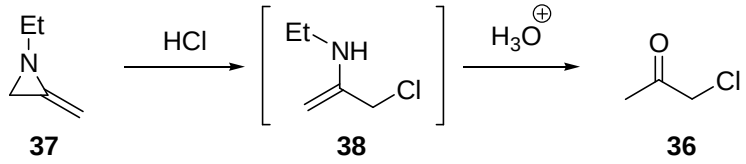
Jongejan *et al*. have shown that *N*-protonation of 1-alkyl-2-methyleneaziridines **1** can occur with FSO_3H/SbF_5 in sulphur dioxide at –78 °C to generate the corresponding methyleneaziridinium fluorosulfate **34** without ring-opening or attack of the exocyclic double bond (Scheme 1.12).[23] Under similar conditions, it was shown that **1** could be *N*-methylated with $[(Me)_2Cl]^+[SbF_5Cl]^-$ to yield **35**. Both **34** and **35** showed surprising thermal stability, no decomposition of either cation being observed by ^{1}H NMR spectroscopy, even when warmed to 50 °C. Methyleneaziridinium cations **34** and **35** were shown to undergo thermally induced isomerisation upon further heating.[24]



Scheme 1.12. Generation of methyleneaziridinium cations.

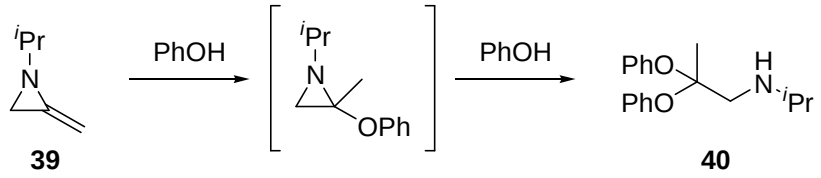
1.3.2 Ring-opening

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]



Scheme 1.13. Chloride ring-opening of methyleneaziridines.

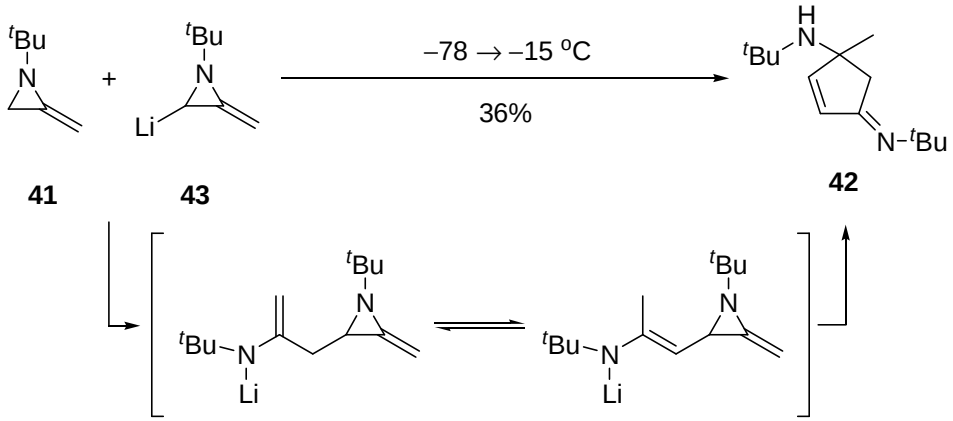
Crandall *et al*. demonstrated that 1-isopropyl-2-methyleneaziridine (**39**) undergoes reaction with excess phenol to generate acetal **40**.[25,26] It was envisioned that the reaction proceeds *via* initial Markovnikov addition of the first equivalent of the phenol across the exocyclic double bond, followed by ring-opening of the aziridine intermediate by the second equivalent of phenol (Scheme 1.14).



39 **40**

Scheme 1.14. Markovnikov addition of phenol to methyleneaziridines.

Vélez and Quast, during their investigations into the alkylation of methyleneaziridines at C-3 *via* lithiation with *sec*-butyllithium, reported the dimerisation of *tert*-butyl-2-methyleneaziridine (**41**) (Scheme 1.15).[27] Formation of dimer **42** was proposed to proceed by nucleophilic ring-opening of **41** by lithiated methyleneaziridine **43**.

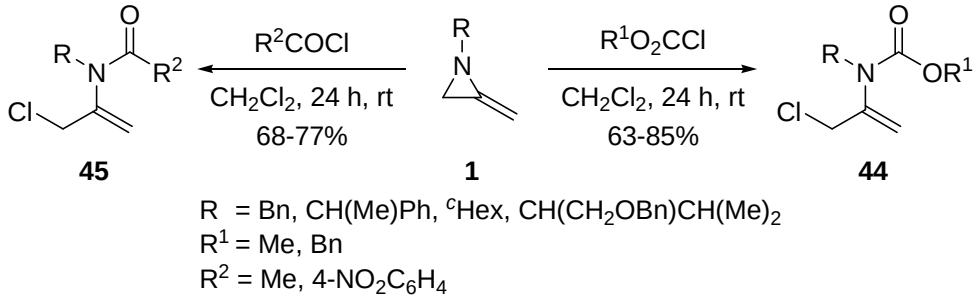


41 **43** **42**

Scheme 1.15. Dimerisation of methyleneaziridines.

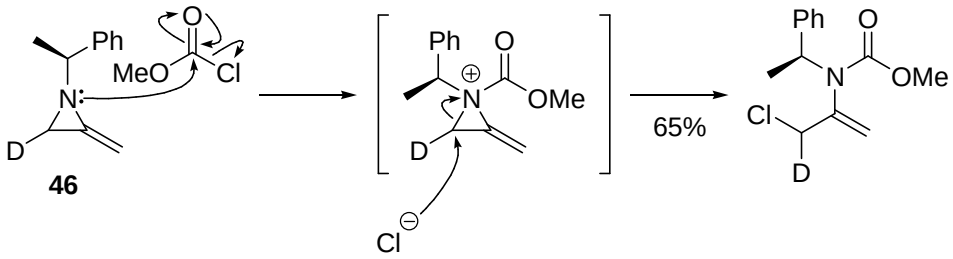
Shipman *et al*. have demonstrated methyleneaziridines can undergo ring-opening by chloroformates to give carbamates **44** (Scheme 1.16).[28] This reaction proceeds well with a variety of *N*-substituents on the methyleneaziridine, however, the sterically crowded trityl-derivative (R = CPh_3) failed 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.



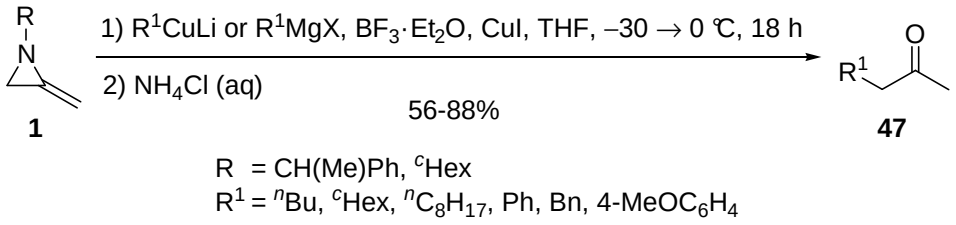
Scheme 1.16. Ring-opening with acid chlorides and chloroformates.

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]



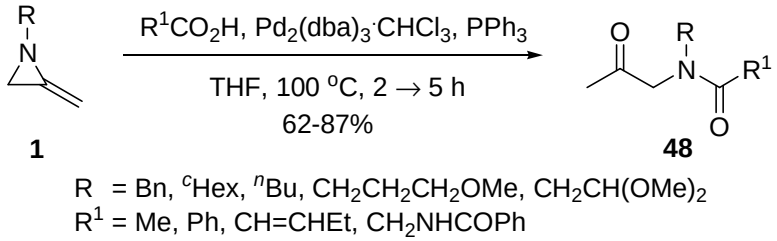
Scheme 1.17. Deuterium labelled ring-opening with chloroformates.

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).



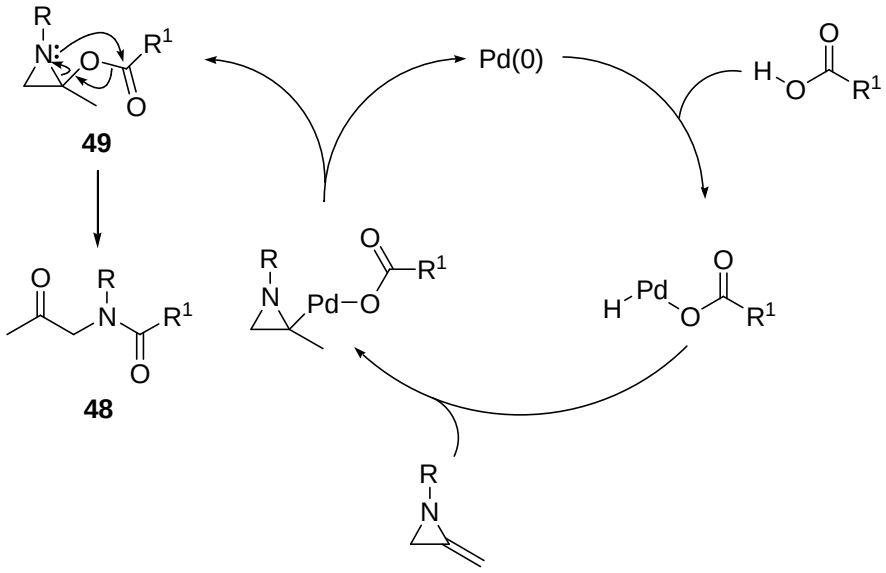
Scheme 1.18. Ring-opening with carbon-based nucleophiles.

Recently, Oh *et al*. reported the palladium catalysed synthesis of α-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 $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and PPh_3 (10 mol%) yielded the corresponding α-amido-ketone **48** (Scheme 1.19).



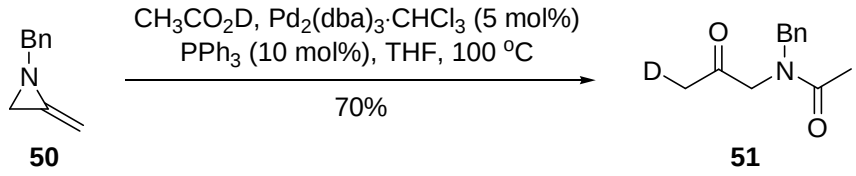
Scheme 1.19. Palladium catalysed synthesis of α-amido-ketones.

The synthesis of α-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 α-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).

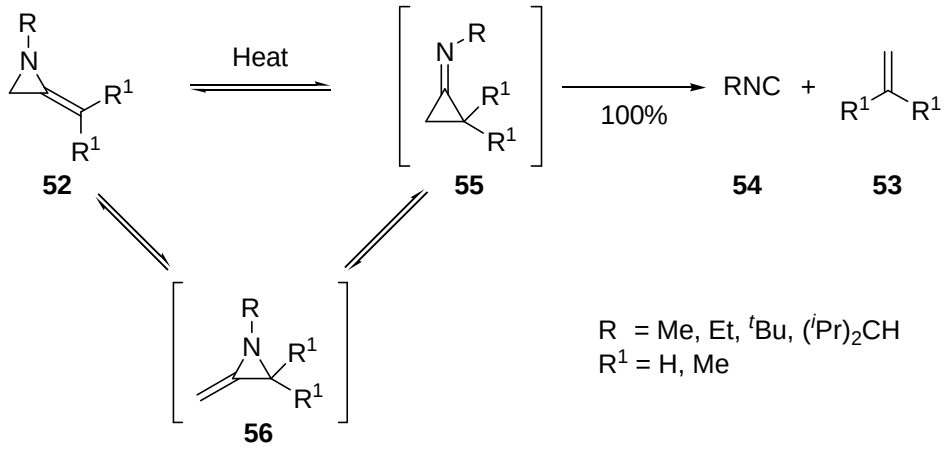


Scheme 1.21. Deuterium labelling studies for the synthesis of α-amido-ketones.

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).[12] These observed products were rationalised by an initial

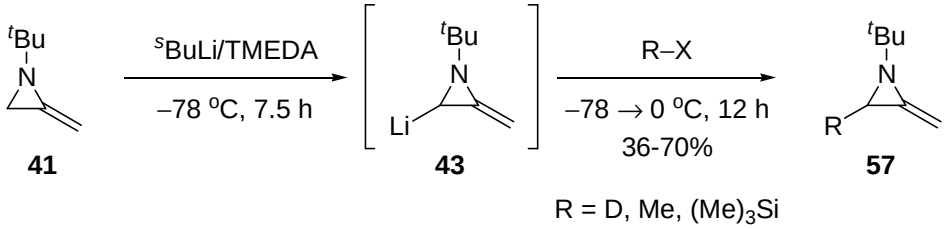
rearrangement to cyclopropanimine intermediate **55** or the structural isomer **56**. Both of these intermediates were detected *via* NMR spectroscopy.



Scheme 1.22. Thermal decomposition of methyleneaziridines.

1.3.4 Ring functionalisations

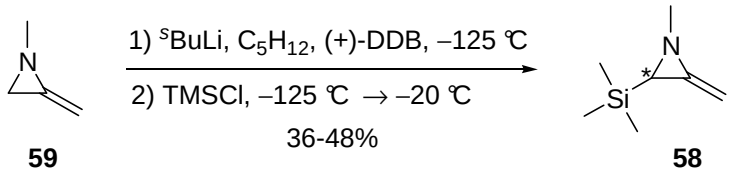
In their studies using *tert*-butyl-2-methyleneaziridine (**41**), Vélez and Quast reported that methyleneaziridines can be lithiated at C-3 with *sec*-butyllithium and tetramethylethylenediamine at –78 °C.[27] Treatment of lithiated species **43** with various electrophiles gave rise to the corresponding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



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

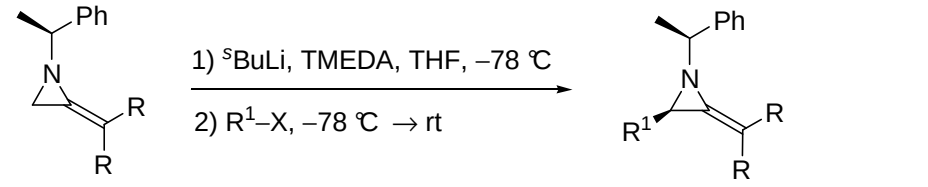
the presence of chiral auxiliary (*S*,*S*)-(+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane ((+)-DDB), followed by anion quenching with trimethylsilyl chloride (Scheme 1.24). However, **58** was isolated in moderate yield with a poor level of stereocontrol (12% ee).[31]



59 **58**

Scheme 1.24. Stereocontrol in the lithiation/alkylation of methyleneaziridines.

Shipman *et al.* achieved much higher levels of stereocontrol using methyleneaziridines bearing chiral *N*-substituents.[11] Methyleneaziridines, **19** and **60**, with a (*S*)-α-methylbenzyl *N*-substituent gave high levels of diastereoselectivity in the corresponding products **61**, when reacted with a range of electrophiles. The highest levels of diastereoselectivity were obtained from **60**, bearing *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, trialkylsilyl 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.[32] However, a second lithiation/alkylation sequence at C-3 was found not to be possible.



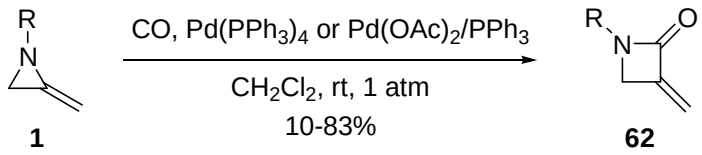
19: R = H
60: R = Me

61a: R = H, R^1 = Bn 70%, 14% de
61b: R = Me, R^1 = Bn 68%, 88% de

Scheme 1.25. Stereoinduction in methyleneaziridine lithiation/alkylation.

1.3.5 Ring expansions

Alpher and Hamel demonstrated that methyleneaziridines can undergo palladium-catalysed carbonylation reactions to give α-methylene-β-lactams.[33] Various *N*-substituted methyleneaziridines **1** were reacted with carbon monoxide in the presence of palladium (0) or palladium (II) and triphenylphosphine catalysts to produce the corresponding methyleneazetidones **62** as single regioisomers (Scheme 1.26).

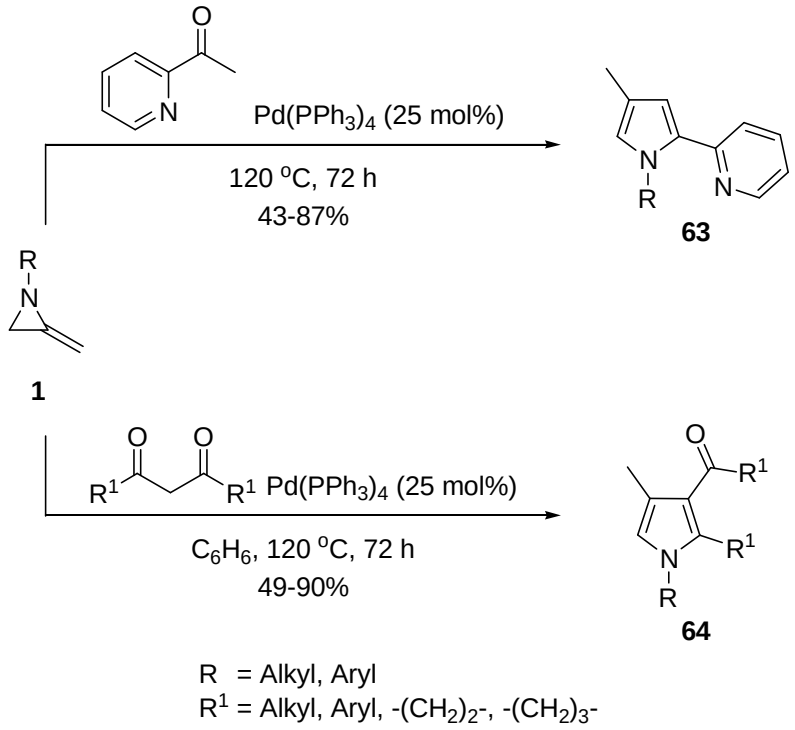


1 **62**

R = ^{n}Bu, ^{n}Hex, Ad, $CH_2CH_2CH_2OMe$, $CH_2CH(OMe)_2$

Scheme 1.26. Palladium catalysed carbonylation of methyleneaziridines.

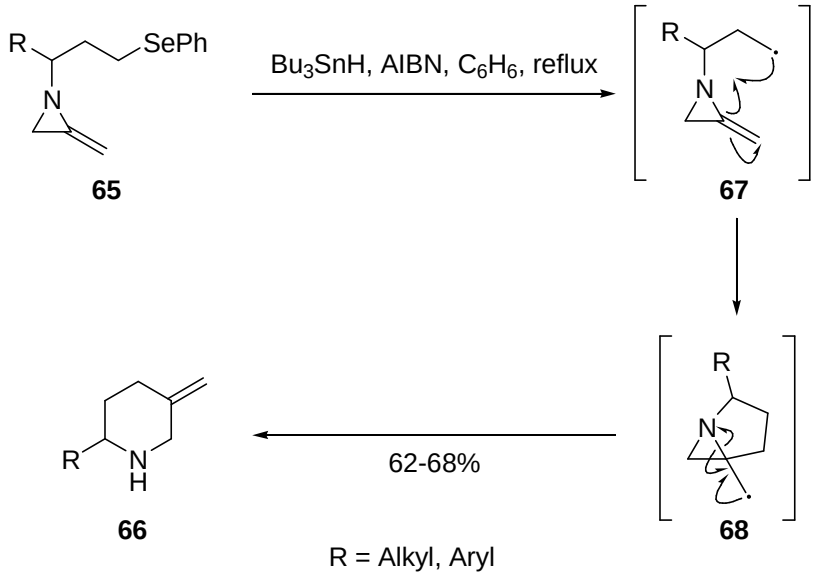
Yamamoto *et al*. expanded the use of palladium catalysis in ring expansion reactions of methyleneaziridines to produce pyrrole derivatives. Palladium catalysed reaction of **1** with *o*-acetylpyridines gave α-pyridinylpyrroles **63**,[34] whilst reaction of **1** with 1,3-diketones led to 1,2,3,4-tetrasubstituted pyrroles **64** (Scheme 1.27).[35]



Scheme 1.27. Palladium catalysed synthesis of pyrrole derivatives.

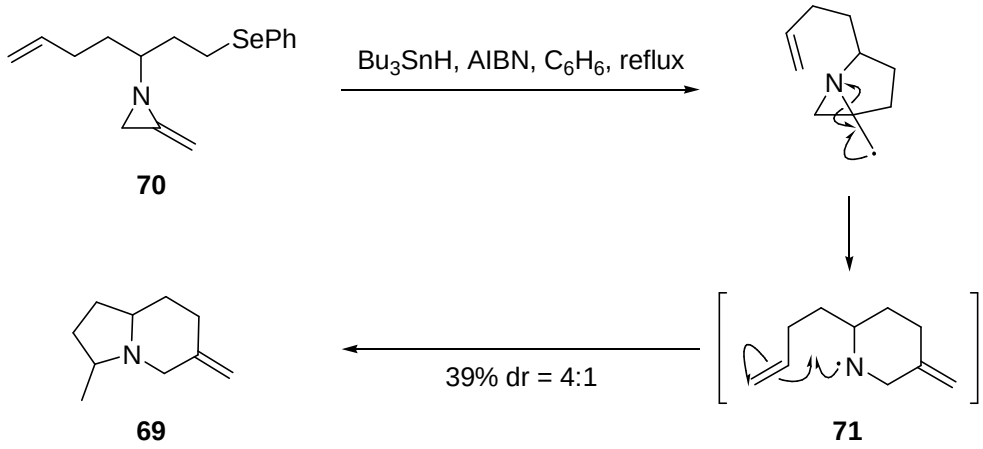
1.3.6 Intramolecular radical rearrangements

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).[7,36]



Scheme 1.28. Radical rearrangement to 3-methylenepiperidines.

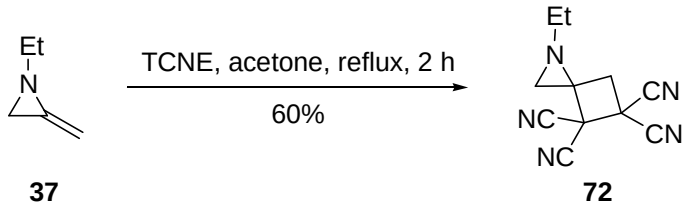
Using the above methodology, Shipman and Prévost achieved a tandem radical process to form indolizidine **69** from methyleneaziridine **70**. Intermediate **71** features an additional radical acceptor, allowing a further 5-*exo*-*trig* cyclisation leading to octahydroindolizine **69** (Scheme 1.29).



Scheme 1.29. Tandem radical cyclisation to an octahydroindolizine.

1.3.7 Reactions of the exocyclic double bond

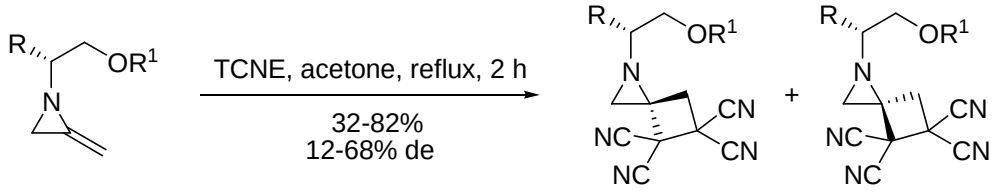
Cookson and co-workers demonstrated that 1-ethyl-2-methyleneaziridine (**37**) can undergo [2π+2π] cycloaddition reactions with electron deficient alkenes.[37] Treatment of **37** with tetracyanoethylene (TCNE) was shown to give the corresponding spiroadduct **72** (Scheme 1.30).



37 **72**

Scheme 1.30. [2π+2π] Cycloaddition reactions with electron deficient alkenes.

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



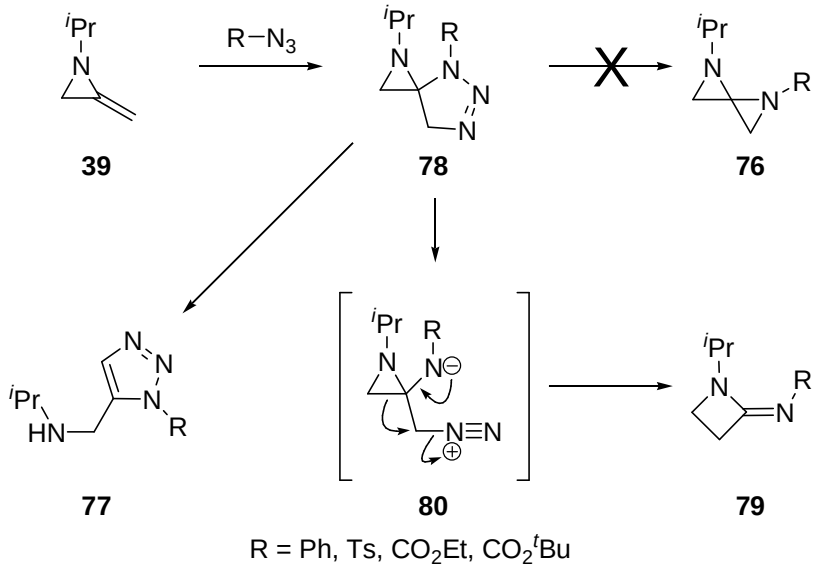
73 **74** **75**

R = Me, ^{i}Pr, ^{i}Bu, Ph
R^{1} = Bn, Si^{t}BuPh$_{2}$

Scheme 1.31. Stereocontrolled [2π+2π] cycloadditions.

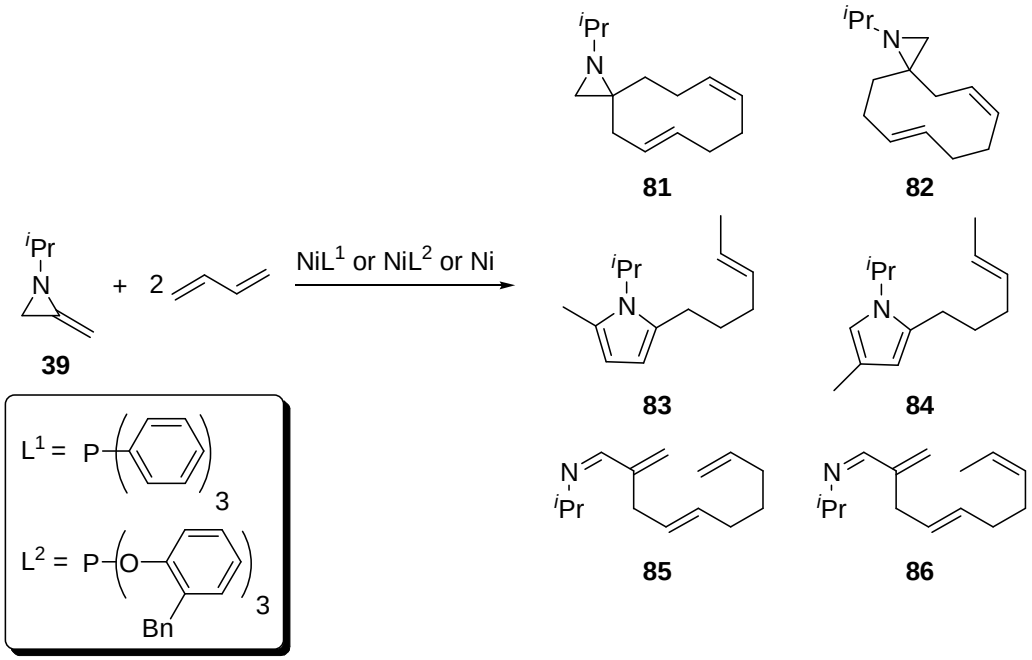
Crandall *et al*. attempted to react 1-isopropyl-2-methyleneaziridine (**39**) with organic azides to give 1,4-diazospiropentanes **76** (Scheme 1.32).[25] However, with phenylazide, reaction with **39** generated triazole **77** as the major product.

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**.



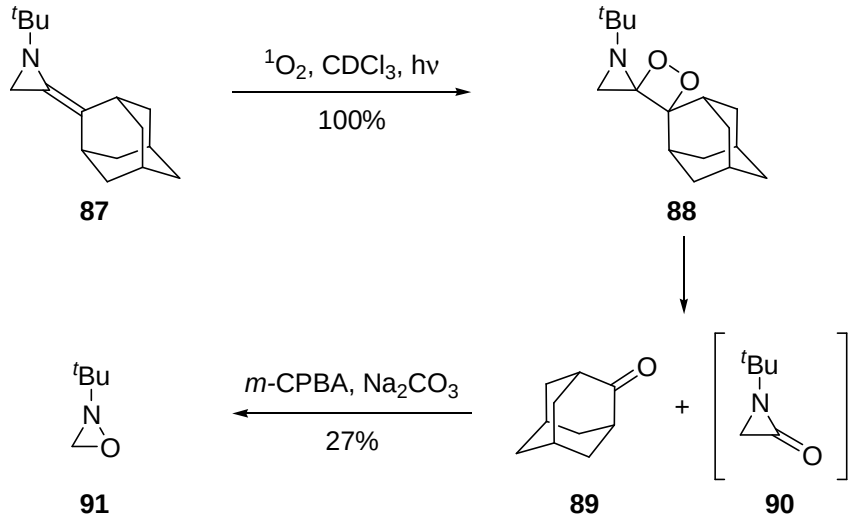
Scheme 1.32. Attempted synthesis of 1,4-diazospiropentanes.

Busch *et al*. developed a nickel-catalysed cyclo-oligomerisation of 1-isopropyl-2-methyleneaziridine (**39**) with excess butadiene.[39] 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.



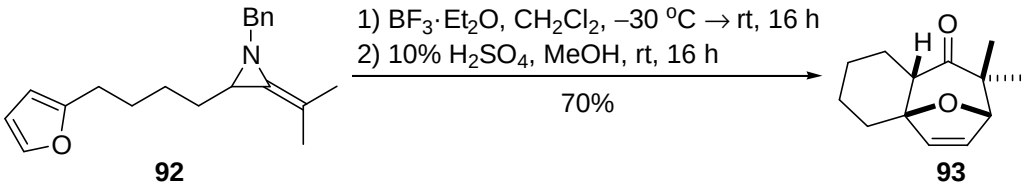
Scheme 1.33. Nickel-catalysed cyclo-oligomerisation.

Ando *et al*. showed that 1-*tert*-butyl-2-adamantylideneaziridine (**87**), when subjected to photooxygenation, underwent oxidative cleavage with singlet oxygen (Scheme 1.34).[40] The reaction initially forms dioxetane **88**, characterised by low temperature NMR spectroscopy. However, above –78 ^{o}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 1.34. Photooxygenation of methyleneaziridines.

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.[41] 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 **92** with $BF_3{\cdot}Et_2O$ yielded tricyclic ketone **93** in good yield as a single stereoisomer after acidic work-up (Scheme 1.35).

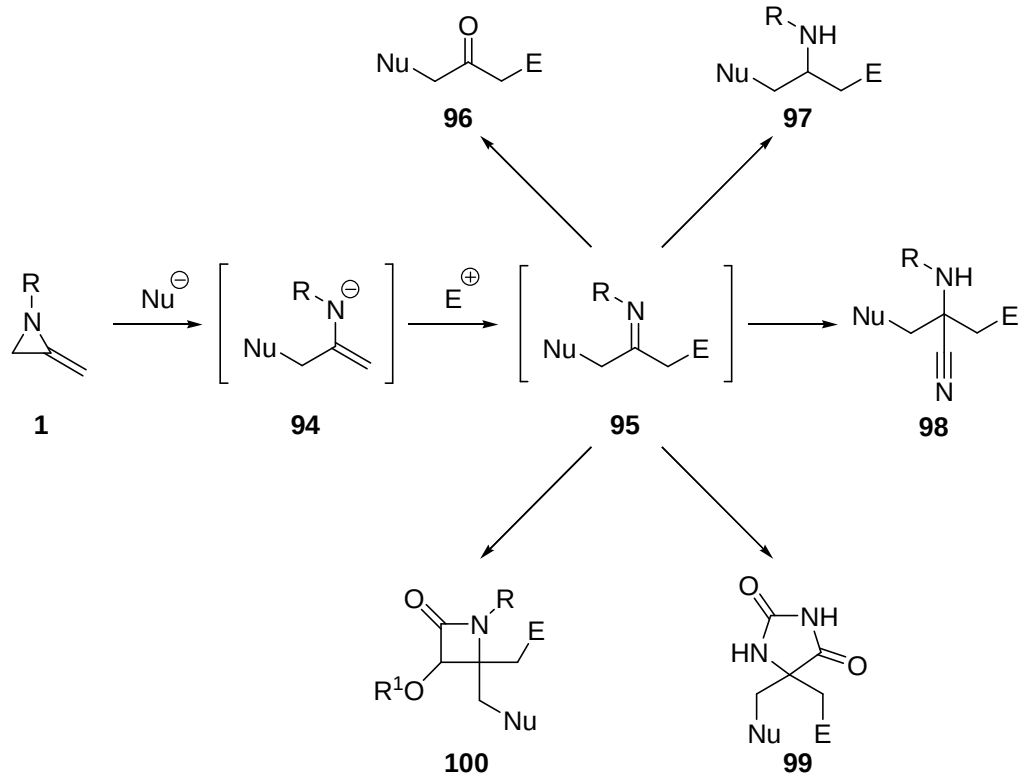


Scheme 1.35. Lewis acid catalysed [4+3] cycloadditions of methyleneaziridines.

