Radical Approaches to *Alangium* and *Mitragyna* Alkaloids

A Thesis Submitted for a PhD

University of York

Department of Chemistry

2010

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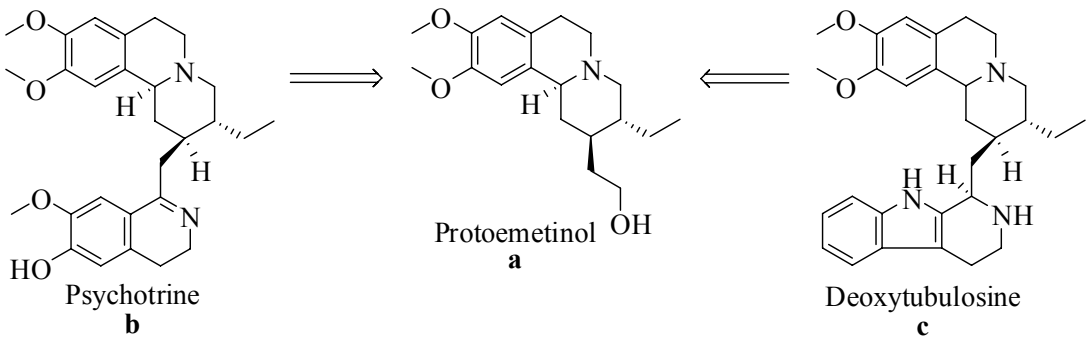
Abstract

The work presented in this thesis has focused on the development of novel and concise syntheses of *Alangium* and *Mitragyna* alkaloids, and especial approaches towards (±)-protoemetinol (**a**), which is a key precursor of a range of *Alangium* alkaloids such as psychotrine (**b**) and deoxytubulosine (**c**). The approaches include the use of a key radical cyclisation to form the tri-cyclic core.

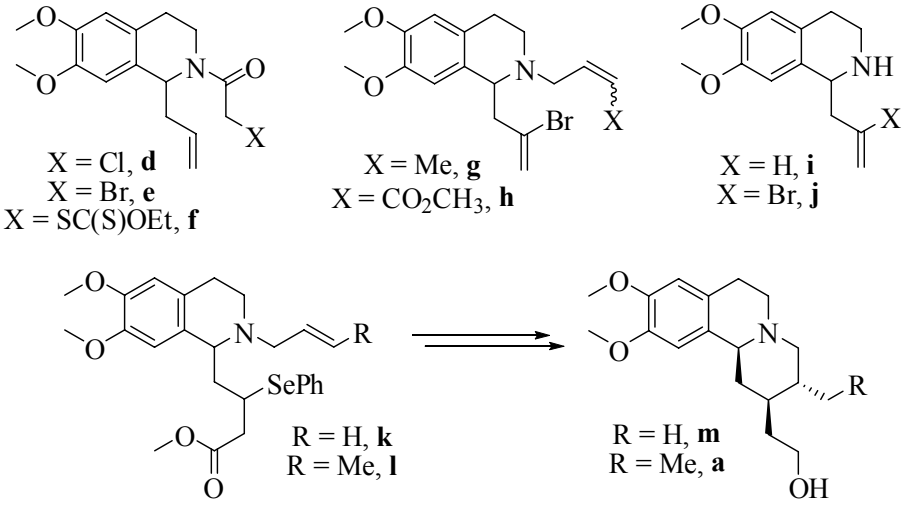


Chapter 1 gives a general overview of radical chemistry and it focuses on the application of radical intermolecular and intramolecular reactions in synthesis. Consideration is given to the mediator of radical reactions from the classic organotin reagents, to more recently developed alternative hydrides. An overview of previous synthetic approaches to a range of *Alangium* and *Mitragyna* alkaloids is then explored.

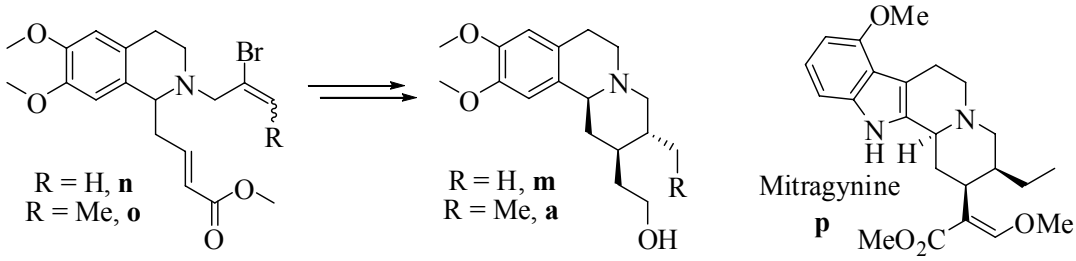
Chapter 2 follows on from previous work within our group, involving the use of phosphorus hydride radical addition reactions, to alkenes or dienes, followed by a subsequent Horner-Wadsworth-Emmons reaction. It was expected that the tri-cyclic core of the *Alangium* alkaloids could be prepared by cyclisation of a 1,7-diene, using a phosphorus hydride to afford the phosphonate or phosphonothioate, however this approach was unsuccessful and it highlighted some limitations of the methodology.

Chapter 3 explores the radical and ionic chemistry of a range of silanes. Initial studies explored the radical addition of a range of silicon hydrides to alkenes to afford the corresponding hydrosilylation products. The chemistry of the hydrosilylation products was then explored – it was hoped that a subsequent Peterson olefination or Fleming-Tamao oxidation would afford the corresponding alkene or alcohol. Subsequent investigations looked into the possibility of combining the radical and ionic reactions, to afford alkenes or alcohols, in a one-pot transformation.

Chapter 4 explores the radical cyclisation of various compounds, including unsaturated alpha-haloamides (**d** and **e**), xanthates (**f**), vinyl bromides (**g** and **h**). For this, a robust and efficient synthesis of an allyl tetrahydroisoquinoline core (**i** and **j**) was developed, following conversion into the desired radical precursors these compounds were treated with tributyltin hydride and a radical initiator. Finally, Chapter 4 investigates the radical cyclisation of some unsaturated phenylselenides (**k** and **l**), which resulted in the isolation of the desired target alkaloid (±)-protoemetinol (**a**) in 4 steps and in 2% overall yield.



Chapter 5, which builds on previous work within Chapter 4, discusses the cyclisation of vinyl bromides bearing an α,β-unsaturated ester (**n** and **o**). This resulted in short 4-step syntheses of both (±)-des-methyl-protoemetinol (**m**) and (±)-protoemetinol (**a**) (along with some epimers). Subsequent studies then expanded the synthetic strategy to include the synthesis of a structurally simpler analogue of mitragynine (**p**).



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Chapter 4 - Tributyltin hydride mediated cyclisation

Chapter 5 - Vinyl bromide approaches to *Alangium* and *Mitragynine* alkaloids

Acknowledgements

Many people have contributed to my years of research at York, all deserve much thanks for their help.

Firstly I would like to show my appreciation to my supervisor Dr Andrew Parsons, first for allowing me to work within his research group. His guidance, knowledge, enthusiasm and most of all proof-reading of this thesis has been invaluable, and with out which this thesis would not be possible.

A great deal of thanks has to go to the technical staff with in the department; Mike and Steve for their friendly banter, and for ensuring a supply of all the required chemicals, Trevor for the mass spectrometry results, Adrian for the X-ray structures, and finally, but most importantly Heather and Amanda for their support with all things NMR related, with out which the experimental would have been possible.

Thanks to all members of the lab past and present, for their friendship and making the past 4 years so entertaining, namely Tony, Danny, Izzi, Peter and Sharifa, and the MChem students over the years Ivor, Mark, Christian and David, and more recently all the POB members for making us feel at home, after our move.

Finally and most importantly a huge thanks you to my family, especially my mum and dad for all their support over the years.

Declaration

I declare that, to the best of my knowledge, the research presented in this thesis is original. Due reference has been made where the work of others is quoted

M. J. Palframan
Aug 2010

Abbreviations

Ac	acetyl
ACCN	1,1'-azobis(cyclohexanecarbonitrile)
AIBN	2,2'-azobisisobutyronitrile
app	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere
BDE	bond dissociation enthalpy
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
B.p.	boiling point
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	carboxybenzyl
CI	chemical ionisation
conc.	concentrated
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dec	decomposition
DEPT	distortionless enhancement by polarisation transfer
DLP	dilauroyl peroxide
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMPU	*N*,*N*'-dimethyl-*N*,*N*'-propylene urea
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
d.s.	diastereoselectivity

E^+	electrophile
ee	enantiomeric excess
EI	electron impact
eq.	equivalent
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
GCMS	gas chromatography mass spectrometry
GCTMS	gas chromatography/time of flight mass spectrometry
h	hour(s)
HMBC	heteronuclear multiple-bond correlation
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple-quantum correlation
hν	irradiation
Im	imidazole
IR	infrared
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
m-	*meta*-
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute(s)
mp	melting point
MS	molecular sieves
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhancement spectroscopy
Nu^-	nucleophile
o-	*ortho*-
p-	*para*-
PG	protecting group
Ph	phenyl

PMB	4-methoxybenzoyl
PNB	4-nitrobenzoyl
ppm	parts per million
Pr	propyl
PTSA	*para*-toluenesulfonic acid
Pyr	pyridine
quant.	quantitative
R_f	retention factor
r.t.	room temperature
sat.	saturated
SET	single electron transfer
t, tert-	tertiary
TBDPS	*t*-butyldiphenylsilyl
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	toluene
TTF	tetrathiafulvalene

Chapter 1 Introduction

1.1 Radical chemistry

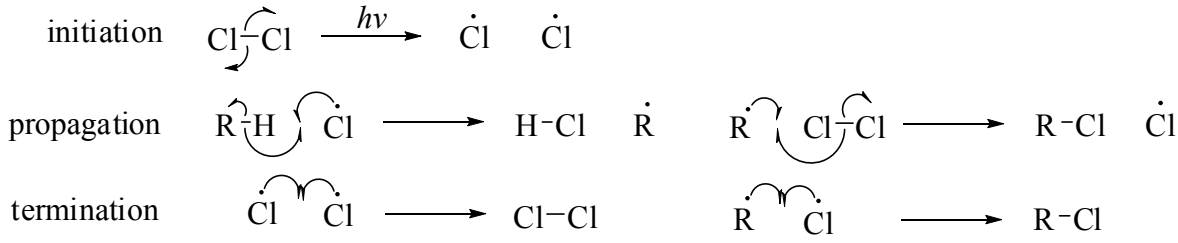
1.1.1 - Overview of radical chemistry

The story of radical chemistry begins over a hundred years ago, with the preparation and isolation of the triphenylmethyl radical by Gomberg in 1900.[1] However his claims that the product was a free radical was greeted with skepticism, and it was not until after the theoretical approaches to covalent bonding that free radicals as odd electron species became believable.[2-4] However it was not till the work by Paneth in 1929 that simple alkyl (methyl and ethyl) free radicals were prepared and studied.[5-7] Paneth showed that heating a stream of tetramethyllead (in a quartz tube) deposited a lead mirror and an "active gas" which is capable of completely volatising a second deposit of lead, and reforming the tetramethyllead. Since these early days radical reactions have developed to become an important tool for the synthetic organic chemist and within the last twenty to thirty years the use of radicals in synthesis has grown enormously. For example, radical processes account for the production of about 75% of the polymers manufactured every year.[8]

We are now at the point where radicals are routinely considered for the preparation of complex target molecules.[9-11] This reflects the fact that radical reactions offer a number of advantages over ionic transformations. Reactions involving cations or anions generally proceed under conditions of high acidity or high basicity respectively, but radical reactions typically proceed under mild or neutral conditions. This allows acid sensitive and chiral substrates to be transformed without decomposition or racemisation. Whereas the solvent usually influences reactions involving ions, radicals are generally less solvated and hence can react similarly in a range of different solvents. As radicals are not solvated they are generally highly reactive, and so can be used to assemble sterically hindered centres within complex target molecules.

1.1.2 - General considerations of radical reactions

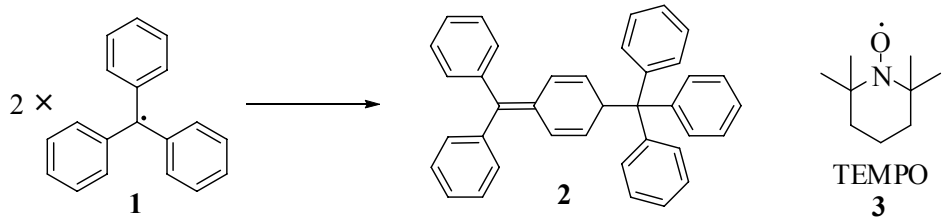
Most synthetically important radical reactions involve chain processes, such as the photolysis of chlorine and alkanes to form alkyl chlorides. Following initiation, the first-formed radical reacts through a series of propagation steps to produce a new radical(s), which ultimately leds to regeneration of the initial radical. Propagation reactions usually involve the formation of strong bonds at the expense of weaker bonds (e.g. the C–Cl bond in an alkyl chloride is stronger than the Cl–Cl bond in chlorine, **Scheme 1**).



Scheme 1

The bond dissociation energies of the bonds that are broken and formed can provide a guide as to whether the process will proceed. Bond dissociation energies can also tell us which radicals are most likely to be generated in initiation steps; the weaker the bond, the more easily the radicals are formed.

Steric factors can play an important part in radical reactions and bulky substituents will reduce the rate at which the radical reacts due to steric hindrance.[12] For example, dimerisation of the methyl radical typically has a rate constant of 3×10^{10} dm^3 mol^{-1} s^{-1} (at rt), whereas the considerably more hindered trityl radical **1** dimerises (head-to-tail, **2, Scheme 2**) with a rate constant of only 3×10^2 dm^3 mol^{-1} s^{-1} (at rt) at the same concentration.[13] Steric hindrance therefore increases the lifetime of radicals, which is exemplified by the stable crystalline TEMPO radical **3**.



Scheme 2

There are numerous methods for initiating radical reactions. Common methods involve the homolytic cleavage of weak bonds by photolysis or thermolysis. Typical examples of radical initiators are peroxides or azo compounds. Although in theory only one molecule of initiator could be used to effectively initiate a chain reaction, due to solvent cage effects, and unwanted termination steps, typically 0.1 equivalents of the initiator is added. A slow addition of the initiator helps the chain reaction to continue as this generates a steady, low concentration of the radical intermediates which reduces the rate of radical-radical termination processes. The choice of initiator is usually decided by its half-life at the temperature of the reaction.[14] AIBN is perhaps the most commonly used initiator with a

half-life of just over 1 h at 80 ˚C, under 5 minutes at 100 ˚C and over 50 h at 60 ˚C. AIBN is commonly used to initiate reactions involving tin hydrides; the nitrile–stabilised radical ($Me_2C(CN)$•) is able to selectively abstract the hydrogen atom in the weak Sn–H bond. Peroxides generate reactive oxygen-centered radicals (RO•)[15, 16] that can abstract hydrogen atoms from various organic molecules and, in some cases, this can led to undesired side reactions and a lack of selectivity. More recently, trialkylboranes (especially triethylborane) in the presence of oxygen/air has been shown to be efficient radical initiators at temperatures down to -78 °C.[17-19]

1.1.3 - Overview of intermolecular additions

Intermolecular radical additions, to form a range of carbon–carbon bonds, commonly involve the addition of carbon-centred radicals to alkenes to form σ-bonds at the expense of weaker π-bonds.[20] Intermolecular radical additions mediated by Bu_3SnH can be difficult to conduct as rather than adding to the C=C bond, the intermediate carbon-centred radical can abstract a hydrogen-atom from Bu_3SnH in a process called simple reduction. Assuming the carbon radical adds to the C=C bond, if the rate of hydrogen-atom abstraction from Bu_3SnH is slow, then alkene polymerisation can occur.

For rapid and high yielding radical additions the polarity of the radical and alkene should be matched. Nucleophilic radicals add faster to electron–poor double bonds due to a dominating SOMO–LUMO interaction. Similarly, electrophilic radicals add faster to electron-rich alkenes due to a dominating SOMO–HOMO interaction (**Figure 1**).

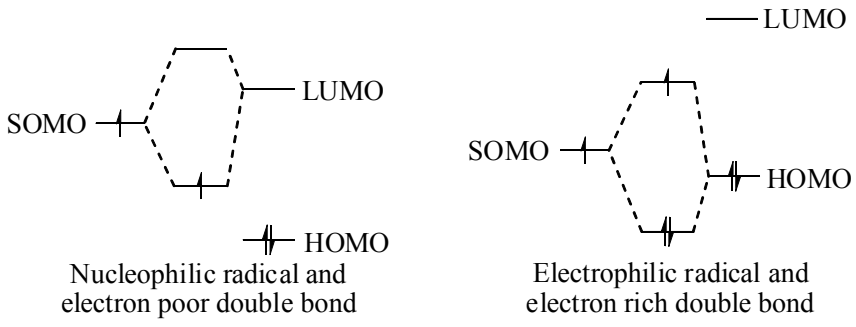
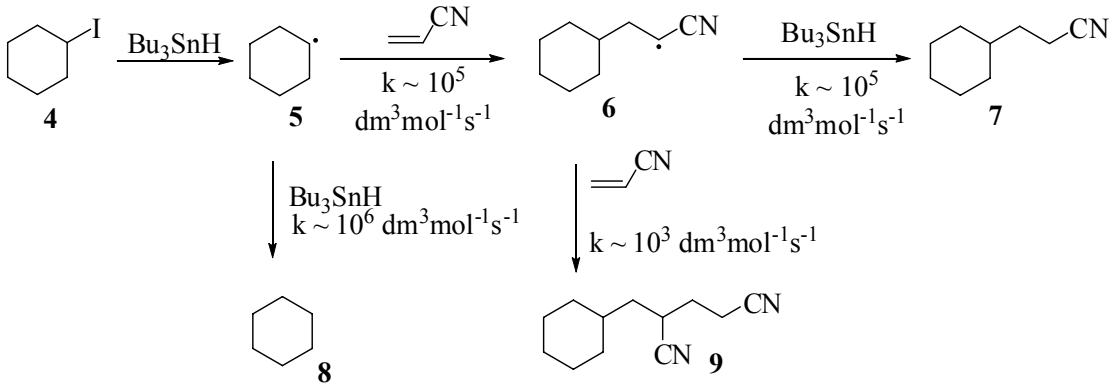


Figure 1

This explains why the nucleophilic *tert*-butyl radical adds to the C=C bond of acrolein over 3000 times faster than to the C=C bond in propene at room temperature. Similarly the rate of addition of a radical to an electron poor double bond depends on the electronic properties of the radical.[21, 22] The more electron-withdrawing the substituent bonded to the

radical, the slower the rate of addition to an electron-poor double bond. This explains the formation of nitrile **7** in 95% yield from reaction of cyclohexyl iodide **4** and acrylonitrile with Bu_3SnCl (0.2 equiv.) and $NaBH_4$ (**Scheme 3**).[23, 24] Addition of the nucleophilic cyclohexyl radical **5** to the electron poor double bond is followed by hydrogen-atom abstraction by radical **6** to afford the nitrile **7**. The polarity of the resulting "electrophilic" radical **6** is incompatible with addition to a second molecule of acrylonitrile that would led to **9**.[25] Steric effects of alkene substituents are also important and, in general, the bulkier the substituents attached to a C=C bond, the slower the rate of radical addition.