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".[42] Famous examples of MCRs include the Strecker,[43] Biginelli,[44] Mannich,[45] Passerini,[46] Ugi[47] and Pauson-Khand[48] 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 monographs[49] 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] achiral[53] and homochiral amines **97**,[54] natural products,[29b,55] heterocycles,[51,52,53,55] α-amino nitriles **98**,[53] hydantoins[51] **99** and β-lactams[52] **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.



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

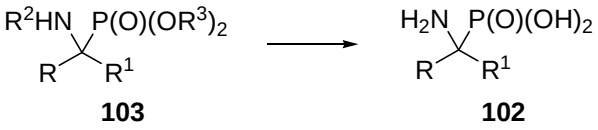
Due to their obvious structural similarities to α-amino acids **101**, α-aminophosphonic acids **102** constitute important motifs in medicinal chemistry (Figure 2.1).[57,58] Many natural and unnatural aminophosphonic acids and their ester and peptide derivatives display a wide range of biological activities.[59] 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.[60] Therefore they serve as inhibitors of enzymes such as proteases and peptide ligases. As such, aminophosphonic acids are known to act as peptide mimics,[61] herbicides,[62] enzyme inhibitors[63] and pharmacological,[64] antibacterial,[65] antiviral,[66] and antitumor agents.[67]

101 **102**

α-amino acid A-aminophosphonic acid

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

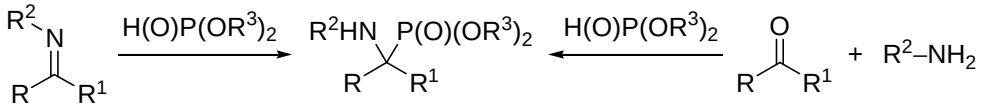
The most common route to α-aminophosphonic acids is *via* chemical manipulation of the corresponding α-aminophosphonates **103** (Scheme 2.1).[68] As such, α-aminophosphonates have become key targets in the synthesis of this compound class. The most common route to α-aminophosphonates, the Kabachnik-Fields reaction[69] is discussed in detail in the following section.



Scheme 2.1. α-Aminophosphonic acids from α-aminophosphonates.

2.1.1 Synthesis of α-aminophosphonates

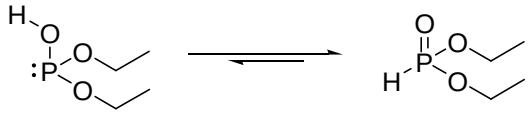
The most common route to α-aminophosphonates remains the hydrophosphonylation of imines (Scheme 2.2).[70] This is achieved by one of two pathways: (i) in a two-component fashion known as the Pudovik reaction[71,72] or (ii) by the Kabachnik-Fields reaction,[69] which combines *in situ* imine formation 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.[73] In fact, Pudovik and Kabachnik both published these groundbreaking observations in the same volume of *Doklady Chemistry* in 1952.



Scheme 2.2. Hydrophosphonylation of imines.

The reaction mechanism for the formation of α-aminophosphonates *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 **104** and phosphonate **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

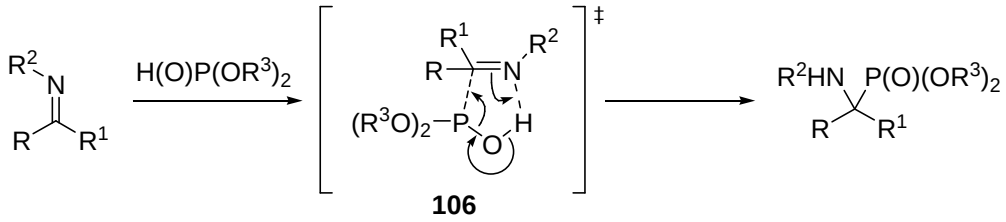
not the phosphonate form is the nucleophilic species.[74] It has been demonstrated that the presence of a base can influence the balance of the equilibrium, allowing for the phosphite form to become more prevalent.[75]



104 **105**

Scheme 2.3. Tautomeric forms of diethyl phosphite.

In the Pudovik reaction,[71] the reaction is considered to go *via* direct insertion of the phosphite into the imine through a five-membered cyclic transition state **106** (Scheme 2.4). Protic and Lewis acidic activators are envisioned to activate the imine to nucleophilic attack.

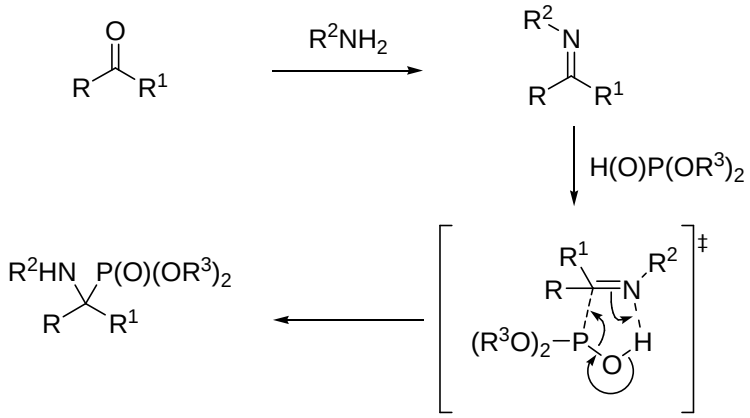


106

Scheme 2.4. Pudovik reaction *via* a five-membered cyclic transition state.

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 α-aminophosphonate. Since its discovery there have been numerous insights into this reaction mechanism,[69,76] and it has been shown that the nature of the aldehyde,[77] the activator,[78] the solvent[79] and the pK_b of the amine[80] all have an effect. However, it is most commonly considered that the reaction

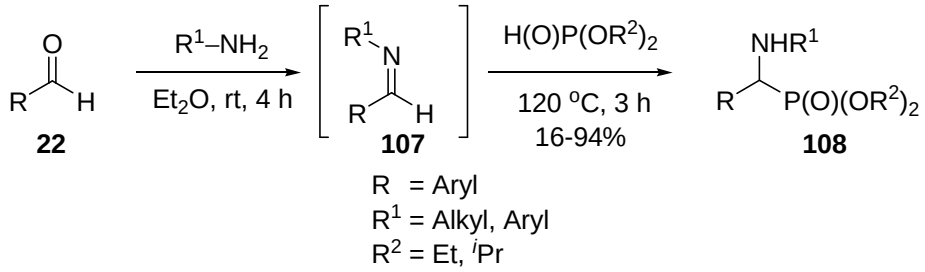
proceeds *via in situ* generation of the imine from condensation of the carbonyl compound with the amine, followed by subsequent nucleophilic attack of the hydrophosphoryl component in a Pudovik style process (Scheme 2.5).



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

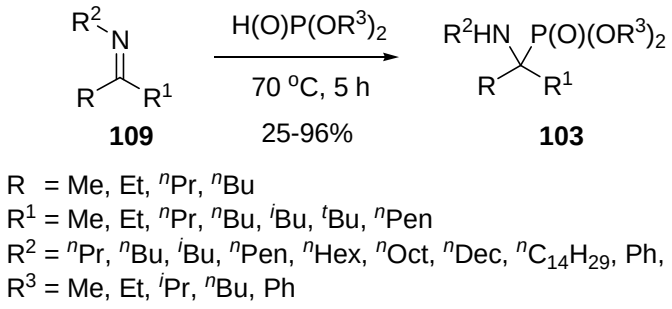
The initial reports published in 1952 on the Pudovik[71] and Kabachnik-Fields[73] reactions have received over 500 citations, revealing substantial interest in these processes. Recent developments relating to these reactions are surveyed below.

Beers *et al*., during their investigations on phosphatase inhibitors, synthesised a range of benzylaminophosphonic acids *via* the corresponding α-aminophosphonates.[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 α-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.



Scheme 2.6. α-Aminophosphonates from aryl aldehydes.

Wieczorek and co-workers have described the synthesis of α-aminophosphonates from ketimines under solvent-free conditions.[82] The reaction of a pre-formed imine **109** with a dialkyl phosphite at 70 ^{o}C was shown to give the corresponding α-aminophosphonate in moderate to very good yields (Scheme 2.7).

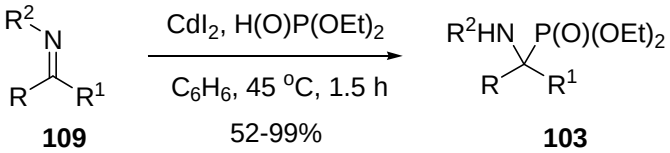


Scheme 2.7. α-Aminophosphonates from ketimines.

Many reports have described the use of Lewis acid catalysts including $TiCl_4$,[83] $AlCl_3$,[84] $InCl_3$,[85] $In(OTf)_3$,[86] Me_2AlCl,[87] $ZrCl_4$,[88] BF_3[89] 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.[90] From screening a range of metal halides they showed that CdI_2 (2 mol%) greatly improved the rate of reaction

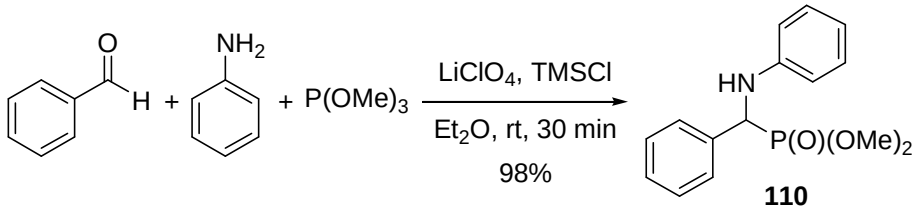
between imines (aldimines and ketimines) **109** and diethyl phosphite (Scheme 2.8).



R = H, ^{c}Hex
R^1 = Et, ^{n}Pr, ^{i}Pr, ^{c}Pen, ^{c}Hex, 3-py, Ph
R^2 = Me, ^{t}Bu, ^{c}Hex, Ph, Bn

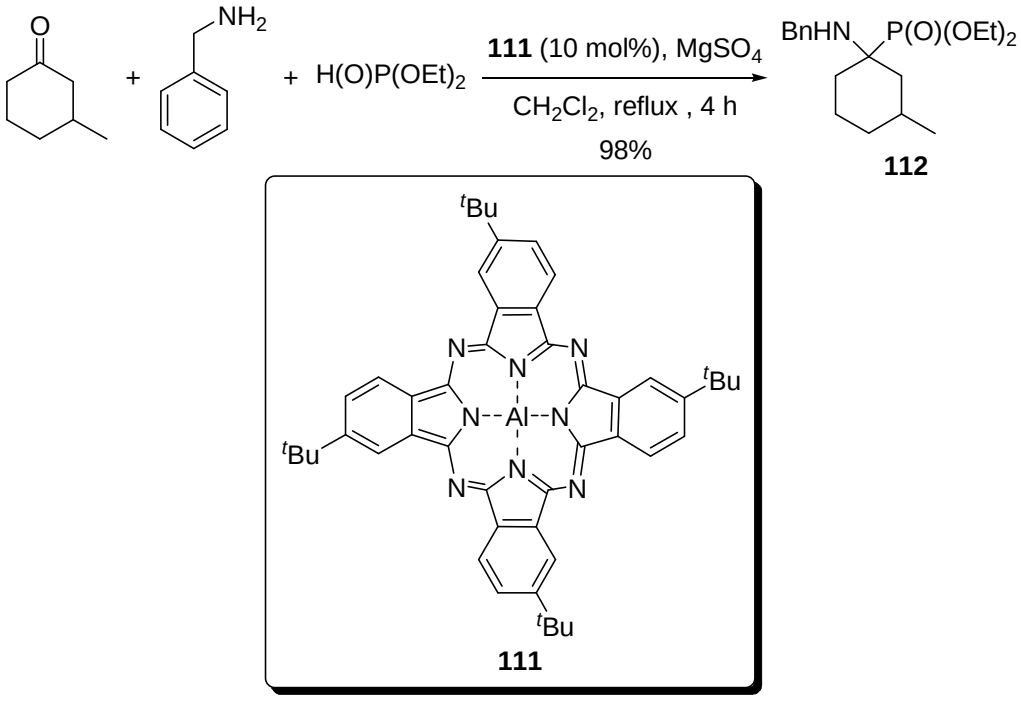
Scheme 2.8. Synthesis of α-aminophosphonates using cadmium iodide.

Lithium perchlorate has been shown to be a very effective Lewis acid for the generation of α-aminophosphonates.[91] As an example, α-aminophosphonate **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).



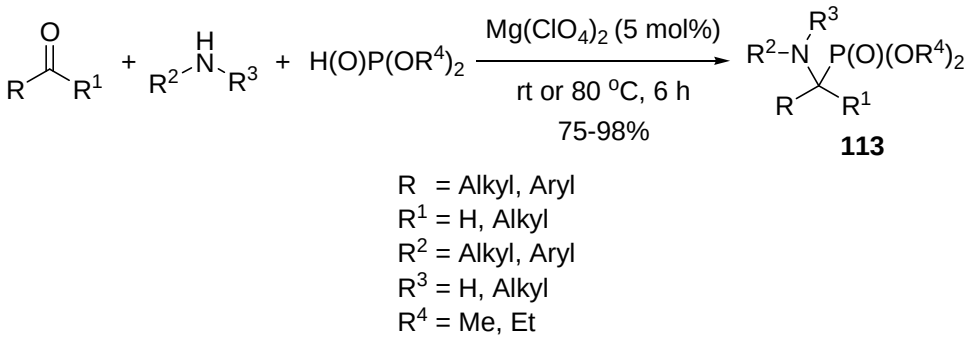
Scheme 2.9. Kabachnik-Fields reaction using lithium perchlorate.

Matveeva *et al*. developed an aluminium based tetra-*tert*-butyl-substituted phthalocyanine **111** Lewis acid for the production of α-aminophosphonates from ketones.[92] For example, the reaction of 3-methylcyclohexanone with benzylamine and diethyl phosphite in the presence of **111** was found to give α-aminophosphonate **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%).



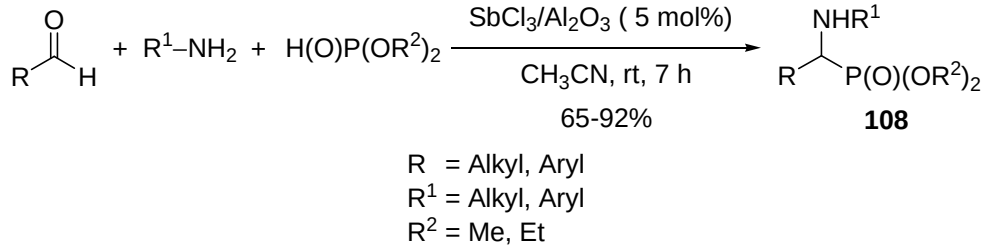
Scheme 2.10. Kabachnik-Fields reaction using an aluminium based catalyst.

Bhagat *et al*. reported that magnesium perchlorate was found to be a highly efficient catalyst in the Kabachnik-Fields reaction under solvent-free conditions.[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 α-aminophosphonates **113** in good yields (Scheme 2.11).



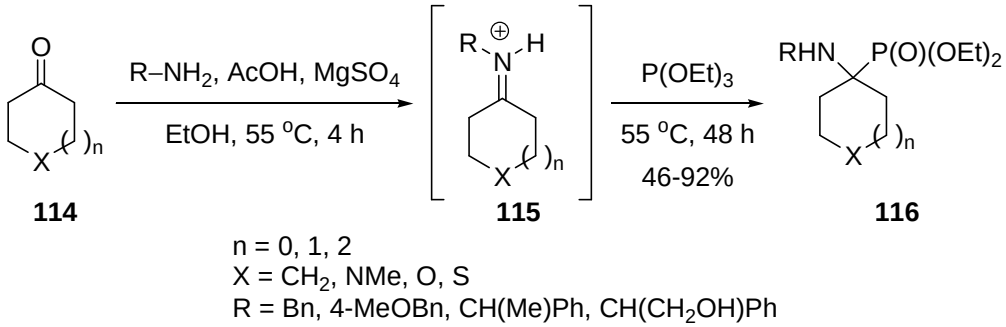
Scheme 2.11. Kabachnik-Fields reaction using magnesium perchlorate.

Recently, Ambica *et al*. reported the use of antimony trichloride adsorbed on alumina as an efficient and recyclable catalyst in a Kabachnik-Fields reaction.[94] They reported that the reaction between aldehydes, amines and dialkyl phosphites led to the corresponding α-aminophosphonates **108** in high yields in the presence of $SbCl_3/Al_2O_3$ (Scheme 2.12).



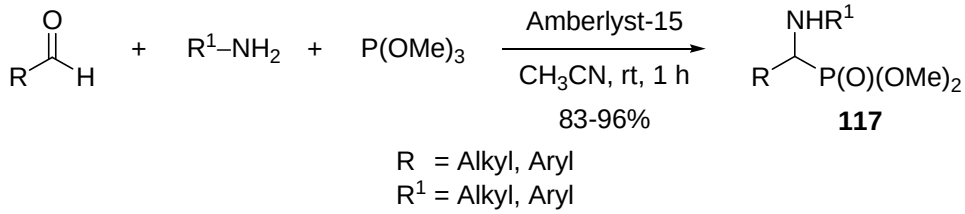
Scheme 2.12. Kabachnik-Fields reaction using $SbCl_3/Al_2O_3$.

Protic acids have also been shown to promote the nucleophilic addition of phosphites into imines.[95] Interestingly, Rabasso and co-workers synthesised a range of cyclic α-aminophosphonates using acetic acid as activator.[96] Sequential reaction of cyclic ketones **114** 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 **115**. Addition of triethyl phosphite was found to give the resultant cyclic product **116** in moderate to good yields (Scheme 2.13).



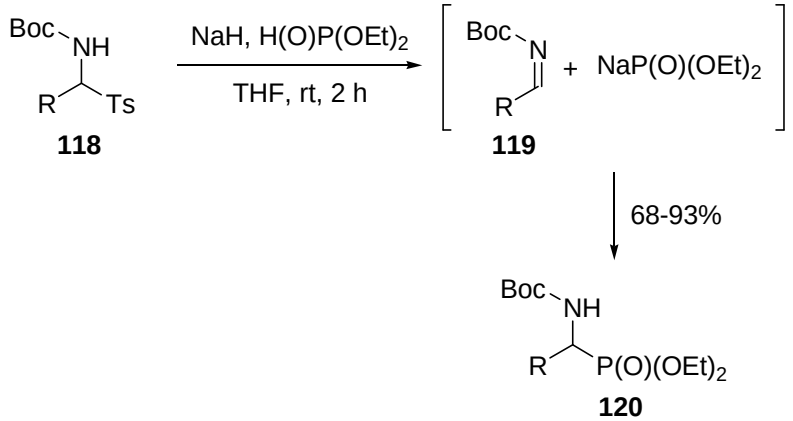
Scheme 2.13. Kabachnik-Fields reaction for cyclic α-aminophosphonates.

Amberlyst-15, containing a sulfonic acid functionality, has been shown to be a highly efficient and recyclable acidic promoter in the Kabachnik-Fields reaction.[97] 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).



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 e*t al*. deployed sodium hydride in their synthesis of *N*-Boc-1-aminoalkylphosphonates (Scheme 2.15).[98] 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-aminoalkylphosphonates **120** in good yields.

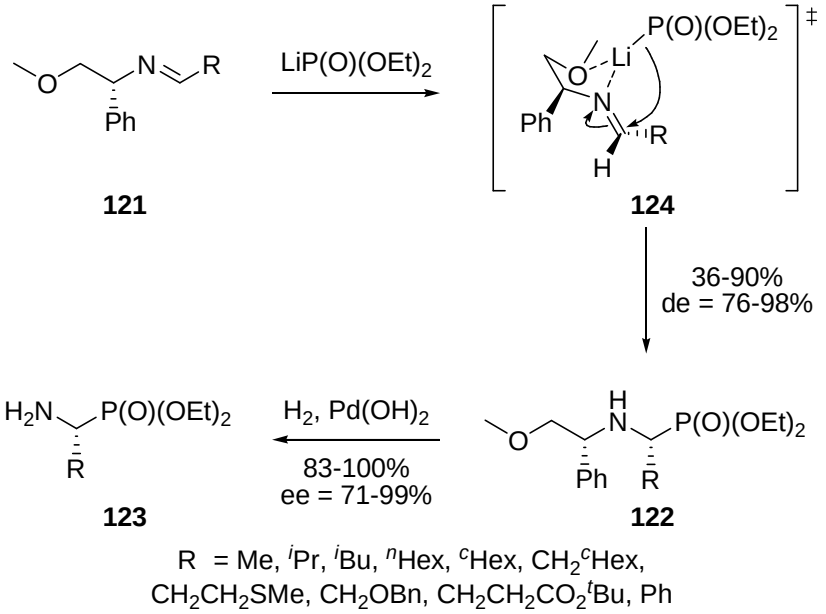


Scheme 2.15. Synthesis of α-aminophosphonates under basic conditions.

2.1.2 Asymmetric synthesis of α-aminophosphonates

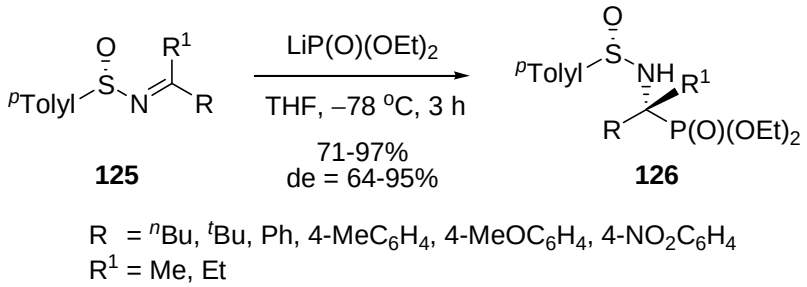
As α-aminophosphonates contain an asymmetric carbon centre there have been many reports on developing asymmetric routes to these systems. As such, the development of enantiocontrolled routes to α-aminophosphonates has received a great deal of attention. Several reviews on this topic have recently been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

Yager *et al*. used amines with a chiral directing group to induce stereochemistry into α-aminophosphonates in a two step process.[100] Reaction of an enantiopure amine with an aldehyde generated chiral imine **121**. Treatment of **121** with lithium diethyl phosphite was found to give the corresponding α-aminophosphonate **122** in moderate to good yields with high levels of diastereomeric excess. Hydrogenolysis of the chiral directing group afforded the corresponding amino ester **123** in good yields and very high levels of enantiomeric purity (Scheme 2.16). The stereocontrol achieved in transition state **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 *Re* face of the imine.



Scheme 2.16. Asymmetric synthesis of α-aminophosphonates.

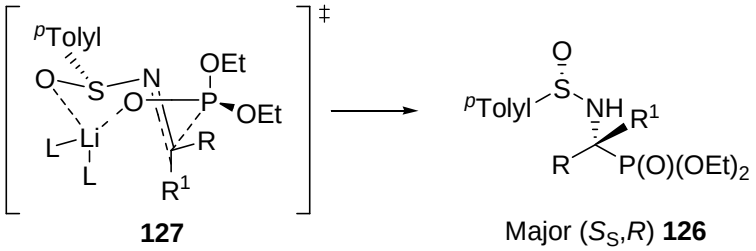
Davis and co-workers used sulfinimines in their asymmetric synthesis of quaternary α-aminophosphonates.[101] They demonstrated that the reaction of enantiopure ketosulfinimines **125** with lithium diethyl phosphite afforded the corresponding *N*-sulfinyl α-aminophosphonates **126** in good yields with high levels of diastereomeric excess (Scheme 2.17).



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

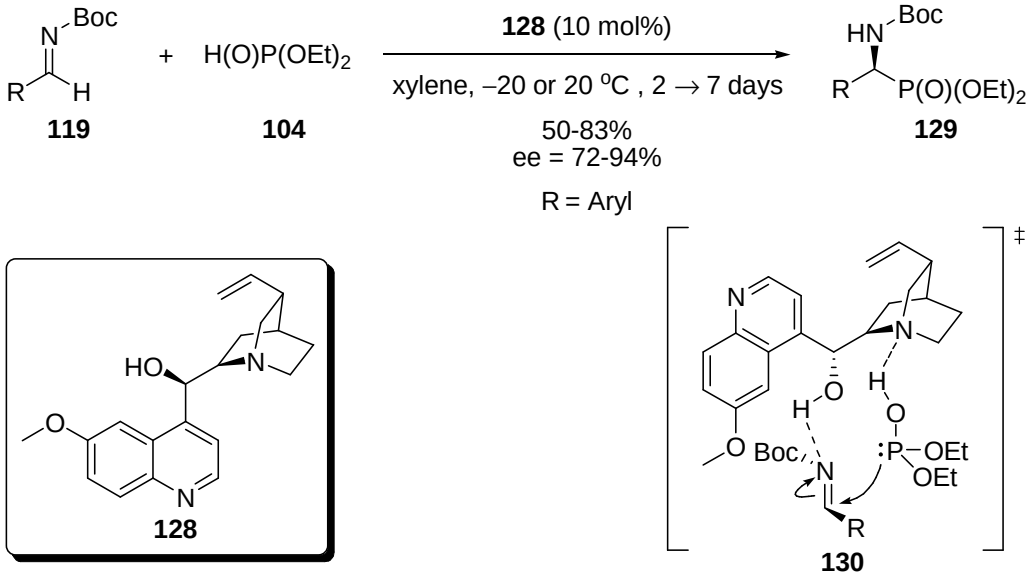
As with the example of Yager, above, the asymmetric induction was believed to have originated from chelation of the lithium cation. In this case, the cation was chelated to the sulfinyl and phosphite oxygens in a seven-membered twisted

chair-like transition state **127**. For the major (S_S,*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.

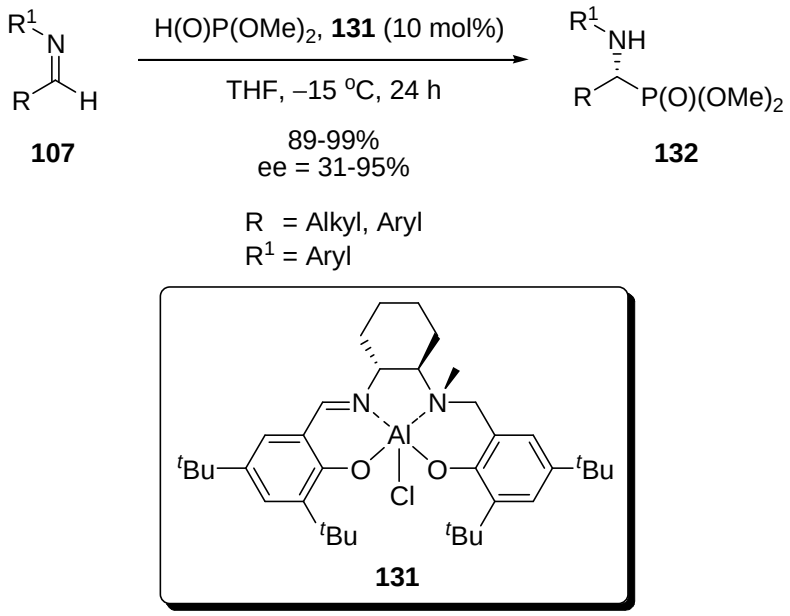
Pettersen *et al*. demonstrated that good enantioselectivities could be obtained in the nucleophilic attack on aldimines by diethyl phosphite using an organocatalytic approach.[102] Using cinchona alkaloid derivative **128** as catalyst, they were able to show that reaction between *N*-Boc imines **119** 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.

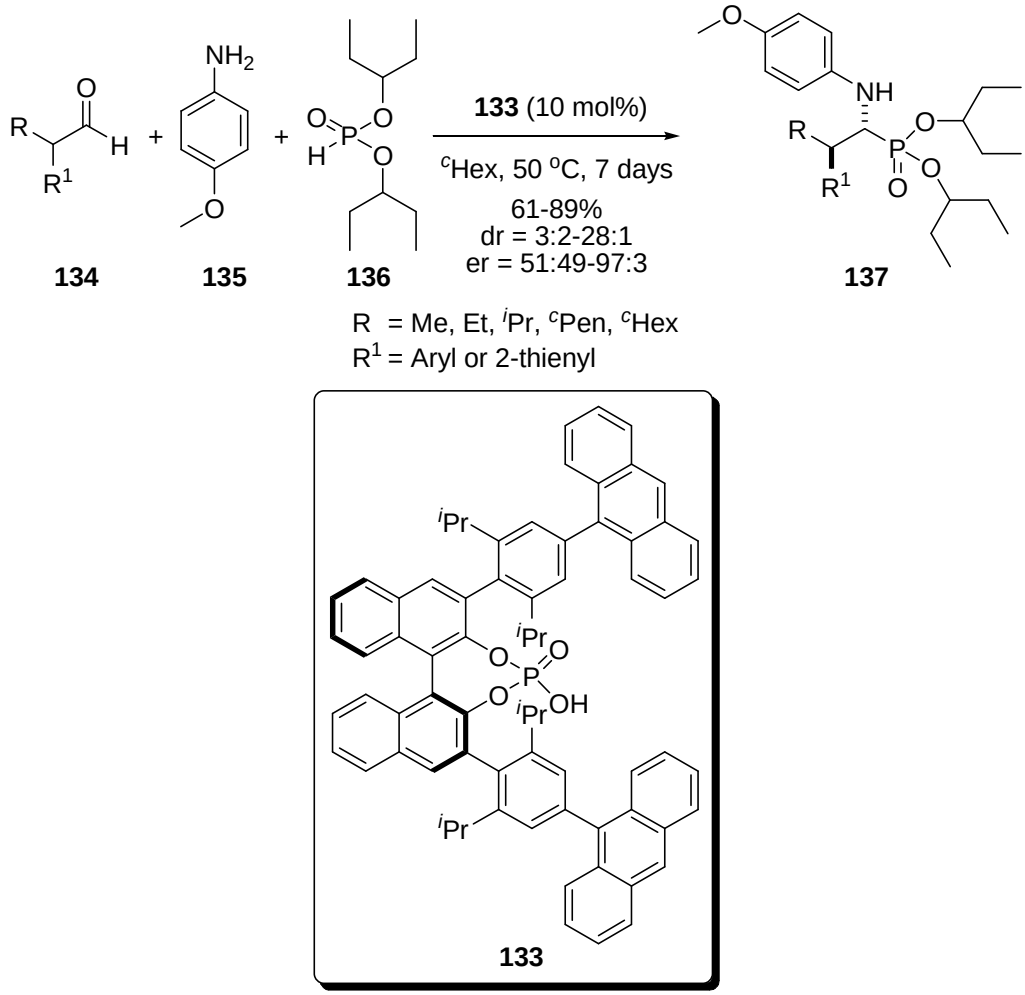
It was proposed that the hydroxyl group and the free nitrogen-lone pair on **128** activated the imine and phosphite *via* hydrogen bonding as shown in transition state **130**. This activation would arise in a stereoselective fashion due to the donor and acceptor positions in the catalyst, giving rise to the observed stereochemical outcome.

Katsuki and co-workers developed an optically active Al(salalen) complex **131** for the enantioselective hydrophosphonylation of aldimines.[103] They showed that **131** catalysed the reaction between aliphatic and aromatic aldimines **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.

Recently, Cheng *et al*. developed a direct catalytic asymmetric three-component Kabachnik-Fields reaction.[104] They found that chiral phosphonic acid **133** catalysed the reaction between aryl substituted aldehydes **134**, *p*-anisidine **135** and di(3-pentyl)phosphite (**136**) to **137** 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.



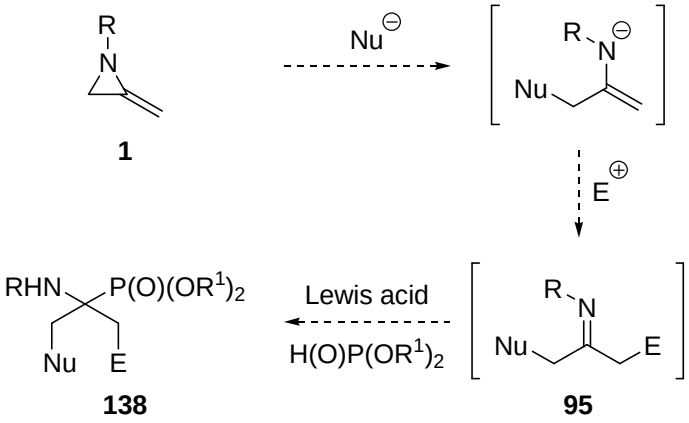
Scheme 2.21. An asymmetric Kabachnik-Fields reaction.

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.

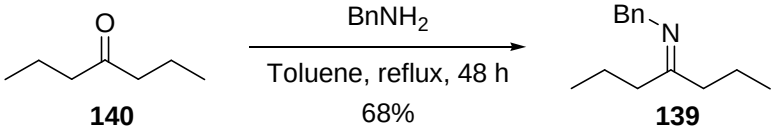
The most common approach to α-aminophosphonates is *via* nucleophilic addition of an alkyl phosphite into an imine. Therefore, it was envisioned that the multi-component reaction of methyleneaziridines (Section 1.3.8) could be adapted to generate α-aminophosphonates. Reaction of methyleneaziridines **1** 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.



Scheme 2.22. Synthesis α-aminophosphonates from methyleneaziridines.

2.2.2 Initial model reactions

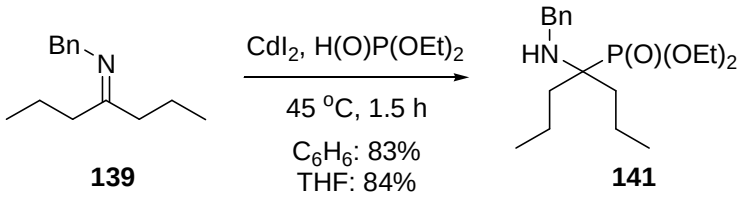
Before attempting to execute the sequence depicted above, we decided to explore the hydrophosphonylation of preformed ketimines using simple activators. Initially, it was decided to examine whether CdI_2, as described by Kabachnik,[90] would be a suitable activator. To examine this proposal, the Pudovik 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 azeotropic removal of water for 48 h. After work-up and purification by distillation, imine **139** was isolated in good yield (Scheme 2.23).



Scheme 2.23. Synthesis of *N*-benzyl-4-heptanimine.

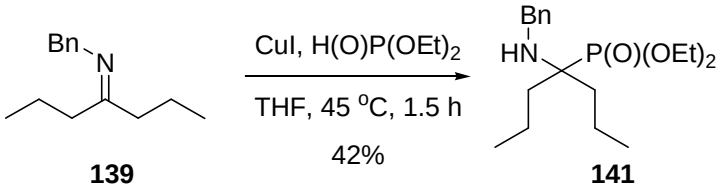
Under the reaction conditions described by Kabachnik,[90] imine **139** (1 equiv.) was dissolved in benzene and treated with CdI_2 (5 mol%) and diethyl phosphite (1 equiv.). After heating at 45 ^{o}C for 1.5 h, α-aminophosphonate **141** was

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 **141** in comparable yield (Scheme 2.24).



Scheme 2.24. Synthesis of an α-aminophosphonate from a preformed ketimine.

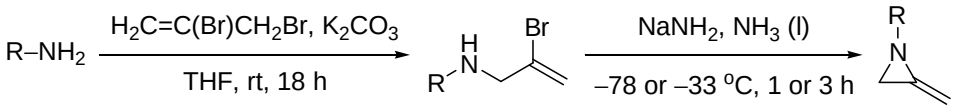
As copper (I) iodide would be present in a MCR involving the ring-opening of methyleneaziridines, we decided to ascertain if this metal salt could be used instead of cadmium iodide. To this end, imine **139** was treated with diethyl phosphite and copper iodide (5 mol%) in tetrahydrofuran under the conditions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



Scheme 2.24. CuI in the synthesis of an α-aminophosphonate.

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 **19**,[10] **50**[9] and **142**[9] were synthesised in two steps from the parent amine according to standard procedures.[6] Amines **143**-**145** were alkylated with 2,3-dibromopropene in tetrahydrofuran in the presence of

K_2CO_3 to generate the corresponding vinyl bromides **146**-**148**. Ring-closure with sodium amide, generated *in situ* from sodium and ammonia in the presence of $Fe(NO_3)_3{\cdot}9H_2O$, in liquid ammonia gave methyleneaziridines **19**, **50** and **142** in good overall yields (Scheme 2.26).



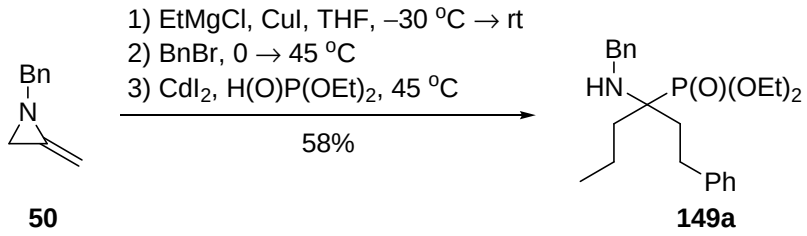
143: R = *S*-CH(Me)Ph
144: R = Bn
145: R = ^{c}Hex

146: 91% (lit. 100%[18])
147: 99% (lit. 98%[18])
148: 70% (lit. 86%[9])

19: 91% (lit. 91%[18])
50: 68% (lit. 78%[18])
142: 63% (lit. 76%[10])

Scheme 2.26. Synthesis of *N*-functionalised methyleneaziridines.

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 ^{o}C and treated with benzyl bromide (1.5 equiv.) and heated to 45 ^{o}C with stirring for 3 h. The resulting mixture was treated with CdI_2 (5 mol%) and diethyl phosphite (1 equiv.) and stirred for 1.5 h at 45 ^{o}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 ^{31}P NMR spectrum and a doublet at 59.7 in the ^{13}C 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.



50 **149a**

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]

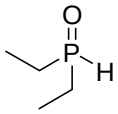
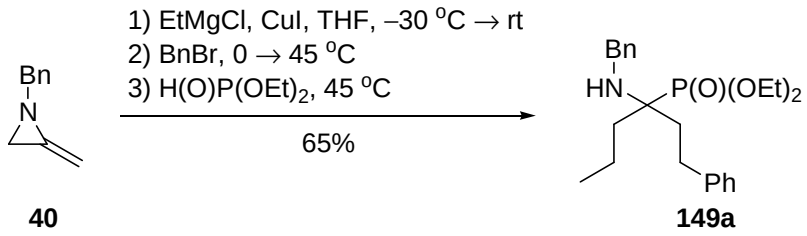


Figure 2.2. Postulated phosphine oxide.

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.

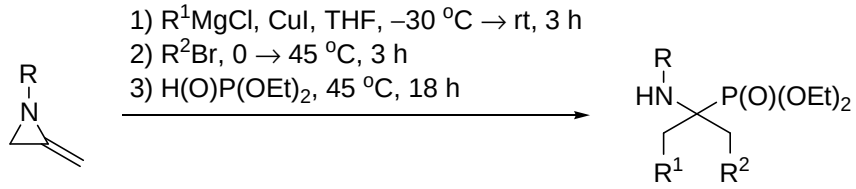


40 **149a**

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.



50 **142** **149a-k**

Scheme 2.29. Multi-component synthesis of α-aminophosphonates.

Entry	Aziridine	R	R^1	R^2	Product	Yield
1	**50**	Bn	Et[a]	Bn	**149a**	65%
2	**142**	[c]Hex	Et[a]	Bn	**149b**	57%
3	**50**	Bn	Et[a]	$THPO(CH_2)_3$	**149c**	60%
4	**50**	Bn	Et[a]	$H_2C{=}CHCH_2$	**149d**	61%
5	**50**	Bn	Et[a]	4-MeOBn	**149e**	62%
6	**50**	Bn	Et[a]	$H_3CC{\equiv}CCH_2$	**149f**	57%
7	**50**	Bn	Et[a]	4-BrBn	**149g**	52%
8	**50**	Bn	[i]Pr[a]	Bn	**149h**	63%
9	**50**	Bn	Bn[a]	Bn	**149i**	62%
10	**50**	Bn	[c]Hex[b]	Bn	**149j**	42%
11	**50**	Bn	$H_2C{=}CHCH_2$[a]	Bn	**149k**	61%

[a] Grignard reagent in THF solution. [b] Grignard reagent in diethyl ether solution.

Table 2.1.

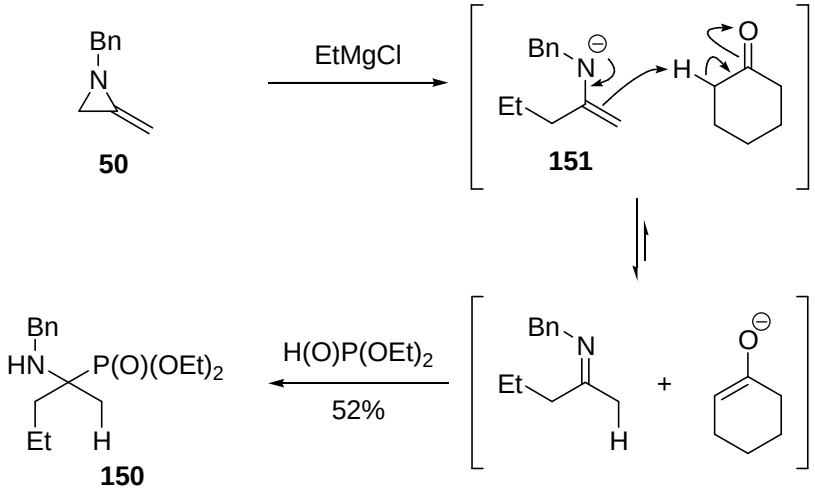
Pleasingly, we were able to readily synthesise a range of α-aminophosphonates in "one-pot" following a single general method. The yields ranged from a moderate 42% (Entry 10) to a very good 65% (Entry 1). The efficiency with respect to each new bond formed is excellent, up to 87%. It was gratifying to 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.[13]

Cyclohexene oxide and iodomethane, which had previously been successfully used in similar MCRs,[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 ^{1}H and ^{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 ^{o}C.

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

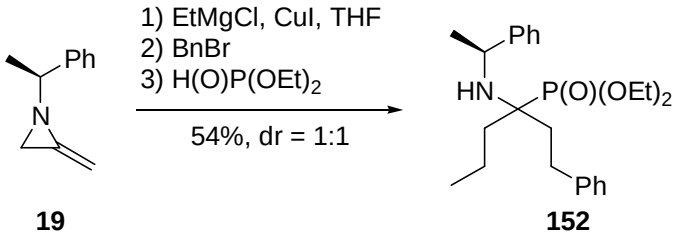


Scheme 2.30. Reaction involving cyclohexanone.

α-Aminophosphonate **150** was initially identified by a doublet at 1.32 ppm (J = 16.4 Hz) integrating for 3 protons in the ^{1}H 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}H–^{31}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

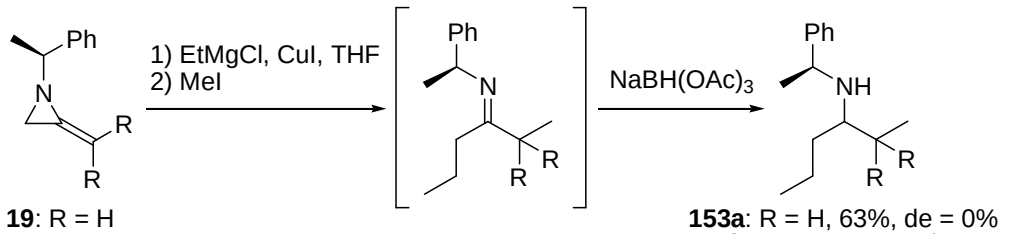
Since asymmetric induction is possible in the synthesis of α-aminophosphonates (Section 2.1.2), we next decided to explore if any stereocontrol could be exerted over the quaternary carbon centre formed in our four-component process. It was envisioned that chiral methyleneaziridine **19** might be a suitable 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}H NMR spectroscopy with two triplets for the terminal CH_3 of the propyl chain at 0.88 and 0.62 ppm.



19 **152**

Scheme 2.31. Attempted asymmetric induction with a chiral methyleneaziridine.

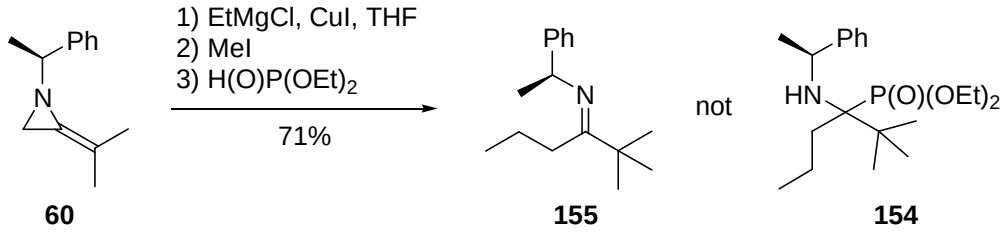
Whilst disappointing, the lack of facial selectivity in the synthesis of **152** was not surprising due to the similar steric size of the propyl and ethyl phenyl chains around the newly formed quaternary carbon centre. This observation is in agreement with the report of Hayes *et al*. who demonstrated that little selectivity was achieved in the synthesis of amine **153a** from methyleneaziridine **19**.[54] 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. Seteric 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-methyleneaziridine[29b] **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 imine[107] **155** was detected as the major product by ^{1}H and ^{13}C NMR spectroscopy (Scheme 2.33). The lack of any signal in the ^{31}P NMR spectrum and a signal of 175.1 in the ^{13}C 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.

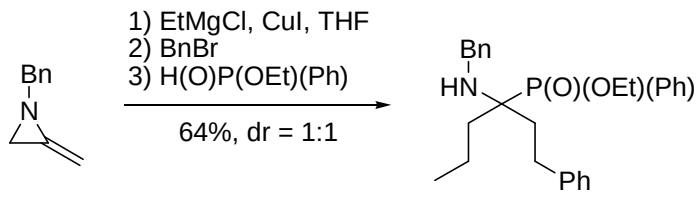


60 **155** **154**

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).

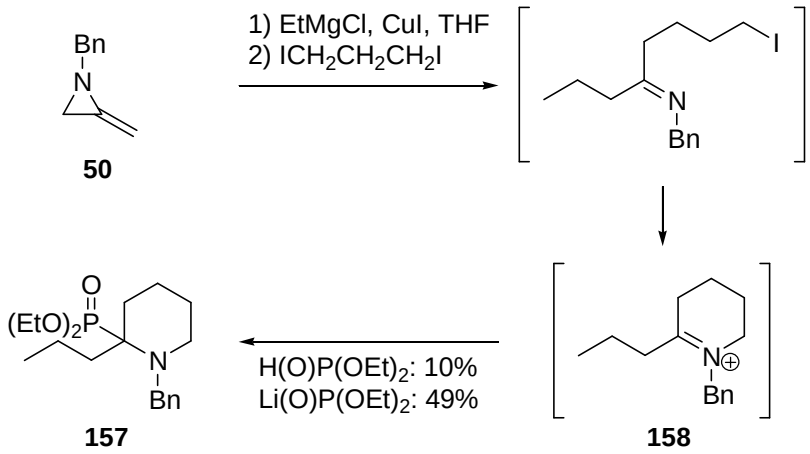


50 **156**

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.[53,55] 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 ^{o}C and treated with 1,3-diiodopropane (2.5 equiv.) and heated to 45 ^{o}C with stirring for 3 h. The reaction mixture was treated with diethyl phosphite (2.5 equiv.) and stirred overnight at 45 ^{o}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.

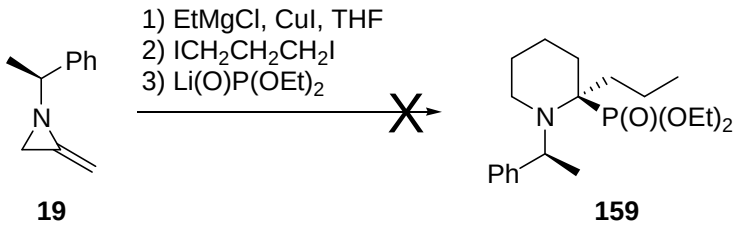


Scheme 2.35. Synthesis of a piperidine derived α-aminophosphonate.

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

ion. 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 ^{o}C and treated with 1,3-diiodopropane and heated to 45 ^{o}C with stirring overnight. In a separate flask, lithium diethyl phosphite was prepared according to the procedure of Yager.[100] Lithium diethyl phosphite was then added *via* cannula to the reaction vessel at room temperature. The reaction mixture was then heated to 45 ^{o}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.

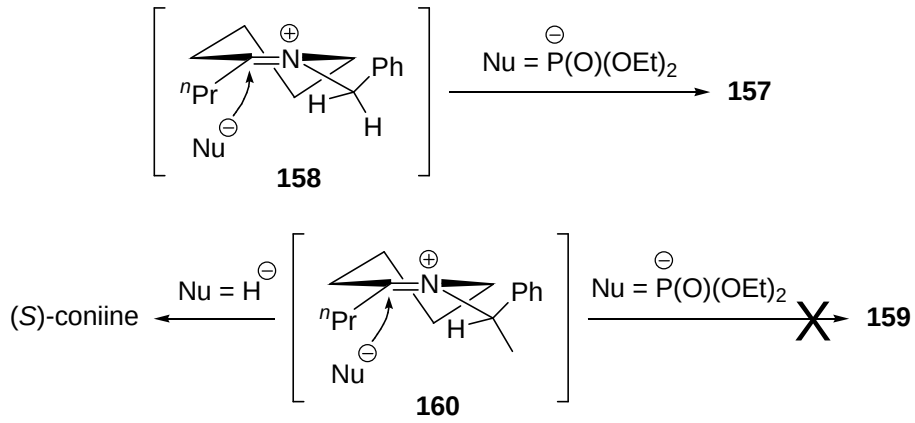
In their multi-component synthesis of (*S*)-coniine, Hayes *et al*. showed that hydride could be added into iminium species such as **158** in a diastereoselective fashion by employment of a chiral auxiliary.[55] Inspired by this report, we sought to examine if diastereocontrol could be realised in the 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 ^{1}H NMR, ^{31}P NMR or mass spectroscopy (Scheme 2.36).



19 **159**

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.[55] They assumed that the iminium cation **160** would adopt a twisted conformation where the allylic 1,3-strain is minimised, allowing for hydride addition to the least hindered *Re*-face (Scheme 2.37). The presence of the extra methyl group on the chiral auxiliary increases the steric bulk around iminium cation **160** compared to iminium cation **158**. Diethyl phosphite anion is a much larger nucleophile than hydride and the extra steric bulk around iminium **158** would crowd out this large phosphite anion leading to failure of the reaction.

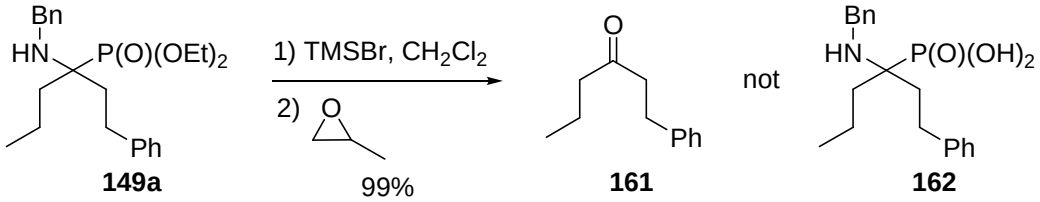


Scheme 2.37. Comparison of cation reactivity.

2.2.6 Deprotection to α-aminophosphonic acids

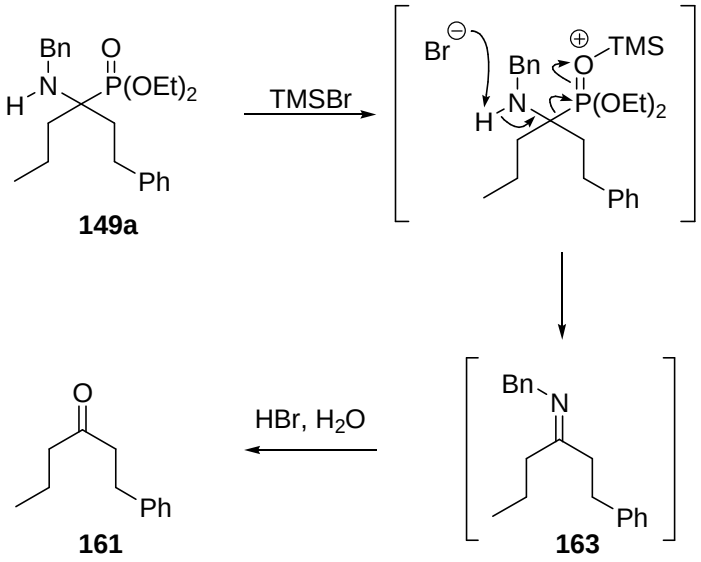
As stated earlier (Section 2.1) the most common route to α-aminophosphonic acids is *via* chemical manipulation of the corresponding α-aminophosphonates. Having demonstrated a general four-component synthesis of α-aminophosphonates, it was expected that α-aminophosphonic acids could be readily accessed from these materials, especially in the case of **149a** and **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 *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 *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 quantative yield (Scheme 2.38). Phosphonic acid **162** was completely undetected.



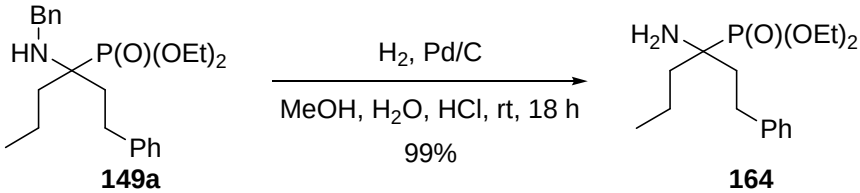
Scheme 2.38. Unexpected ketone formation.

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).



Scheme 2.38. Postulated rationalisation of ketone formation.

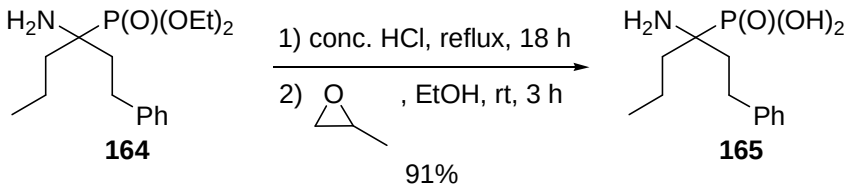
It was believed that the *N*-benzyl group could be readily removed by catalytic hydrogenation. Phosphonate **149a** was dissolved in methanol, water and aqueous hydrogen chloride, subjected to a hydrogen atmosphere in the presence of palladium on activated carbon and stirred at room temperature overnight. 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 **164** in concentrated aqueous hydrogen chloride was heated to reflux overnight. After cooling to room temperature and removal of the solvent *in vacuo* the residue was redissolved in ethanol, treated with excess propylene oxide and stirred at room temperature for 3 h. α-Aminophosphonic acid **165** was then collected as a white solid in 91% yield (Scheme 2.41). Phosphonic acid **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.

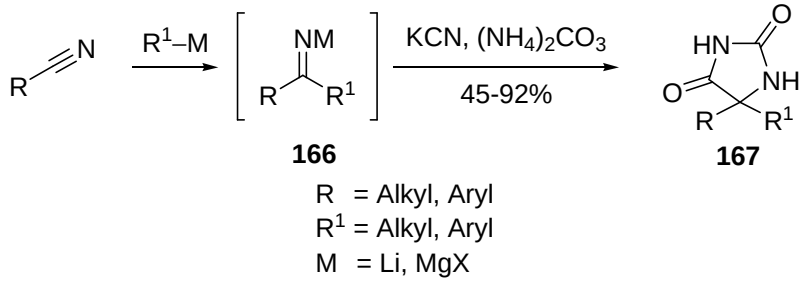


Scheme 2.41. Synthesis of an α-aminophosphonic acid.

Due to time constrains, the deprotection sequence outlined above was only conducted with phosphonate **149a**. However, it is believed that this sequence would be readily applicable to α-aminophosphonates **149c-k** and **157**.

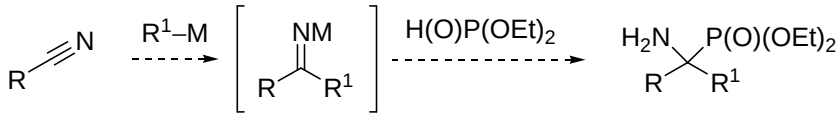
2.3 Alternative MCR to α-aminophosphonates from nitriles

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



Scheme 2.42. A modified Bucherer-Bergs reaction.

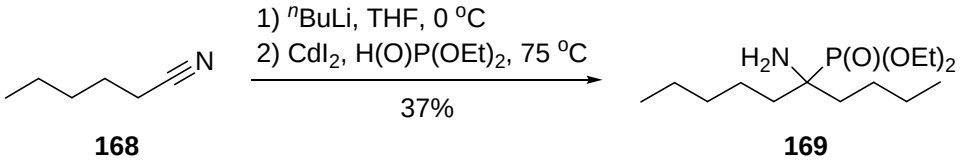
We reasoned that α-aminophosphonates could be generated in an analogous fashion from nitriles *via* a modified Pudovik reaction (Scheme 2.43). This chemistry would be complementary to that described above, allowing access to aryl substituted α-aminophosphonates.



Scheme 2.43. Proposed synthesis of α-aminophosphonates from nitriles.

To test these ideas, *n*-butyl lithium (1.2 equiv.) was cooled to 0 ^{o}C in tetrahydrofuran then reacted with *n*-hexane nitrile (**168**) (1 equiv.). The reaction mixture was stirred at 0 ^{o}C for 30 min then cadmium iodide (10 mol%) and diethyl phosphite (1.2 equiv.) were added. The mixture was rapidly heated to 75 ^{o}C in a pre-heated oil bath and stirred overnight. Upon cooling to room

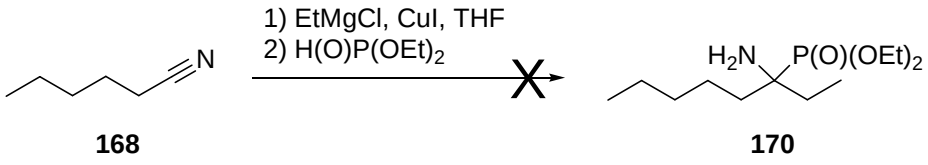
temperature and after work-up and purification, α-aminophosphonate **169** was isolated in an encouraging 37% yield (Scheme 2.44). A further control reaction performed in the absence of CdI_2 failed to yield any of **169**.



168 **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.



168 **170**

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.[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 diastereocontrol 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 **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

α-aminophosphonic acids could conceivably be formed quickly and efficiently from methyleneaziridines in three operations.

Finally, a simple three-component synthesis of α-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 α-aminophosphonates. As such, further research into this methodology may be warranted.

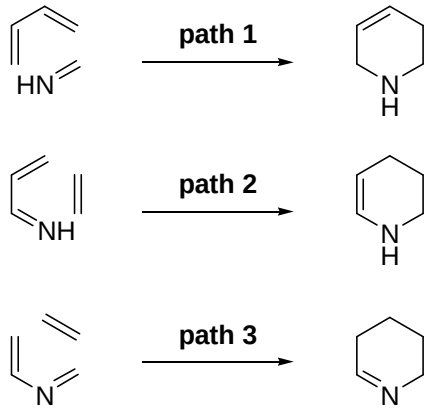
Chapter 3:

Attempted MCR to

2,3-Dihydro-4-pyridones

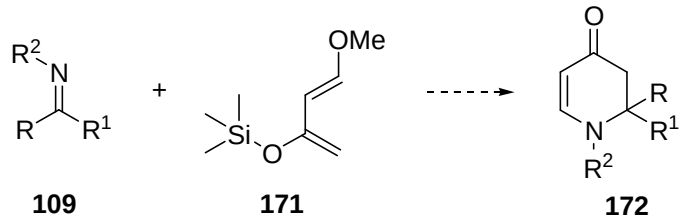
3.1 Introduction to Imino-Diels-Alder Reactions

The imino Diels-Alder reaction is a common method for the construction of functionalised heterocyclic rings.[112] High levels of regio-,[113] diastereo-[114] and enantio-selectivity[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[117] (path 2), or 2-azadienes (path 3).[118]



Scheme 3.1. Imino Diels-Alder reactions.

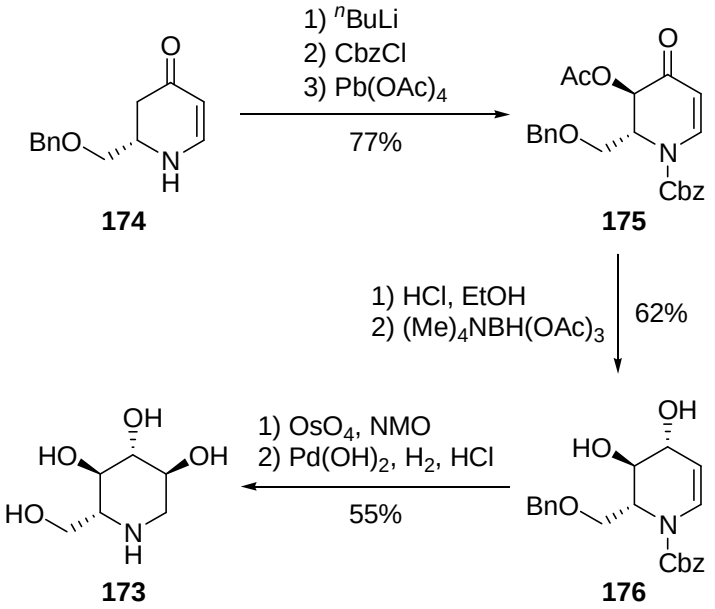
Of particular interest to us was the imino Diels-Alder reaction of imines **109** acting as the dienophiles (path 1) towards electron-rich dienes such as Danishefsky's diene[119] (**171**) to give 2,3-dihydro-4-pyridones **172** (Scheme 3.2). We anticipated that such systems could be constructed by a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



Scheme 3.2. Synthesis of 2,3-dihydro-4-pyridones.

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.[120]

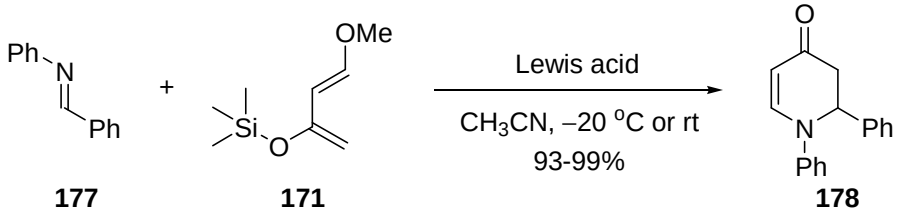
For example, Comins *et al*. synthesised polyhydroxy piperidine alkaloid (-)-deoxynojirimycin (**173**) *via* chiral pyridone **174**.[121] Cbz protection of **174**, followed by stereoselective acetoxylation provided *trans*-3-acetoxy-2,3-dihydropyridone **175**. Ester hydrolysis of **175** followed 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).



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.

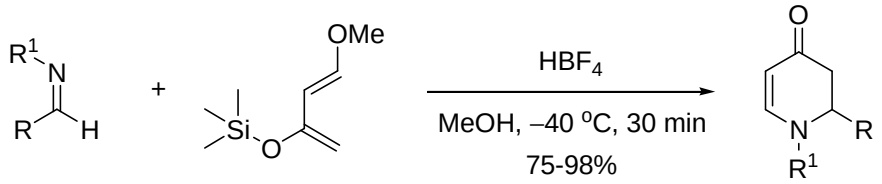
Much of the research into the imino Diels-Alder reaction has focused on the use of Lewis acid activators. A number of metal triflates have been successfully deployed in the reaction of imine **177** with Danishefsky's diene (**171**) to give pyridone **178** (Scheme 3.4). Examples include $In(OTf)_3$,[122] $Yb(OTf)_3$ and $Sc(OTf)_3$[123] under various reaction conditions.