Scheme 3

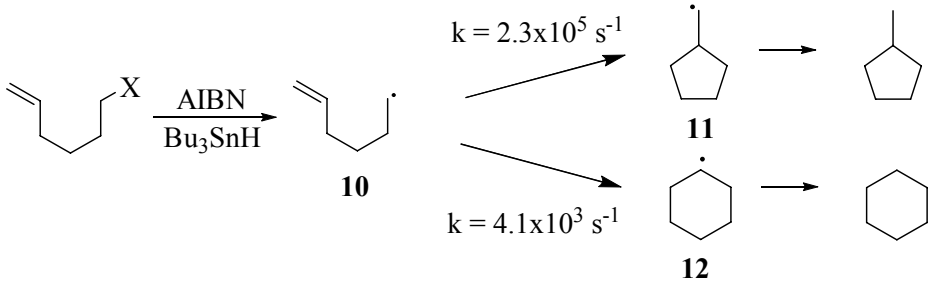
Finally, intermolecular radical addition to alkynes is slower than for alkenes, as vinyl radicals are less stable than alkyl radicals. For example, the *tert*-butyl radical adds to the double bond of methyl acrylate around 5.5 times faster than to the triple bond of methyl propiolate at the same temperature.[26]

1.1.4 - Overview of radical cyclisations

The development of cyclisations that are mild and versatile has been a recurring theme in organic synthesis. Although only recognized relatively recently, intramolecular addition reactions of radicals are among the most powerful methods for forming rings.[9, 27]

Efficient radical cyclisations require selective radical generation and rapid propagation steps. Cyclisations are often easier to conduct than bimolecular reactions, as many cyclisations are so rapid, compared to the rate of simple reduction, that it is hard to trap initial radicals with standard reagents (such as tin hydrides) before ring closure. Often, the products from competing bimolecular reactions are not observed because these reactions proceed at a much slower rate than cyclisation.

A common and reliably useful radical reaction is the cyclisation of unsaturated halides and similar compounds to form mainly 5- and 6-membered rings. An example is the cyclisation of the hex-5-en-1-yl radical **10**, which forms the primary radical **11** in a 5-*exo* cyclisation rather than the more stable secondary radical **12**, **Scheme 4**.[28] In both cases, the reaction leds to the formation of a C–C σ-bond at the expense of the weaker π-bond.



Scheme 4

The preference for 5-*exo* cyclisation can be rationalised by the stereoelectronically controlled chair-like transition state, where the 5-*exo* transition state favours overlap between the SOMO of the radical and the LUMO of the alkene, **Figure 2**. This places the angle of attack at 106°, which is close to the angle observed in a comparable intermolecular reaction (109°), however the orbital overlap of the SOMO and LUMO for the 6-*endo* cyclisation is less efficient.[29-31]

Beckwith-Houk chair transition state

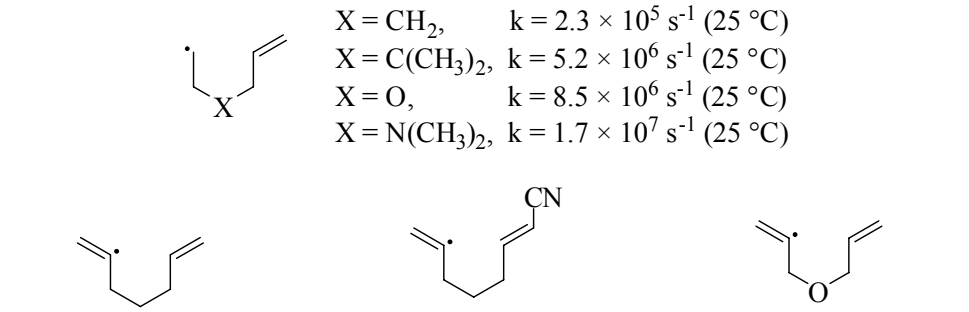
Figure 2

Following cyclisation, radicals **11** and **12** abstract a hydrogen atom from Bu_3SnH at approximately the same rate to form the cycloalkane, with the tributyltin radical continuing the chain. The major process in competition with cyclisation is the direct reduction to form hex-1-ene, which depends on the concentration of Bu_3SnH. Formation of the hex-1-ene would be a problem if Bu_3SnH was added in a single portion, however the yield of hex-1-ene can be minimised *via* slow addition of tributyltin hydride which increases the lifetime of the first-formed carbon-centred radical allowing more time for cyclisation which is independent of the Bu_3SnH concentration. Other competitive processes include the

addition of Bu_3Sn• to the double bond, however unlike halogen atom abstraction, this is reversible and fragmentation regenerates the tributyltin radical and alkene. Radical coupling reactions can also be minimised by using a low concentration of reactants.

Radical cyclisation mediated by Bu_3SnH has proven to be an effective method for forming 5-membered rings. The rate of 5-*exo* radical cyclisation can be increased by:

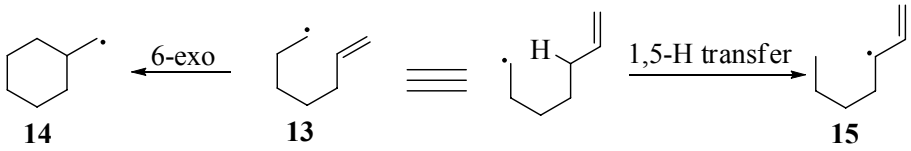
1. using vinyl/aryl radical precursors;
2. introducing alkyl groups, particularly geminal dialkyl groups, within the carbon chain;
3. introducing an oxygen or nitrogen atom within the carbon chain;
4. attaching an electron-withdrawing group to the acceptor bond.



Scheme 5[32-34]

The increased reactivity of sp^2 vinyl and aryl radicals leds to rapid bond formation.[32-34] The introduction of alkyl groups or a heteroatom changes the bond angles and/or lengths of the chain; these differences led to better orbital overlap in the 5-*exo* chair transition state and faster cyclisation.[35] The effect of the nitrile group can be explained by polarity:[36] The high-energy SOMO of the nucleophilic alkyl radical can interact more effectively with the relatively low energy LUMO orbital of the electron-poor double bond,[10] and the cyclic secondary radical is mesomerically stabilised by the nitrile triple bond.

Similarly, the radical cyclisations of 1-halohept-6-enes can form the 6-membered ring **14**, **Scheme 6,** however the rate of 6-*exo* cyclisation is around 40 times slower than that of 5-*exo* cyclisation.[37, 38] In addition, the hept-6-en-1-yl radical **13** can undergo competitive 1,5-hydrogen-atom abstraction to form a resonance-stabilised allylic radical **15**.



Scheme 6

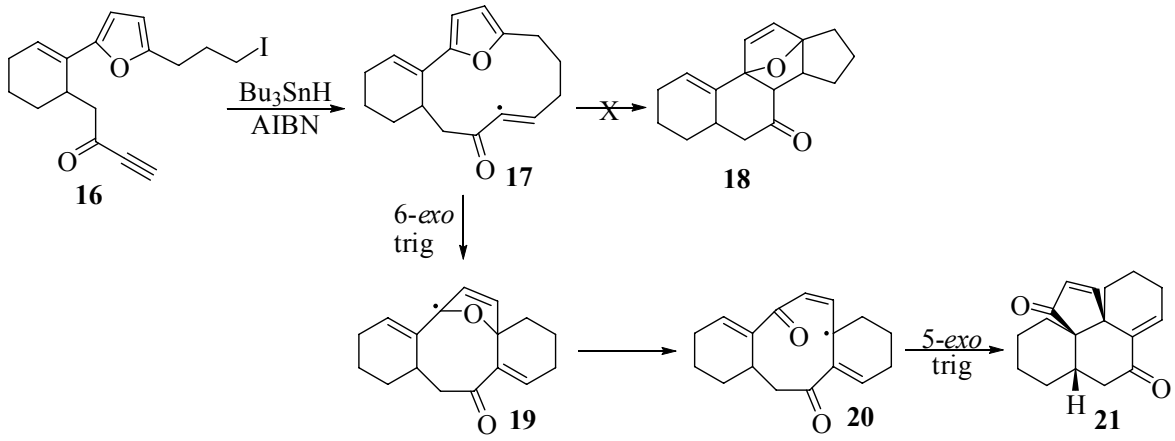
Cyclisation using alternative precursors to alkenes (including alkynes, nitriles, imines, oximes and hydrazones) are also possible. Radical cyclisation onto alkynes and nitriles are slightly slower than for alkenes,[39] however imines and related compounds usually undergo faster cyclisation.[40] This trend largely reflects the order of stability of the cyclic radicals produced.

1.1.5 – Organotin radicals in synthesis

Tin hydrides (especially Bu_3SnH) are the most common reagents used to mediate radical reactions, including intermolecular radical additions using alkyl halides and unsaturated compounds like alkenes and alkynes, which is partly due to the large amount of kinetic data on radicals derived from tin hydrides. This has also led to the development of a wide range of novel radical initiators, to generate tin-centred radicals under mild conditions.

1.1.5.1 - Additions to carbon-carbon multiple bonds

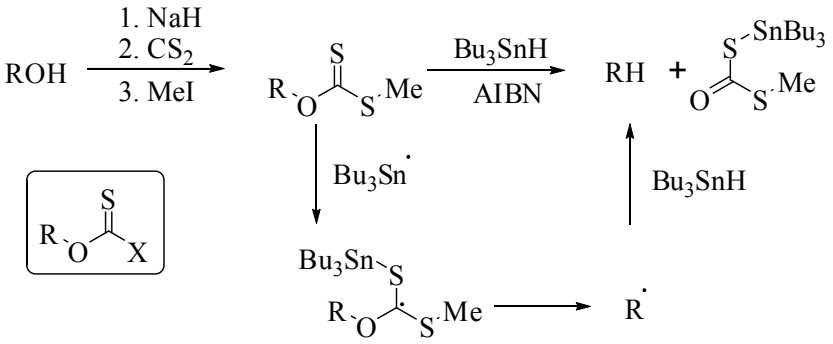
To illustrate the application of radical reactions in synthetic chemistry an example from the Pattenden group is presented in **Scheme 7**.[41] Following previous work, the furan-based iodoynone **16** was anticipated to undergo a radical Diels-Alder like cyclisation reaction to give the steroidal analogue **18**. However, the tetracyclic ketone **21** was isolated. The tetracycle was probably produced *via* initial 13–*endo*–dig macrocyclisation to form vinyl radical **17**, followed by a 6–*exo*–trig transannular addition of the vinyl radical onto the furan, subsequent fragmentation, 5–*exo* cyclisation and H-atom abstraction. The driving force for the formation of **19** from **17** lies in the stabilisation of radical **19** by the adjacent oxygen atom, while the formation of **20** can be explained by the stability of the resonance-stabilised allylic radical.



Scheme 7

1.1.5.2 - Addition to a carbon–heteroatom double bond

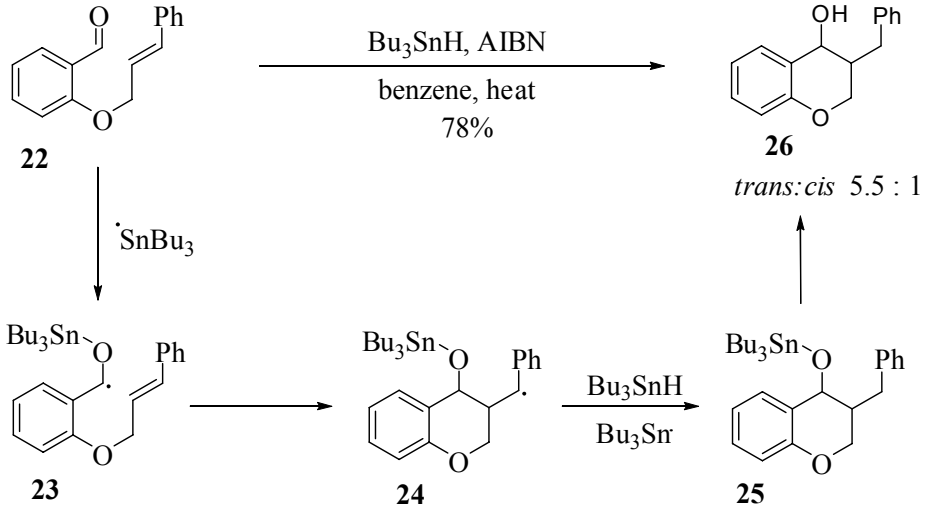
As well as halogen atom abstractions, tin centred radicals can also add to a range of carbon-carbon and carbon-heteroatom double bonds.[42-45] Perhaps the best known example of the ability of tin-centred radicals to add to C=S double bonds is in the Barton-McCombie deoxygenation of alcohols.[46] This is a mild method of reducing primary and secondary alcohols via xanthates (X = SMe), thiobenzoates (X = Ph) or thiocarbonyl imidazoles (X = imidazolyl). The reaction proceeds via reversible addition of the tin radical to the thiocarbonyl sulfur atom, which undergoes β-scission to give the corresponding carbonyl compound and an alkyl radical, which subsequently abstracts a hydrogen atom from the tin hydride (**Scheme 8**).



Scheme 8

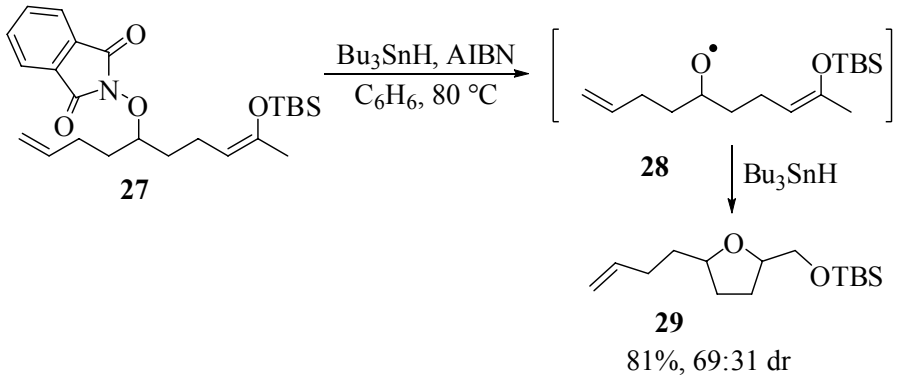
Tin-centred radicals can also add reversibly to carbonyl double bonds as illustrated in the synthesis of chromanol **26** via the cyclization of 2-(cinnamyloxy)benzaldehyde **22** (**Scheme 9**).[47] The tributyltin radical adds to the oxygen atom of the carbonyl to afford benzylic radical **23**, which is then able to undergo a 6-*exo* cyclisation to afford **24**. The intermediate benzylic radical **24** can fragment to regenerate the initial carbon-centred

radical **23**. Although the rate of fragmentation is faster than the 6-*exo* cyclisation, the benzylic radical **24** reacts with Bu_3SnH faster than the corresponding benzylic radical **24**. Hydrolysis of the organotin adduct **25** results in the formation of chromanol **26**.



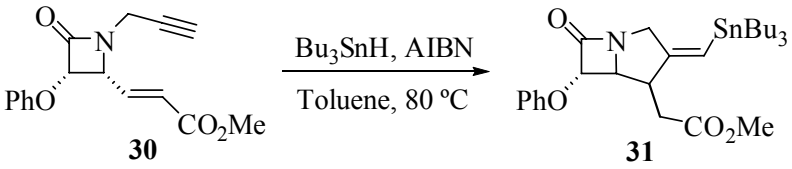
Scheme 9

In more recent work, on developing approaches to tetrahydrofurans and tetrahydropyrans, Sammis and coworkers have reported cyclisation of an oxygen-centred radical onto silyl enol ethers.[48] The inclusion of an oxygen substituent on the alkene provides both a synthetic handle for further functionalisation, whilst increasing the rate of cyclisation, by increasing the electron density of the alkene (an alkoxyl-radical is electrophilic).[49] The generation of the oxygen-centered radical was achieved by cleavage of the N-OR bond in an *N*-alkoxyphthalimide **27** by the addition of a tributyltin radical, to the carbonyl oxygen. The high degree of chemoselectivity of the electrophilic alkoxyl-radical **28**, is demonstrated by the cyclisation of silyl enol ether **28**, where both a simple alkene and the more electron rich silyl enol ether are present, which leds to the selective formation of only tetrahydrofuran **29**, **Scheme 10**.



Scheme 10

Tin-centred radicals also add to alkenes and alkynes, with addition to electron-poor bonds being favoured because tin-centred radicals are typically nucleophilic. These addition reactions are generally reversible due to the formation of weak Sn-C bonds (e.g. Sn-Me has a bond enthalpy of only 278 kJ mol^{-1}).[26] Bachi and co-workers used a hydrostannylation reaction to prepare fused bicyclic β-lactam **31** from alkyne **30** (**Scheme 11**).[50] Hydrostannylation chemistry is growing in importance due to the use of organotin compounds in many transition-metal catalysed reactions such as in the Stille coupling.



Scheme 11

However, competitive addition of tin-centred radicals to alkenes and alkynes is not usually seen in radical cyclisations of most unsaturated organohalides, as addition of $Bu_3Sn•$ to unsaturated CC bonds is reversible unlike the irreversible abstraction of a halogen atom.

1.1.5.3 - Problems associated with tributyltin hydrides

Currently, organotin reagents dominate the area of synthetic radical chemistry and are the automatic choice for many radical reactions. However, there are several major drawbacks associated with tin-based reagents. Organostannanes compounds are known to be very neurotoxic, and so require careful handling and disposal. For use in the pharmaceutical industry commercial drugs should contain tin levels below the ppb level. This level of purity is difficult to achieve because the tin halide by-products decompose to form tin oxides, which streak on silica. This has resulted in minimal use of tin hydrides in the pharmaceutical industry.

Several methods have been developed to overcome the problems associated with tin hydrides. One solution has been to retain the use of tributyltin hydride but to lower the amount of the hydride and hence lower the amount of tin byproducts. This has been achieved by using catalytic quantities of tributyltin hydride followed by reduction of the tributyltin halide by-product with a stoichiometric reducing agent, usually $NaCN(BH_3)$.[51-54]

Alternatively, methods have been developed to aid the separation of tin residues from reaction mixtures.[55, 56] For example, the use of solid supported reagents, where the tin hydride is attached to a polymer support and after the radical reaction has been performed, the tin by-product can be efficiently removed from the product by simple filtration,[57-62] and if required, the tin hydride can be regenerated by reduction. An alternative method is to attach the organic substrate to a solid support – after the radical reaction, the tin residues are removed by thorough washing, before cleaving the product from the support.[63] Another alternative is the use of fluorous tin hydrides. Once the radical chemistry has been performed, a fluorous phase extraction is used to remove most of the tin by-products from the product.[64, 65] Alternatively, it has been shown that filtering the crude reaction mixture though a KF-Silica plug removes most of the tin-containing byproducts.[66] Although useful on a small scale, these solutions are not practical on larger scales.

The problems, and limited range of solutions related to the use of tin hydrides has triggered a search for alternative approaches of generating free radicals that circumvent the use of tin hydrides. In recent years a wide range of potential hydride replacements for tributyltin hydride (as radical chain mediators) have been explored, which include the use of thiols, silanes, cyclohexadienes[67] and phosphorus hydrides. Another area that has attracted interest is the generation of radicals via single electron transfer reactions (SET).

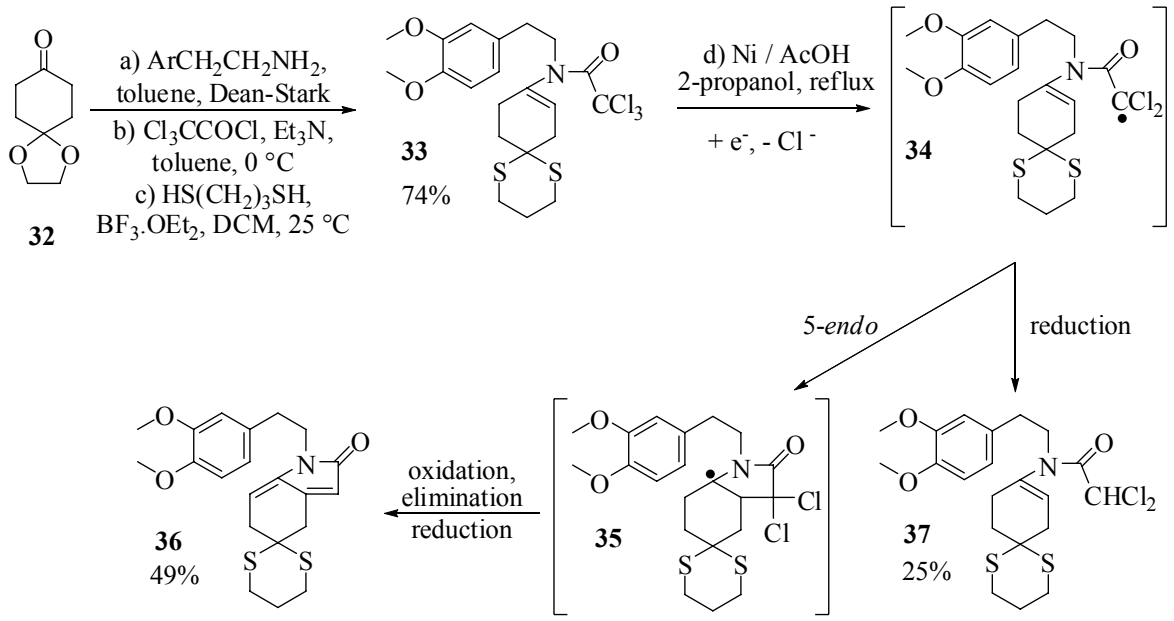
1.1.6 - Single electron transfer reactions

Single electron transfer reactions have become an increasingly common method of radical generation. There are two variations of a SET reaction, either reductive or oxidative, depending on whether, for example, a metal-containing reactant loses or gains an electron. A few examples of the use of SET reactions towards the synthesis of natural products are discussed.

1.1.6.1 - Nickel mediated reactions

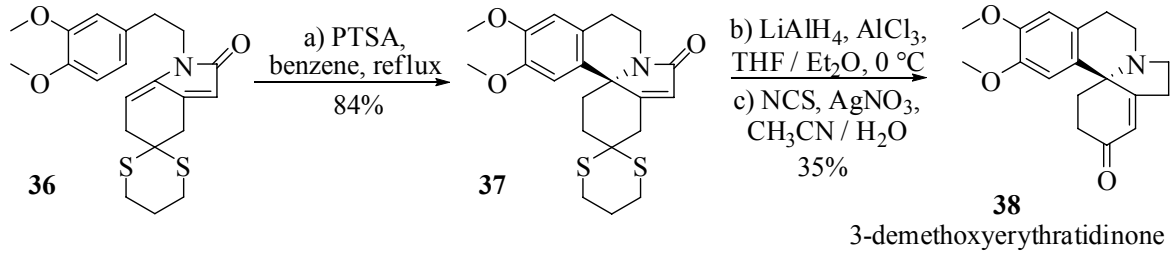
Zard and co-workers have shown that nickel powder with acetic acid in refluxing 2-propanol can be used to generate radicals derived from trichloroacetamides, which can undergo cyclisations.[68] This has been applied to the synthesis of the *erythrina* alkaloid 3-demethoxyerythratidinone (**Scheme 12** and **Scheme 13**). Treatment of trichloroacetamide **33**, obtained in 3 steps from cyclohexanone **32**, with nickel and acetic acid resulted in reduction to form intermediate radical **34**,[69-71] which then cyclises to give the *5-endo* product **35**. Subsequent oxidation generates a cation, which undergoes elimination, and

after further C-Cl bond reduction yields lactam **36**, in 49% yield, together with a 25% yield of the direct reduction material **37**.



Scheme 12

The synthesis was completed by treatment of the lactam **36** with *p*-toluenesulfonic acid to trigger a Pictet-Spengler reaction to afford the pentacycle **37** (**Scheme 13**). Reduction of the amide moiety using alane and subsequent removal of the dithioketal with migration of the C=C bond gave 3-demethoxyerythratidinone (**38**), in 7 steps starting from the cyclohexadione **32** (in 10% overall yield).

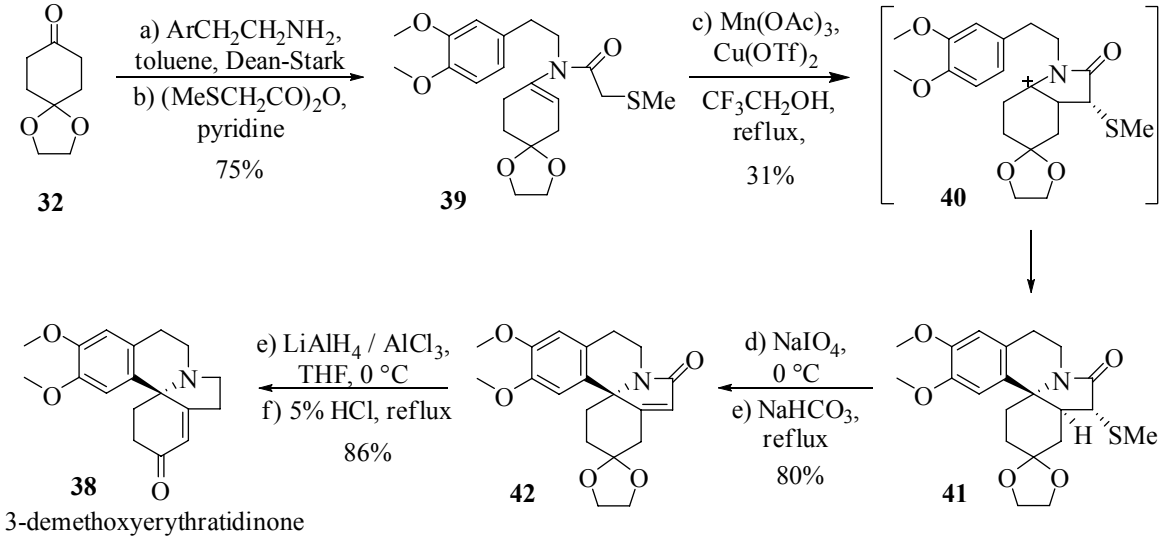


Scheme 13

1.1.6.2 - Manganese(III) acetate mediated reactions

An alternative SET approach to 3-demethoxyerythratidinone **38** has been reported by Ishibashi and co-workers, who focussed on the cyclisation of a methylthio amide (derived from cyclohexanone **32**) mediated by manganese(III) acetate (**Scheme 14**). On treatment with manganese(III) acetate and copper(II) triflate in refluxing 2,2,2-trifluoroethanol, methylthio amide **39**, afforded pentacycle **41** in 31% yield, via cation **40**.[72] Conversion to

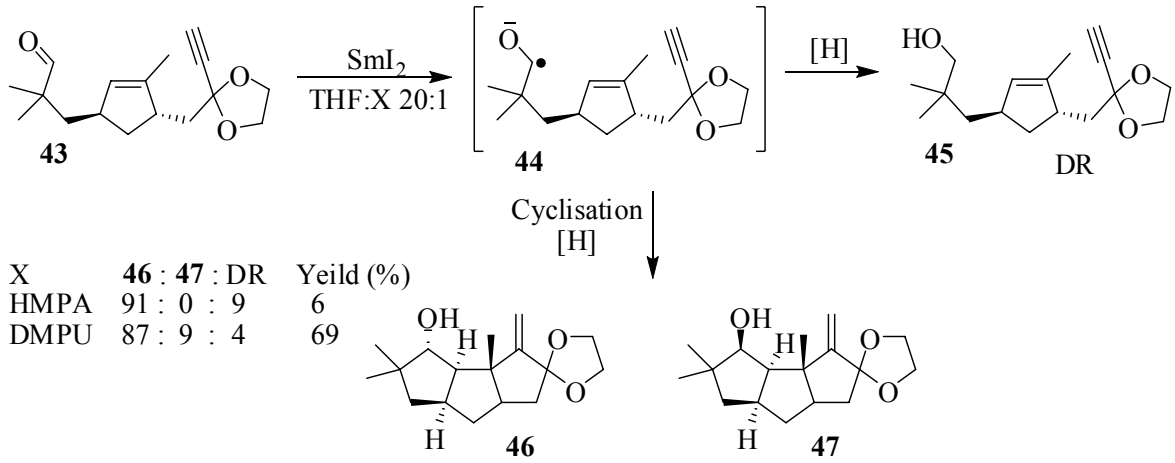
3-demethoxyerythratidinone (**38**) was achieved using a previously developed procedure, via oxidation of the sulfide to the sulfoxide, and thermal elimination to afford unsaturated amide **42.** Subsequent reduction of the amide with alane and acetal deprotection afforded 3-demethoxyerythratidinone **38**.[73]



Scheme 14

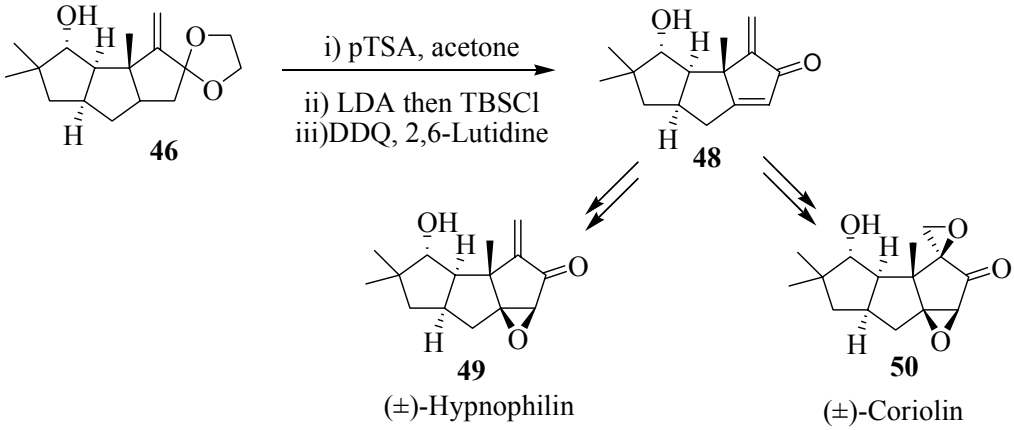
1.1.6.3 - Samarium(II) mediated reactions

Samarium(II)-mediated radical reactions have been known for some time and their synthetic use is exemplified by the total synthesis of (±)-hypnophilin (**49**) and the formal synthesis of (±)-coriolin (**50**) (**Schemes 15** and **16**).[74] Samarium(II) iodide (in the presence of a co-solvent) donates an electron to the unsaturated aldehyde **43**, to afford the intermediate radical anion **44**, which undergoes a sequential 5-*exo*-trig, 5-*exo*-dig cyclisation to afford the tricyclic ketals **46** and **47**, along with alcohol **45**, from direct reduction of the aldehyde.



Scheme 15

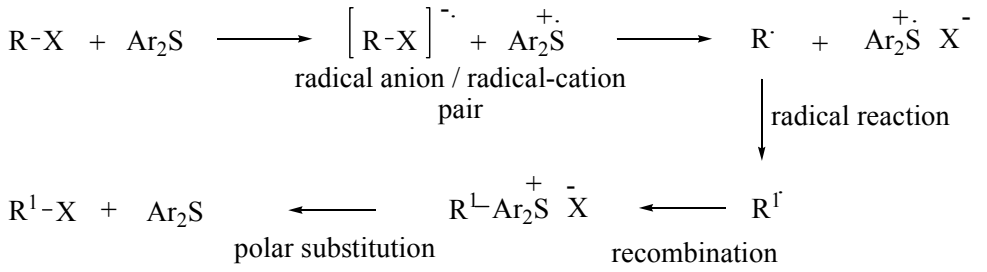
Completion of the synthesis was achieved by conversion of the tricyclic alcohol **46** into the conjugated dienone **48** (**Scheme 16**), from which selective epoxidation afforded (±)-coriolin (**50)** and (±)-hypnophilin (**49**). Treatment of alcohol **46** with *p*-toluenesulfonic acid in acetone resulted in cleavage of the ketal protecting group to afford the α,β-unsaturated system, subsequent treatment with LDA and TBS-C1, followed by oxidation using DDQ/2,6-lutidine afforded the conjugated dienone **48**.



Scheme 16

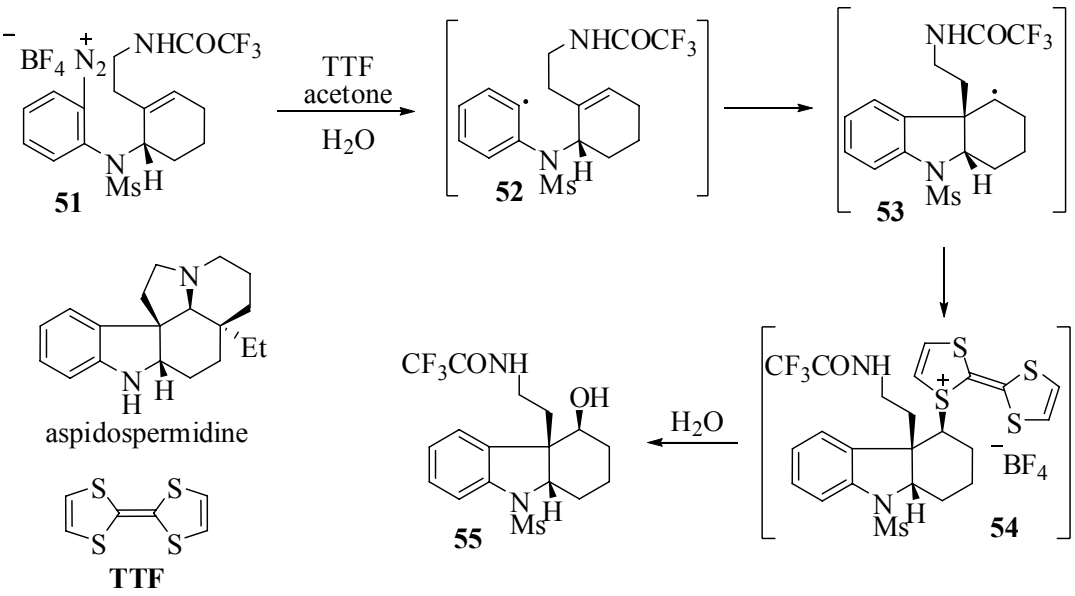
1.1.6.4 Tetrathiofulvalenes

Murphy and co-workers have developed the Radical-Polar Crossover-Reaction,[75] which combines radical and ionic steps in one-pot (**Scheme 17**).[76-81] For example, an easily oxidised sulfide can undergo electron transfer to an appropriate substrate, to generate a radical-cation/radical anion pair, which can fragment to afford the radical (R·) which either recombines with the radical cation or undergoes further radical reactions before recombination to give the sulfonium salt. The sulfonium salt then undergoes a polar substitution reaction to expel the sulfide.