177 **171** **178**

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

Akiyama *et al.* have shown that Brönsted 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).



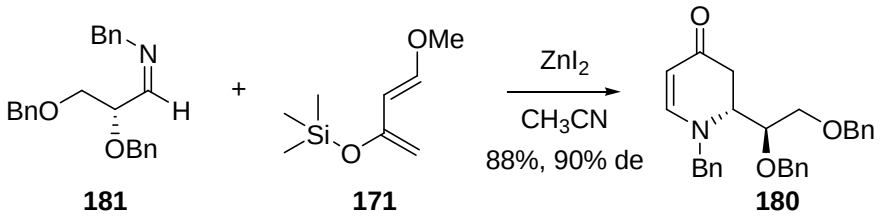
107 **171** **179**

R = Ph, 4-$MeOC_6H_4$
R^1 = Ph, 4-$NO_2C_6H_4$, 4-MeC_6H_4, PhCH=CH, ^{c}Hex

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

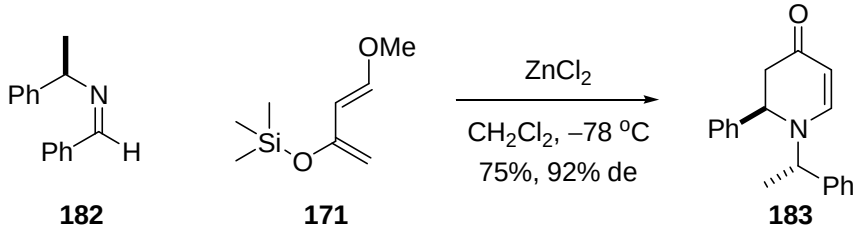
Stereoselectivity in the imino Diels-Alder reaction can be achieved in a number of ways. Badorrey *et al.* showed that stereo-induction can arise from using imines derived from chiral aldehydes.[125] For example, pyridone **180** was

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.

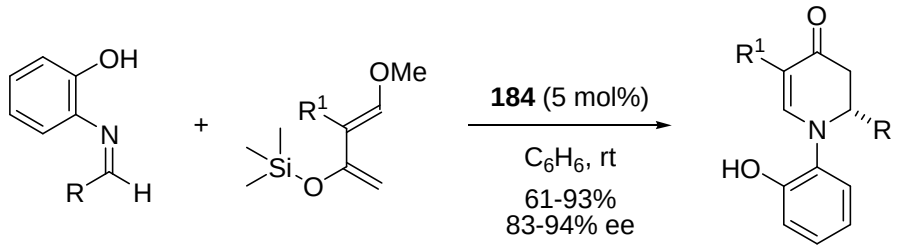
Imines derived from chiral amines have also been shown to impart stereoselectivity under Lewis acid catalysis.[126,127] In particular imines derived from aldehydes and α-phenylethylamine were shown to give pyridones in high selectivities, although in only moderate yields. Several Lewis acids were screened, including $BF_3{\cdot}Et_2O$, $TiCl_2(i\text{-}OPr)_2$, $B(OPh)_3$ 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 (Scheme3.7).[128]



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

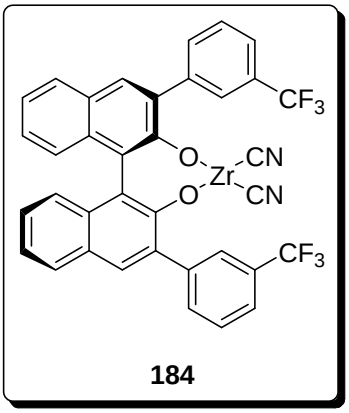
Chiral Lewis acids have also been used to induce selectivity in imino Diels-Alder reactions.[129,130] Kobayashi *et al*. showed that chiral Lewis acid **184** imparted good enantioselectivities in the reaction of aldimines **185** with

Danishefsky-type dienes **186** to give pyridones **187** in good yields (Scheme 3.8).[131]



185 **186** **187**

R = ^{c}Hex, Ph, 4-MeC$_6$H$_4$, Napth, 2-thiophene
R^1 = H, Me



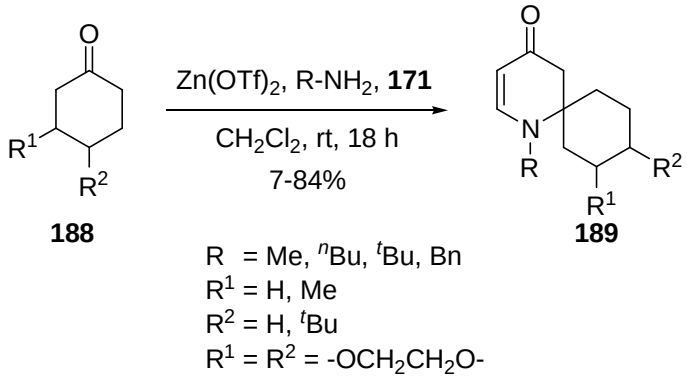
184

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 *et al.* have reported that unactivated imines derived from cyclic ketones undergo cycloaddition with Danishefsky's diene in the presence of Zn(OTf)$_3$.[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 = Me or *n*-Bu) gave

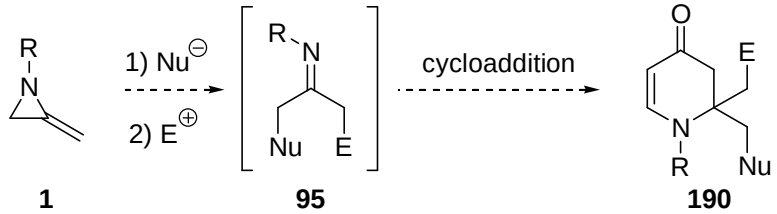
good yields, however with larger groups (R = Bn or *tert*-Bu), only moderate yields were obtained at best (Scheme 3.9). Moreover, no reaction was observed with 2-substituted ketones.



Scheme 3.9. Synthesis of pyridones from cyclohexanones.

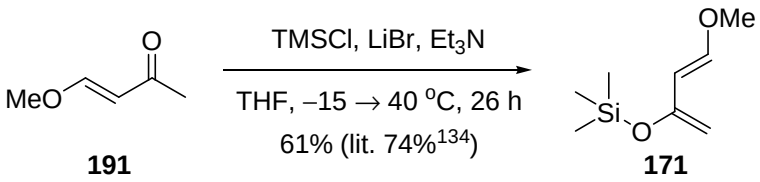
3.2 Pyridone Synthesis Attempt *via* Methyleneaziridine MCRs

Since it has been shown that pyridones can be accessed from the imino Diels-Alder reaction of ketimines with an electron-rich diene,[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.



Scheme 3.10. Proposed approach to pyridones *via* an imino Diels-Alder MCR.

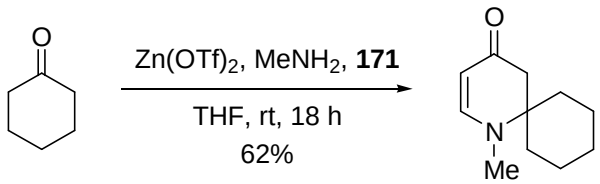
Many of the reports of imino Diels-Alder reactions employ Danishefsky's diene (**171**) and so this material was selected for our studies. This diene can be readily made using published methods.[119,133,134] Thus, treatment of *trans*-4-methoxy-but-3-en-2-one **191** with lithium bromide and chlorotrimethylsilane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



191 **171**

Scheme 3.11. Synthesis of Danishefsky's diene.

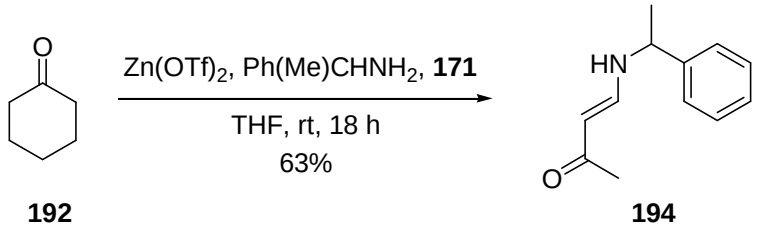
To develop a methyleneaziridine based MCR approach to pyridones, the first challenge was to explore if an imino Diels-Alder reaction could be effected in tetrahydrofuran. To this end, zinc triflate catalysed reaction of cyclohexanone derived imines with diene **171** was repeated according to Huang's method[132] in tetrahydrofuran (Scheme 3.12). Cyclohexanone (**192**) in tetrahydrofuran was treated with $Zn(OTf)_2$ (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%).[132]



192 **193**

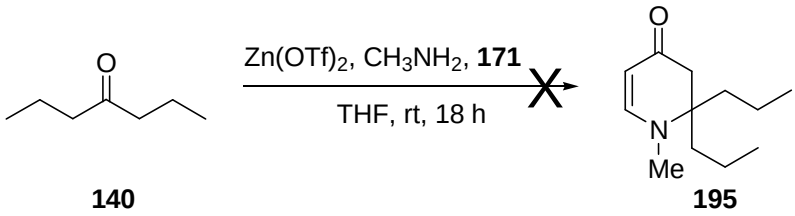
Scheme 3.12. Solvent compatibility test reaction.

In agreement with Huang,[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[135] **194** was isolated as the major product (Scheme 3.13). This result suggested that methyleneaziridines bearing no branching at the α-carbon would be needed to realise the proposed new MCR (Scheme 3.11).



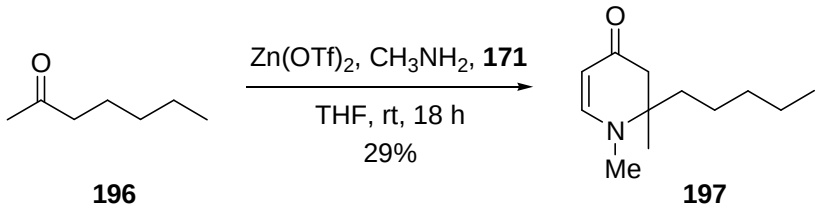
Scheme 3.13. Probing *N*-substituent size.

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 ^1H NMR or mass spectroscopy (Scheme 3.14).



Scheme 3.14. Unsuccessful use of 4-heptanone.

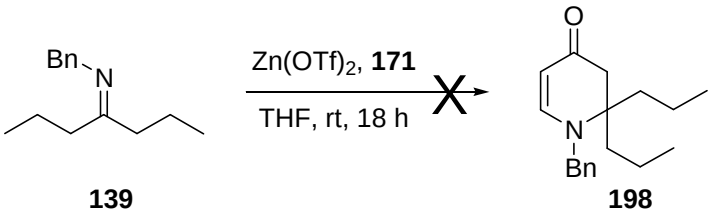
Using 2-heptanone (**196**) under the same conditions, pyridone **197** was isolated in a modest 29% yield (Scheme 3.15).



Scheme 3.15. Synthesis of a pyridone from 2-heptanone.

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 ^1H NMR or mass spectroscopy (Scheme 3.16).



Scheme 3.16. Attempted synthesis of pyridones form ketimines.

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[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.

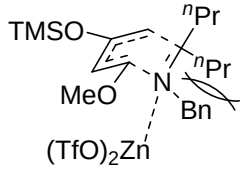


Figure 3.1. Steric clashing in the synthesis of pyridones from ketimines.

3.3 Conclusion

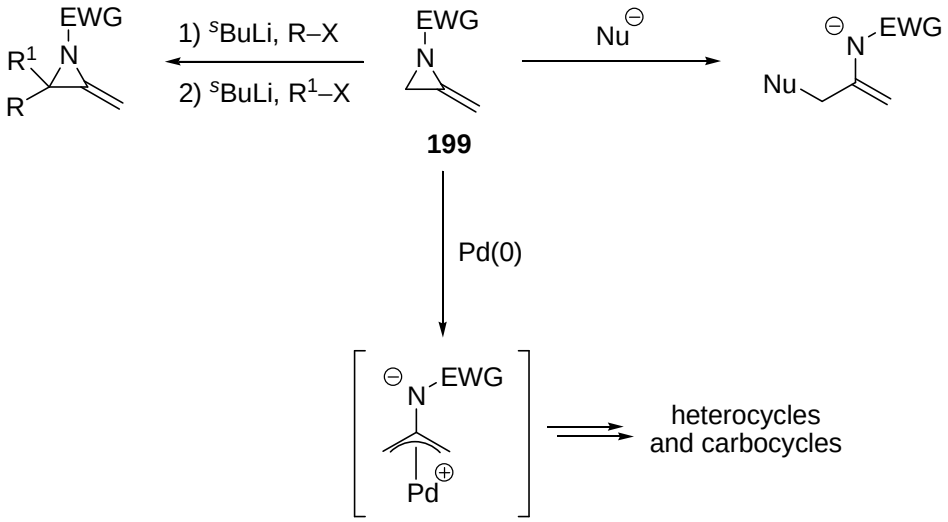
Experiments to ascertain if a MCR route to pyridones *via* an imino Diels-Alder reaction from methyleneaziridines have met with failure. Model studies indicated that acyclic ketimines that would be used as intermediates in these reactions are poor substrates for imino Diels-Alder reactions. Although 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* *N*-Functionalisation of Methyleneaziridines

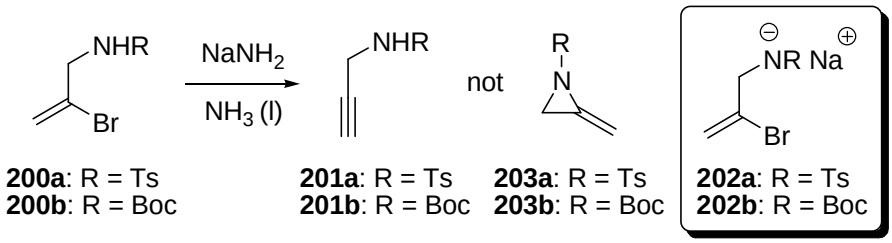
4.1 Introduction

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.[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* π-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.

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.[10] When the ring-closure of *N*-tosyl **200a** and *N*-Boc **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 **201** (Scheme 4.2).

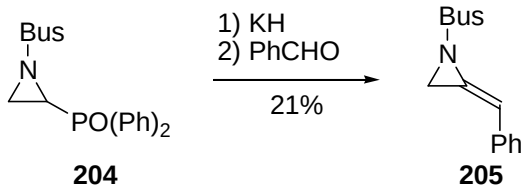


Scheme 4.2. Undesired generation of acetylenes.

The increased acidity of the NH within **200** means that these vinyl bromides would become irreversibly deprotonated to generate the corresponding sodium anions **202** rather than ring-close to methyleneaziridines **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[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[136] type strategy.[137] Aziridine **204** (made in three

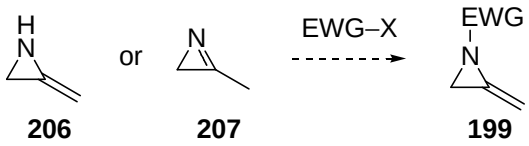
steps from the corresponding vinyl phosphonate) when treated with potassium hydride and benzaldehyde yielded the corresponding methyleneaziridine **205** in a modest yield as a single geometric isomer (Scheme 4.3). The structure of this derivative has been confirmed by X-ray crystallography. Whilst these results are encouraging, the length of this sequence, and low yields led us to consider alternate strategies.



204 **205**

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).



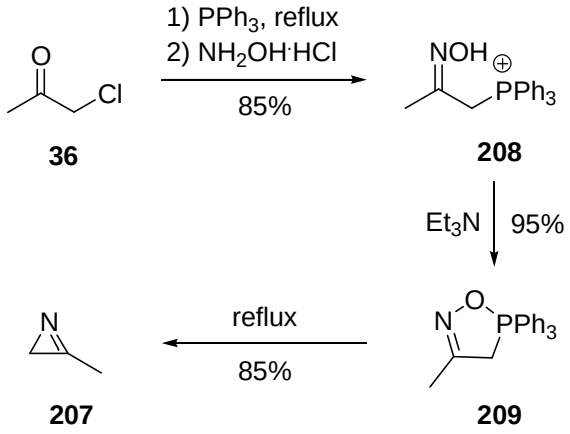
206 **207** **199**

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. *endo*cyclic 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 *exo*- or *endo*cyclic unsaturation.

Hassner *et al*. reported the synthesis of 2-methylazirine (**207**) from α-halo ketoximes *via* oxazaphospholoes.[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).

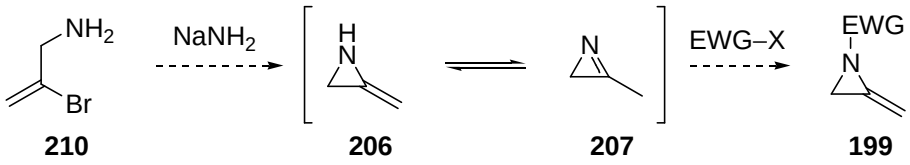


Scheme 4.5. Synthesis of 2-methylazirine.

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.

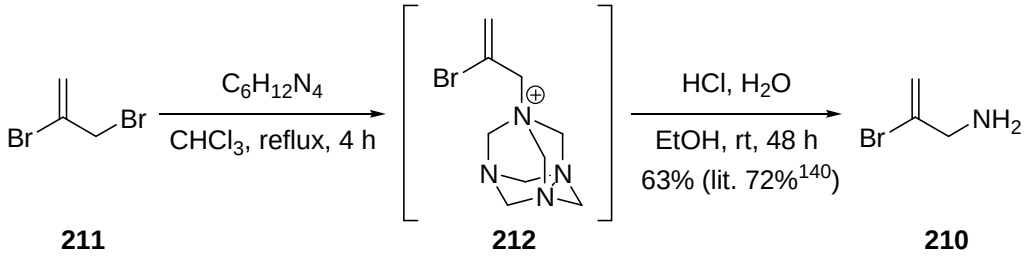
4.2 Attempted *in situ* functionalisation to 2-methyleneaziridines

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).



Scheme 4.6. Proposed *in situ* alkylation of 2-methyleneaziridine.

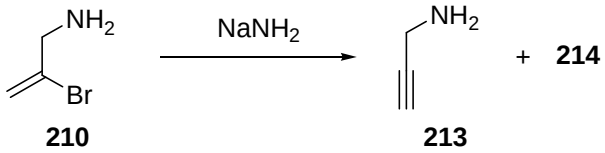
In order to explore the approach outlined above it was required to synthesise vinyl bromide **210**. This was achieved according to the procedure first described by Bottini *et al.*[140] Reaction of 2,3-dibromopropene **211** with hexamethylenetetramine under reflux led to quaternary ammonium salt **212**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



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 ^{o}C at 1 atm[139]) making isolation potentially difficult. The organic soluble extract was also obtained by partitioning between $D_2O/CDCl_3$. 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.



Scheme 4.8. Attempted ring-closure of *N*-(2-bromoallyl)-amine.

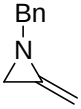
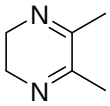
Entry	Na (equiv.)	Time (min)	Temperature (^{o}C)	Product Ratio[a]					
				D_2O			$CDCl_3$		
				210	213	214	210	213	214
1	2.5	10	–33	1	-	-	-	-	-
2	2.5	60	–33	1	-	-	2.6	1	-
3	2.5	60	–78	1	-	-	1.9	1	0.1
4	2.5	120	–33	1	-	-	4.1	1	-
5	2.5	360	–33	1	-	-	3	1	-
6	3.5	60	–33	1	-	-	1	-	-
7	5	60	–33	1	-	-	1.2	1	0.1
8	5	120	–33	-	-	-	-	1	1.2
9	6	60	–33	-	-	-	-	1	1.9

[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 ^{o}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.

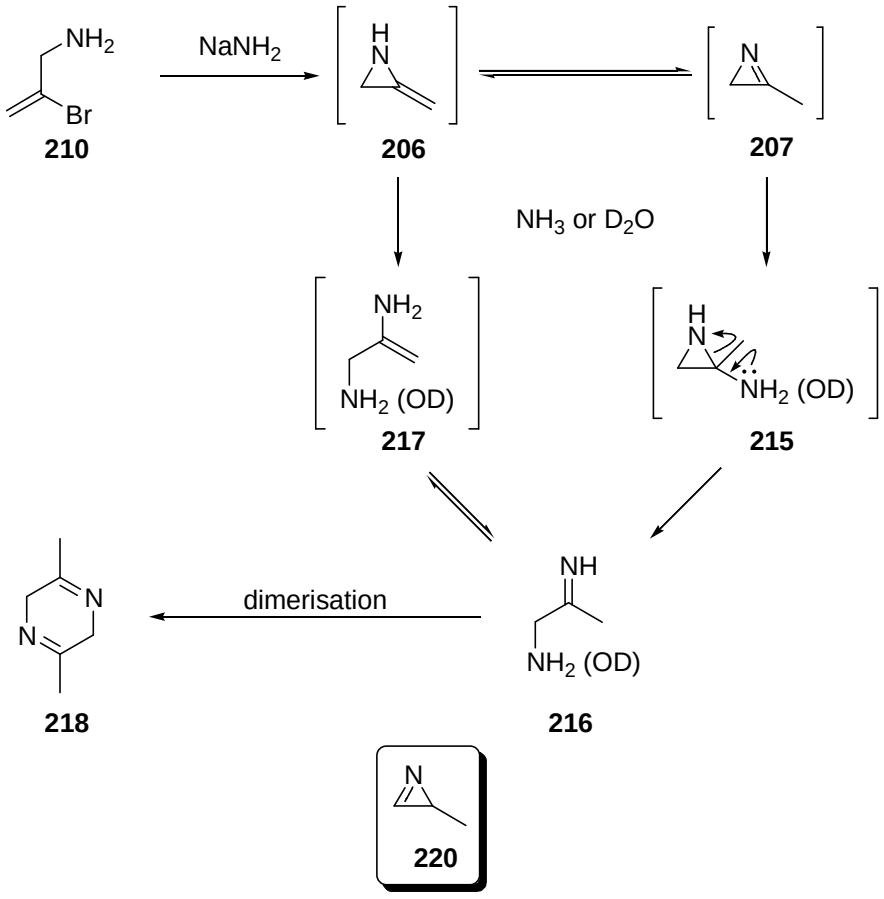
Entry	Compound	Structure	δ_H ($CDCl_3$)	δ_C ($CDCl_3$)
1	**214**	-	3.99 (2H), 2.00 (3H)	167.5 (C/CH_2), 52.1 (C/CH_2), 24.3 (CH/CH_3)
2	**207**		2.50 (3H), 1.35 (2H)[139]	-[a]
3	**50**		4.72 (2H), 2.06 (2H)[9]	137.0 (C), 83.5 ($=CH_2$), 30.6 (ring CH_2)[9]
4	**219**		3.35 (4H), 2.15 (6H)[142]	160.2 (C), 45.8 (CH_2), 24.0 (CH_3)[142]

[a] ^{13}C NMR data for **207** was not reported.[139]

Table 4.2

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.[143] Consequently, aziridines formed in this process could be susceptible to further ring-opening reactions.[144] Hence, 2-methylazirine (**207**) could undergo nucleophilic addition with NH_3 or D_2O 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.[145] It was also

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[142] **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.

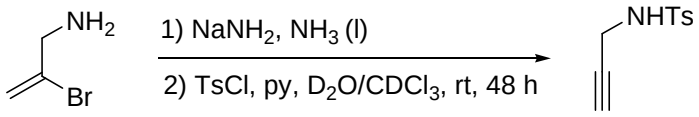
Whilst structures **216** and **218** bear reasonable resemblance to **214**, there are still considerable discrepancies on comparing the observed data to known analogues (Table 4.2). As such, it is difficult to determine the identity of **214**, although the

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).

216 **218**

Figure 4.1. Tentatively proposed imine products.

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* ^1H NMR spectroscopy in both the organic and aqueous phases (Scheme 4.10).



210 **201a**

Scheme 4.10. Attempted *in situ* tosylation.

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 *in vitro* and *in vivo* formation of THBCs within brain and other tissue cells.[153]

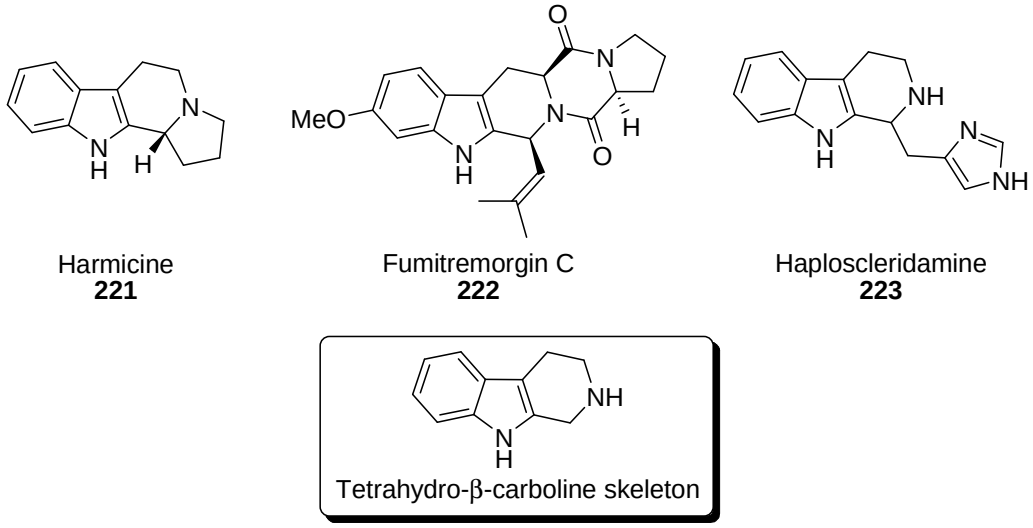


Figure 5.1. Selected β-carboline containing natural products.

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]

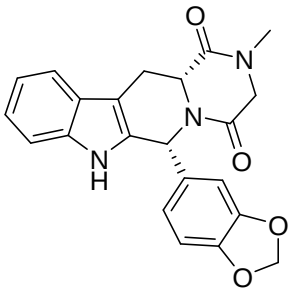


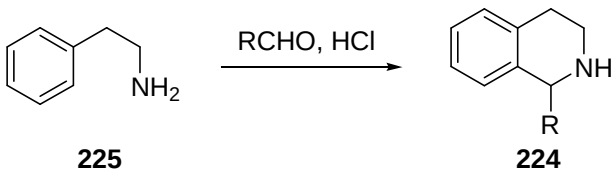
Figure 5.2. Tadalafil.

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[157] and as such only highlights are discussed herein.

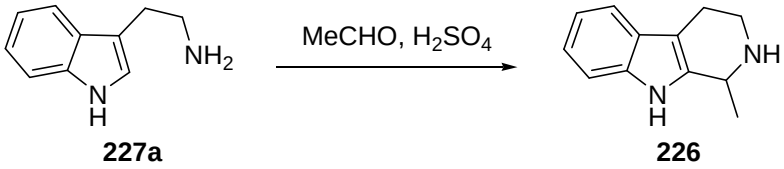
The Pictet-Spengler cyclisation involves the condensation of an aldehyde or ketone with a β-arylethylamine, typically under Brönsted or Lewis acid catalysis, to give an electrophilic iminium ion, which undergoes electrophilic aromatic substitution. This reaction was first reported in 1911 by Pictet and Spengler in their synthesis of tetrahydroisoquinolines **224** from phenethylamine (**225**) and aldehydes under acidic conditions. (Scheme 5.1).[158]



225 **224**

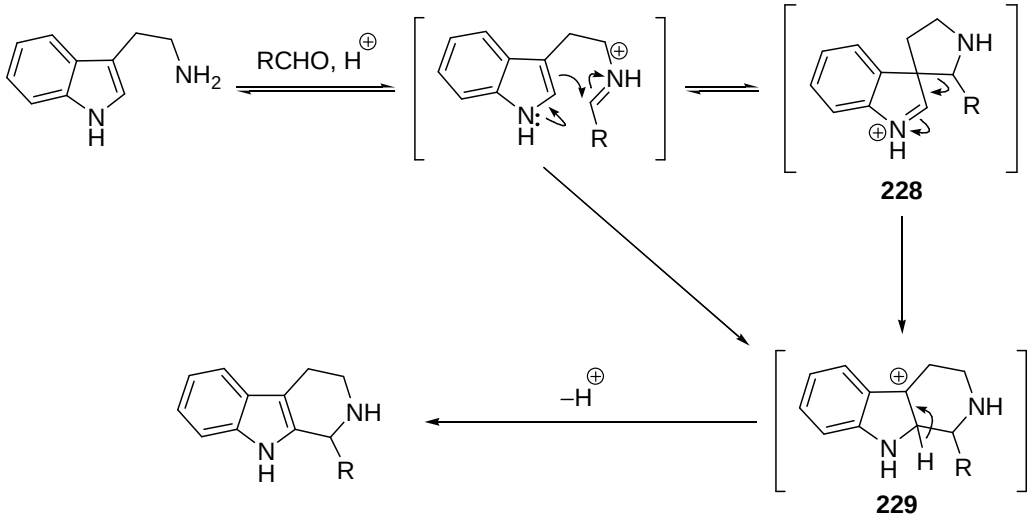
Scheme 5.1. Pictet and Spengler's synthesis of tetrahydroisoquinolines.

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).[159]



Scheme 5.2. Tatsui's synthesis of tetrahydro-β-carbolines.

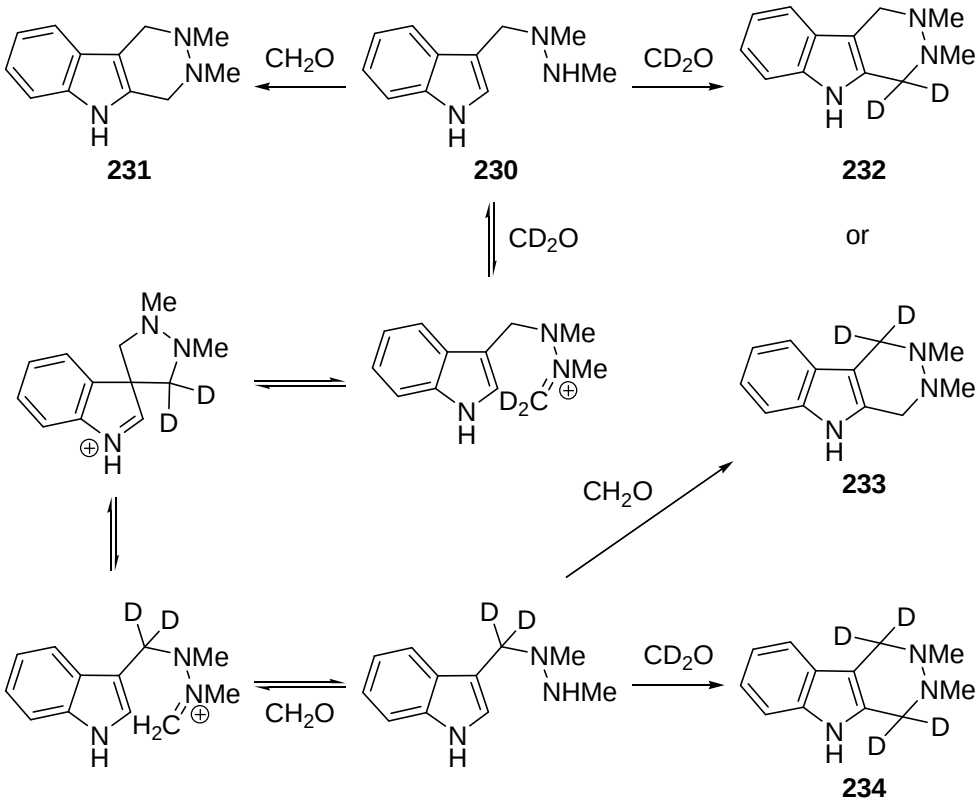
The precise mechanism of the synthesis of THBCs has yet to be fully defined, although it is widely accepted that it proceeds through a *spiro*-indolenine intermediate **228**,[160] which collapses to form the carboline (Scheme 5.3). However, direct attack at C-2 of the indole by reactive electrophiles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



Scheme 5.3. Accepted mechanism of the Pictet-Spengler cyclisation.