Scheme 17

The most commonly used sulfide is tetrathiafulvalene (TTF), which is able to donate an electron to an arenediazonium salt. This route has been used to prepare aspidospermidine from the diazonium salt **51** (**Scheme 18**)[82]. Electron transfer and subsequent loss of N_2 affords the aryl radical **52**, which undergoes 5-e*xo*-trig cyclisation to give secondary radical **53**, which then combines with tetrathiafulvalene to give the sulfonium salt **54**. An S_N1 substitution reaction of **54** using water as the nucleophile affords alcohol **55**, which is transformed into aspidospermidine using conventional methods.[80]



Scheme 18

1.1.7 - Alternative hydrides

The most investigated solution to many of the problems of tin hydrides has been the development of alternative hydrides that are non-toxic. The weak Sn-H bond (~310 kJ mol^{-1}) makes tin hydrides extremely versatile radical reagents, as the bond is weak enough for a variety of carbon-centred radicals to be able to rapidly abstract a hydrogen atom from the tin, forming a stronger C-H bond, thereby continuing the chain by regenerating the tin-centred radical. Alternative radical reagents must have a comparably weak hydride bond.

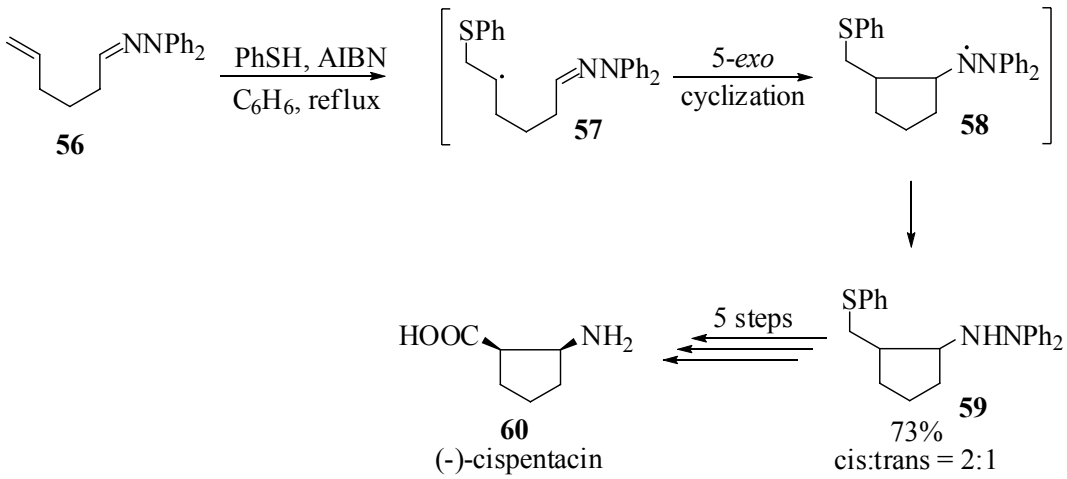
1.1.7.1 - Germanium hydrides

Investigations have been performed into the use of less toxic trialkylgermanium hydrides. Tributylgermanium hydride has a relatively strong Ge–H bond (~370 kJ mol^{-1}),[83, 84] often resulting in low levels of simple reduction of unsaturated organohalides. So addition of C-centered radicals to alkenes can proceed with essentially equimolar amounts of the halide and alkene, and slow addition is not usually required.[85] The lower reactivity of germanium-

centred radicals limits this methodology to predominantly iodides.[86] Further problems are the relatively high expense of tributylgermanium hydride and the relatively fast rate of addition of Bu_3Ge• to alkenes.[87, 88] A more reactive germanium hydride is tris(trimethylsilyl)germane [$(Me_3Si)_3GeH$],[89-91] which is able to reduce a wider variety of functional groups but, the rate of hydrogen abstraction from $(Me_3Si)_3GeH$ is faster than from tributyltin hydride, and so this can led to increased levels of simple reduction, which limits its usefulness.

1.1.7.2 - Thiols

A range of alkyl and aryl thiols can act as hydrogen-atom donors on reaction with carbon-centred radicals – a relatively weak S-H bond is broken (~370 kJ mol^{-1}) and a stronger C-H bond is formed (~400 kJ mol^{-1}).[92] The use of thiol-mediated radical reactions has been explored in a recent review by Majumdar and Debnath,[93, 94] and especially their use in the synthesis of carbocycles and heterocycles. Sulfur-centred radicals are unable to abstract a halogen atom from an alkyl halide at a rate to maintain a chain reaction. Consequently, most synthetic applications of thiols rely on their ability to add rapidly and reversibly to multiple bonds,[95-99] such as in Naito's synthesis of (-)-cispentacin (**60**) (**Scheme 19**).[100] The initially formed PhS• radical undergoes (reversible) addition to the alkene **56**, giving a secondary radical **57**, that undergoes 5-*exo* cyclisation to afford a nitrogen centred radical **58**, which abstracts a hydrogen atom from thiophenol to afford **59**. The synthesis of (-)-cispentacin (**60**) is then completed in 5 subsequent steps.



Scheme 19

1.1.7.3 - Silanes

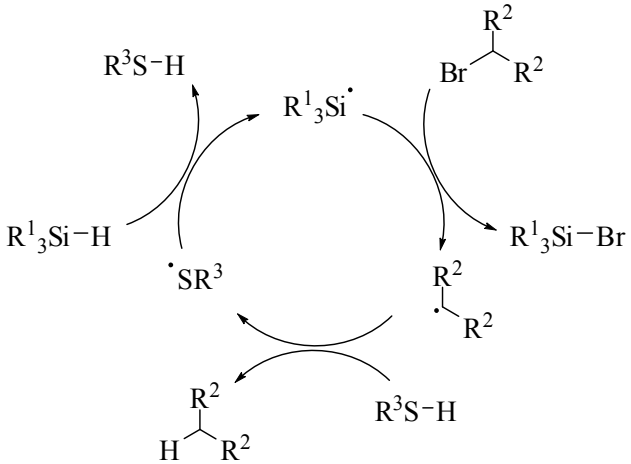
Silanes are the most widely studied alternatives to tin hydrides, principally because they are easily prepared, non-toxic and silicon-centred radicals react rapidly with a range of functional groups, including alkyl halides and double bonds.[84, 101] However, in a hydrosilylation reaction using a trialkylsilane, the intermediate β-silylalkyl radical usually reacts relatively slowly with R_3SiH and so the yields of hydrosilylated products can be low. This is because simple triorganosilanes like triethylsilane possess a relatively strong Si–H bond (398 kJ mol^{-1} for Et_3SiH) and so they are poor hydrogen atom donors.[102]

However, Roberts[103] showed that, in conjunction with a thiol catalyst, alkyl or aryl-silanes can serve as replacements for tin hydrides for the reduction of alkyl halides and related compounds, including double and triple bonds. In the absence of a thiol catalyst, the abstraction of the electron-rich hydrogen atom bonded to silicon, by a nucleophilic alkyl radical (step 1), is slow because of polar effects, and is usually too slow to maintain the chain. In the presence of a thiol, the slow direct hydrogen-transfer step is replaced by two faster steps (2 and 3) that benefit from favourable polar effects (**Scheme 20**).

$$R^{\bullet} + R'_3SiH \rightarrow RH + R'_3Si^{\bullet} \quad (1)$$

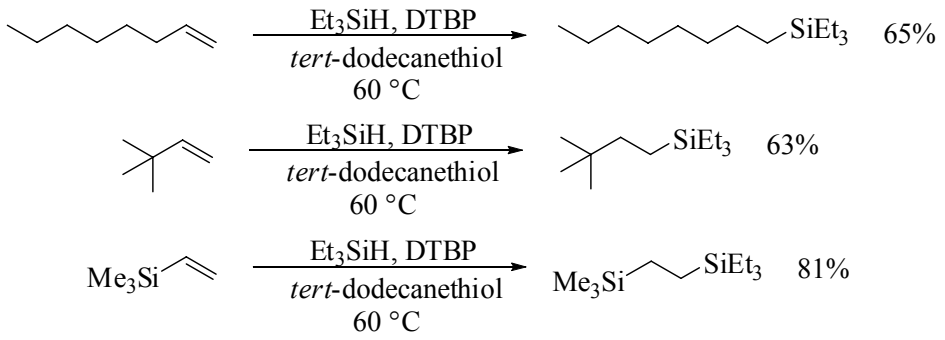
$$R^{\bullet} + R''SH \rightarrow RH + R''S^{\bullet} \quad (2)$$

$$R''S^{\bullet} + R'_3SiH \rightarrow R''SH + R'_3Si^{\bullet} \quad (3)$$



Scheme 20

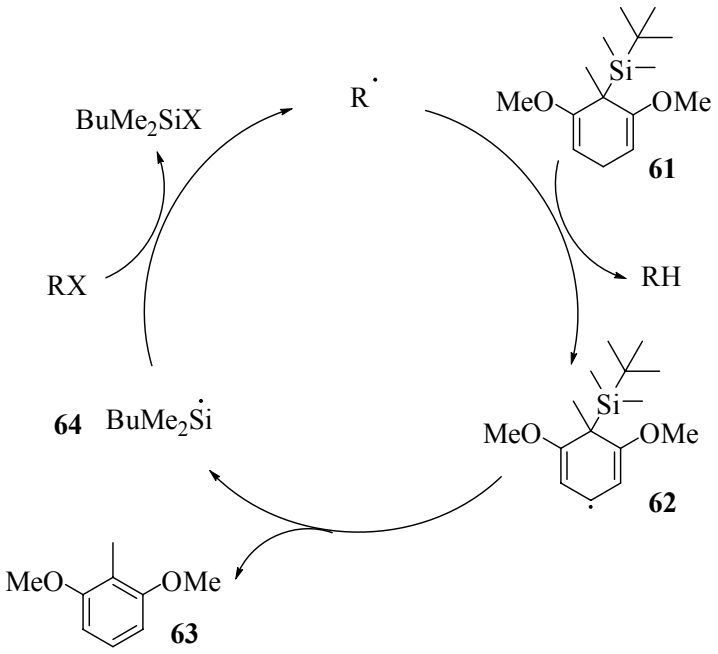
This method has also been applied to the hydrosilylation of various simple alkenes with a range of silanes.[104] For Et_3SiH, it was found that the highest yields were obtained when using Et_3SiH as the solvent and the reaction initiated by di-*tert*-butyl peroxide (DTBP) (**Scheme 21**).



Scheme 21

1.1.7.4 - Silylated cyclohexadienes

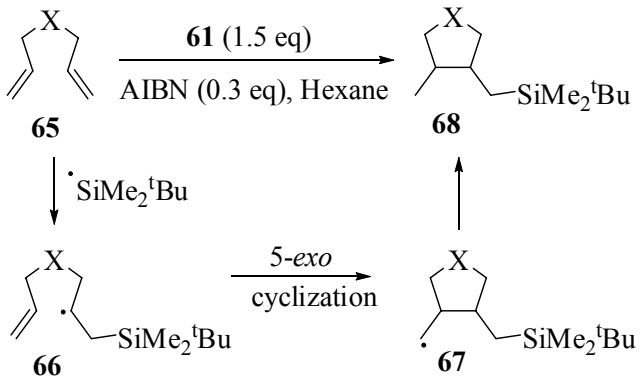
It is known that cyclohexadienes can act as hydrogen atom donors in alkyl radical reductions.[105, 106] However, the intermediate cyclohexadienyl radical cannot abstract a halogen atom, and so 1,4-cyclohexadienes cannot reduce alkyl halides. However, Studer has introduced silylated cyclohexadienes[107-109] that can mediate radical dehalogenations, deselenations, deoxygenations, and intermolecular additions.[110] Abstraction of a hydrogen atom from the silylated cyclohexadiene **61** affords a cyclohexadienyl radical **62**, which aromatises to afford the dimethoxytoluene **63** with expulsion of the silyl radical **64**, that propagates the chain by reaction with the starting organohalide (**Scheme 22**).



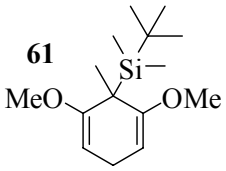
Scheme 22

Alternatively, if the silyl radical (formed in the aromatisation step) is allowed to react with an alkene the corresponding hydrosilylation product is formed. This hydrosilylation could be regarded as a transfer-hydrosilylation. This work has been applied to the cyclisation of

1,6-dienes **65**, affording cyclised products **68** in up to 80% yield as a mixture of diastereoisomers, **Scheme 23**.[111] The initially formed silyl radical adds to a C=C bond of the diene to form a β-silylalkyl radical **66** which undergoes a 5-*exo*-cyclization to give primary radical **67** that is reduced by the silylated cyclohexadiene. The formation of the *cis*-isomer as the major isomer is in accordance with the Beckwith-Houk model for 5-*exo*-cyclisations.[28, 112, 113]

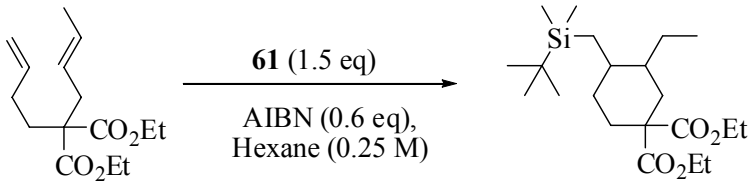


X	Yield (%)	*cis/trans*
$C(CO_2Et)_2$	80	43:10
O	71	25:10
N-Ts	76	20:10
$C(CH_2OH)_2$	62	23:10



Scheme 23

It has been shown that silylated cyclohexadiene **61** reduces primary carbon-centred radicals about 55 times slower than Bu_3SnH does.[107] This allows the study of slower radical chain reactions. For instance, on hydrosilylation/cyclisation of 1,7-diene **69**, the product **70** was isolated in 61% yield as a 1:1 mixture of diastereoisomers, **Scheme 24**. The silyl radical addition occurs highly regioselectively at the less-hindered terminal double bond and this is followed by a 6-*exo*-cyclisation. The product of mono-hydrosilylation, without cyclisation, was not observed.



70 - 61%, dr 1:1

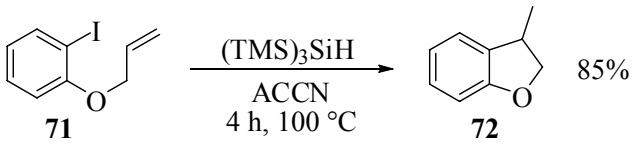
Scheme 24

1.1.7.5 - Tris(trimethylsilyl)silane

The most successful and widely used replacement for tributyltin hydride is tris(trimethylsilyl)silane (TTMSS).[102, 114-116] TTMSS is non-toxic and the silicon byproducts from organohalide reductions are generally easier to separate from organic products. An added benefit is the slightly stronger Si–H bond (about 20 kJ mol^{-1} stronger

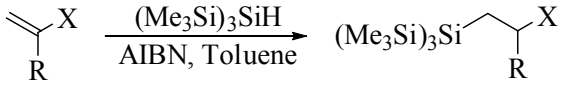
than the Sn–H bond in tributyltin hydride) produces fewer by-products of direct reduction, allowing radical additions to be accomplished with a stoichiometric amount of the silane in the reaction mixture, removing the need for syringe pumping and high-dilution techniques usually required for tin hydrides.

Recently, Chatgilialoglu and coworkers have shown that $(Me_3Si)_3SiH$ can mediate the reduction of iodides and bromides, hydrosilylate alkenes and carbonyls, in aqueous media using ACCN as the initiator at 100 °C. An amphiphilic thiol ($HOCH_2CH_2SH$) was needed for the reaction of water-soluble compounds[117] and the reaction could be applied to the radical cyclisation of 1-allyloxy-2-iodobenzene (**71**) to furnish furan **72** (**Scheme 25**).



Scheme 25

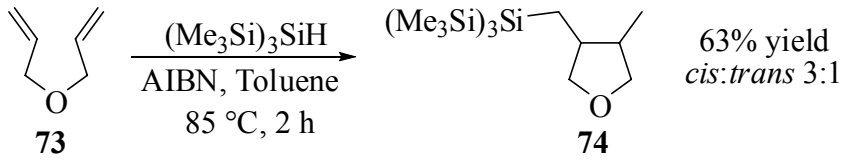
Like other silicon-centred radicals, the $(Me_3Si)_3Si$• radical can add rapidly to multiple bonds and it has been used successfully in hydrosilylation reactions, with both electron rich and poor alkenes (**Scheme 26 and Table 1**).[118, 119] Reaction of a range of alkenes has been carried out by using a slight excess of tris(trimethylsilyl)silane in toluene at 80-90 °C in the presence of AIBN to give the corresponding hydrosilylation products in good to excellent yield. A slight excess of tris(trimethylsilyl)silane (1.2 equiv) was sufficient to avoid polymerisation of the alkenes.



X	R	Yield %	X	R	Yield %
$(CH_2)_7CH_3$	H	81	OAc	H	80
Ph	H	74	SPh	H	78
CN	H	85	Ph	Me	79
CO_2Me	H	79	CO_2Me	Me	77

Scheme 26 and Table 1

Cyclisation of dienes, including diallyl ether **73**, has also been accomplished (**Scheme 27**). The alkyl radical formed after the addition of the silyl radical to a C=C bond, cyclises to give the tetrahydrofuran derivative **74** in 63% yield (as a mixture of *cis*:*trans* isomers in the ratio 3:1).



73 **74**

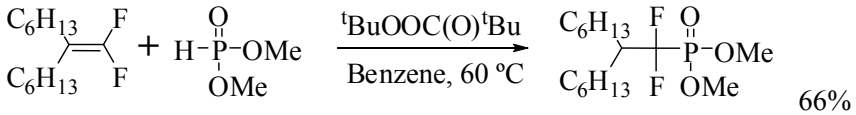
Scheme 27

However, there are several disadvantages with using TTMSS, including the cost (it is approximately 5 times more expensive than Bu_3SnH) and it is prone to aerial oxidation. Also, before the hydrosilylation method can become of general synthetic use, methods need to be developed for the transformation of the $(Me_3Si)_3Si$ group into useful functionality (see Chapter 3).

1.1.7.6 - Organophosphorus hydrides

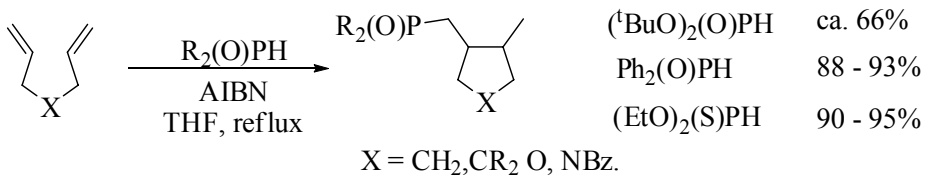
Relatively weak P–H bonds are found in a variety of organophosphorus compounds[106] including dialkylphosphines and phosphites [$(RO)_2P(O)H$], which are easily handled, non-toxic, commercially available, and cheaper than many of the group 14 hydrides. Phosphorus centred radicals are formed from hydrides under mild conditions with commercially available initiators, many commercially available organophosphorus compounds are easy to derivatise,[120] and a number of chiral and fluorous examples have been reported in the literature.[121]

Phosphorus-centred radicals are known to add to alkenes. For example, Piettre[122] has shown that addition of dimethyl phosphite to fluoro-alkenes is an excellent route to 2,2-disubstituted-1,1-difluorophosphonates (**Scheme 28**).



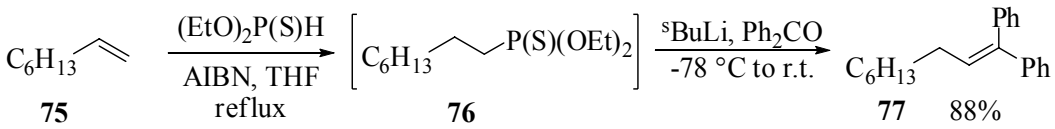
Scheme 28

Phosphites, thiophosphites and phosphine oxides have all been shown to add regioselectively to a range of alkenes, including 1,6-dienes resulting in 5-*exo* cyclisations to yield 5-membered rings (**Scheme 29**).[123,124]



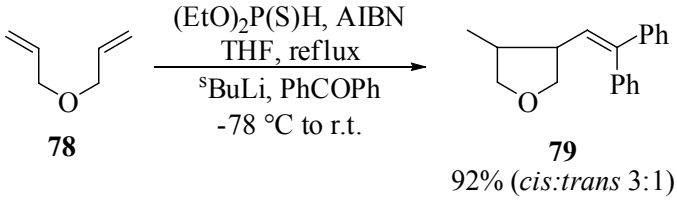
Scheme 29

The resulting phosphonates or phosphonothioates can undergo Horner-Wadsworth-Emmons-type (HWE) reactions to form alkenes. It is even possible to combine the radical addition and HWE reactions in a one-pot reaction (**Scheme 30**). For example, heating oct-1-ene (**75**) with diethyl thiophosphite and AIBN forms phosphonothioate **76**, which is immediately reacted with ^{s}BuLi and benzophenone to give 1,1-diphenylnon-1-ene (**77**) in an 88% yield.[121, 125, 126]



Scheme 30

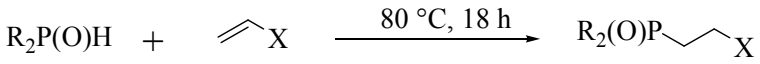
Combined stereoselective radical cyclisations and intermolecular HWE reactions are also possible as are consecutive radical addition/alkylation/HWE reactions.[121, 125, 126] Such as the addition of diethyl thiophosphite to allyl ether (**78**) and a subsequent HWE reaction to afford the alkene **79** (**Scheme 31**).



Scheme 31

Typically, the addition of a phosphine oxide or a phosphinate to an alkene requires a radical initiator such as benzoyl peroxide, AIBN, or more recently, the use of microwaves. However, Han has reported that a small amount of air/oxygen can initiate the addition of secondary phosphine oxides and H-phosphinates to alkenes.[127] Under a pure nitrogen atmosphere (less than 1 ppm of oxygen), diphenylphosphine oxide and 1-decene did not react at 80 °C after 18 h, but when a trace amount of air was introduced an 85% yield of the addition product was isolated. The addition also proceeded in air, although the yield of

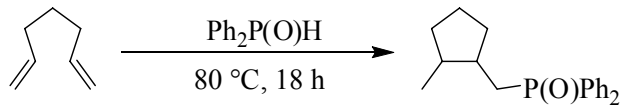
product was only 28%. This method was found to be applicable to both secondary phosphine oxides and phosphinates (but not phosphonates), and to a wide range of alkenes (**Scheme 32**).



R_2P = $^nBu_2P$, Ph(^{t}Bu)P, Ph_2P, Ph(OEt)P
X = $(CH_2)_4OH$, $(CH_2)_4CN$, $(CH_2)_4CO_2Et$, $SiEt_3$, O^{n}Bu, S(O)Ph, $P(O)Ph_2$,
44 - 98%, mostly 80 - 90%

Scheme 32

Additionally, it is possible to perform a radical cyclisation of 1,6-heptadiene (**80**), to yield the corresponding phosphonate **81**, although in moderate yields (**Scheme 33**).

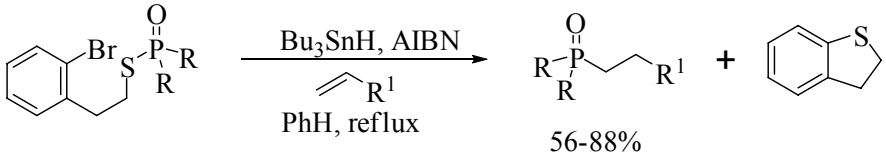


80 **81**

air/nitrogen: 38%, d.r. 2.9/1
10 mol% AIBN: 52%, d.r. 2.7/1

Scheme 33

The groups of Fensterbank, Lacote and Malacria have reported the homolytic cleavage of P-S bonds to generate phosphorus-centered radicals, which can add to alkenes, thereby allowing the synthesis of phosphonates (**Scheme 34**). The key step is a homolytic substitution on a sulfur atom and the dihydrobenzothiophene by-product could be easily separated from the desired products.[128-134]

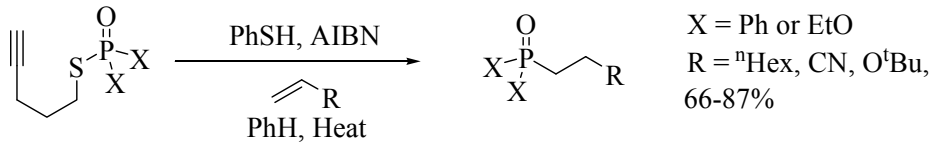


56-88%

R = Ph or EtO, R^1 = ^{n}Hex, CN or O^{t}Bu,

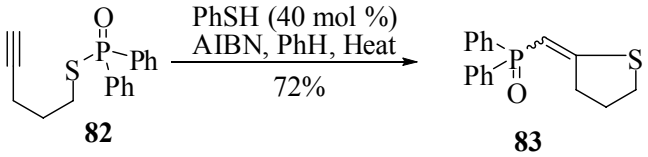
Scheme 34

Reaction of a thiol with an alkyne, in the absence of tributyltin hydride, resulted in an efficient radical substitution following initial addition of the thiyl radical to the triple bond (**Scheme 35**).[128] This new cascade sequence delivered good yields of phosphorus-containing products.



Scheme 35

Finally, phosphinoyl radicals have been shown to add to triple bonds as illustrated by the formal cycloisomerisation of the thiophosphine oxide **82** to afford the thiophene **83** shown in **Scheme 36**.



82 **83**

Scheme 36

1.2 Alkaloids

Alkaloid is the general name of all natural products containing a free, basic nitrogen atom. Alkaloids are produced as secondary metabolites by a large number of organisms, including bacteria, fungi, animals and plants. Alkaloids are typically divided into three subgroups; true alkaloids, proto alkaloids and pseudo alkaloids. True alkaloids are derived biosynthetically from amino acids and the nitrogen is part of a heterocyclic ring (e.g. nicotine). Proto alkaloids are derived biosynthetically from amino acids, however the nitrogen is outside of a ring system (e.g. amphetamines). Pseudo alkaloids are not directly derived biosynthetically from amino acids, but instead purines, (e.g. caffeine).[135] Alkaloids can be further classified based on two different systems;

- either based on their chemical structure, i.e. their core framework, such as pyrrolidines, pyridines, tropanes, pyrrolizidines, isoquinolines, indoles, quinolines, terpenoids and steroids; or
- By the biological origin, such as the opium alkaloids from the opium poppy (*Papaver somniferum*) or the ergot alkaloids from the ergot fungus (*Claviceps*).

Many alkaloids have pharmacological effects, ledding to their uses as medications and recreational drugs, such as those shown below (**Figure 3**).

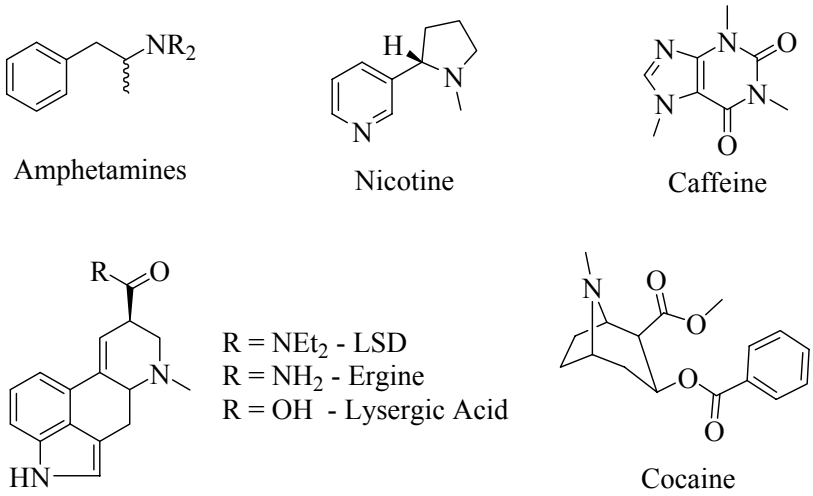
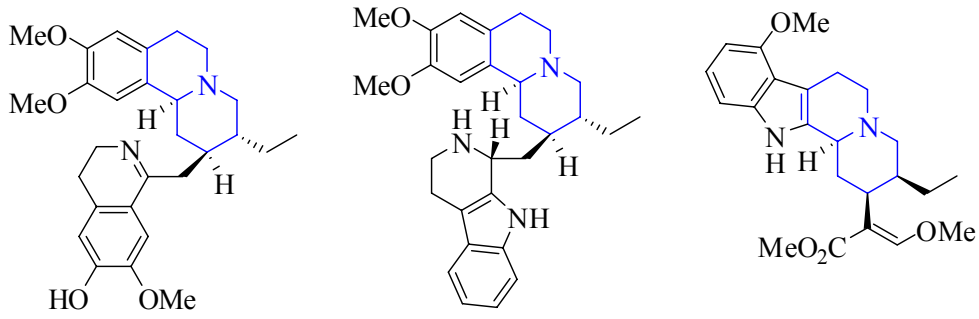


Figure 3

1.2.1 –Overview of *Alangium* and *Mitragyna* alkaloids

The *Alangium* family of alkaloids have attracted interest due to their use as folk remedies for numerous ailments (including dystentery) and a number of benzo[a]quinolizidine alkaloids, exhibit potent biological activities.[136] For example, psychotrine (**84**) (**Figure 4**),

isolated from the root of the Ipecacuanha plant, is a potent inhibitor of HIV-1 reverse transcriptase,[137, 138] and deoxytubulosine (**85**) has cytotoxic properties. Mitragynine (**86**) is isolated from the plant *Mitragyna speciosa*, which is traditionally used in tropical areas as a stimulant like coca or as a substitute for opium. The unique properties of this medicinal plant have attracted considerable interest. Recently, mitragynine (**86**) has been found to exhibit potent analgesic activity principally against μ-opioid receptors.[139-141]



Psychotrine
84
Potent inhibitor of HIV-1 reverse transcriptase

Deoxytubulosine
85
cytotoxic properties and is an inhibitor of thymidylate synthase

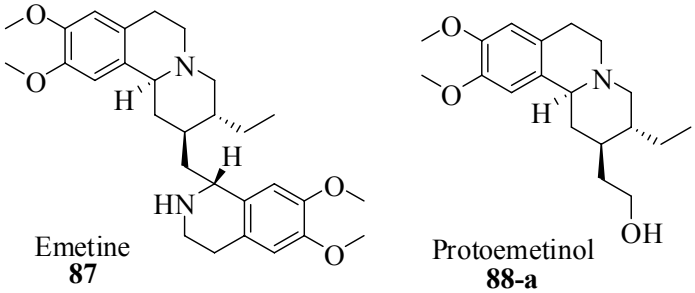
Mitragynine
86
exhibit potent analgesic activity, principally against opioid receptors.

Figure 4 (original in colour)

1.2.2 - *Alangium* alkaloids

1.2.2.1 - Synthesis of *Alangium* alkaloids and related compounds

Battersby,[142-146] Fujii[147,148] and Brossi[149] from the 1960s to 70s published around 50 papers based on synthetic methods to the *Alangium* family of alkaloids including psychotrine (**84**), deoxytubulosine (**85**), emetine (**87**) and other related compounds (**Figures 4** and **5**). These racemic routes are long-winded, in excess of 10 steps. There are a few recent papers on the synthesis of *Alangium* alkaloids including psychotrine (**84**), deoxytubulosine (**85**) and emetine (**87**). The following are some recent examples that show methods for the synthesis of the tricyclic core of these types of alkaloids, often proceeding via protoemetinol (**88**) (**Figure 5**).[144]



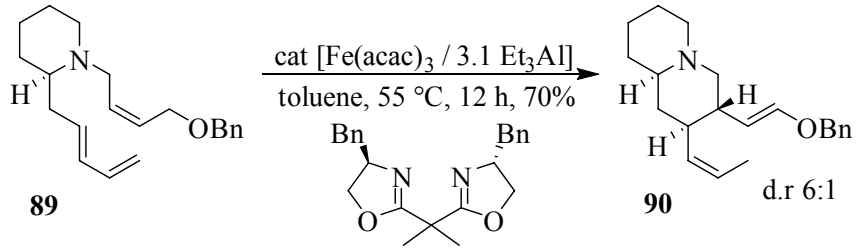
Emetine
87

Protoemetinol
88-a

Figure 5

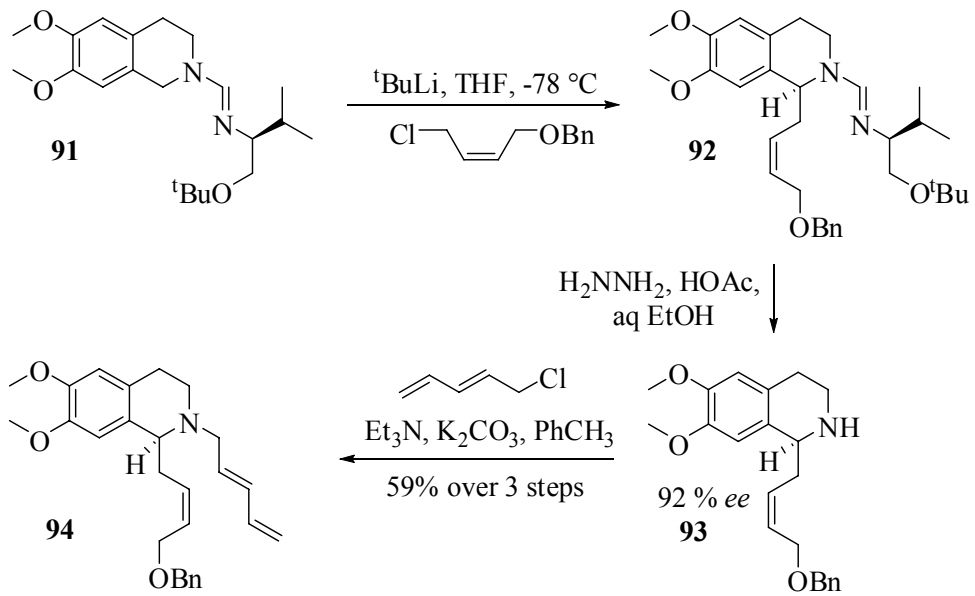
1.2.2.2 - Iron catalysed cyclisation

Takacs and coworkers have developed novel cyclisation methods using catalytic metal-mediated reactions, including iron catalysts, which are attractive due to their low toxicity and availability. An example of a catalytic iron-mediated reaction is the cyclisation of enediene **89** to afford the substituted quinolizidine **90** in 70% yield, as a 6:1 mixture of diastereomers (**Scheme 37**).[150]



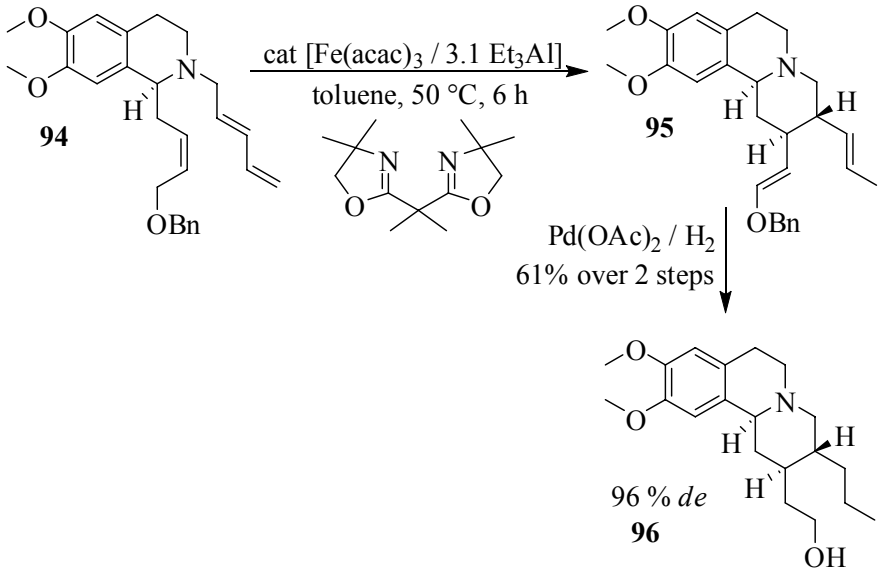
Scheme 37

It was envisioned that this methodology could be applied to the synthesis of the tricyclic core of the *Alangium* alkaloids (**Schemes 38** and **39**). The synthesis began following previous work by Meyers who devised an efficient route for the diastereoselective alkylation of chiral tetrahydroisoquinolines bearing a formamidine auxiliary.[151,152] Deprotonation of tetrahydroisoquinoline **91** and subsequent alkylation with (*Z*)-1-chloro-4-benzyloxy-2-butene affords the desired substituted tetrahydroisoquinoline **92**. Without purification, the chiral auxiliary was then removed to yield the free tetrahydroisoquinoline **93**. To complete the enediene synthesis, the free tetrahydroisoquinoline **93** was *N*-alkylated with (*E*)-pentadienyl chloride to afford enediene **94** in 59% yield over 3 steps.