Bailey obtained evidence for the *spiro*-indolenine intermediate through deuterium labelling studies (Scheme 5.4).[163] It was found *via* NMR and mass

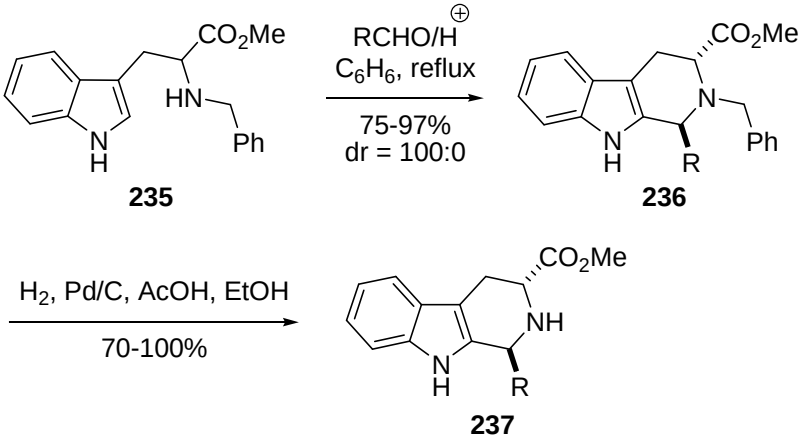
spectroscopy studies that reaction of indolic hydrazine **230** with isotopically enriched formaldehyde gave a roughly equal mixture of **231**, **232**, **233**, and **234**. This statistical mixing is consistent with an equilibrium between a spiro intermediate and reversible imine formation/hydrolysis. 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.

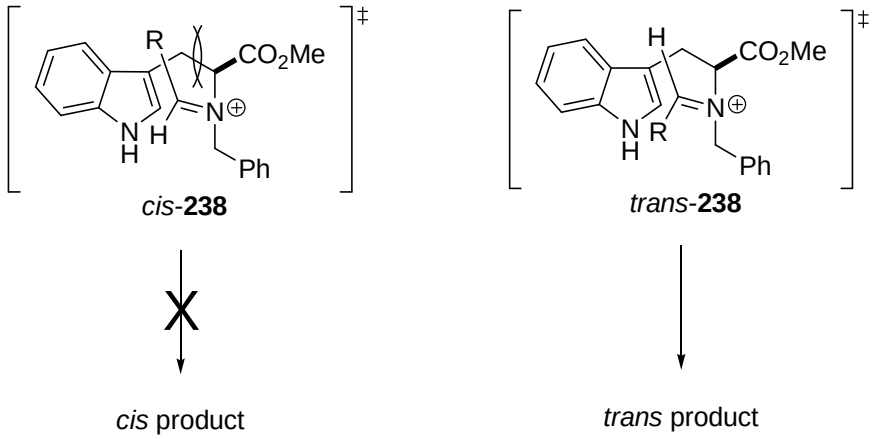
5.2.2 Stereocontrol in Pictet-Spengler cyclisations

In 1981, Ungemach *et al*. reported the stereospecific synthesis of *trans*-1,3-disubstituted THBCs.[164] *N*-Benzyltryptophan methyl ester (**235**) was condensed with aldehydes in a stereospecific fashion. Catalytic hydrogenation of *N*-benzyl derivatives **236** gave *trans*-β-carbolines **237** in good yields and high selectivities (Scheme 5.5).



Scheme 5.5. Ungemach's synthesis of *trans*-1,3-disubstituted THBCs.

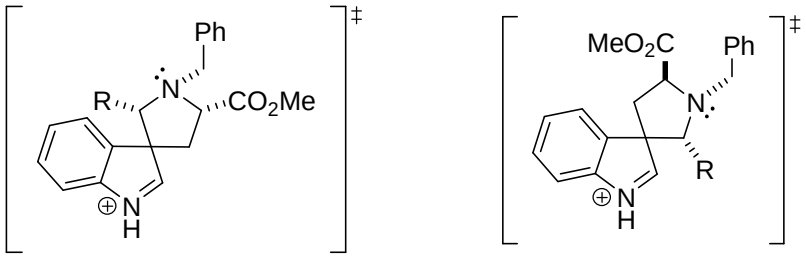
The stereochemical preference in this cyclisation was rationalised by examination of the likely transition states. When the 1- and 3-substituents lie *cis* there would be appreciable 1,3-interactions between the R and ester groups in transition state *cis*-**238**. However, when the substituents adopt 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).



Scheme 5.6. Rational for the selective formation of *trans*-**236**.

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

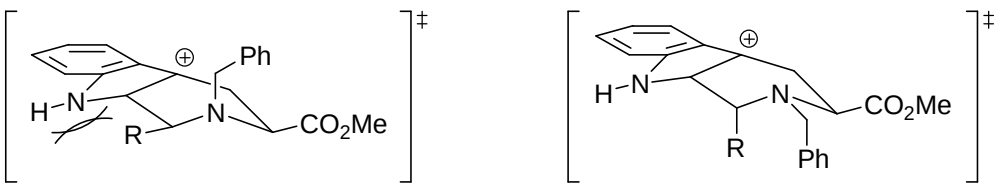
postulated to proceed through spiroindolenine intermediate **239**. Attack of the top face of the iminium double bond in *trans*-**238** would result in spiroindolenine **239a** with the substituents ecoming eclipsed and hence more crowded. Attack of the bottom face would proceed *via* **239b** which would result in far less steric crowding, favouring the formation of *trans*-**236**.



239a **239b**

Figure 5.3. Consideration of attack from C-3 of indole double bond.

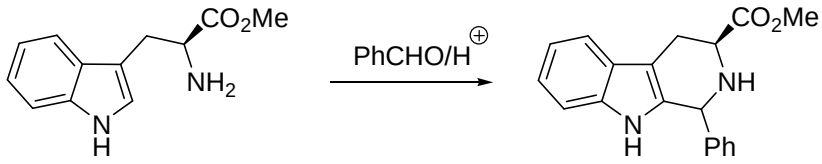
When considering direct electrophilic attack from C-2 of the indole double bond of the top face of the iminium double bond in *trans*-**238**, Ungemach postulated that carbocation **240a** would result. This carbocation would feature equatorial C-1 and C-3 substituents but also a disfavoured axial N-2 substituent. Moreover, **240a** would suffer from unfavourable $A^{1,2}$ 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 $A^{1,2}$ strain, thus **240b** would be the more stable cation intermediate.



240a **240b**

Figure 5.4. Consideration of attack from C-2 of indole double bond.

Bailey *et al*. also reported complete stereochemical control in Pictet-Spengler cyclisations to 1,3-disubstituted THBCs.[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 *trans*-isomer of **242** is formed preferentially, whereas in dichloromethane at 0 ^{o}C, the *cis*-isomer is favoured (Scheme 5.7).



241 **242**

C_6H_6, 80 ^{o}C: 76%, *cis*:*trans* = 37:63
CH_2Cl_2, 0 ^{o}C: 74%, *cis*:*trans* = 82:18

Scheme 5.7. Stereochemical control in the Pictet-Spengler cyclisation.

Bailey *et al*. have provided an explanation for these observations.[160b] At high temperatures the reaction is reversible and a slight preference for the *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).

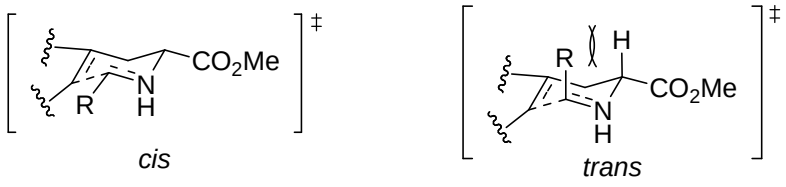
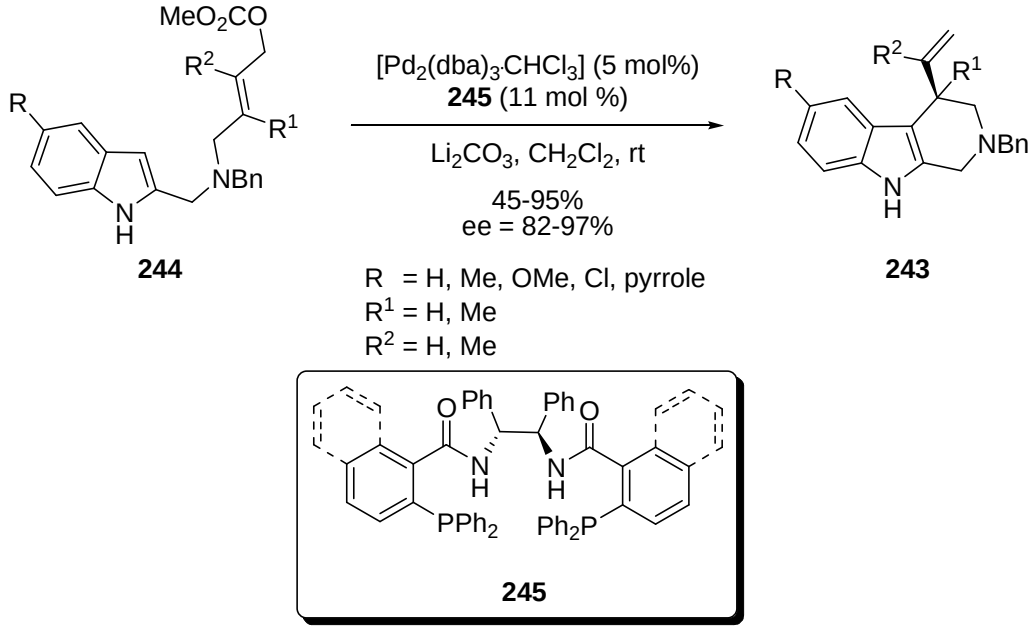


Figure 5.5. Preference for *cis* configuration under kinetic control.

5.2.3 Intramolecular allylic alkylation

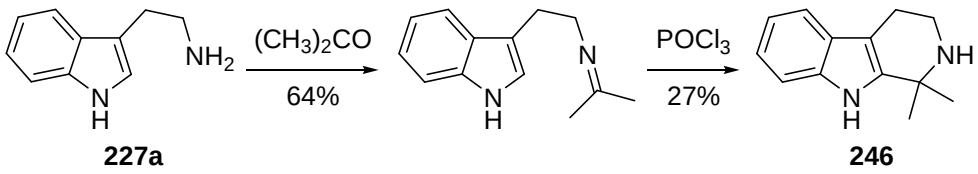
In 2005, Bandini *et al*. reported the first enantioselective metallo-catalysed synthesis of THBCs **238** and tetrahydro-γ-carbolines (Scheme 5.8).[166] This was achieved by palladium-catalysed intramolecular allylic alkylation of indolyl carbonates **239** with DPPBA-based Trost's[167] ligand **240**.



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

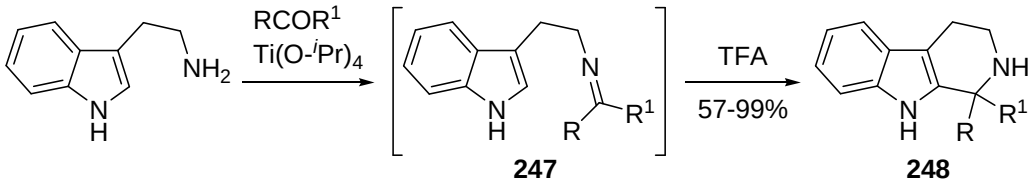
5.2.4 Synthesis of 1,1-disubstituted tetrahydro-β-carbolines

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).[168] However, this process is rather inefficient.



Scheme 5.9. Synthesis of 1,1-disubstituted THBCs with $POCl_3$.

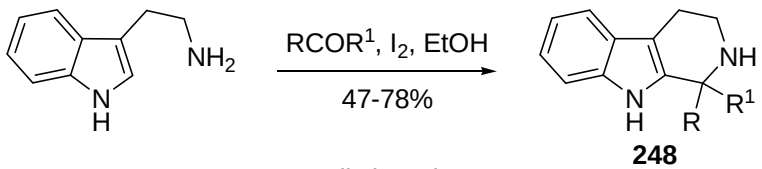
The first significant advance came in 2003, when Horiguchi *et al*. reported the use of titanium (IV) isopropoxide as iminating agent for the generation of indole functionalised ketimines **242**.[169] Further cyclisation promoted by TFA led to simple 1,1-disubstituted THBCs **243** (Scheme 5.10).



R = Me, Ph
R^1 = Me, Et, Ph, CH_2SPh
R = R^1 = $-(CH_2)_5-$, $-(CH_2)_6-$

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

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 **248** from simple, unactivated ketones (Scheme 5.11).[170]

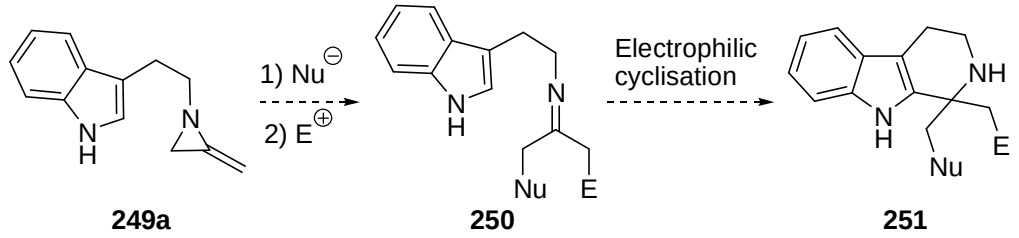


R = Alkyl, Aryl
R^1 = Alkyl, Aryl

Scheme 5.11. Lingam's conditions utilising I_2.

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).

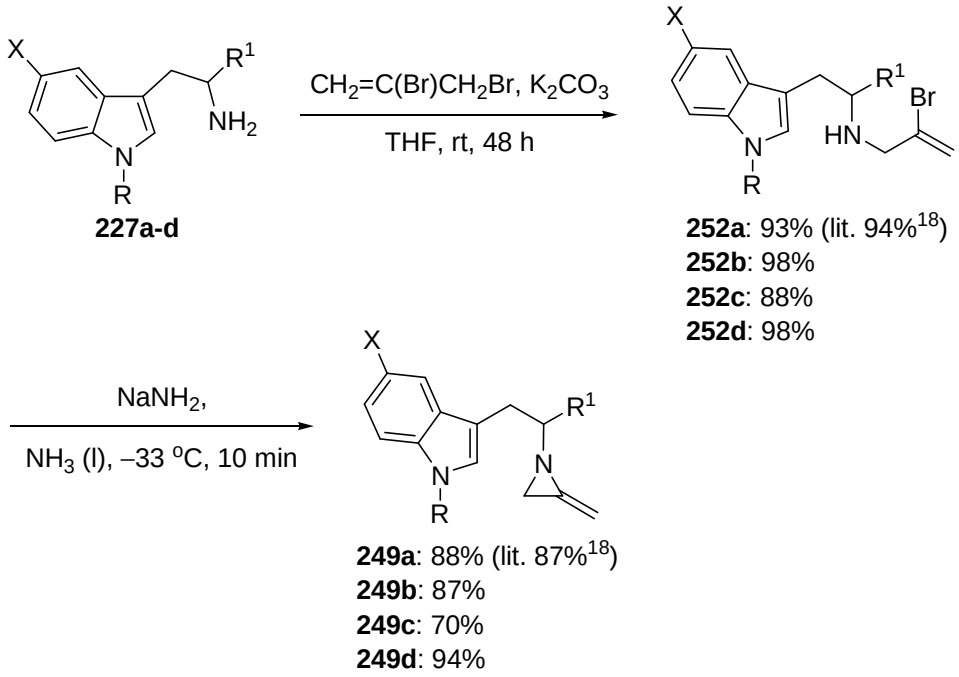


Scheme 5.12. Proposed formation of THBCs *via* a 3-CR.

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**.[18] 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 ^{o}C afforded known methyleneaziridine **249a** in 88% yield after

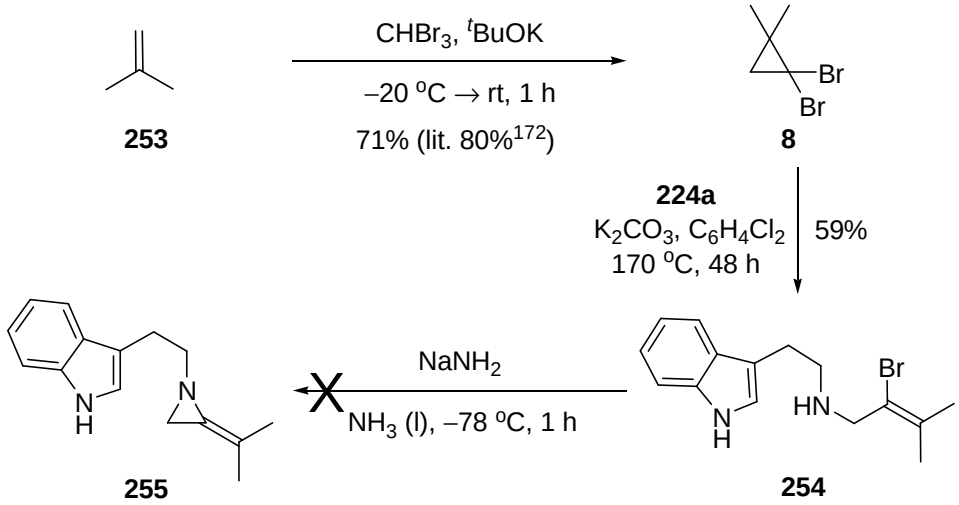
bulb-to-bulb distillation. Three novel derivatives were made using the same general approach. Thus, methoxy-derivative **249b** was prepared from 5-methoxytryptamine (**227b**) in 85% overall yield using the same sequence. Similarly, **249c** was made in 62% overall yield from *N*-2-(1-methyl-1*H*-indol-3-yl)ethylamine[171]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



Scheme 5.13. Synthesis of indole tethered methyleneaziridines.

It is known that primary amines can be converted to methyleneaziridines bearing a *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_2CO_3 in 1,2-dichlorobenzene at 170 °C for 48 hours. After work-up and purification, **254** was isolated in 59% yield. Unfortunately,

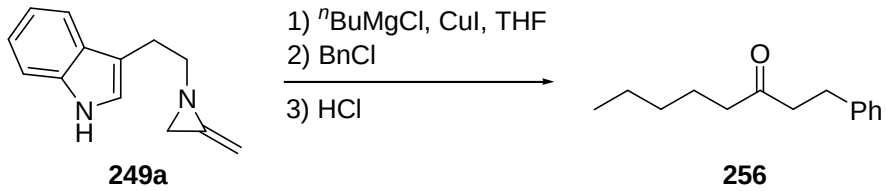
attempted aziridination of **254** under the standard conditions failed to furnish **255** (Scheme 5.14).



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

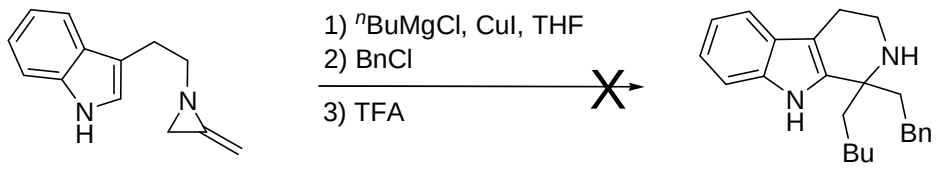
5.3.2 Initial model reactions

Methyleneaziridine **249a** has been shown to be a suitable substrate for the formation of 1,3-disubstituted propanone **256** (Scheme 5.15).[18]



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

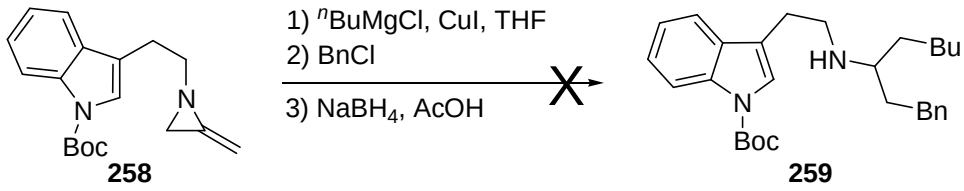
However, the use of **249a** in a modified MCR failed to yield any of the desired 1,1-disubstituted THBC **257** using trifluoroacetic acid[169] to induce the final cyclisation (Scheme 5.16).[18]



249a **257**

Scheme 5.16. Unsuccessful Pictet-Spengler MCR.

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).[18]

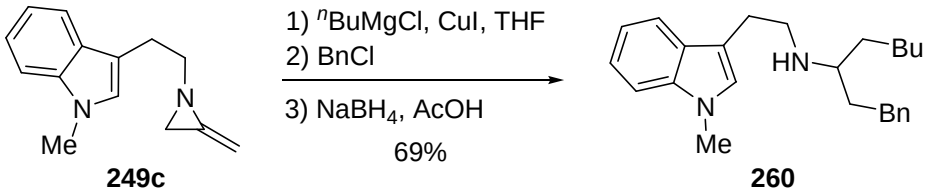


258 **259**

Scheme 5.17. Unsuccessful amine forming MCR.

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. *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 *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).

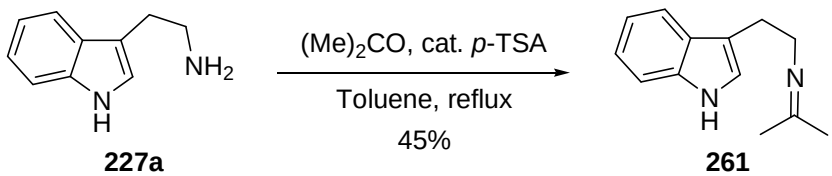


249c **260**

Scheme 5.18. Amine formation from indole functionalised aziridine.

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.

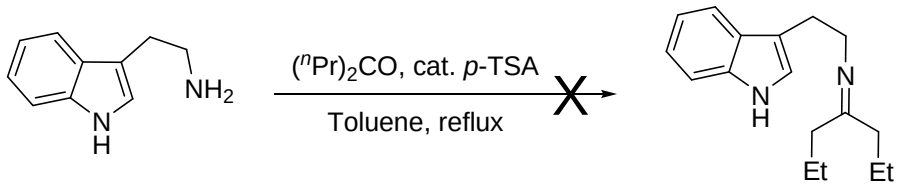
In order to test new conditions, imine **261** was made as a substrate for model cyclisations. Hester had synthesised indole functionalised imines by the condensation reaction of acetone and tryptamine (**227a**) in refluxing benzene in the presence of *p*-toluenesulfonic acid, to give 3-(2-isopropylideneaminoethyl)indole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



227a **261**

Scheme 5.19. Synthesis of indole tethered ketimines.

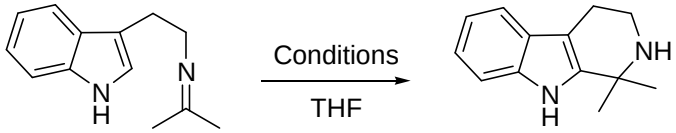
We also attempted to synthesise imine **262**, as it would more closely resemble the imines resulting from the MCR. Tryptamine (**227a**), 4-heptanone and catalytic *p*-TSA were refluxed in toluene with azeotropic distillation of water. Surprisingly, this reaction failed to yield the expected product.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



227a **262**

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.



261 **246**

Scheme 5.21. Pictet-Spengler cyclisation of **261**.

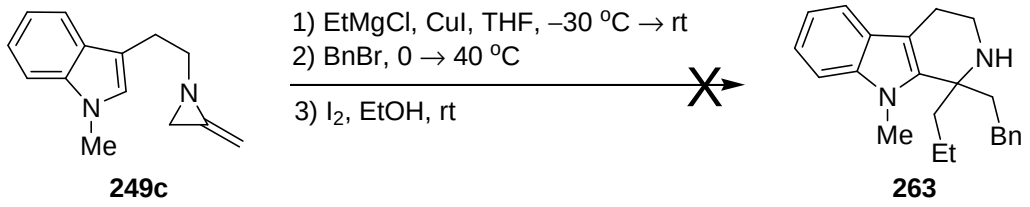
Entry	Activator	Solvent	Temp.	Yield
1	$POCl_3$[168]	THF	Reflux	-
2	$Sc(OTf)_3$[174]	THF	Reflux	-
3	$B(Bu)_3$[175]	THF	–78 °C	-
4	c. H_2SO_4[176]	MeOH/THF	0 °C	91%
5	I_2[170]	EtOH/THF	Rt	56%

Table 5.1.

The most suitable conditions were identified as I_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.

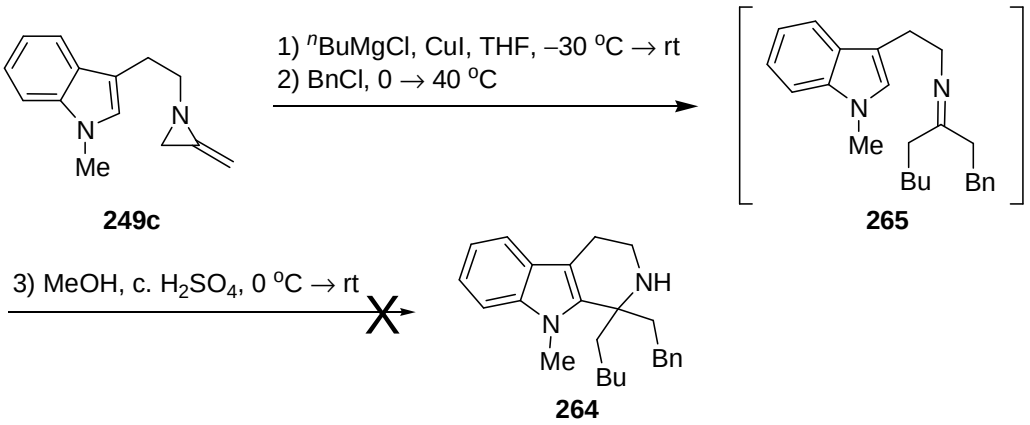
As an initial test, Lingam's[170] cyclisation conditions of I_2 in EtOH were applied to the MCR. These conditions were chosen initially as they were considered to be milder than concentrated sulphuric acid in methanol.[176] Methyleneaziridine **249c** in tetrahydrofuran was ring-opened with ethylmagnesium 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.

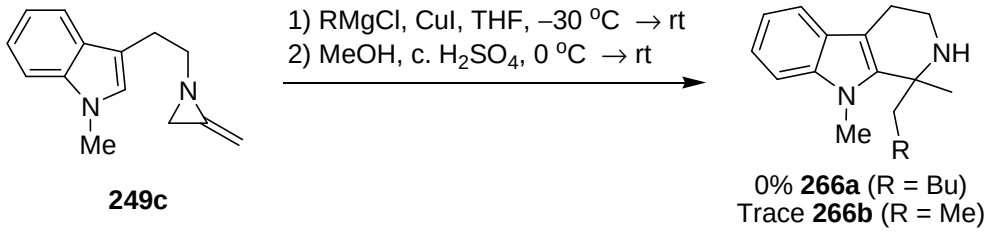
Using the conditions of Rodríguez,[176] methyleneaziridine **249c** was reacted with *n*-butylmagnesium chloride, copper (I) iodide (20 mol%) and benzyl chloride as described above. Treatment with methanol and concentrated sulphuric acid at 0 °C with subsequent warming to room temperature, again after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



Scheme 5.23. Unsuccessful acid activated Pictet-Spengler MCR.

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.

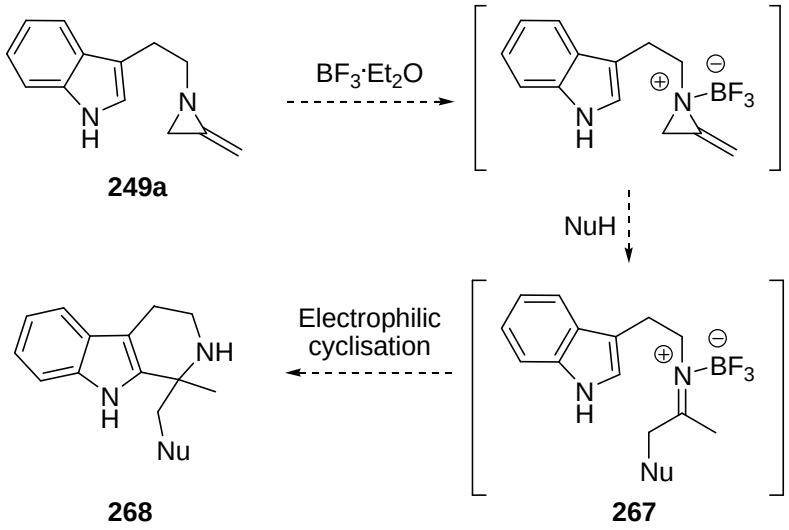


Scheme 5.24. Attempted 2 component Pictet-Spengler reactions.

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.[177] 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.[18]

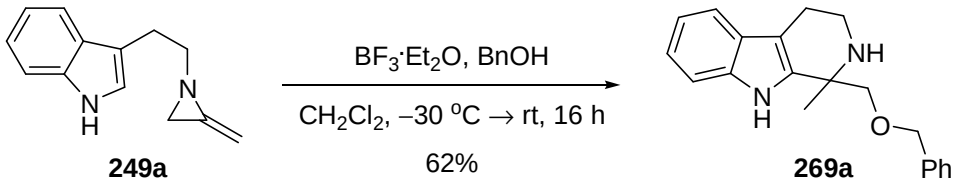
5.4 Synthesis of 1,1-Disubstituted β-Carbolines

It is known that $BF_3{\cdot}OEt_2$ 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 $BF_3{\cdot}OEt_2$ 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)



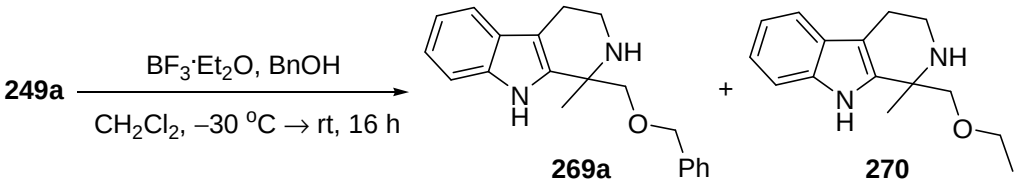
Scheme 5.25. Re-evaluated approach to THBCs.

To test this idea, methyleneaziridine **249a** was dissolved in dichloromethane, cooled to –30 ^{o}C and treated with $BF_3{\cdot}Et_2O$ (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 $BF_3{\cdot}OEt_2$ 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.



Scheme 5.27. Optimisation of reaction equivalents of benzyl alcohol.

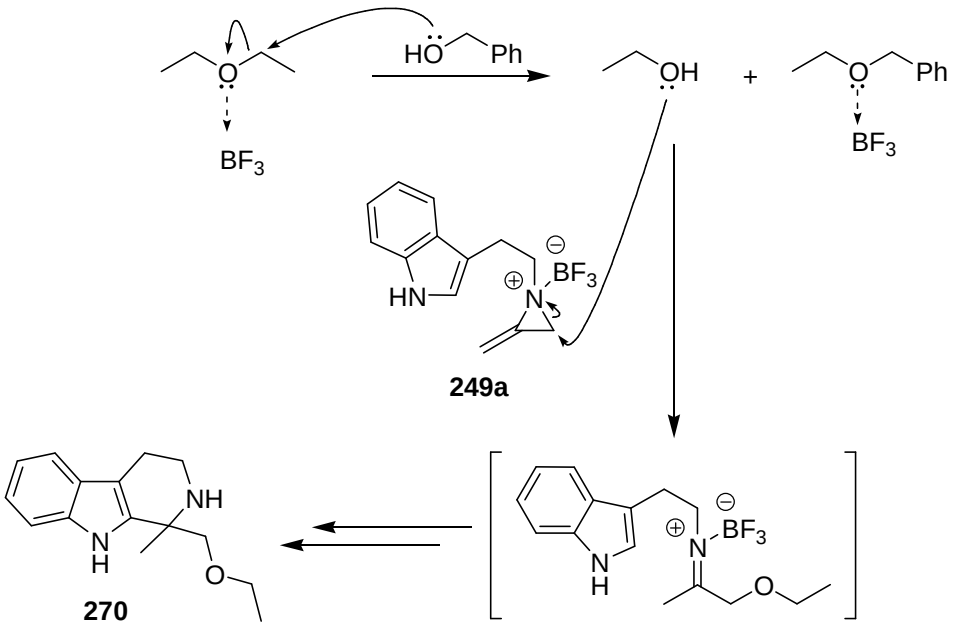
Entry	BnOH (equiv.)	Yield	
		269a	**270**
1	1.1	54%	14%
2	1.5	61%	8%
3	2	73%	-

Table 5.2.