Scheme 38

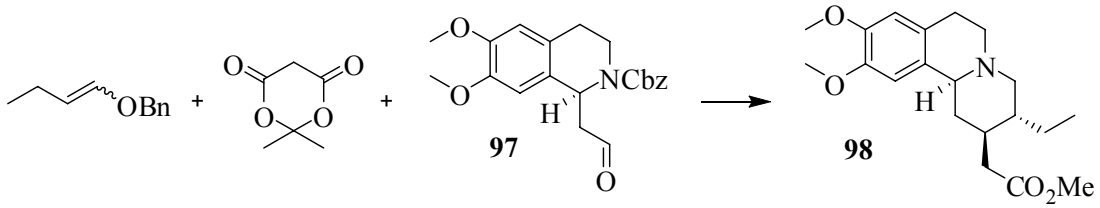
Treatment of enediene **94** with a bisoxazoline-modified iron catalyst afforded the desired tricycle **95**, although purification was problematic due to the labile enol ether (**Scheme 39**). Analysis of the vicinal coupling constants from the ^{1}H NMR spectrum established the stereochemistry as depicted. All that remained was reduction of the two double bonds followed by reductive cleavage of the benzyl ether moiety. The one-pot palladium-catalysed reduction and debenzylation of crude tricycle **95** was efficient and afforded the corresponding alcohol **96** in 61% yield over the two steps.



Scheme 39

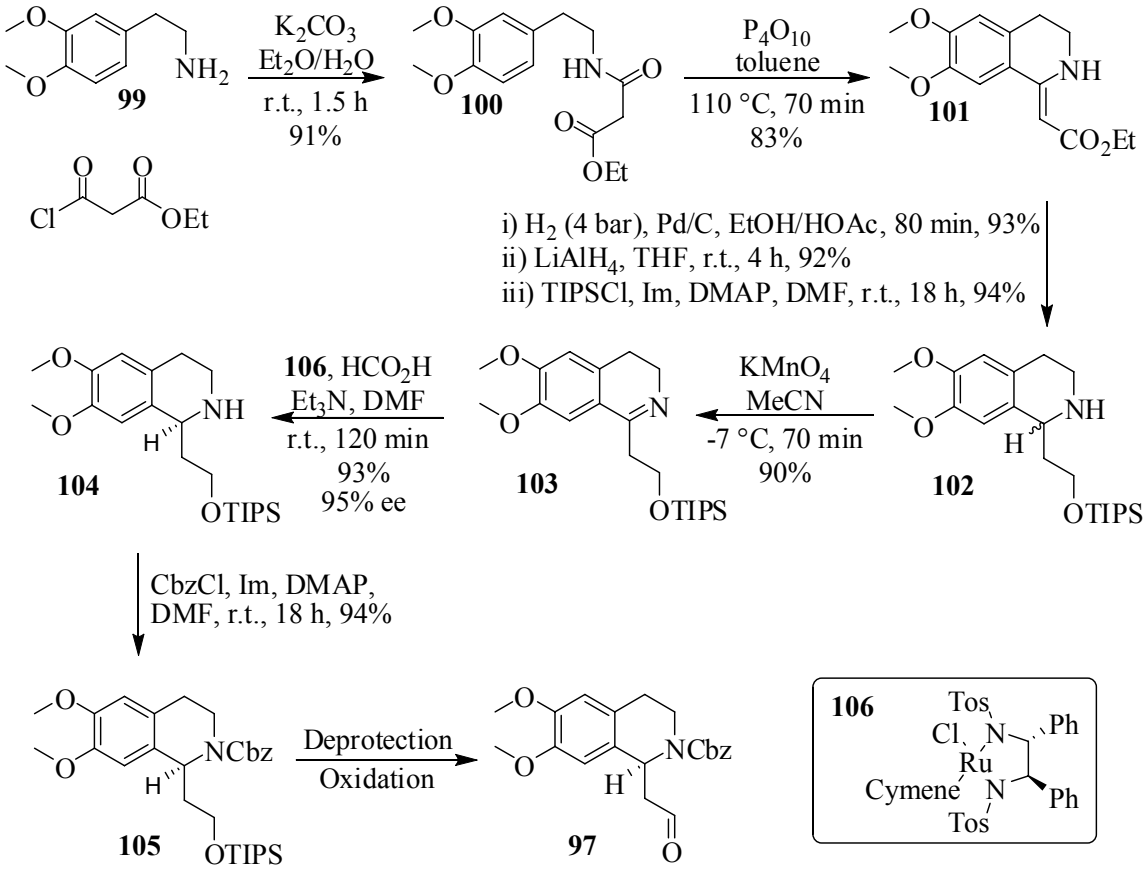
1.2.2.3 A domino hetero-Diels-Alder reaction

In 2004 Tietze reported the synthesis of *Alangium* alkaloids employing an enantioselective catalytic transfer hydrogenation of an imine, followed by a domino Knoevenagel/hetero-Diels-Alder reaction in the key cyclisation step.[153] This resulted in the synthesis of a common intermediate **98**, which could be elaborated to either emetine (**87**) or deoxytubulosine (**85**) (**Scheme 40**).



Scheme 40

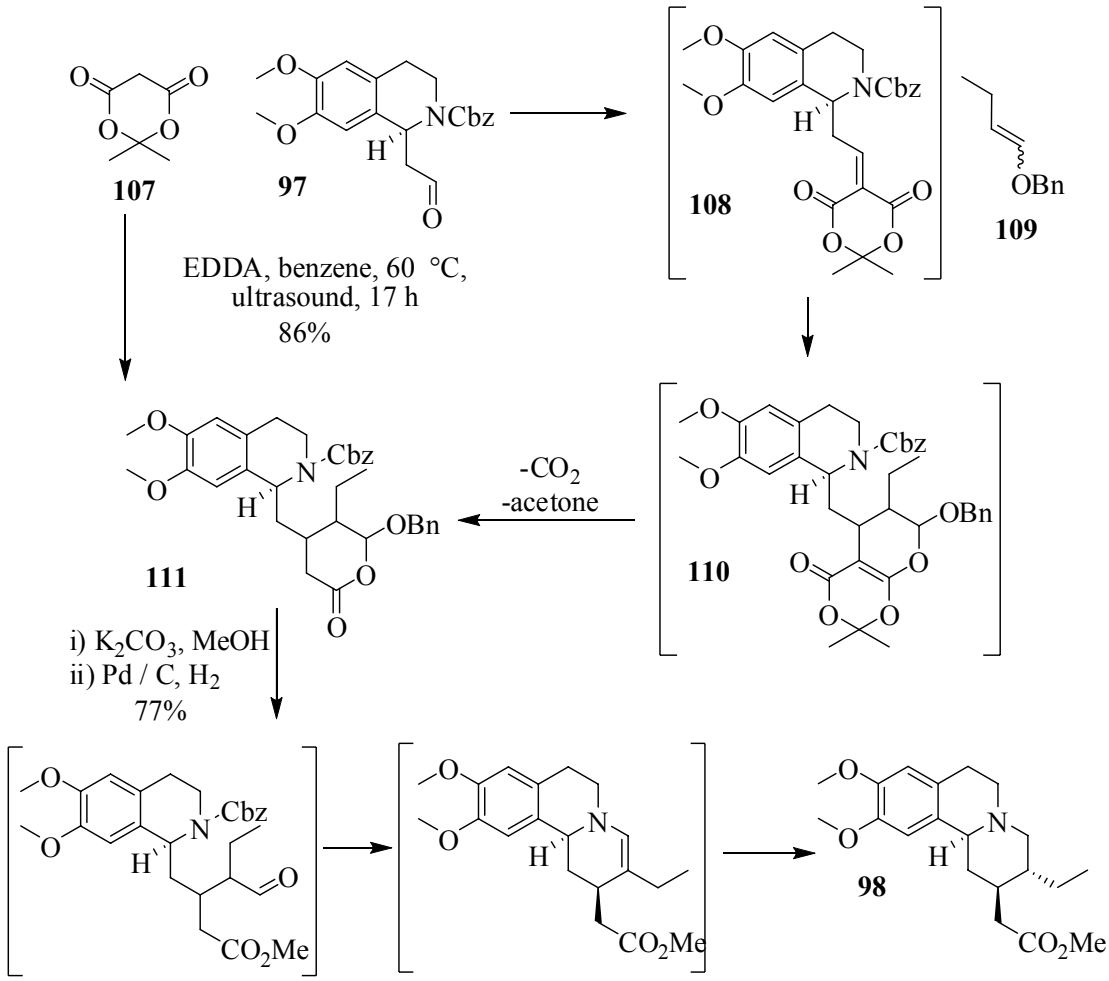
The enantiopure NCbz protected tetrahydroisoquinoline **97** was prepared by initial synthesis of the racemic OTIPS tetrahydroisoquinoline **102** (**Scheme 41**). This was accomplished by reaction of 2-(3,4-dimethoxyphenyl)ethanamine (**99**) with ethyl 2-(chlorocarbonyl)acetate to afford ethyl 2-(3,4-dimethoxyphenethylcarbamoyl)acetate (**100**) and subsequent Bischler-Napieralski cyclisation affords tetrahydroisoquinoline **101**. Reduction of the α,β-unsaturated system and TIPS protection gave silyl ether **102** which was oxidised with $KMnO_4$ to give the imine **103** in 55% yield over 6 steps from 2-(3,4-dimethoxyphenyl)ethanamine (**99**). Transfer hydrogenation with triethylammonium formate in the presence of a chiral ruthenium catalyst **106** afforded the tetrahydroisoquinoline **104** in 93% yield with 95% ee. Cbz protection of the nitrogen followed by TIPS deprotection and oxidation of the alcohol gave the desired tetrahydroisoquinoline-aldehyde **97**.



Scheme 41

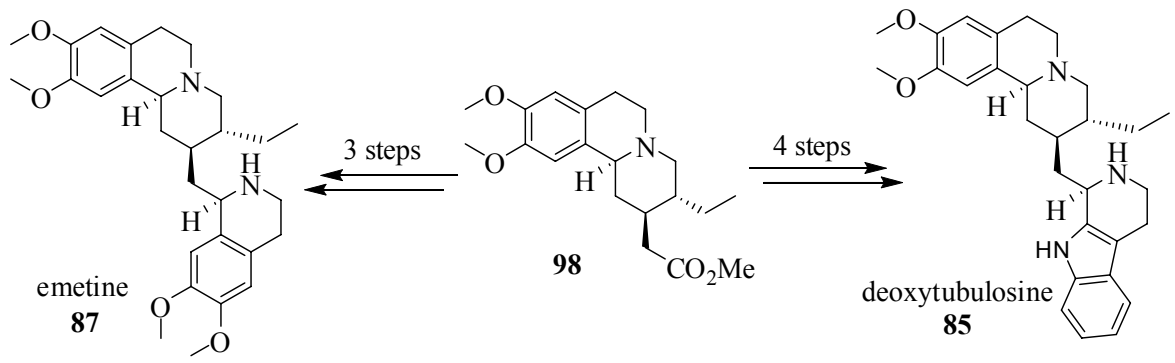
The reaction of tetrahydroisoquinoline-aldehyde **97**, Meldrum's acid (**107**) and enol ether **109** in benzene and a catalytic amount of ethylene diammonium diacetate in a sonic bath resulted in the formation of tetrahydroisoquinoline **111** (**Scheme 42).** Formation of the tetrahydroisoquinoline **111** proceeds via the 1-oxa-1,3-butadiene **108**, which undergoes a

hetero-Diels-Alder reaction with enol ether **109** (with inverse electron demand) to afford **110** with undergoes a subsequent loss of CO_2 and acetone. Tetrahydroisoquinoline **111** is not isolated, but treated with K_2CO_3/MeOH and a catalytic amount of Pd/C under a hydrogen atmosphere to yield the benzoquinolizidine **98**, along with two other diastereomers.



Scheme 42

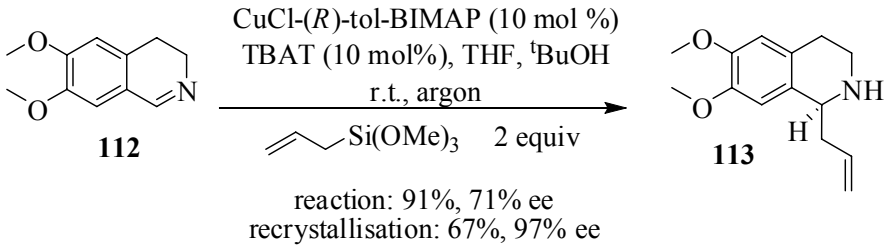
The benzoquinolizidine **98** can be converted into either emetine (**87**) or deoxytubulosine (**85**), in 3 or 4 steps, respectively, by subsequent functionalisation of the methyl ester with the appropriate substituent followed by Pictet-Spengler reactions to obtain the cyclised material and then reductions to obtain the correct oxidation levels (**Scheme 43**).



Scheme 43

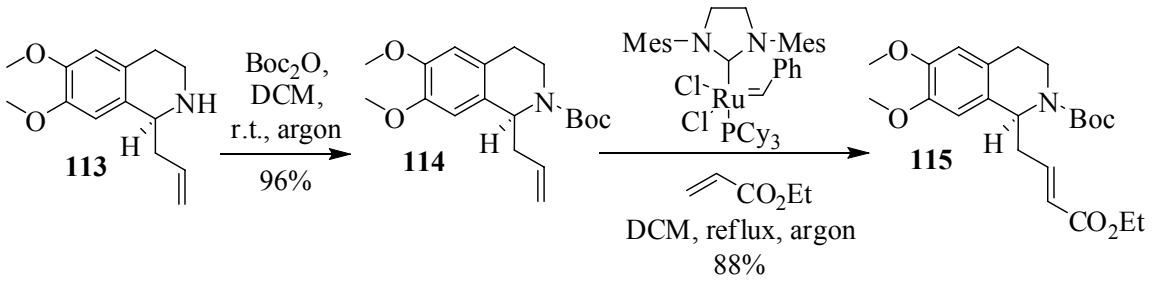
1.2.2.4 Catalytic asymmetric allylation

Recently, Itoh and workers reported the formal synthesis of (-)-emetine (**87**) (**Schemes 44-46**).[154] Their strategy built on recent work by Shibasaki and coworkers who used allyltrimethoxysilane and a catalytic amount of a Cu(I) salt for the allylation of ketones and aldehydes.[155] Itoh applied this protocol to the stereoselective allylation of 6,7-dimethoxy-3,4-dihydroisoquinoline (**112**) (**Scheme 44**). Various phosphine derivatives were investigated as chiral ligands, with tol-BINAP in THF at room temperature giving the best result. It should be noted that although the stereoselectivity is moderate, this was the first example of a catalytic allylation reaction using a cyclic imine, and recrystallisation of the (-)-dibenzoyl-L-tartaric acid salt gave an improved enantiomeric excess.



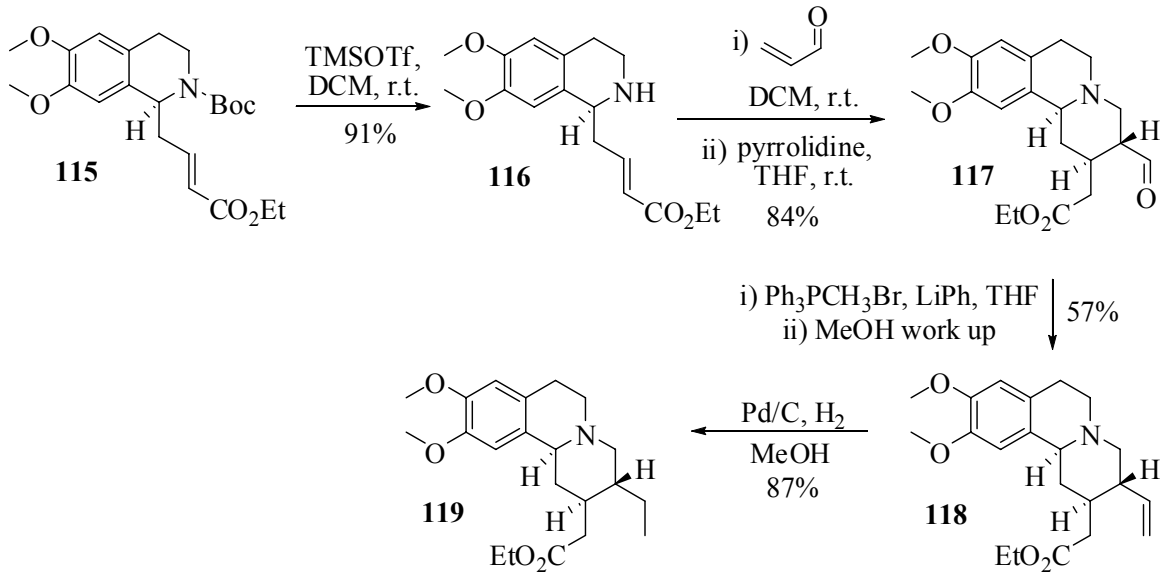
Scheme 44

In order to functionalise the allyl group in **113** it was necessary to protect the tetrahydroisoquinoline nitrogen with a Boc group to give **114**, after which a cross-metathesis reaction (using the second-generation Grubbs' catalyst) was carried out to give a high yield of the desired alkene **115** (**Scheme 45**).



Scheme 45

Deprotection of alkene **115** afforded the free amine **116**, subsequent slow addition of acrolein and treatment with pyrrolidine afforded the tricyclic formyl derivate **117** in good yield (**Scheme 46**). The formyl derivative **117** was subjected to a Wittig reaction with the ylide derived from methyltriphenylphosphonium bromide followed by treatment with methanol to give alkene **118**. Finally, a Pd/C catalysed hydrogenation gave ester **119**, which is an intermediate for the synthesis of (-)-emetine (**87**).