From these results, we ascertained that using an equimolar quantity of $BF_3{\cdot}OEt_2$, and 2 equivalents of benzyl alcohol were optimal. Using less benzyl alcohol (Entries 1 and 2), a side product **270**, was isolated.

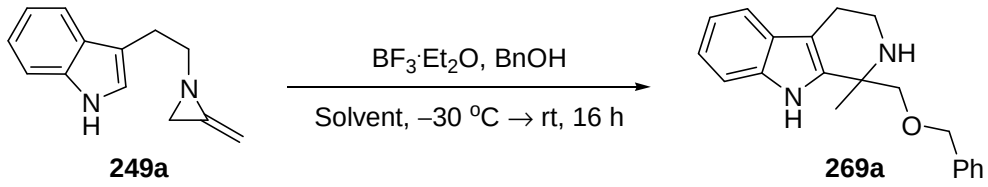
β-Carboline **269a** was identified by a distinct quaternary carbon at 53.4 ppm in the ^{13}C NMR spectrum and the presence of two AB systems (4.54, 4.50, 3.55 and 3.51 ppm) in the ^{1}H NMR spectrum. These AB systems were readily assigned as the benzylic CH_2 and the CH_2 bonded to the quaternary carbon. 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 carboline **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 $BF_3{\cdot}OEt_2$. A plausible mechanism is that activated by the BF_3, the diethyl ether undergoes a transetherification reaction, liberating ethanol and producing benzyl ethyl ether as by-product (Scheme 5.28).



Scheme 5.28. Speculated mechanism for the formation of **270**.

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 $BF_3{\cdot}OEt_2$ and 2 equivalents of benzyl alcohol (Scheme 5.29). The results are summarised in Table 5.3.



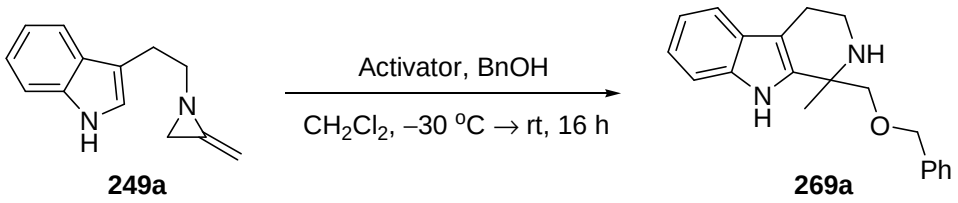
249a **269a**

Scheme 5.29. Solvent optimisation.

Entry	Solvent	Yield 269a
1	CH_2Cl_2	73%
2	$C_6H_5CH_3$	38%
3	$ClCH_2CH_2Cl$	44%
4	$CHCl_3$	32%
5	MeCN	52%

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.



249a **269a**

Scheme 5.30. Screening of Lewis/Brönsted acids.

Entry	Activator	Yield 269a
1	$BF_3{\cdot}OEt_2$	73%
2	$BF_3{\cdot}THF$	41%
3	$BF_3{\cdot}SMe_2$	-
4	$Sc(OTf)_3$	-
5	$AlMe_3$	-
6	TFA	28%
7	TCA	-
8	H_2SO_4	-
9	AcOH	-
10	CH_3SO_3H	-

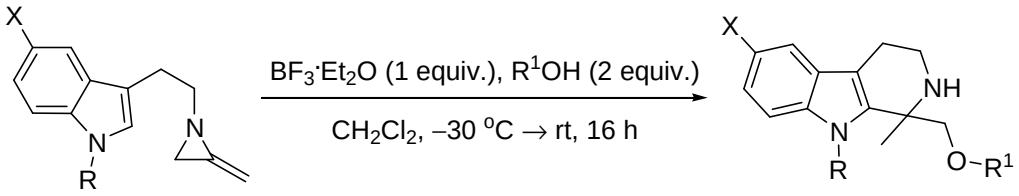
Table 5.4.

Clearly, $BF_3{\cdot}OEt_2$ was the best activator for the cyclisation (Entry 1). Lower conversions were observed with $BF_3{\cdot}THF$ and TFA (Entries 2 and 6). None of the other activators produced any of the desired product by ^1H NMR or mass spectroscopy.

To summarise, the best conditions involved the use of equimolar amounts of methyleneaziridine and $BF_3{\cdot}OEt_2$, 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.

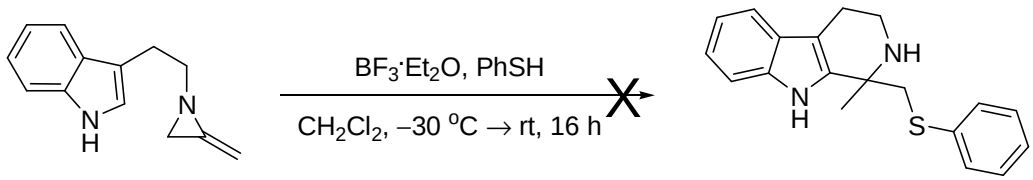
Entry	Aziridine	R	X	R^1OH	Product	Yield
1	**249a**	H	H	BnOH	**269a**	73%
2	**249a**	H	H	^{n}PrOH	**269b**	83%
3	**249a**	H	H	^{c}HexOH	**269c**	63%
4	**249a**	H	H	^{t}BuOH	**269d**	58%
5	**249a**	H	H	$H_2C{=}CHCH_2OH$	**269e**	80%
6	**249a**	H	H	$HC{\equiv}C(CH_2)_3OH$	**269f**	71%
7	**249b**	H	OMe	BnOH	**269g**	66%
8	**249c**	Me	H	BnOH	**269h**	43%
9	**249c**	Me	H	$H_2C{=}CHCH_2OH$	**269i**	37%

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.[177] 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).

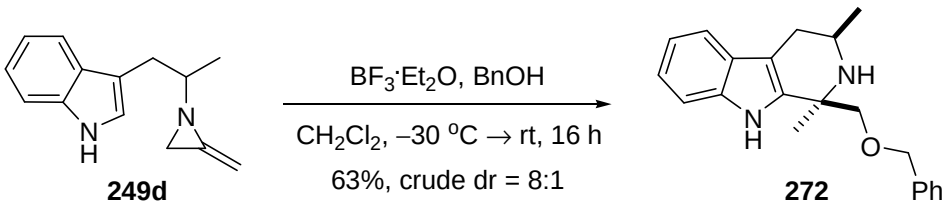


249a **271**

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.[165] Thus, we thought that the presence of a "chiral handle" in the 3-position of the cyclised ring might lead to some diastereocontrol.

Gratifyingly, reaction of methyleneaziridine **229d** with benzyl alcohol (2 equiv.) in the presence of $BF_3{\cdot}OEt_2$ (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 C*H*$_2$OBn hydrogens and the methyl group at C-3, as well as between the methyl group at C-1 and H-3 (Figure 5.6).

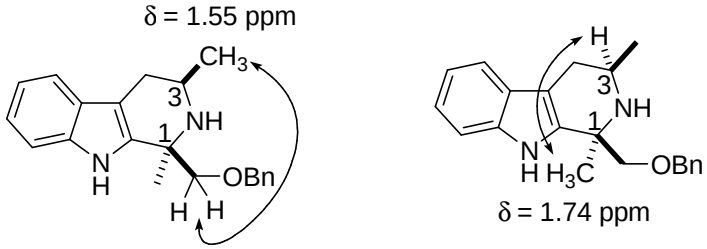


Figure 5.6. Depiction of NOESY correlations.

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 CH_3 and CH_2OBn. Thus, rationalising the preference for the CH_3 to be axial and the CH_2OBn to be equatorial is difficult, even if the reaction is considered to be under kinetic control (Figure 5.7).

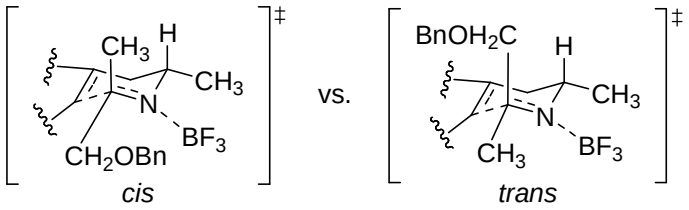
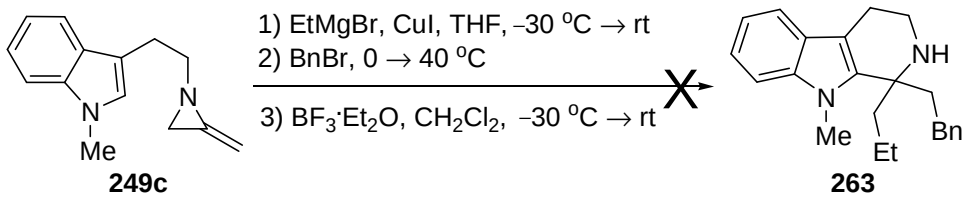


Figure 5.7. Depiction of *cis* and *trans* conformations.

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, $BF_3{\cdot}OEt_2$ 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 ^{o}C and a dichloromethane solution of $BF_3{\cdot}OEt_2$ (1 equiv.) added (Scheme 5.34). Unfortunately, after work-up none of the desired product **263** was identified by ^{1}H NMR or mass spectroscopy.



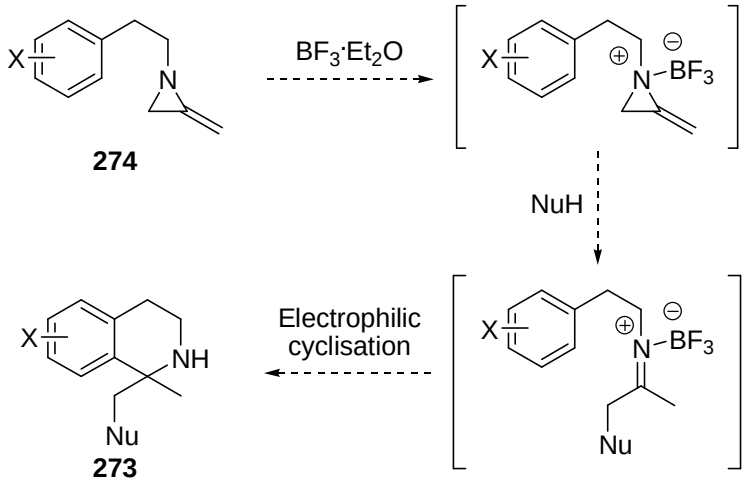
Scheme 5.34. Attempted Pictet-Spengler MCR with $BF_3{\cdot}OEt_2$ activation.

The reaction was repeated, as described above, but with the tetrahydrofuran removed and the residue re-dissolved in dichloromethane before addition of $BF_3{\cdot}OEt_2$. 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).

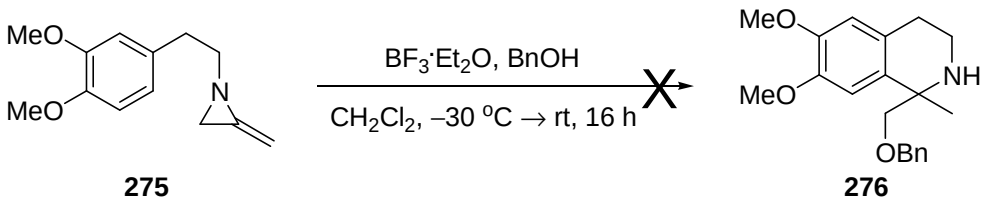
5.5 Attempted Synthesis of Tetrahydroisoquinolines

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).



Scheme 5.35. Approach to tetrahydroisoquinolines from methyleneaziridines.

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.[18] Unfortunately, reaction of an existing sample of **275** with $BF_3{\cdot}OEt_2$ (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 form further explaining the origin of this failure.



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.[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^{TM} 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 ^{o}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.[180]

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 F_{254}) 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.

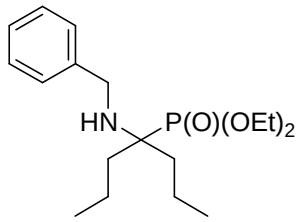
^{1}H, ^{13}C and ^{31}P NMR spectra were recorded at 300 MHz, 75 MHz and 121 MHz respectively on a Bruker DPX-300; at 400 MHz, 100 MHz and 161 MHz respectively on a Bruker DPX-400. Signals in the ^{1}H and ^{13}C NMR spectra are reported as singlets (s), doublets (d), triplets (t), etc, which refer 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

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.

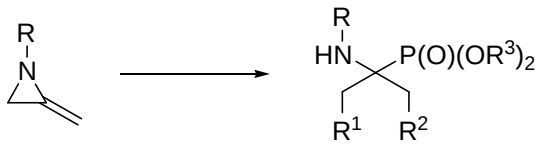
Diethyl [4-(benzylamino)heptan-4-yl]phosphonate (141)



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 ^{o}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 Et_3N) afforded **141** (705 mg, 84%) as a pale yellow oil. R_f = 0.36 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2960, 1711, 1454, 1226, 1022 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.21 (5H, m, Ar), 4.16 (4H, dt, *J* = 7.2, 14.7 Hz, 2 x OCH_2), 3.87 (2H, d, *J* = 2.6 Hz, NCH_2), 1.79-1.61 (4H, m, CH_2CCH_2), 1.55-1.39 (4H, m, 2 x C*H*$_2$CH$_3$), 1.34 (6H, t, *J* = 7.0 Hz, 2 x OCH_2CH_3), 0.92 (6H, t, *J* = 7.2 Hz, 2 x CH_2CH_3) ppm; δ_C NMR (100 MHz, $CDCl_3$) 141.3 (C, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 126.8 (CH, Ar), 61.9 (OCH_2, d, J_{CP} = 7.6 Hz), 59.7 (C, d, J_{CP} = 134.8 Hz), 47.3 (NCH_2, d, J_{CP} = 2.9 Hz), 35.9 (CH_2, d, J_{CP} = 4.2 Hz), 16.7 (CH_3, d, J_{CP} = 5.6 Hz), 16.4 (CH_2, d, J_{CP} = 5.6 Hz), 14.8 (CH_3) ppm; δ_P NMR (161 MHz, $CDCl_3$) 31.2 ppm; MS (ES$^+$) *m/z* = 341.1 [MH$^+$]; HRMS (ES$^+$) *m/z* calcd for $C_{18}H_{32}NNaO_3P$ [MNa$^+$]: 364.2012; found: 364.2015.

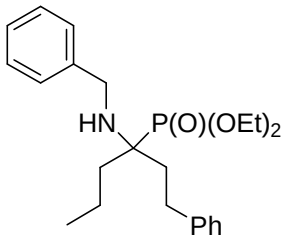
Synthesis of α-aminophosphonates from methyleneaziridines

General Method 1:



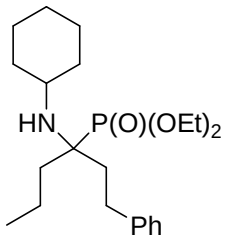
Re-purified Copper (I) iodide (20 mol%) in a round-bottomed flask was flame dried under vacuum and then purged with nitrogen (three cycles performed). THF (2 mL) was added and the mixture cooled to –30 ^{o}C, whereupon the Grignard reagent (2.5 equiv.) was added. After 10 min, methyleneaziridine **19**, **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_2O (20 mL) and washed with a saturated aqueous solution of NH_4Cl (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 α-aminophosphonate was achieved by column chromatography with silica pre-treated with Et_3N.

Diethyl [3-(benzylamino)-1-phenylhexan-3-yl]phosphonate (149a).



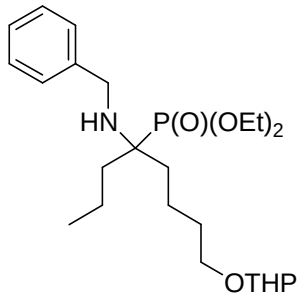
Methyleneaziridine **50** (102 mg, 0.70 mmol) was reacted with CuI (26 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 880 μL, 1.76 mmol), benzyl bromide (130 μL, 1.09 mmol) and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149a** (185 mg, 65%) as a pale yellow oil. R_f = 0.37 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2958, 1603, 1453, 1230, 1049 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.44-7.23 (10H, m, Ar), 4.24 (4H, dt, *J* = 7.6, 14.6 Hz, 2 x OCH_2), 3.97 (2H, s, NCH_2), 2.91-2.76 (2H, m, CH_2Ar), 2.13-1.99 (2H, m, CCH_2), 1.93-1.75 (2H, m, CCH_2), 1.62-1.55 (3H, m, CH_2 + NH), 1.41 (6H, t, *J* = 6.9 Hz, 2 x OCH_2CH_3), 1.01 (3H, t, *J* = 7.3 Hz, CH_2CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 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 (OCH_2, d, J_{CP} = 7.6 Hz), 59.7 (C, d, J_{CP} = 135.7 Hz), 47.6 (NCH_2, d, J_{CP} = 2.8 Hz), 35.9 (CH_2, d, J_{CP} = 4.0 Hz), 35.8 (CH_2, d, J_{CP} = 4.4 Hz), 29.7 (CH_2, d, J_{CP} = 5.4 Hz), 16.7 (CH_3, d, J_{CP} = 5.6 Hz), 16.5 (CH_2, d, J_{CP} = 7.6 Hz), 14.7 (CH_3) ppm; δ_P (161 MHz, $CDCl_3$) 30.6 ppm; MS (ES^+) *m/z* 404 [MH^+]; HRMS (ES^+) calcd for $C_{23}H_{35}NO_3P$ [MH^+]: 404.2349; found: 404.2345.

Diethyl [3-(cyclohexylamino)-1-phenylhexan-3-yl]phosphonate (149b).



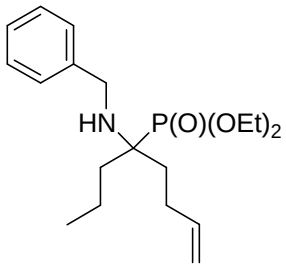
Methyleneaziridine **142** (104 mg, 0.76 mmol) was reacted with CuI (29 mg, 0.15 mmol), ethylmagnesium chloride (2M in THF, 950 μL, 1.90 mmol), benzyl bromide (140 μL, 1.18 mmol) and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149b** (171 mg, 57%) as a pale yellow oil. R_f = 0.47 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2972, 1602, 1449, 1230, 1021 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30-7.16 (5H, m, Ar), 4.14 (4H, dt, *J* = 7.2, 14.4 Hz, 2 x OCH_2), 2.91-2.67 (3H, m, CH_2Ar + CH), 2.05-1.46 (12H, m, 5 x CH_2 + NH + CH*H*), 1.33 (6H, t, *J* = 7.1 Hz, 2 x OCH_2CH_3), 1.28-1.05 (5H, m, 2 x CH_2 + C*H*H), 0.94 (3H, t, *J* = 7.2 Hz, CH_2CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 142.8 (C, Ar), 128.41 (CH, Ar), 128.38 (CH, Ar), 125.7 (CH, Ar), 61.7 (OCH_2, d, J_{CP} = 7.8 Hz), 61.6 (OCH_2, d, J_{CP} = 7.6 Hz), 60.3 (C, d, J_{CP} = 135.8 Hz), 50.8 (CH), 36.81 (CH_2), 36.76 (CH_2), 36.7 (CH_2, d, J_{CP} = 4.8 Hz), 29.9 (CH_2Ar, d, J_{CP} = 5.4 Hz), 25.8 (CH_2), 25.7 (CH_2), 16.7 (CH_2) 16.7 (CH_3, d, J_{CP} = 5.2 Hz), 14.8 (CH_3) ppm; δ_P (161 MHz, $CDCl_3$) 31.6 ppm; MS (ES^+) *m/z* 396 [MH^+]; HRMS (ES^+) calcd for $C_{22}H_{39}NO_3P$ [MH^+]: 396.2662; found: 396.2677.

Diethyl [5-(benzylamino)-1-(tetrahydro-2*H*-pyran-2-yloxy)octan-5-yl] phosphonate (149c).



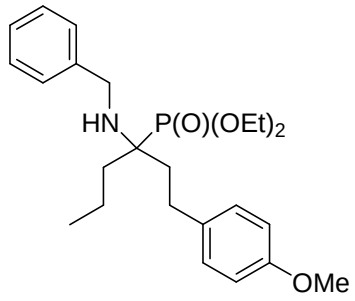
Methyleneaziridine **50** (106 mg, 0.73 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 920 μL, 1.84 mmol), 2-(3-bromopropoxy)-tetrahydro-2*H*-pyran (250 mg, 1.12 mmol) and diethyl phosphite (240 μL, 1.86 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149c** (201 mg, 60%) as a pale yellow oil. R_f = 0.29 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2938, 1453, 1231, 1119, 1021 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.21 (5H, m, Ar), 4.58 (1H, s, OCH), 4.16 (4H, dt, *J* = 7.2, 14.6 Hz, 2 x OCH_2), 3.87 (3H, m, NC*H*$_2$ + OCH*H*), 3.78-3.73 (1H, m, OC*H*H), 3.51-3.48 (1H, m, OCH*H*), 3.43-3.37 (1H, m, OC*H*H), 1.85-1.41 (17H, m, 8 x CH_2 + NH), 1.34 (6H, t, *J* = 7.0 Hz, 2 x OCH_2CH_3), 0.92 (3H, t, *J* = 7.2 Hz, CH_2CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 141.3 (C, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 126.8 (CH, Ar), 98.8 (OCH, d, J_{CP} = 3.9 Hz), 67.3 (OCH_2, d, J_{CP} = 5.8 Hz), 62.3 (OCH_2), 61.6 (OCH_2, d, J_{CP} = 7.7 Hz), 59.7 (C, d, J_{CP} = 135.8 Hz), 47.4 (NCH_2, d, J_{CP} = 2.9 Hz), 35.9 (CH_2, d, J_{CP} = 3.7 Hz), 33.3 (CH_2, d, $J_{C\text{-}P}$ = 4.3 Hz), 30.8 (CH_2), 30.4 (CH_2), 25.5 (CH_2), 19.7 (CH_2), 19.6 (CH_2), 16.7 (CH_3, d, J_{CP} = 5.6 Hz), 16.4 (CH_2, d, J_{CP} = 3.7 Hz), 14.8 (CH_3) ppm; δ_P (161 MHz, $CDCl_3$) 31.1 ppm; MS (ES^+) *m/z* 456 [MH^+]; HRMS (ES^+) calcd for $C_{24}H_{43}NO_5P$ [MH^+]: 456.2873; found: 456.2894.

Diethyl [5-(benzylamino)oct-1-en-5-yl]phosphonate (149d).



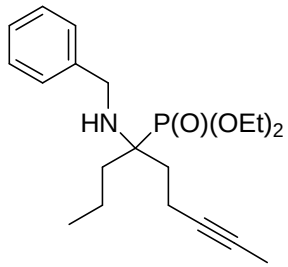
Methyleneaziridine **50** (104 mg, 0.72 mmol) was reacted with CuI (26 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 900 μL, 1.80 mmol), allyl bromide (93 μL, 1.08 mmol) and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149d** (155 mg, 61%) as a pale yellow oil. R_f = 0.33 (50% ethyl acetate in petroleum ether); υ_{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*H*), 4.95 (1H, d, *J* = 9.4 Hz, =C*H*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_2CH), 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_2CH_3), 0.93 (3H, t, *J* = 7.4 Hz, CH_2CH_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_{CP} = 7.7 Hz), 59.5 (C, d, J_{CP} = 136.1 Hz), 47.3 (NCH_2, d, J_{CP} = 2.9 Hz), 35.8 (CH_2, d, J_{CP} = 4.3 Hz), 32.7 (CH_2, d, J_{CP} = 4.3 Hz), 27.4 (CH_2, d, J_{CP} = 5.7 Hz), 16.7 (CH_3, d, J_{CP} = 5.3 Hz), 16.4 (CH_2, d, J_{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 $C_{19}H_{33}NO_3P$ [MH^+]: 354.2193; found: 354.2202.

Diethyl [3-(benzylamino)-1-(4-methoxyphenyl)hexan-3-yl]phosphonate (149e).



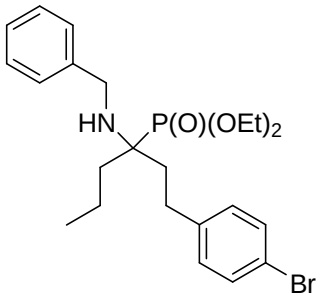
Methyleneaziridine **50** (105 mg, 0.72 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 910 μL, 1.82 mmol), 4-methoxybenzyl bromide (160 μL, 1.14 mmol) and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149e** (195 mg, 62%) as a pale yellow oil. R_f = 0.30 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2955, 1611, 1511, 1453, 1231 cm^{-1}; δ_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_2Ar), 2.08-1.97 (2H, m, CH_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 $OCH_2C\mathit{H}_3$), 0.95 (3H, t, *J* = 7.2 Hz, $CH_2C\mathit{H}_3$) ppm; δ_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_2Ar, 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; δ_P (161 MHz, $CDCl_3$) 30.9 ppm; MS (ES^+) *m/z* 434 [MH^+]; HRMS (ES^+) calcd for $C_{24}H_{37}NO_4P$ [MH^+]: 434.2455; found: 434.2463.

Diethyl [6-(benzylamino)non-2-yn-6-yl]phosphonate (149f).



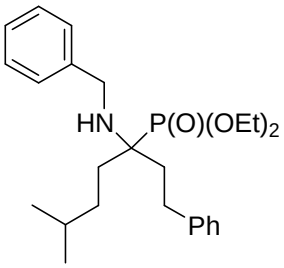
Methyleneaziridine **50** (103 mg, 0.71 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 890 μL, 1.78 mmol), 1-bromo-2-butyne (100 μL, 1.14 mmol) and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149f** (147 mg, 57%) as a pale yellow oil. R_f = 0.35 (50% ethyl acetate in petroleum ether); υ_{max} 2960, 1603, 1452, 1230, 1019 cm^{-1}; δ_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 $OCH_2C\mathit{H}_3$), 0.92 (3H, t, *J* = 7.2 Hz, $CH_2C\mathit{H}_3$) ppm; δ_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 ($\mathit{C}H_2C$≡, d, J_{CP} = 6.7 Hz), 3.5 ($C\mathit{C}H_3$) ppm; δ_P (161 MHz, $CDCl_3$) 30.1 ppm; HRMS (ES^+) calcd for $C_{20}H_{33}NO_3P$ [MH^+]: 336.2193; found: 336.2206.

Diethyl [3-(benzylamino)-1-(4-bromophenyl)hexan-3-yl]phosphonate (149g).



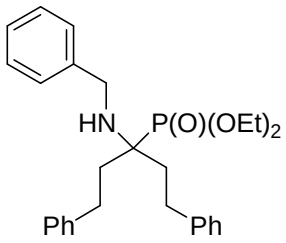
Methyleneaziridine **50** (101 mg, 0.70 mmol) was reacted with CuI (27 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 880 μL, 1.76 mmol), 4-bromobenzyl bromide (260 mg, 1.04 mmol) in THF (30 μL), and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (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); υ_{max} 2959, 1487, 1453, 1229, 1048 cm^{-1}; δ_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_2Ar), 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 $OCH_2C\mathit{H}_3$), 0.96 (3H, t, *J* = 7.3 Hz, $CH_2C\mathit{H}_3$) ppm; δ_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_2Ar, 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; δ_P (161 MHz, $CDCl_3$) 30.4 ppm; MS (ES^+) *m/z* 482 [MH^+, ^{79}Br], 484 [MH^+, ^{81}Br]; HRMS (ES^+) calcd for $C_{23}H_{34}{}^{81}BrNO_3P$ [MH^+]: 484.1437; found: 484.1453.

Diethyl [3-(benzylamino)-6-methyl-1-phenylheptan-3-yl]phosphonate (149h).



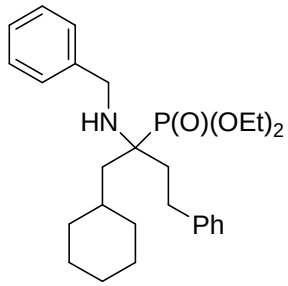
Methyleneaziridine **50** (104 mg, 0.72 mmol) was reacted with CuI (27 mg, 0.14 mmol), isobutylmagnesium chloride (2M in THF, 900 μL, 1.80 mmol), benzyl bromide (130 μL, 1.09 mmol) and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149h** (197 mg, 63%) as a pale yellow oil. R_f = 0.40 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2953, 1603, 1453, 1228, 1020 cm^{-1}; δ_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_2Ar), 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 $OCH_2C\mathit{H}_3$), 0.93 (6H, d, *J* = 6.4 Hz, 2 x $CH_2C\mathit{H}_3$) ppm; δ_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_2Ar, d, J_{CP} = 5.6 Hz), 28.8 (CH), 22.7 (CH_3), 16.7 (CH_3, d, J_{CP} = 5.2 Hz) ppm; δ_P (161 MHz, $CDCl_3$) 30.7 ppm; MS (ES^+) *m/z* 432 [MH^+]; HRMS (ES^+) calcd for $C_{25}H_{39}NO_3P$ [MH^+]: 432.2662; found: 432.2665.

Diethyl [3-(benzylamino)-1,5-diphenylpentan-3-yl]phosphonate (149i).



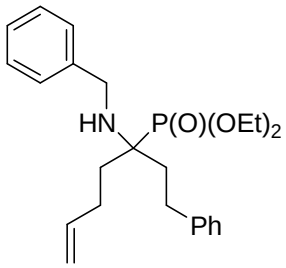
Methyleneaziridine **50** (103 mg, 0.71 mmol) was reacted with CuI (26 mg, 0.14 mmol), benzylmagnesium chloride (2M in THF, 890 μL, 1.78 mmol), benzyl bromide (130 μL, 1.09 mmol) and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149i** (205 mg, 62%) as a white solid. m.p. 69-70 ^{o}C (from ethyl acetate/petroleum ether); R_f = 0.32 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2923, 1601, 1451, 1221, 1022 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.41-7.17 (15H, m, Ar), 4.22 (4H, dt, *J* = 7.3, 14.5 Hz, 2 x OCH_2), 3.96 (2H, s, NCH_2), 2.92-2.76 (4H, m, 2 x CH_2Ar), 2.21-2.03 (4H, m, 2 x CH_2), 1.70 (1H, br s, NH), 1.37 (6H, t, *J* = 7.1 Hz, 2 x $OCH_2C\mathit{H}_3$) ppm; δ_C (100 MHz, $CDCl_3$) 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 (OCH_2, d, J_{CP} = 7.4 Hz), 59.7 (C, d, J_{CP} = 136.4 Hz), 47.4 (NCH_2, d, J_{CP} = 3.2 Hz), 35.9 (CH_2, d, J_{CP} = 4.6 Hz), 29.8 (CH_2Ar, d, J_{CP} = 5.4 Hz), 16.8 (CH_3, d, J_{CP} = 8.6 Hz) ppm; δ_P (161 MHz, $CDCl_3$) 30.2 ppm; MS (ES^+) *m/z* 466 [MH^+]; HRMS (ES^+) calcd for $C_{28}H_{37}NO_3P$ [MH^+]: 466.2506; found: 466.2519. Anal. Calcd for $C_{28}H_{36}NO_3P$: 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).



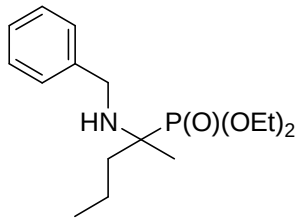
Methyleneaziridine **50** (103 mg, 0.71 mmol) was reacted with CuI (26 mg, 0.14 mmol), cyclohexylmagnesium chloride (2M in diethyl ether, 890 μL, 1.78 mmol), benzyl bromide (130 μL, 1.09 mmol) and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149j** (137 mg, 42%) as a pale yellow oil. R_f = 0.30 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2921, 1602, 1450, 1225, 1021 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39-7.16 (10H, m, Ar), 4.19 (4H, dt, *J* = 7.2, 14.4 Hz, OCH_2), 3.93 (2H, d, *J* = 1.9 Hz, NCH_2), 2.86-2.73 (2H, m, CH_2Ar), 2.11-2.03 (2H, m, CH_2), 1.94 (1H, d, *J* = 12.2 Hz, CH), 1.84-1.52 (8H, m, 4 x CH_2), 1.36 (6H, t, *J* = 7.0 Hz, 2 x $OCH_2C\mathit{H}_3$), 1.29-1.05 (5H, m 2 x CH_2 + NH) ppm; δ_C (100 MHz, $CDCl_3$) 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 (OCH_2, d, J_{CP} = 8.0 Hz), 61.7 (OCH_2, d, J_{CP} = 7.8 Hz), 60.7 (C, d, J_{CP} = 134.6 Hz), 47.5 (NCH_2, d, J_{CP} = 2.8 Hz), 40.5 (CH_2, d, J_{CP} = 3.8 Hz), 36.4 (CH_2, d, J_{CP} = 4.4 Hz), 35.8 (CH_2), 35.6 (CH_2), 32.6 (CH, d, J_{CP} = 7.4 Hz), 30.1 (CH_2, d, J_{CP} = 5.0 Hz), 26.6 (CH_2), 26.3 (CH_2), 16.7 (CH_3, d, J_{CP} = 5.4 Hz) ppm; δ_P (161 MHz, $CDCl_3$) 30.5 ppm; MS (ES^+) *m/z* 458 [MH^+]; HRMS (ES^+) calcd for $C_{27}H_{41}NO_3P$ [MH^+]: 458.2819; found: 458.2814.

Diethyl [3-(benzylamino)-1-phenylhept-6-en-3-yl]phosphonate (149k).



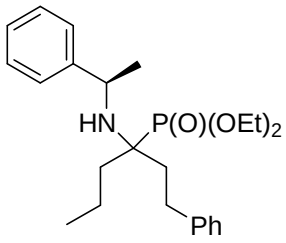
Methyleneaziridine **50** (102 mg, 0.70 mmol) was reacted with CuI (26 mg, 0.14 mmol), allylmagnesium chloride (2M in THF, 880 μL, 1.76 mmol), benzyl bromide (130 μL, 1.09 mmol) and diethyl phosphite (230 μL, 1.79 mmol) as described in General Method 1. Purification on silica gel (30% ethyl acetate in petroleum ether) afforded **149k** (178 mg, 61%) as a pale yellow oil. R_f = 0.34 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2976, 1602, 1452, 1232, 1020 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.43-7.21 (10H, m, Ar), 5.94-5.84 (1H, m, CH), 5.10 (1H, d, *J* = 17.0 Hz, CH*H*), 5.02 (1H, d, *J* = 10.2 Hz, C*H*H), 4.24 (4H, dt, *J* = 7.2, 14.4 Hz, 2 x OCH_2), 3.96 (2H, s, NCH_2), 2.91-2.76 (2H, m, CH_2Ar), 2.41-2.25 (2H, m, CH_2), 2.17-2.03 (2H, m, CH_2), 2.01-1.86 (2H, m, CH_2), 1.65 (1H, br s, NH), 1.40 (6H, t, *J* = 7.0 Hz, 2 x $OCH_2C\mathit{H}_3$) ppm; δ_C (100 MHz, $CDCl_3$) 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_2), 61.9 (OCH_2, d, J_{CP} = 7.7 Hz), 59.5 (C, d, J_{CP} = 136.0 Hz), 47.3 (NCH_2, d, J_{CP} = 2.9 Hz), 35.8 (CH_2, d, J_{CP} = 3.8 Hz), 32.7 (CH_2, d, J_{CP} = 4.8 Hz), 29.7 (CH_2, d, J_{CP} = 5.3 Hz), 27.6 (CH_2, d, J_{CP} = 5.8 Hz), 16.7 (CH_3, d, J_{CP} = 5.3 Hz) ppm; δ_P (121 MHz, $CDCl_3$) 29.6 ppm; MS (ES^+) *m/z* 416 [MH^+]; HRMS (ES^+) calcd for $C_{24}H_{35}NO_3P$ [MH^+]: 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. R_f = 0.23 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2959, 1604, 1453, 1225, 1021 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.21 (5H, m, Ar), 4.22-4.13 (4H, m, 2 x OCH_2), 3.93 (1H, dd, *J* = 2.0, 12.7 Hz, NCH*H*), 3.85 (1H, dd, *J* = 1.74, 12.7 Hz, NC*H*H), 1.82-1.39 (5H, m, CH_2CH_2 + NH), 1.34 (6H, t, *J* = 7.0 Hz, 2 x OCH_2CH_3), 1.32 (3H, d, *J* = 16.4 Hz, CCH_3), 0.94 (3H, t, *J* = 7.2 Hz, CH_2CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 141.2 (C, Ar), 128.3 (CH, Ar), 128.2 (CH), 126.8 (CH), 62.0 (OCH_2, d, J_{CP} = 7.2 Hz), 61.7 (OCH_2, d, J_{CP} = 7.9 Hz), 56.5 (C, d, J_{CP} = 140.9 Hz), 47.5 (NCH_2, d, J_{CP} = 3.6 Hz), 36.9 (CH_2, d, J_{CP} = 4.3 Hz), 20.8 (CCH_3, d, J_{CP} = 2.3 Hz), 16.7 (OCH_2CH_3, d, J_{CP} = 2.2 Hz), 16.6 (OCH_2CH_3, d, J_{CP} = 2.1 Hz), 15.8 (CH_2CH_3, d, J_{CP} = 8.4 Hz), 14.6 (CH_2CH_3) ppm; δ_P (161 MHz, $CDCl_3$) 31.1 ppm; MS (ES^+) *m/z* = 314.0 [MH^+]; HRMS (ES^+) *m/z* calcd for $C_{16}H_{28}NNaO_3P$ [MNa^+]: 336.1699; found: 336.1713.

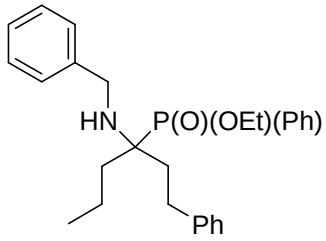
Diethyl [3-(1-phenylethylamino)-1-phenylhexan-3-yl]phosphonate (152).



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); υ_{max} (film) 2960, 1602, 1452, 1229, 1020 cm^{-1}; δ_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_2Ar), 2.63-2.41 (1.5H, m, ¾ x CH_2Ar), 1.99-1.48 (6H, m, 3 x CH_2), 1.37-1.32 (10H, m, 2 x $OCH_2C\mathit{H}_3$ + $CHC\mathit{H}_3$ + NH), 0.88 (1.5H, t, *J* = 6.9 Hz, ½ x $CH_2C\mathit{H}_3$), 0.62 (1.5H, t, *J* = 6.9 Hz, ½ x $CH_2C\mathit{H}_3$) ppm; δ_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_2Ar, 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; δ_P (161 MHz, $CDCl_3$)

31.2, 31.1 ppm; MS (ES^+) *m/z* 418 [MH^+]; HRMS (ES^+) calcd for $C_{24}H_{37}NO_3P$ [MH^+]: 418.2506; found: 418.2521.

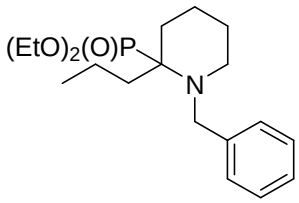
Ethyl [3-(benzylamino)-1-phenylhexan-3-yl](phenyl)phosphinate (156).



Methyleneaziridine **50** (104 mg, 0.72 mmol) was reacted with CuI (26 mg, 0.14 mmol), ethylmagnesium chloride (2M in THF, 900 μL, 1.80 mmol), benzyl bromide (130 μL, 1.09 mmol) and freshly distilled ethyl phenylphosphinate (270 μL, 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 ^1H and ^{31}P NMR spectroscopy. R_f = 0.29 (50% ethyl acetate in petroleum ether); υ_{max} (film) 2957, 2362, 1602, 1453, 1210, 1023 cm^{-1}; δ_H (400 MHz, C_6D_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*H*), 3.80-3.69 (1H, m, OC*H*H), 3.14-2.89 (2H, m, CH_2Ar), 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_2CH_3), 0.98 (1.5H, t, *J* = 7.4 Hz, ½ x CH_2CH_3), 0.97 (1.5H, t, *J* = 7.0 Hz, ½ x CH_2CH_3) ppm; δ_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_2Ar, 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; δ_P (161 MHz, C_6D_6) 58.8, 58.7 ppm; MS (ES^+) *m/z* 436 [MH^+]; HRMS (ES^+) calcd for $C_{27}H_{34}NNaO_2P$ [MNa^+]: 458.2219; found: 458.2228.

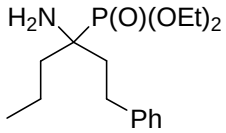
Diethyl (1-benzyl-2-propylpiperidiny-2-yl)-2-phosphonate (157).



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 μL, 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-diiodopropane (210 μL, 1.83 mmol) was added dropwise, then the mixture heated at 45 ^oC 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 μL, 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 ^oC. Upon cooling to room temperature, the mixture was diluted with Et_2O (20 mL) then washed with saturated aqueous NH_4Cl 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); υ_{max} (film) 2959, 1654, 1450, 1230, 1017 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35-7.18 (5H, m, Ar), 4.23 (5H, m, 2 x OCH_2 + NCH*H*), 3.60 (1H, dd, *J* = 4.8, 15 Hz, NC*H*H), 2.93-2.85 (1H, m, ring NCH*H*), 2.55-2.52 (1H, m, ring NC*H*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_2CH_3), 1.35 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 0.89 (3H, t, *J* = 7.0 Hz, CH_2CH_3) ppm; δ_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_{CP} = 122.3 Hz), 61.4 (OCH_2, d, J_{CP} = 8.0 Hz), 60.6 (OCH_2, d, J_{CP} = 8.0 Hz), 54.9 (CH_2), 46.7 (NCH_2), 36.6 (CH_2, d, J_{CP} = 6.3 Hz), 31.2 (CH_2), 25.9 (CH_2), 21.1 (CH_2, d, J_{CP} = 2.6 Hz), 16.8 (CH_3, d, J_{CP} = 6.0 Hz), 16.7 (CH_3, d, J_{CP} = 6.3 Hz), 15.7 (CH_2, d, J_{CP} = 6.7 Hz), 14.8 (CH_3) ppm; δ_P (161 MHz, $CDCl_3$) 32.5 ppm; MS (ES^+) *m/z* 354 [MH^+]; HRMS (ES^+) calcd for $C_{19}H_{33}NO_3P$ [MH^+]: 354.2193; found: 354.2200.

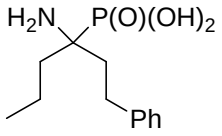
Diethyl (3-amino-1-phenylhexan-3-yl)phosphonate (164).



Palladium, 10 wt.% on activated carbon (52 mg) was added to α-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®, 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); υ_{max} (film) 2959,

1603, 1454, 1224, 1020 cm^{-1}; δ_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_2Ar), 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_2CH_3), 0.99 (3H, t, *J* = 7.3 Hz, CH_2CH_3) ppm; δ_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_2Ar, 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; δ_P (161 MHz, d_4-MeOD) 31.1 ppm; MS (ES^+) *m/z* 314 [MH^+]; HRMS (ES^+) calcd for $C_{16}H_{29}NO_3P$ [MH^+]: 314.1880; found: 314.1890.

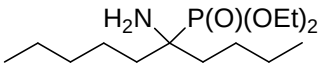
(3-Amino-1-phenylhexan-3-yl)phosphonic acid (165).



α-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 ^oC (from ethanol/propylene oxide); υ_{max} (film) 2961, 2872, 1603, 1525, 1496, 1454, 1147 cm^{-1}; δ_H (400 MHz, d_4-AcOD) 7.32-7.19 (5H, m, Ar), 2.91-2.77 (2H, m, CH_2Ar), 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; δ_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

(CH_2), 29.3 (CH_2Ar), 16.1 (CH_2, d, J_{CP} = 4.5 Hz), 13.5 (CH_3) ppm; δ_P (161 MHz, d_4-AcOD) 17.1 ppm; MS (ES^+) *m/z* 258.0 [MH^+]; HRMS (ES^+) calcd for $C_{12}H_{21}NO_3P$ [MH^+]: 258.1254; found: 258.1255.

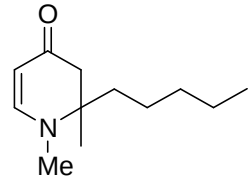
5-(Ethoxy(ethylperoxy)phosphino)decan-5-amine (169).



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 ^oC, whereupon hexanenitrile (100 μL, 0.84 mmol) was added. The reaction mixture was stirred for 30 min at 0 ^oC. 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 ^oC (preheated bath). After 24 h the mixture was cooled to room temperature and poured into H_2O (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (3 x 20 ml), dried over $MgSO_4$, 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. R_f = 0.58 (10% methanol in dichloromethane); υ_{max} (film) 2954, 1607, 1458, 1229, 1022 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.17-4.10 (4H, m, OCH_2), 1.67-1.19 (22H, m, 7 x CH_2 + 2 x CH_3 + NH_2), 0.94-0.88 (6H, m, 2 x CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 62.0 (OCH_2, d, J_{CP} = 7.6 Hz), 54.8 (C, d, J_{CP} = 143.3 Hz), 54.7 (C, d, J_{CP} = 143.0 Hz), 35.3 (CH_2, d, J_{CP} = 3.4 Hz), 35.0 (CH_2, d, J_{CP} = 3.4 Hz), 32.4 (CH_2), 24.2 (CH_3, d, J_{CP} = 5.6 Hz), 23.3 (CH_2), 22.6 (CH_2, d, J_{CP} = 5.6 Hz), 22.5 (CH_2), 16.5 (OCH_2CH_3, d, J_{CP} = 5.6 Hz), 14.0

(CH_3), 13.9 (CH_3); δ_P (161 MHz, $CDCl_3$) 31.9 ppm; MS (ES^+) *m/z* = 294.0 [MH^+]; HRMS (ES^+) *m/z* calcd for $C_{14}H_{32}NNaO_3P$ [MNa^+]: 316.2012; found: 316.2020.

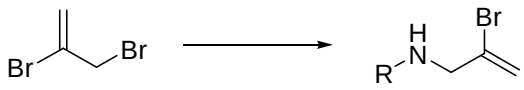
2,3-Dihydro-1,2-dimethyl-2-pentylpyridin-4(1H)-one (197).



To a stirred solution of 2-heptanone (70 μL, 0.52 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (5 mL) and a saturated solution of NH_4Cl (5 mL) added. The reaction mixture was stirred for 2 h and the organic layer separated and the aqueous layer extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried over Na_2SO_4, 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. R_f = 0.12 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 6.80 (1H, d, *J* = 7.4 Hz, =CHN), 4.84 (1H, d, *J* = 7.5 Hz, =CH), 2.86 (3H, s, NCH_3), 2.50 (1H, d, *J* = 16.2 Hz, COC*H*H), 2.20 (1H, d, *J* = 16.0 Hz, COCH*H*), 1.25-1.19 (8H, m, 4 x CH_2), 1.16 (3H, s, CCH_3), 0.82 (3H, t, *J* = 6.7 Hz, CH_2CH_3) ppm; MS (ES^+) *m/z* = 196.1 [MH^+].

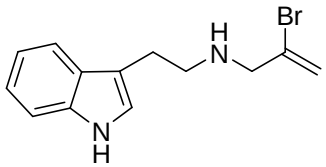
Preparation of *N*-(2-bromo-2-propenyl)-alkylamines

General Method 2:



To a stirred suspension of amine (2 equiv.) and K_2CO_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_2O (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_3N.

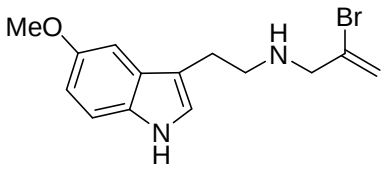
3-[2-(2-Methyleneaziridin-1-yl)ethyl]indole (252a).[18]



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); υ_{max} (film) 3413, 3168, 2917, 2844, 1627, 1455 cm^{-1}; δ_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), 6.99 (1H, d, *J* = 2.3 Hz, Ar), 5.71 (1H, d, *J* = 1.8 Hz, =C*H*H), 5.50 (1H, d, *J* = 1.8 Hz, =CH*H*), 3.47 (2H, s, NCH_2CBr), 3.00-2.88 (4H, m, CH_2CH_2), 1.57 (1H, br s, NH) ppm; δ_C (100 MHz, $CDCl_3$) 136.4 (C,

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 (=CH_2), 113.8 (C, Ar), 111.2 (CH, Ar), 57.5 (NCH_2), 48.1 (NCH_2), 25.8 ($ArCH_2$) ppm; MS (ES^+) *m/z* 281 [MH^+, ^{81}Br], 279 [MH^+, ^{79}Br]; HRMS (ES^+) calcd for $C_{13}H_{16}BrN_2$ [MH^+, ^{79}Br]: 279.0491; found: 279.0489. Anal. calcd for $C_{13}H_{15}BrN_2$: C, 55.93; H, 5.42; N, 10.03%. Found: C, 55.56; H, 5.32; N, 9.72%.

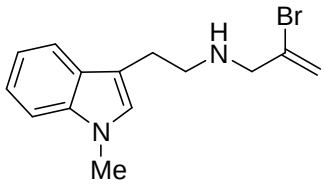
2-Bromo-*N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]prop-2-en-1-amine (252b).



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. R_f = 0.23 (ethyl acetate); υ_{max} (film) 3176, 2910, 1624, 1484, 1456, 1438 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, =C*H*H), 5.52 (1H, d, *J* = 1.5 Hz, =CH*H*), 3.86 (3H, s, CH_3), 3.48 (2H, s, NCH_2CBr), 2.97-2.88 (4H, m, CH_2CH_2), 1.71 (1H, br s, NH) ppm; δ_C (100 MHz, $CDCl_3$) 153.9 (CO), 133.5 (CBr), 131.5 (C, Ar), 127.8 (C, Ar), 122.7 (CH, Ar), 117.5 (=CH_2), 113.5 (C, Ar), 112.3 (CH, Ar), 111.9 (CH, Ar), 100.7 (CH, Ar), 57.4 (NCH_2), 55.9 (CH_3O), 47.9 (NCH_2), 25.8 ($ArCH_2$) ppm; MS (ES^+) *m/z* 309 [MH^+, ^{79}Br], 311 [MH^+, ^{81}Br]; HRMS (ES^+) calcd for $C_{14}H_{18}BrN_2O$ [MH^+,^{79}Br]:

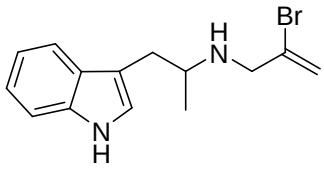
309.0597; found: 309.0596. Anal. calcd for $C_{14}H_{17}BrN_2O$: C, 54.38; H, 5.54; N, 9.06%. Found: C, 54.12; H, 5.35; N, 8.94%.

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



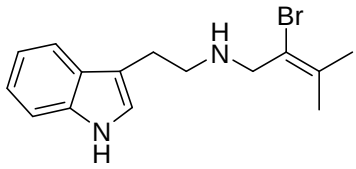
N-2-(1-Methyl-1*H*-indol-3-yl)ethylamine[171] (**227c**) (1.62 g, 9.31 mmol) was reacted with potassium carbonate (0.64 g, 4.65 mmol) and 2,3-dibromopropene (0.48 mL, 4.65 mmol) as described in General Method 2. Purification on silica gel (ethyl acetate) afforded **252c** (1.19 g, 88%) as a brown oil. R_f = 0.22 (ethyl acetate); υ_{max} (film) 3054, 2911, 2824, 1625, 1472 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.60 (1H, d, *J* = 7.6 Hz, Ar), 7.28 (1H, d, *J* = 8.2 Hz, Ar), 7.22 (1H, ddd, *J* = 1.1, 6.9, 8.0 Hz, Ar), 7.10 (1H, ddd, *J* = 1.0, 6.8, 7.9 Hz, Ar), 6.91 (1H, s, Ar), 5.73 (1H, d, *J* = 1.4 Hz, =C*H*H), 5.51 (1H, d, *J* = 1.4 Hz, =CH*H*), 3.74 (3H, s, CH_3), 3.47 (2H, s, NCH_2CBr), 2.99-2.88 (4H, m, CH_2CH_2), 1.63 (1H, br s, NH) ppm; δ_C (100 MHz, $CDCl_3$) 137.1 (C, Ar), 133.4 (CBr), 127.8 (C, Ar), 126.7 (CH, Ar), 121.6 (CH, Ar), 119.0 (CH, Ar), 118.7 (CH, Ar), 117.4 ($=CH_2$), 112.2 (C, Ar), 109.2 (CH, Ar), 57.4 (NCH_2), 48.2 (NCH_2), 32.6 (NCH_3) 25.7 ($ArCH_2$) ppm; MS (EI^+) *m/z* 292 [MH^+,^{79}Br], 294 [MH^+,^{81}Br]; HRMS (EI^+) calcd for $C_{14}H_{17}BrN_2$ [MH^+,^{79}Br]: 292.0575; found: 292.0575. Anal. calcd for $C_{14}H_{17}BrN_2$: C, 57.35; H, 5.84; N, 9.55%. Found: C, 57.57; H, 5.85; N, 9.42%.

***N*-[1-(1*H*-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_f = 0.39 (ethyl acetate); υ_{max} (film) 2961, 2907, 1625, 1455, 1355 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, =C*H*H), 5.47 (1H, d, *J* = 1.2 Hz, =CH*H*), 3.47 (2H, s, NCH_2CBr), 3.10-3.02 (1H, m, CH), 2.88-2.79 (2H, m, CH_2CH), 1.78 (1H, br s, NH), 1.11 (3H, d, *J* = 6.6 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 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_2), 113.2 (C, Ar), 111.1 (CH, Ar), 54.8 (NCH_2), 50.9 (NCH), 33.2 (CH_3), 20.2 ($ArCH_2$) ppm; MS (ES^+) *m/z* 293 [MH^+,^{79}Br], 295 [MH^+,^{81}Br]; HRMS (ES^+) calcd for $C_{14}H_{18}BrN_2$ [MH^+,^{79}Br]: 293.0648; found: 293.0650. Anal. calcd for $C_{14}H_{17}BrN_2$: C, 57.35; H, 5.84; N, 9.55%. Found: C, 57.20; H, 5.73; N, 9.40%.

_N_-(2-(1_H_-Indol-3-yl)ethyl)-2-bromo-3-methylbut-2-en-1-amine (254).

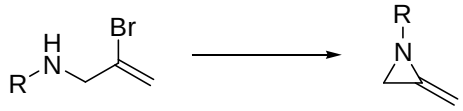


To a stirred solution of 1,1-dibromo-2,2-dimethyl-cyclopropane[172] (**8**) (10.0 g, 43.9 mmol) in 1,2-dichlorobenzene (80 mL) was added tryptamine (**227a**) (15.5 g, 96.5 mmol) and potassium carbonate (6.67 g, 48.3 mmol). The mixture was then heated at 170 ^{o}C for 48 h. On cooling to room temperature, 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 ^{o}C/15 mmHg) prior to purification on silica gel, pre-treated with Et_3N (ethyl acetate), which afforded **254** (7.95 g, 59 %) as a brown solid. m.p. 97-98 ^{o}C (from ethyl acetate); R_f = 0.19 (ethyl acetate); υ_{max} (film) 2921, 2839, 1618, 1448, 1109, 742 cm^{-1}; δ_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_2CBr), 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; δ_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/z* 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 $C_{15}H_{19}BrN_2$: C, 58.64; H, 6.23; N, 9.11%. Found: C, 58.76; H, 6.25; N, 9.06%.

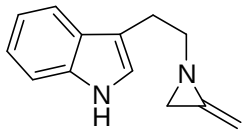
Preparation of 2-Methyleneaziridines

General Method 3:



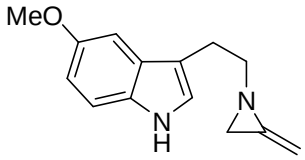
An oven-dried 3-neck flask was fitted with an oven-dried cold-finger condenser and gas inlet. Iron (III) nitrate nonahydrate (0.10 mol%) was added and the system flushed with anhydrous ammonia. Ammonia was then condensed into the flask by the addition of dry-ice to the condenser. Sodium metal (3.5 equiv.) 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 ^{o}C a solution of vinyl bromide **252** in Et_2O (1:1 w/v) was added and the solution stirred for 10 min. The mixture was diluted with Et_2O (20 mL) and quenched by the dropwise addition of water (20 mL) (CAUTION). Once the ammonia had evaporated, Et_2O (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 $MgSO_4$, 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).[18]



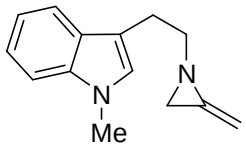
Sodium amide, generated from sodium (1.08 g, 47.1 mmol) and iron (III) nitrate nonahydrate (2.0 mg, 5.0 μmol) in ammonia (100 mL), was reacted with vinyl bromide **252a** (3.76 g, 13.5 mmol) as described in General Method 3. Purification by bulb-to-bulb distillation (175 °C, 0.1 Torr) afforded **249a** (2.36 g, 88%) as a clear colourless oil. υ_{max} (film) 3412, 1766, 1619, 1455, 1339 cm^{-1}; δ_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, =C*H*H), 4.69 (1H, s, =CH*H*), 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; δ_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/z* 199 [MH^+]; HRMS (ES^+) calcd for $C_{13}H_{15}N_2$ [MH^+]: 199.1230; found 199.1231.

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



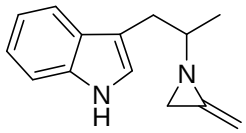
Sodium amide, generated from sodium (585 mg, 25.4 mmol) and iron (III) nitrate nonahydrate (12.0 mg 29.7 μmol) in ammonia (50 mL), was reacted with vinyl bromide **252b** (2.25 g, 7.27 mmol) as described in General Method 3. **249b** (1.44 g, 87%) was isolated as a brown oil which was characterised and used without further purification. υ_{max} (film) 2938, 1766, 1623, 1583, 1484 cm^{-1}; δ_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, =C*H*H), 4.69 (1H, s, =CH*H*), 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; δ_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 $C_{14}H_{17}N_2O$ [MH^+]: 229.1335; found 229.1333.

1-Methyl-3-[2-(2-methyleneaziridin-1-yl)ethyl]-1*H*-indole (249c).



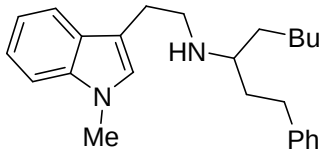
Sodium amide, generated from sodium (403 mg, 17.5 mmol) and iron (III) nitrate nonahydrate (12.0 mg, 29.7 μmol) in ammonia (50 mL), was reacted with vinyl bromide **252c** (1.47 g, 5.0 mmol) as described in General Method 3. Purification by bulb-to-bulb distillation (185 °C, 0.1 Torr) gave **249c** (741 mg, 70%) as a yellow oil. υ_{max} (film) 3051, 1765, 1615, 1472, 1173 cm^{-1}; δ_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, =C*H*H), 4.68 (1H, s, =CH*H*), 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; δ_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 ($=CH_2$), 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]-1*H*-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. υ_{max} (film) 2967, 1771, 1454, 1162, 1089 cm^{-1}; δ_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, =C*H*H), 4.67 (1H, s, =CH*H*), 3.16 (1H, dd, *J* = 5.1, 14.1 Hz, ArC*H*H), 2.91 (1H, dd, *J* = 8.0, 14.1 Hz, ArCH*H*), 2.27-2.18 (1H, m, CH), 2.06 (1H, s, ring C*H*H), 2.00 (1H, s, ring CH*H*), 1.20 (3H, d, *J* = 6.6 Hz, CH_3) ppm; δ_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).

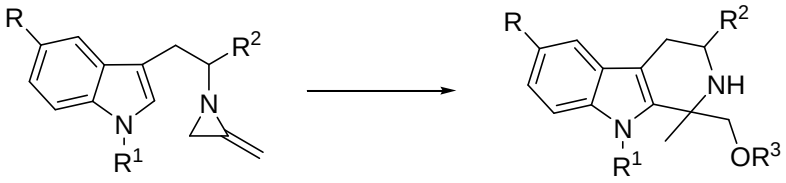


Re-purified Copper (I) iodide (36 mg, 0.19 mmol) in a round-bottomed flask was flame dried under vacuum and then purged with nitrogen (three cycles performed). THF (4 mL) was added and the mixture cooled to –30 ^{o}C, whereupon *n*-butylmagnesium chloride (2M in THF, 1.06 mL, 2.12 mmol) was added. After 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 ^{o}C, benzyl chloride (0.16 mL, 1.39 mmol) was added dropwise, and the mixture heated at 40 ^{o}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 ^{o}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 NH_4Cl solution (3 x 20 mL), saturated $NaHCO_3$ solution (3 x 20 mL) and brine (3 x 30 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification on silica gel (5% methanol in dichloromethane) afforded **260** (228 mg, 69%) as a brown oil. R_f = 0.23 (5% methanol in dichloromethane); υ_{max} (film) 2927, 1585, 1454, 1327, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, NCH_3), 2.94-2.84 (4H, m, C*H*$_2$C*H*$_2$NH), 2.51-2.45 (3H, m, CH_2Ar + CH), 1.68-1.62 (2H, m, CHC*H*$_2$), 1.37 (1H, br s, NH), 1.18-1.22 (8H, m, 4 x CH_2), 0.76 (3H, t, *J* = 6.9 Hz, CH_3) ppm; δ_C (100 MHz, $CDCl_3$)

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.

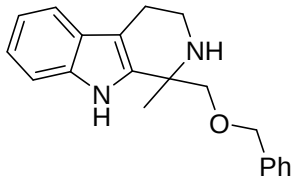
Synthesis of 1,1 disubstituted tetrahydro-β-carbolines.

General Method 4:



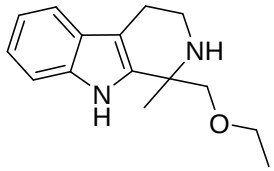
To a stirred solution of methyleneaziridine **249** (1 equiv.) in CH_2Cl_2 (2 mL) at –30 °C was added $BF_3{\cdot}Et_2O$ (1 equiv.) dropwise. After 5 minutes, the alcohol (2 equiv.) was added dropwise and the solution was allowed to warm to room temperature and stirred for 16 hours. The mixture was poured into 10% NaOH (20 mL), at which point a colour change from red to yellow was observed. The mixture was extracted with CH_2Cl_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_3N.

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



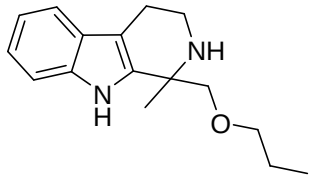
Methyleneaziridine **249a** (200 mg, 1.01 mmol) was reacted with $BF_3{\cdot}Et_2O$ (130 μL, 1.03 mmol) and benzyl alcohol (210 μL, 2.03 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded **269a** (226 mg, 73%) as a brown oil. R_f = 0.22 (5% methanol in dichloromethane); υ_{max} (film) 2853, 1724, 1452, 1297, 1092 cm^{-1}; δ_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, OC*H*H), 4.50 (1H, d, *J* = 11.9 Hz, OCH*H*), 3.55 (1H, d, *J* = 8.5 Hz, OC*H*H), 3.51 (1H, d, *J* = 8.5 Hz, OCH*H*), 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; δ_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_2O), 53.4 (C), 39.9 (CH_2CH_2), 25.5 (CH_3), 22.9 (CH_2CH_2) ppm; MS (ES^+) *m/z* 307 [MH^+]; HRMS (ES^+) for $C_{20}H_{23}N_2O$ [MH^+]: 307.1805; found 307.1802.

1-(Ethoxymethyl)-2,3,4,9-tetrahydro-1-methyl-1H-pyrido[3,4-b]indole (270).