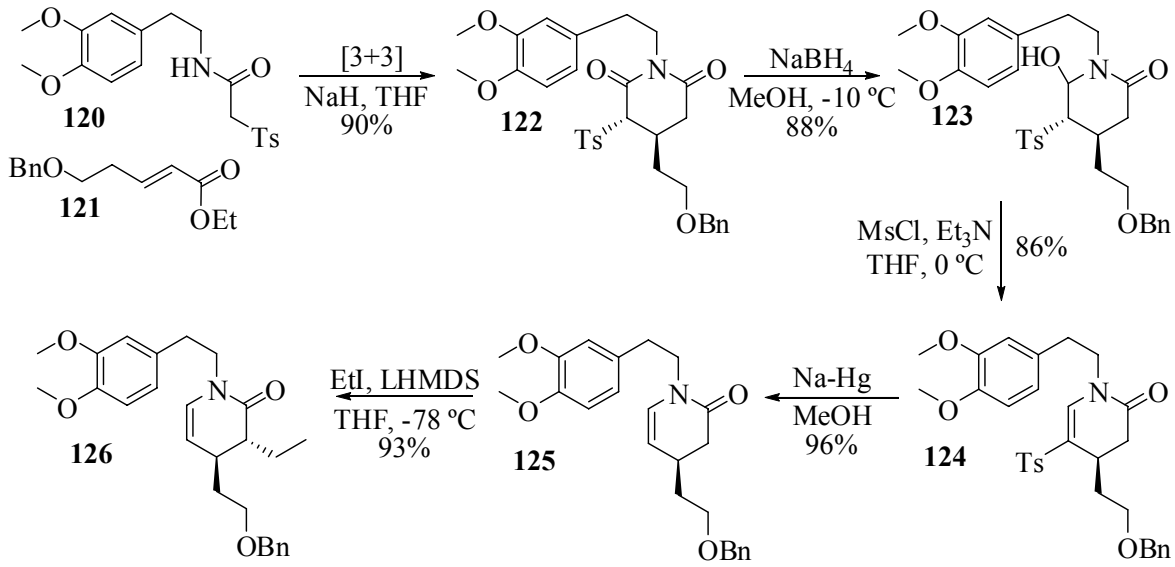


Scheme 46

1.2.2.5 - [3+3] Annulation followed by acid-catalysed cyclisation

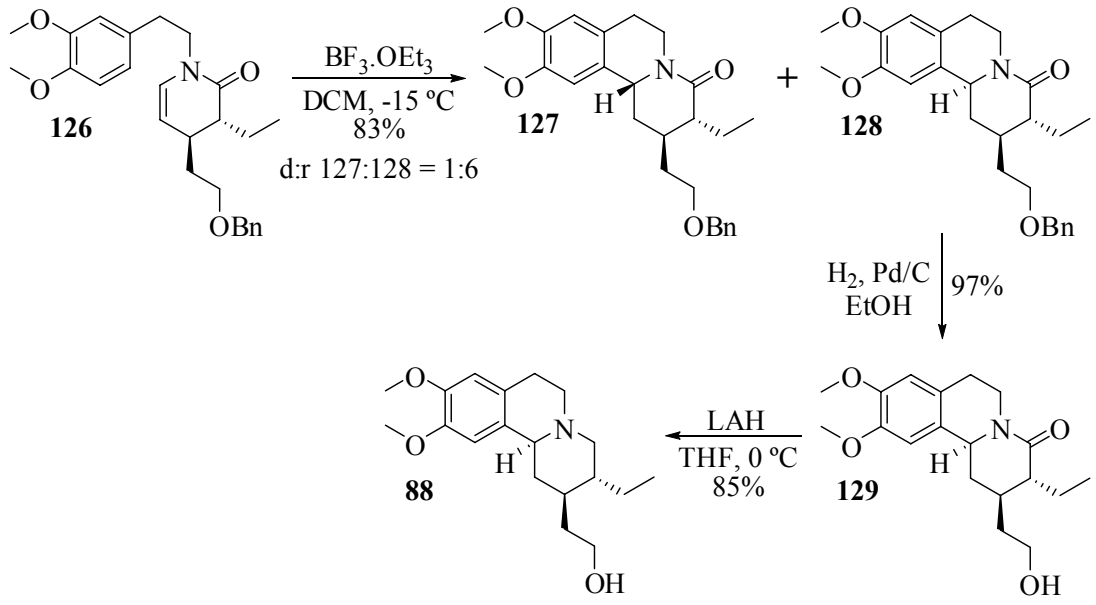
Recently the group of Chang has reported the total synthesis of (±)-protoemetinol **(88)** using an acid-catalysed intramolecular cyclisation of enlactam **126** to form the tricyclic core **127** (**Schemes 47** and **48**).[156] Their synthesis started with the [3+3] annulation of sulfonyl acetamide **120** using α,β-unsaturated ester **121** (**Scheme 47**), followed by the regioselective reduction of the carbonyl α to the sulfonyl group in **122** with sodium borohydride to afford hydroxylactam **123**. Subsequent mesylation and elimination furnished enlactam **124**, which on treatment with sodium amalgam resulted in

desulfonation to afford the corresponding enlactam **125**. Alkylation using LHMDS and iodoethane afforded **126** as a single diastereomer.



Scheme 47

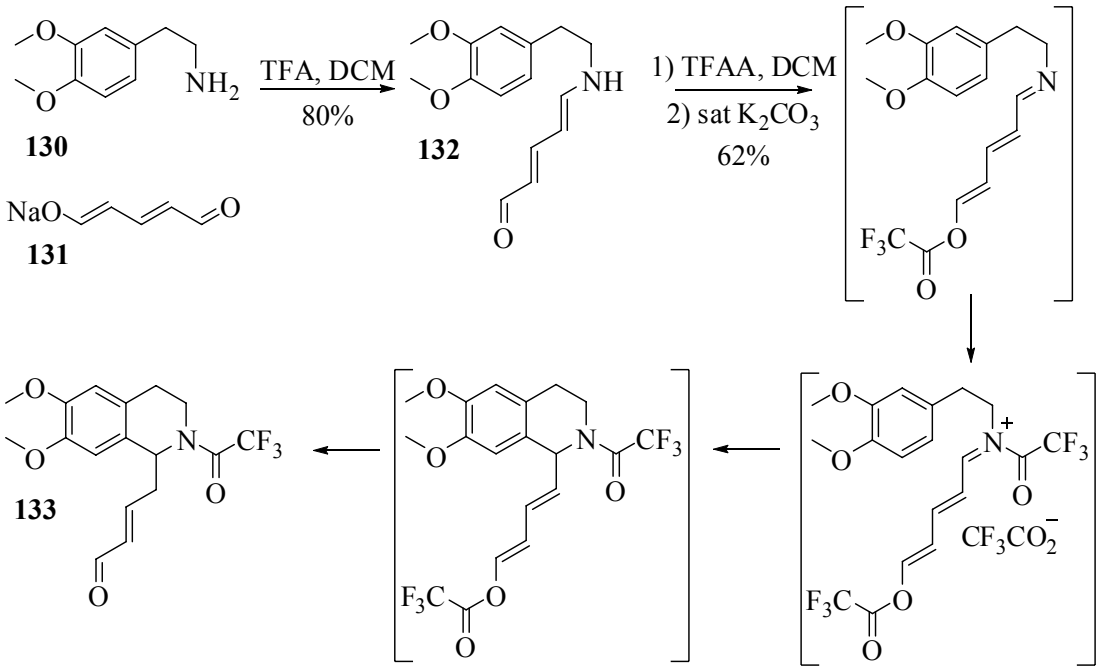
The tricyclic core of protoemetinol (**88**) was formed by the Lewis acid catalysed cyclisation of **126** using boron trifluoride diethyl etherate, which produced a 1:6 mixture of **127** and **128** in an excellent 83% yield. To complete the synthesis of (±)-protoemetinol (**88**) debenzylation was achieved by treatment of **128** with palladium on carbon and hydrogen to afford alcohol **129** and finally, reduction with lithium aluminum hydride afforded (±)-protoemetinol (**88**) (**Scheme 48**), in 8-steps in a total yield of 36% from sulfonyl acetamide **120**.



Scheme 48

1.2.2.6 - Pictet-Spengler and subsequent Strecker reaction

More recently, Delpech and coworkers have developed a route to trifluoroacetyl protected tetrahydroisoquinolines via aminopentadienals, formed from the condensation of homoveratrylamine (or tryptamine) with glutaconaldehydes when treated with trifluoroacetic anhydride,[157] proceeding via a Pictet-Spengler reaction. Subsequently, this methodology has been applied to the synthesis of protoemetinol (**88**) (and related tetrahydroisoquinolines). Their synthesis started with the formation of trifluoroacetyl protected tetrahydroisoquinoline **133** in two steps (**Scheme 49**). First, treatment of homoveratrylamine (**130**) and glutaconaldehyde sodium salt (**131**) in the presence of trifluoroacetic acid afforded aminopentadienal **132**, which on treatment with 2 equivalents of trifluoroacetic anhydride[a] and a subsequent basic hydrolysis led to the isolation of tetrahydroisoquinoline **133**.

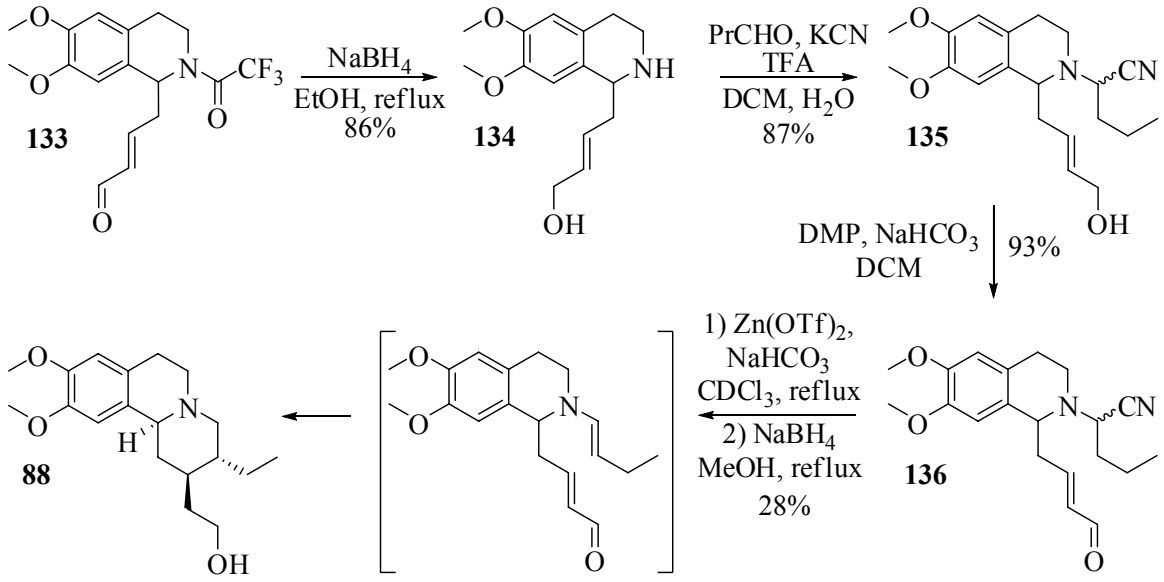


Scheme 49

To complete the synthesis of protoemetinol (**88**), reduction of the trifluoroacetyl and aldehyde groups afforded the secondary amine **134** (**Scheme 50**). A protected form of the enamine was introduced by the formation of an aminonitrile **135** via a Strecker reaction and oxidation of the allylic alcohol to the enal **136** was achieved by the use of Dess-Martin periodinane and $NaHCO_3$. Treatment of the enal **136** with 0.5 equiv of $Zn(OTf)_2$,[b] in the presence of $NaHCO_3$, led to cyclisation followed by trapping of the resulting iminium salt

[a] Treatment with one equivalent resulted in half the yield of product **133**
[b] Use of $Zn(OTf)_2$ as a Lewis acid increases the electrophilicity of the enal by coordination to oxygen

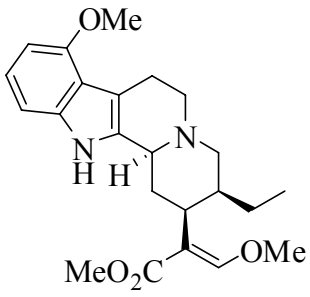
by the cyanide ion. Finally, both the aldehyde and the masked iminium groups were reduced by $NaBH_4$ to afford protoemetinol (**88**) and its C-3 epimer in a moderate 28% yield.



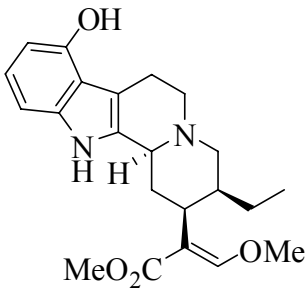
Scheme 50

1.2.3 The *Mitragyna* alkaloid mitragynine (86)

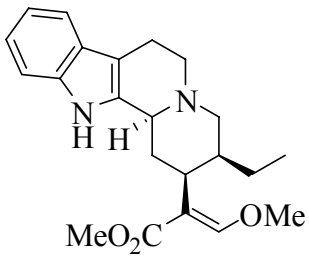
Mitragynine (**86**) was first isolated in 1907 by Hooper,[158] and then given its name following a subsequent isolation by Field.[159] However, it was not until 1965 that the structure of mitragynine (**86**) was identified by X-ray crystallography of the hydroiodide salt.[160] In small doses it has been shown to act as a stimulant, while in higher doses it has more opiate-like activity. Recent studies have shown that the methoxy group is essential for the analgesic activity.[141, 161] Mitragynine (**86**) was found to be an opioid agonist, which acts on both μ- and δ-opioid receptors, (μ-receptors are responsible for the enjoyable effects of opiates, analgesia and physical dependence). De-methyl mitragynine (**137**, also known as 9-hydroxy-corynantheidine) exhibits high affinity for μ-opioid receptors but is only a partial agonist. De-methoxy mitragynine (**138**, also know as corynantheidine) does not exhibit any opioid agonistic activity, but it reverses the morphine-inhibited twitch contraction,[141] and so is classified as an opioid receptor antagonist.



Mitragynine
86



De-methyl mitragynine
or 9-hydroxy-corynantheidine
137



De-methoxy mitragynine
or Corynantheidine
138

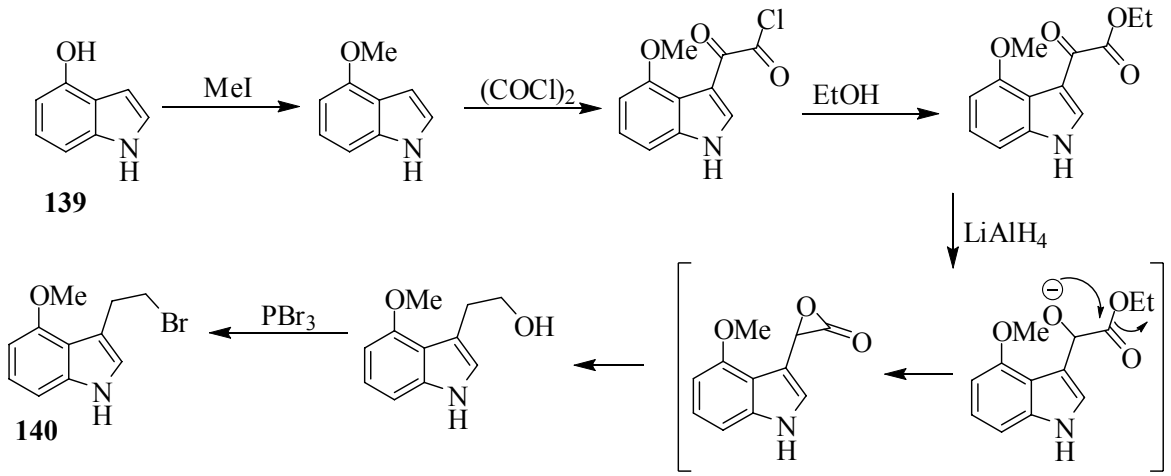
Figure 6

1.2.3.1 - Synthesis of mitragynine (86) and related compounds

To-date there are two reported total syntheses of mitragynine (**86**) and a few syntheses of related de-methoxy compounds. This is a result of the lack of availability of 4-methoxytryptophan required for the synthesis of the indole core. Currently, 4-methoxytryptophan can only be obtained in high optical purity by the use of immobilized penicillin G acylase, in a kinetic resolution.[162, 163]

1.2.3.2 - First total synthesis of mitragynine (86)

Takayama reported the first total synthesis of mitragynine (**86**) in 1995[164] using 4-methoxytryptophyl bromide (**140**) and a chiral pyridine alcohol **141** as key starting materials (**Schemes 51 - 54**). The optically pure pyridine alcohol **141** was isolated using an enzymatic process, while the 4-methoxytryptophyl bromide (**140**) fragment was prepared from 4-hydroxyindole **139** via a five-step operation. This involved *O*-methylation followed by reaction with oxalyl chloride, ethanolysis, reduction with $LiAlH_4$ and finally, bromination (**Scheme 51**).