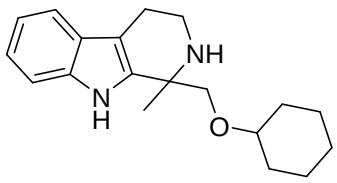
Methyleneaziridine **249a** (200 mg, 1.01 mmol) was reacted with $BF_3{\cdot}Et_2O$ (130 μL, 1.03 mmol) and benzyl alcohol (110 μL, 1.11 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded **269a** (169 mg, 54%) as a brown oil, with the data described above. Further elution afforded **270** (33 mg, 14%) as a brown oil. R_f = 0.21 (5% methanol in dichloromethane); υ_{max} (film) 2971, 2869, 1451, 1296, 1104 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, CH_2OCH_2), 3.22-3.11 (2H, m, NCH_2), 2.70 (2H, t, *J* = 5.6 Hz, $ArCH_2$), 2.06 (1H, br s, NH), 1.47 (3H, s, CCH_3), 1.21 (3H, t, *J* = 6.9 Hz, $CH_2C\mathit{H}_3$) ppm; δ_C (100 MHz, $CDCl_3$) 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 (OCH_2), 67.1 (OCH_2), 53.4 (C), 39.8 (NCH_2), 25.4 ($C\mathit{C}H_3$), 22.9 ($ArCH_2$), 15.3 ($CH_2\mathit{C}H_3$) ppm; MS ($LSIMS^+$) *m/z* 245.1 [MH^+]; HRMS ($LSIMS^+$) calculated for $C_{15}H_{20}DN_2O$ [MD^+]: 246.1711; found 246.1714.

1-Methyl-1-(propoxymethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (269b).



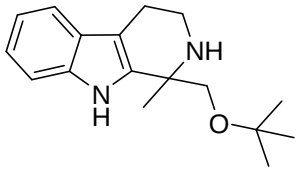
Methyleneaziridine **249a** (200 mg, 1.01 mmol) was reacted with $BF_3{\cdot}Et_2O$ (130 μL, 1.03 mmol) and propan-1-ol (150 μL, 2.01 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded **269b** (217 mg, 83%) as a brown oil. R_f = 0.22 (5% methanol in dichloromethane); υ_{max} (film) 2962, 2919, 2850, 1452, 1297 cm^{-1}; δ_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_2OCH_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_2CH_3), 1.49 (3H, s, CCH_3), 0.95 (3H, t, *J* = 7.3 Hz, CH_2CH_3) ppm; δ_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_2CH_3), 22.90 ($ArCH_2$), 10.8 (CH_2CH_3) ppm; MS ($LSIMS^+$) *m/z* 259 [MH^+]; HRMS ($LSIMS^+$) calculated for $C_{16}H_{23}N_2O$ [MH^+]: 259.1810; found 259.1820.

1-(Cyclohexyloxymethyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (269c).



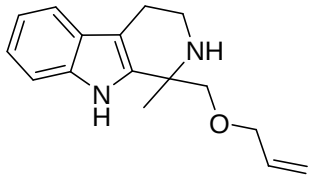
Methyleneaziridine **249a** (200 mg, 1.01 mmol) was reacted with $BF_3{\cdot}Et_2O$ (130 μL, 1.03 mmol) and cyclohexanol (210 μL, 1.99 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded **269c** (191 mg, 63%) as a brown oil. R_f = 0.20 (5% methanol in dichloromethane); υ_{max} (film) 2928, 2853, 1449, 1297, 1093 cm^{-1}; δ_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, OC*H*H), 3.55 (1H, d, *J* = 8.2 Hz, OCH*H*), 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; δ_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 $C_{19}H_{27}N_2O$ [MH^+]: 299.2118; found 299.2121.

1-(*tert*-Butoxymethyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (269d).



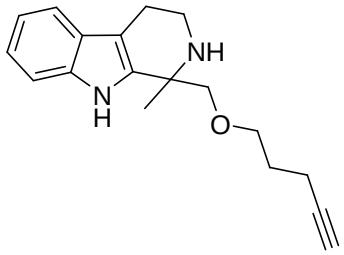
Methyleneaziridine **249a** (200 mg, 1.01 mmol) was reacted with $BF_3{\cdot}Et_2O$ (130 μL, 1.03 mmol) and 2-methyl-propanol (190 μL, 1.99 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded **269d** (160 mg, 58%) as a brown oil. R_f = 0.28 (5% methanol in dichloromethane); υ_{max} (film) 2848, 1431, 1363, 1192, 1093 cm^{-1}; δ_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, OC*H*H), 3.39 (1H, d, *J* = 7.8 Hz, OCH*H*), 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; δ_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 $C_{17}H_{25}N_2O$ [MH^+]: 273.1967; found 273.1973.

1-(Allyloxymethyl)-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (269e).



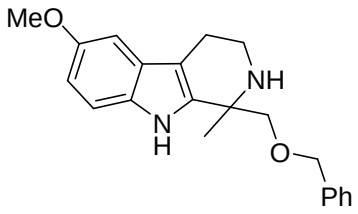
Methyleneaziridine **249a** (200 mg, 1.01 mmol) was reacted with $BF_3{\cdot}Et_2O$ (130 μL, 1.03 mmol) and allyl alcohol (140 μL, 2.06 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded **269e** (206 mg, 80%) as a brown oil. R_f = 0.22 (5% methanol in dichloromethane); υ_{max} (film) 2972, 2901, 1451, 1297, 1075 cm^{-1}; δ_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, =C*H*CH_2), 5.33-5.23 (1H, m, =C*H*H), 5.19-5.09 (1H, m, =CH*H*), 4.05-3.96 (2H, m, OCH_2), 3.52 (1H, d, *J* = 8.6 Hz, OC*H*H), 3.49 (1H, d, *J* = 8.6 Hz, OCH*H*), 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; δ_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 $C_{16}H_{21}N_2O$ [MH^+]: 257.1648; found 257.1648.

1-Methyl-1-[(pent-4-ynyloxy)methyl]-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (269f).



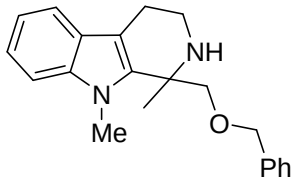
Methyleneaziridine **249a** (200 mg, 1.01 mmol) was reacted with $BF_3{\cdot}Et_2O$ (130 μL, 1.03 mmol) and 4-pentyn-1-ol (190 μL, 2.04 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded **269f** (201 mg, 71%) as a brown oil. R_f = 0.22 (5% methanol in dichloromethane); υ_{max} (film) 3287, 2862, 1620, 1452, 1297 cm^{-1}; δ_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, OC*H*H), 3.48 (1H, d, *J* = 8.4 Hz, OCH*H*), 3.26-3.14 (2H, m, NCH_2), 2.73 (2H, t, *J* = 5.7 Hz, $ArCH_2$), 2.39-2.25 (2H, m, $CH_2C\mathit{H}_2CH_2$), 2.01 (1H, t, *J* = 2.8 Hz, ≡CH), 1.88-1.80 (2H, m, $C\mathit{H}_2C{\equiv}CH$), 1.65 (1H, br s, NH), 1.51 (3H, s, CH_3) ppm; δ_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 ($\mathit{C}H_2C{\equiv}CH$), 25.4 (CH_3), 22.9 ($ArCH_2$), 15.5 ($CH_2\mathit{C}H_2CH_2$) ppm; MS ($LSIMS^+$) *m/z* 283 [MH^+]; HRMS ($LSIMS^+$) calcd for $C_{18}H_{23}N_2O$ [MH^+]: 283.1806; found 283.1810.

1-(Benzyloxymethyl)-6-methoxy-1-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4 indole (269g).



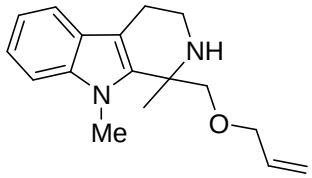
Methyleneaziridine **249b** (412 mg, 1.80 mmol) was reacted with $BF_3{\cdot}Et_2O$ (230 μL, 1.81 mmol) and benzyl alcohol (370 μL, 3.58 mmol) as described in General Method 4. Purification on silica gel (3% methanol in dichloromethane) afforded **269g** (401 mg, 66%) as a brown oil. R_f = 0.21 (5% methanol in dichloromethane); υ_{max} (film) 2935, 1705, 1625, 1590, 1453 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, OC*H*H), 4.51 (1H, d, *J* = 12.2 Hz, OCH*H*), 3.84 (3H, s, OCH_3), 3.56 (1H, d, *J* = 8.4 Hz, OC*H*H), 3.53 (1H, d, *J* = 8.4 Hz, OCH*H*), 3.23-3.11 (2H, m, NCH_2), 2.69 (2H, t, *J* = 5.7 Hz, $ArCH_2$), 1.92 (1H, br s, NH), 1.49 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 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 (OCH_2), 73.7 (OCH_2), 56.1 (OCH_3), 53.5 (C), 39.8 (NCH_2), 25.4 (CH_3), 22.8 ($ArCH_2$) ppm; MS (ES^+) *m/z* 337 [MH^+]; HRMS (ES^+) calcd for $C_{21}H_{25}N_2O_2$ [MH^+]: 337.1911; found 337.1911.

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



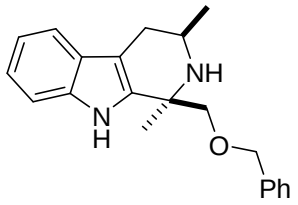
Methyleneaziridine **249c** (200 mg, 0.94 mmol) was reacted with $BF_3{\cdot}Et_2O$ (120 μL, 0.95 mmol) and benzyl alcohol (195 μL, 1.89 mmol) as described in General Method 4. Purification on silica gel (2% methanol in dichloromethane) afforded **269h** (130 mg, 43%) as a brown oil. R_f = 0.25 (5% MeOH in CH_2Cl_2); υ_{max} (film) 2928, 1705, 1469, 1453, 1091 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, OC*H*H), 4.49 (1H, d, *J* = 12.3 Hz, OCH*H*), 3.87 (1H, d, *J* = 9.7 Hz, OC*H*H), 3.63 (3H, s, NCH_3), 3.58 (1H, d, *J* = 9.7 Hz, OCH*H*), 3.22-3.07 (2H, m, NCH_2), 2.77 (2H, t, *J* = 5.7 Hz, $ArCH_2$), 1.93 (1H, br s, NH), 1.49 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 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 (OCH_2), 73.3 (OCH_2), 55.0 (C), 39.4 (NCH_2), 31.6 (NCH_3), 23.9 (CH_3), 23.3 ($ArCH_2$) ppm; MS (ES^+) *m/z* 321 [MH^+]; HRMS (ES^+) calcd for $C_{21}H_{25}N_2O$ [MH^+]: 321.1961; found 321.1962.

1-(Allyloxymethyl)-1,9-dimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (269i).



Methyleneaziridine **249c** (200 mg, 0.94 mmol) was reacted with $BF_3{\cdot}Et_2O$ (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. R_f = 0.23 (5% methanol in dichloromethane); υ_{max} (film) 2930, 1647, 1470, 1364, 1237 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, =C*H*CH_2), 5.25-5.15 (2H, m, =CH_2), 3.99 (2H, d, *J* = 5.8 Hz, OCH_2), 3.89 (1H, d, *J* = 9.6 Hz, OC*H*H), 3.78 (3H, s, NCH_3), 3.59 (1H, d, *J* = 9.6 Hz, OCH*H*), 3.25-3.09 (2H, m, NCH_2), 2.77 (2H, t, *J* = 5.7 Hz, $ArCH_2$), 1.95 (1H, br s, NH), 1.51 (3H, s, CH_3) ppm; δ_C (100 MHz, $CDCl_3$) 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 (=CH_2), 110.0 (C, Ar), 108.7 (CH, Ar), 74.9 (OCH_2), 72.4 (OCH_2), 55.0 (C), 39.3 (NCH_2), 31.8 (NCH_3), 23.9 (CH_3), 23.3 ($ArCH_2$), ppm; MS (ES^+) *m/z* 271 [MH^+]; HRMS (ES^+) calcd for $C_{17}H_{23}N_2O$ [MH^+]: 271.1805; found 271.1802.

(1*R,3*R**)-1-[(Benzyloxy)methyl]-2,3,4,9-tetrahydro-1,3-dimethyl-1*H*-pyrido[3,4-*b*]indole (272).**



Methyleneaziridine **249d** (200 mg, 0.94 mmol) was reacted with $BF_3{\cdot}Et_2O$ (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 (1*R**,3*R**)-**272** (190 mg, 63%) as a light brown oil. R_f = 0.25 (5% methanol in dichloromethane); υ_{max} (film) 2862, 1707, 1453, 1307, 1092 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, OC*H*H), 4.58 (1H, d, *J* = 11.6 Hz, OCH*H*), 4.00-3.88 (2H, m, OCH_2), 3.63-3.53 (1H, m, NCH), 2.92 (1H, dd, *J* = 4.1, 15.7 Hz, ArCH_{eq}H), 2.76-2.73 (1H, m, ArCH_{ax}H), 1.74 (3H, s, CCH_3), 1.55 (3H, d, *J* = 6.3 Hz, CHCH_3), 1.25 (1H, br s, NH) ppm; δ_C (100 MHz, $CDCl_3$) 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 (OCH_2), 73.7 (OCH_2), 55.5 (C), 45.1 (CH), 30.6 (CCH_3), 25.1 ($ArCH_2$), 22.6 (CHCH_3) ppm; MS (ES^+) *m/z* 321 [MH^+]; HRMS (ES^+) calcd for $C_{21}H_{25}N_2O$ [MH^+] 321.1961, found 321.1960.

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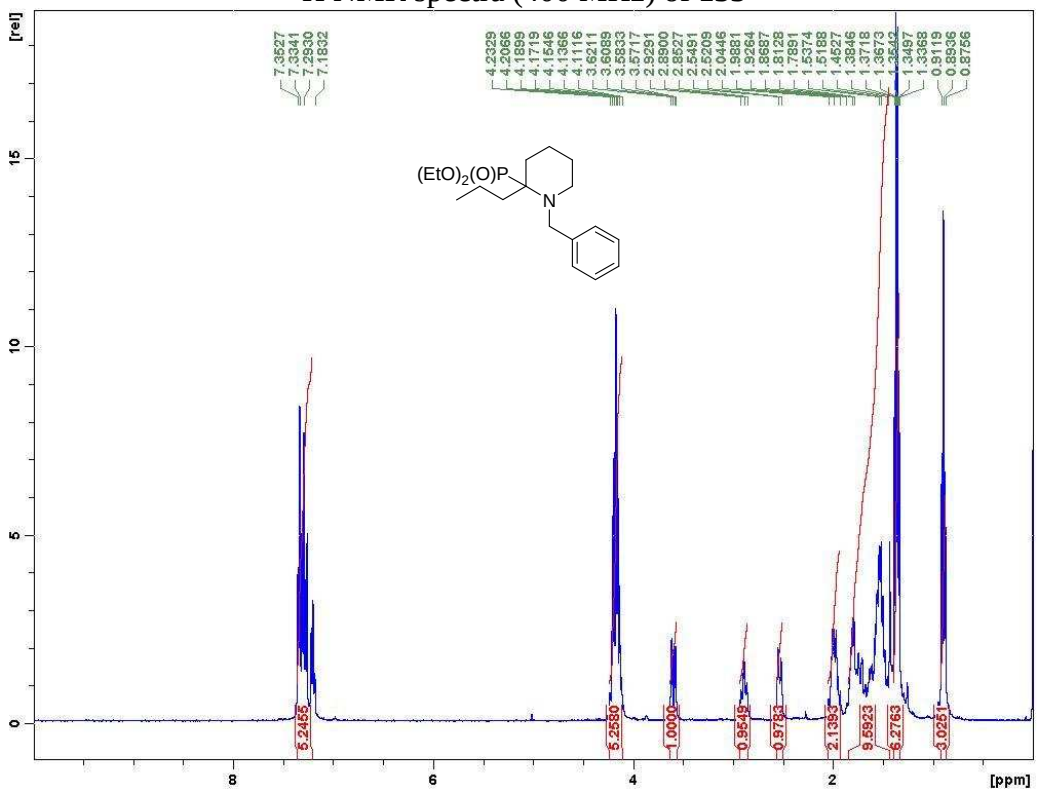
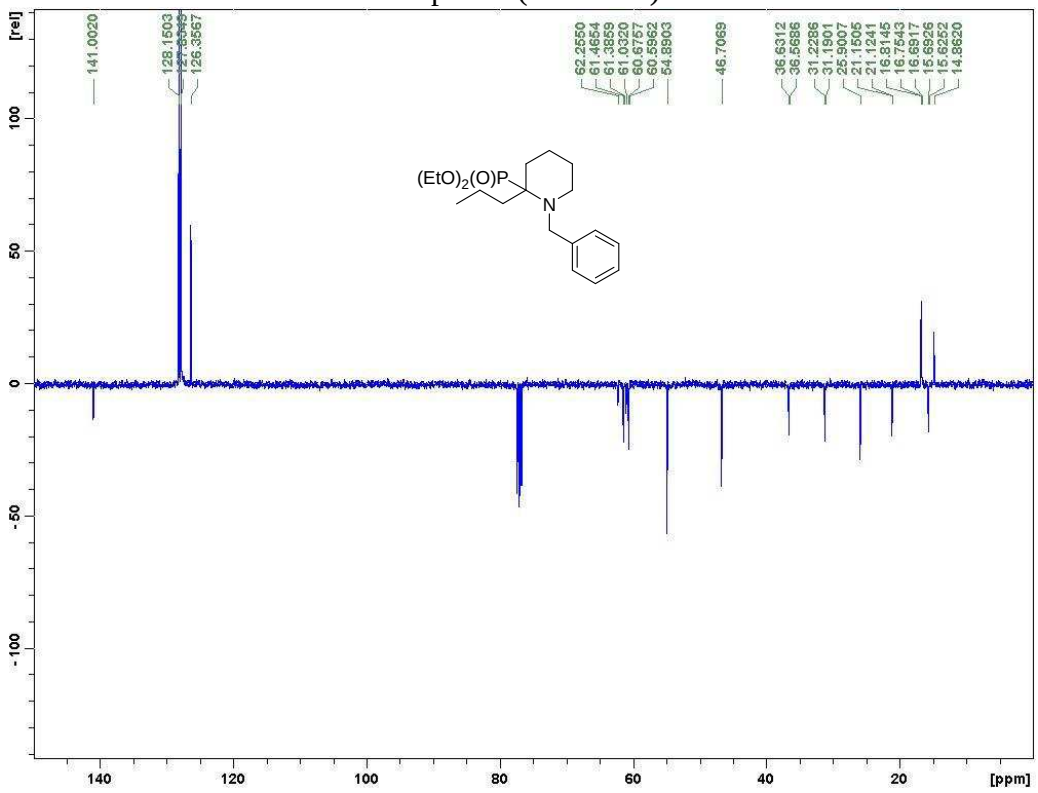
Appendix

^{1}H NMR spectra (400 MHz) of **155**



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



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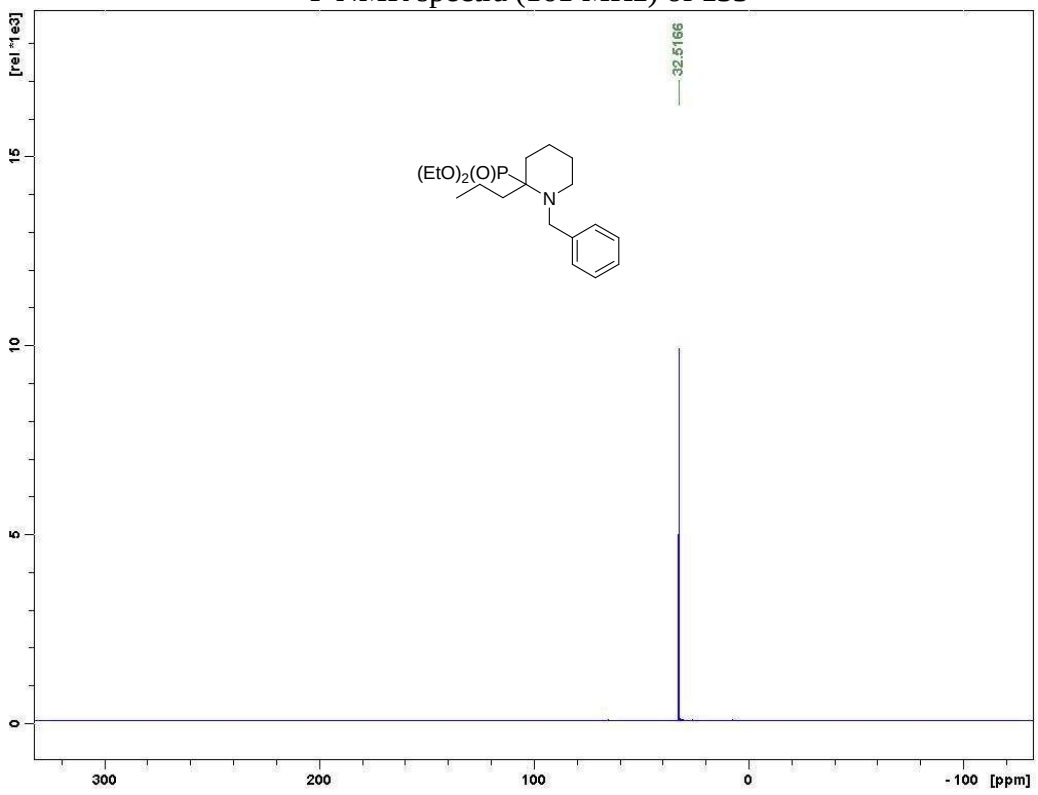

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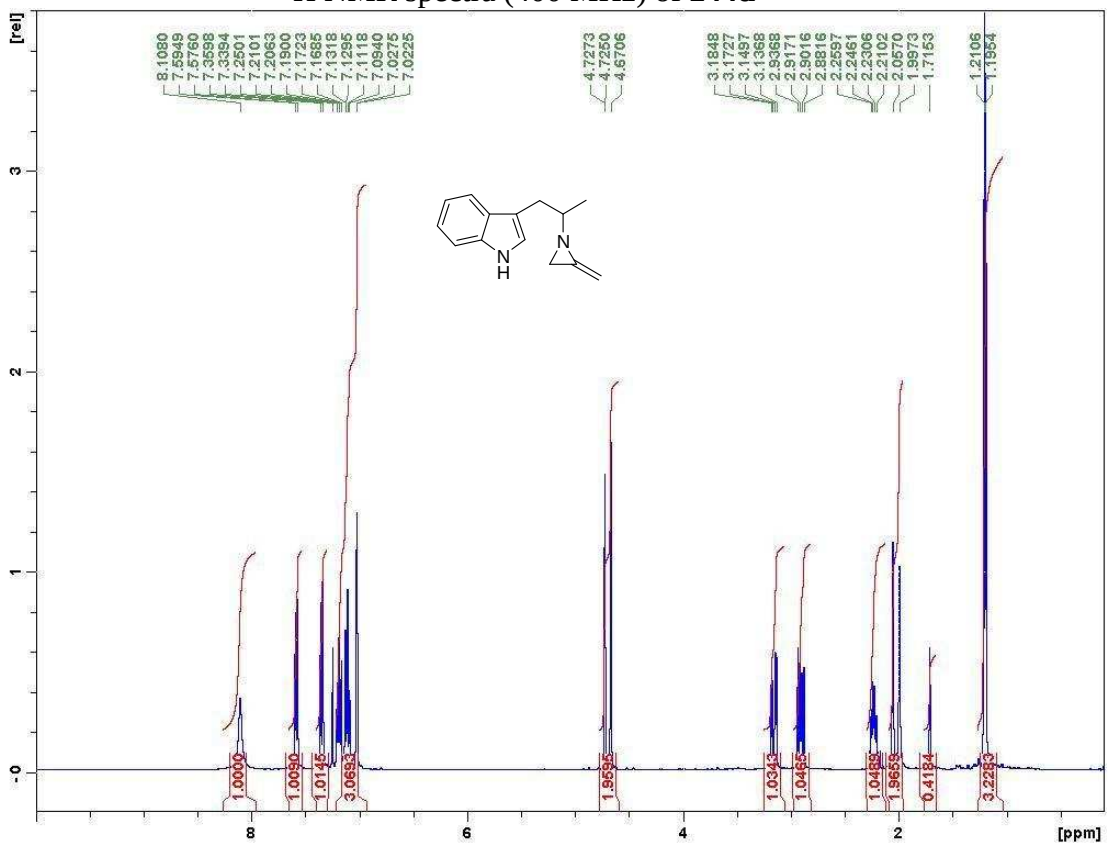

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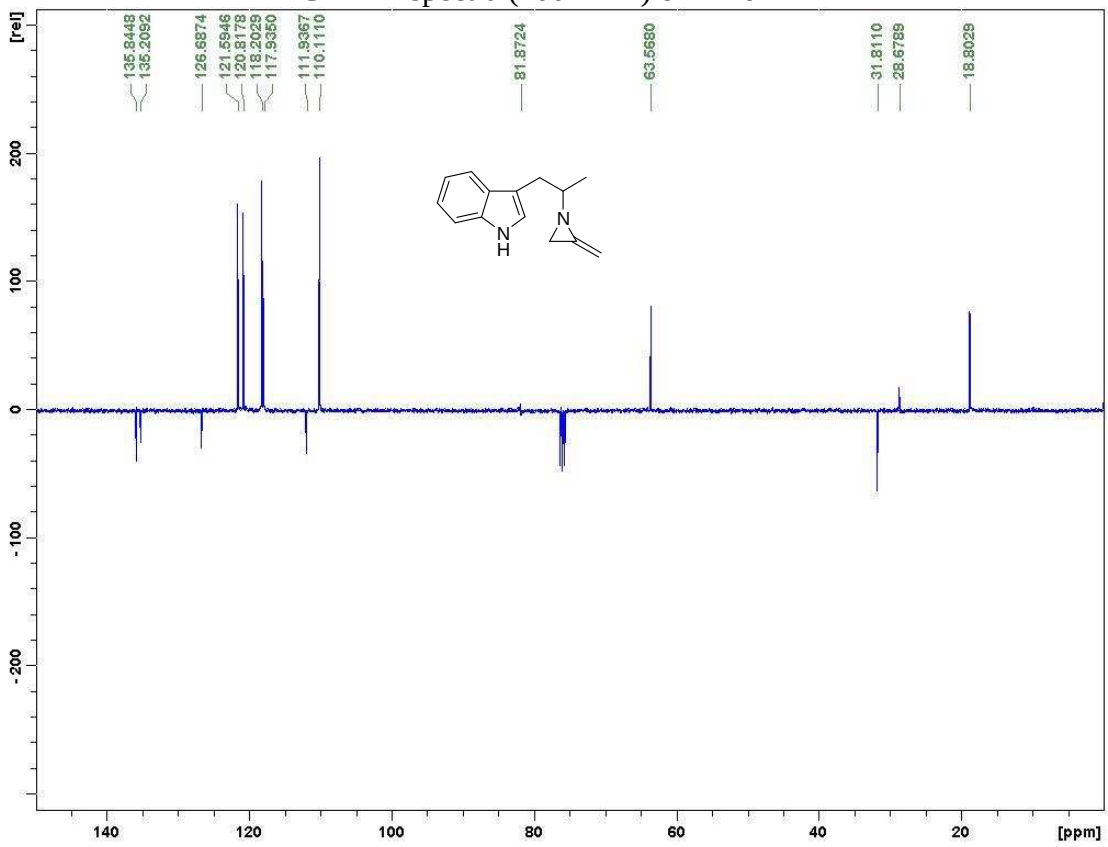
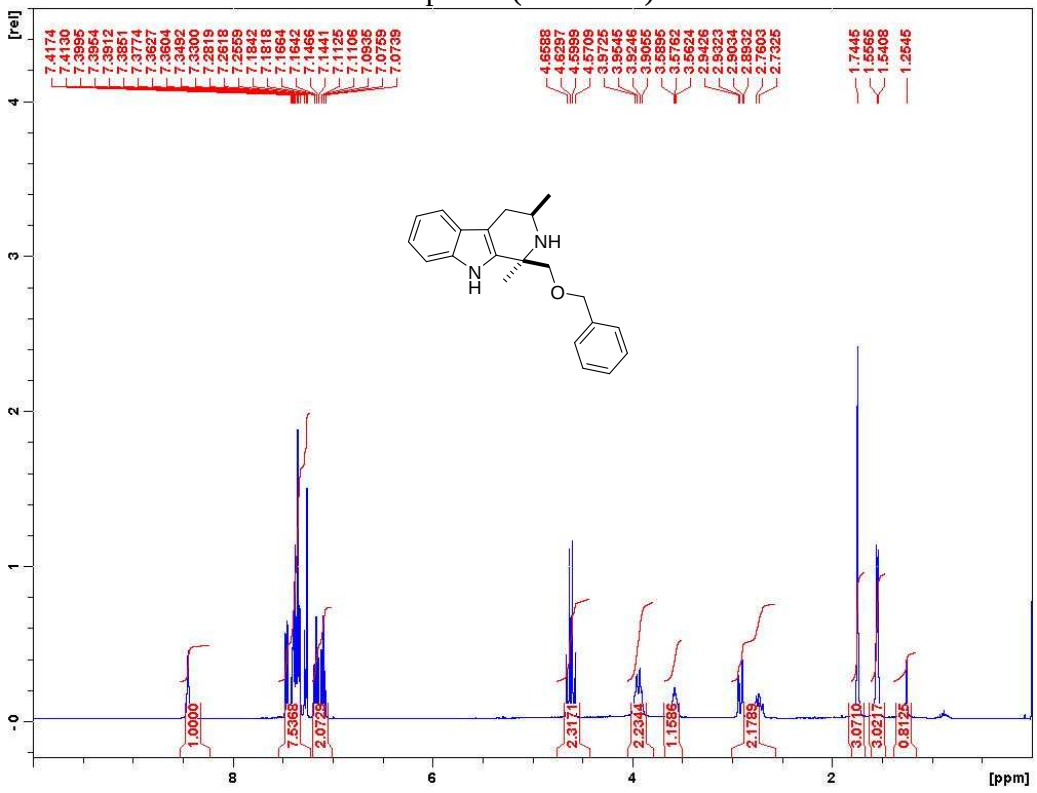


^{1}H NMR spectra (400 MHz) of **267**



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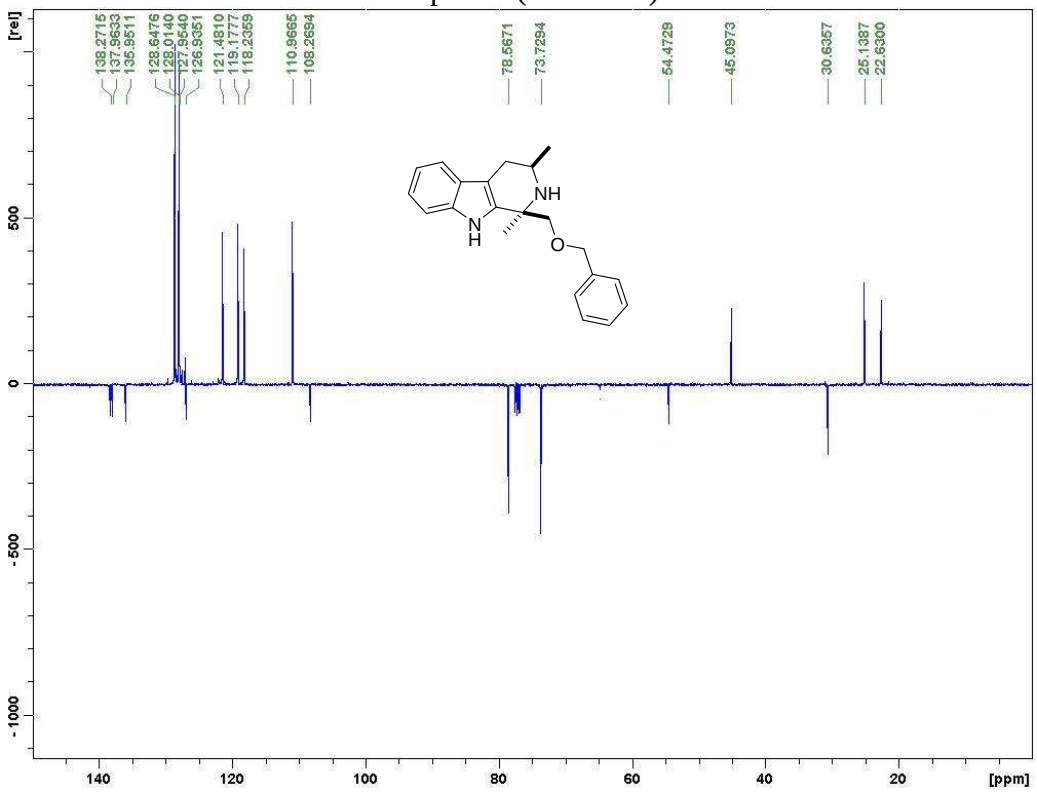

NOSEY correlation (400 MHz) of **267**