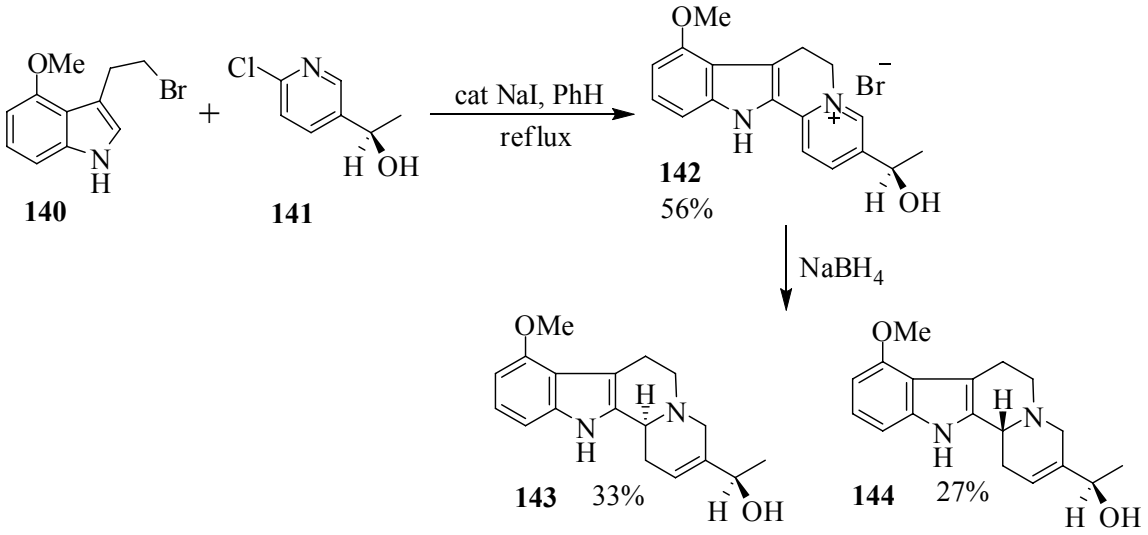


139

140

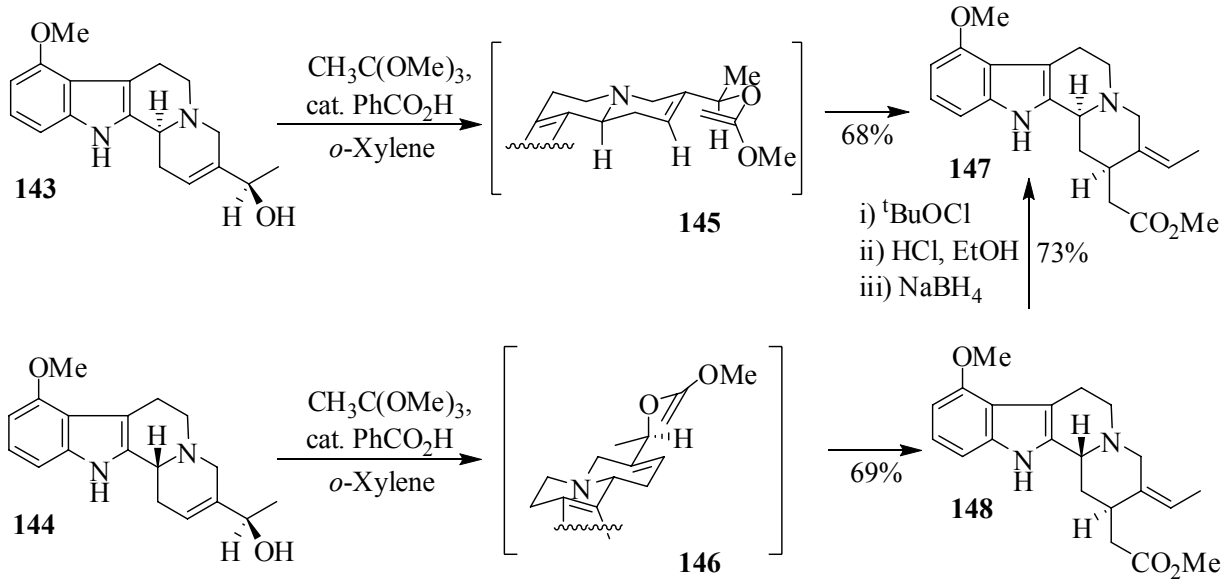
Scheme 51

The 4-methoxytryptophyl bromide (**140**) and the pyridine alcohol **141** were condensed in refluxing benzene in the presence of a catalytic amount of sodium iodide to give pyridinium salt **142**, which was reduced with sodium borohydride to yield the two alcohols, **143** and **144**, in 33% and 27% yield, respectively (**Scheme 52**).



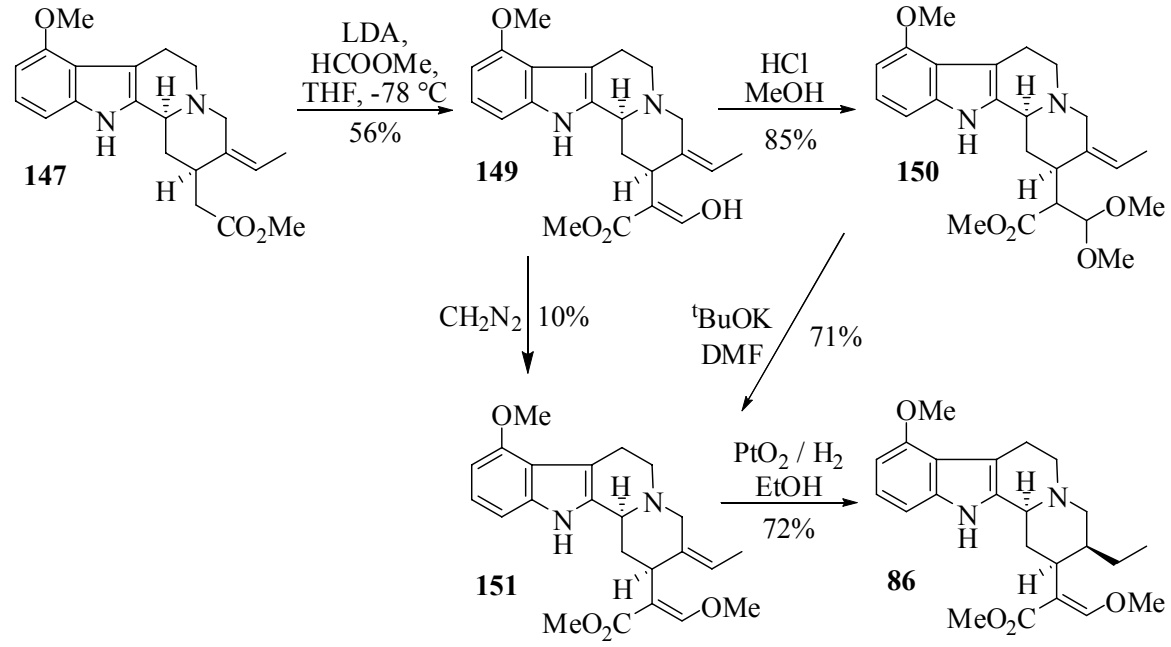
Scheme 52

Although two isomers were formed in the reduction, it was anticipated that the chiral centre from the starting pyridine alcohol **141** would control the stereochemistry in a subsequent Claisen rearrangement (expected to proceed via chair-like transition states **145** and **146**) (**Scheme 53**). To this end, the allylic alcohols **143** and **144** were subjected to a Claisen rearrangement, by heating with trimethyl orthoacetate in the presence of a catalytic amount of benzoic acid in *o*-xylene. Isomer **148**, with the wrong configuration at position C-2, could be transformed into the desired isomer **147** by an oxidation/reduction sequence via the 3,4-dehydroiminium salt.



Scheme 53

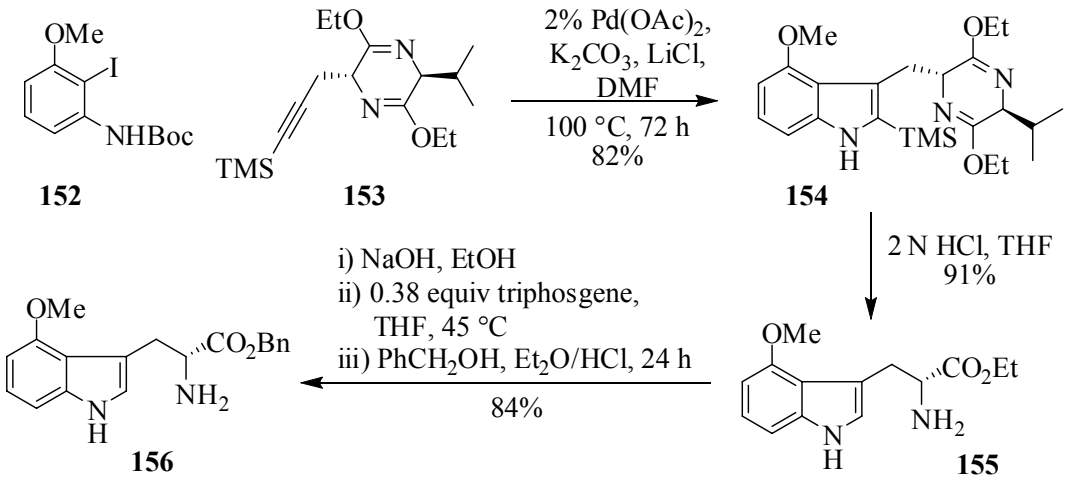
Introduction of the formyl group was then achieved using LDA and HCOOMe to afford **149** (**Scheme 54**). Subsequent attempts at *O*-methylation of the enol system in **149** using diazomethane were inefficient. So, the formyl group was converted into a dimethyl acetal **150**, which was treated with KO^tBu to give the desired methyl enol ether **151**. Finally, the C=C bond of the alkene was reduced using PtO_2 under a hydrogen atmosphere to afford mitragynine (**86**).



Scheme 54

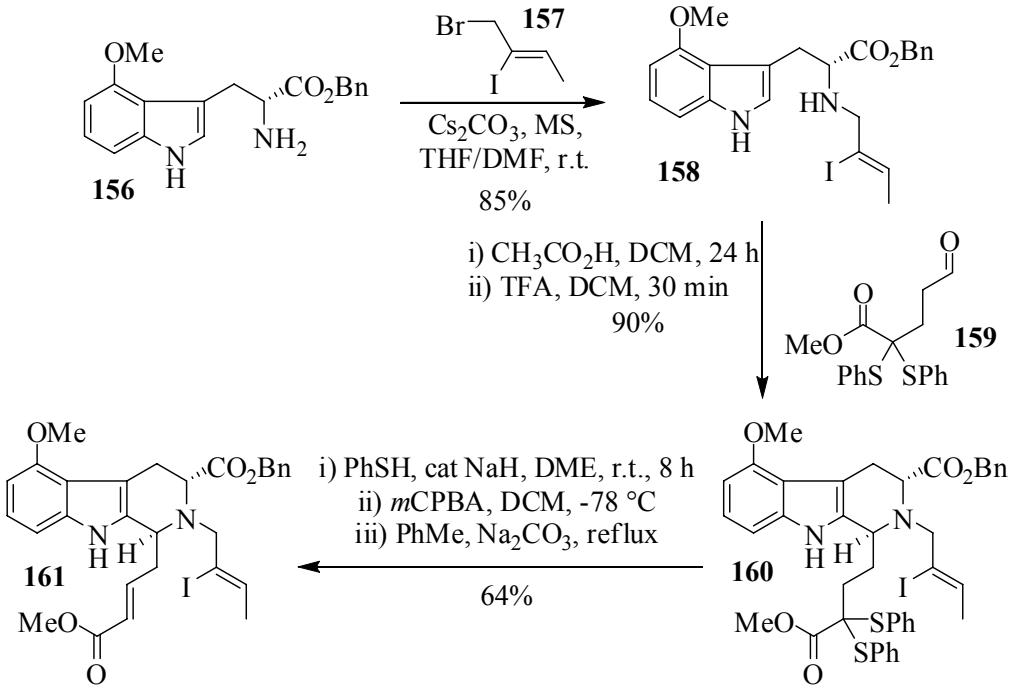
1.2.3.3 - Second total synthesis of mitragynine (86)

More recently, Cook has reported the enantiospecific synthesis of 4-methoxytryptophan using the Larock heteroannulation,[165, 166] which has been employed in the total synthesis of mitragynine (**86**) and related alkaloids,[167] based on an approach used in previous work for the synthesis of de-methoxy mitragynine (**138**, corynantheidine).[168] The Larock heteroannulation is a method for the synthesis of substituted indole derivatives. The advantage of the Larock process stems from the high regioselectivity achieved when a bulky silyl-substituted internal alkyne is employed as a substrate - the regioselectivity is explained by steric interactions between the ortho aromatic hydrogen atom (or, in the Larock heteroannulation, the methoxyl group) and the substituent on the alkyne. The desired 4-methoxy-indole **154** was obtained in 82% yield by reaction of Boc-protected 2-iodo-3-methoxyaniline (**152**) with TMS alkyne **153** to give the *N*-Boc-protected indole derivative after 6 h, although if the reaction mixture was stirred for 3 days, this led to deprotection of the *N*-Boc group (**Scheme 55**). Hydrolysis of **154** using 2 N HCl in THF cleanly afforded 4-methoxy-D-tryptophan ethyl ester (**155**) in 91% yield. The ethyl ester was then hydrolysed and converted into the benzyl ester **156**.



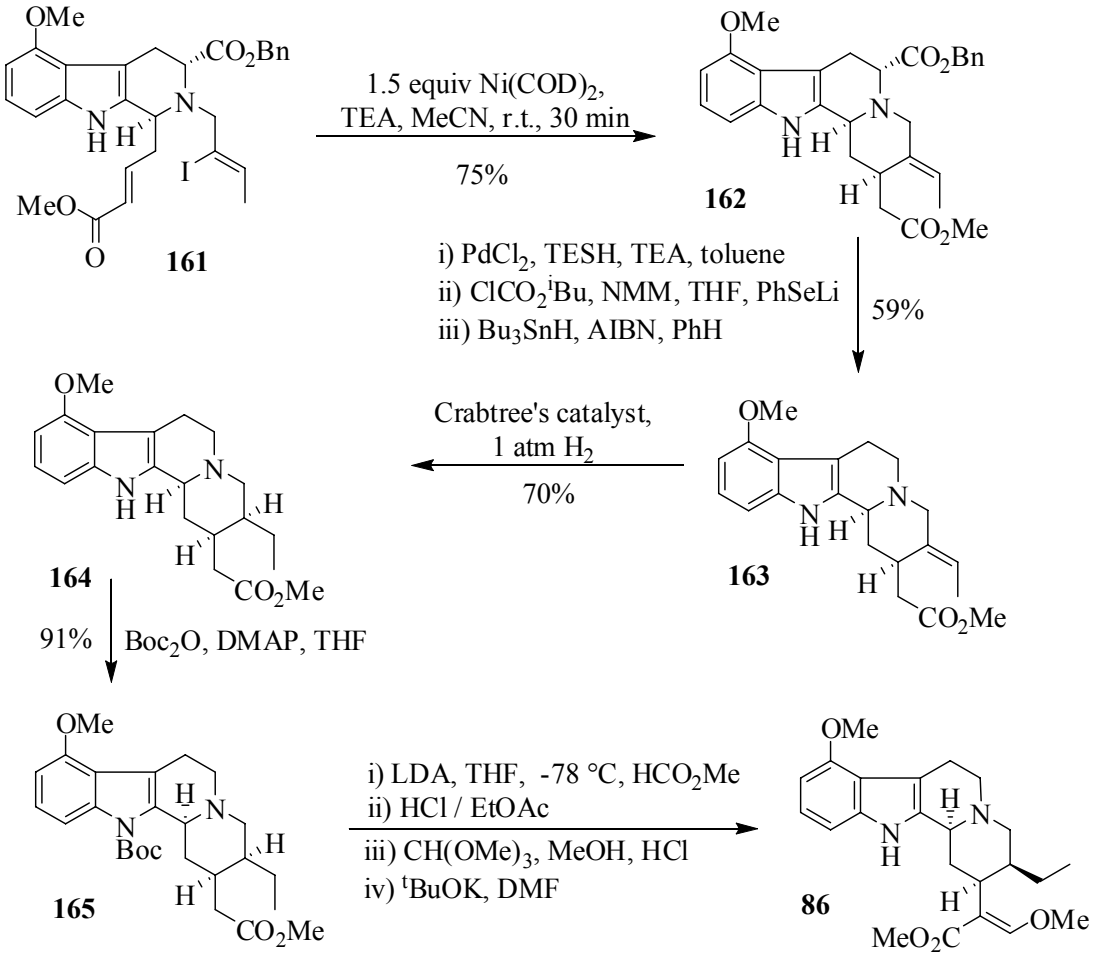
Scheme 55

Monoalkylation of indole **156** with allylic bromide **157** and Cs_2CO_3 in DMF/THF afforded the secondary amine **158** in 85% yield (**Scheme 56**). An asymmetric Pictet-Spengler reaction[169] between the secondary amine **158** and aldehyde **159** furnished tricyclic diester **160**. Diester **160** was then converted into the desired α,β-unsaturated ester **161** in 64% overall yield via removal of one of the thiophenol groups, followed by oxidation with *m*-CPBA and elimination of the resulting sulfoxide.



Scheme 56

The α,β-unsaturated ester **161** was then subjected to a $Ni(COD)_2$-mediated cyclisation to provide the tetracyclic skeleton **162** in 75% yield (**Scheme 57**). The benzyl group of the ester **162** was removed by treatment with $PdCl_2$ in the presence of triethylsilane and the corresponding carboxylic acid was converted into the tetracyclic ester **163** via the Barton-Crich decarboxylation process. Reduction of the alkene in **163** was achieved using Crabtree's catalyst and the resulting tetracycle **164** was treated with $(Boc)_2O$ and a catalytic amount of DMAP to afford the *N*-Boc tetracycle **165**. Subsequent formylation and *N*-Boc deprotection followed by acetal formation and elimination of MeOH provided mitragynine (**86**).

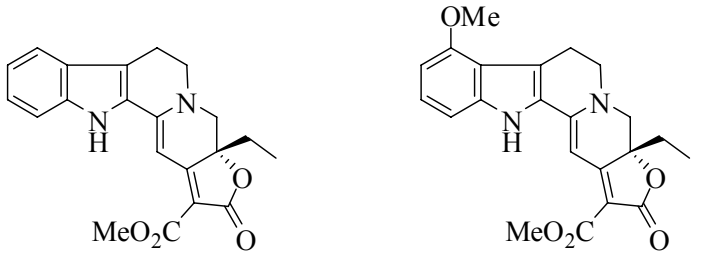


Scheme 57

1.2.3.4 - Synthesis of related alkaloids

1.2.3.4.1 - Synthesis of (-)-9-methoxymitralactonine (167)

Recently, mitralactonine (**166**) and (-)-9-methoxymitralactonine (**167**) (**Figure 7**) have been isolated (from the young leaves of Malaysian, *Mitragyna speciosa Korth*) and synthesised by Takayama and coworkers.[170]

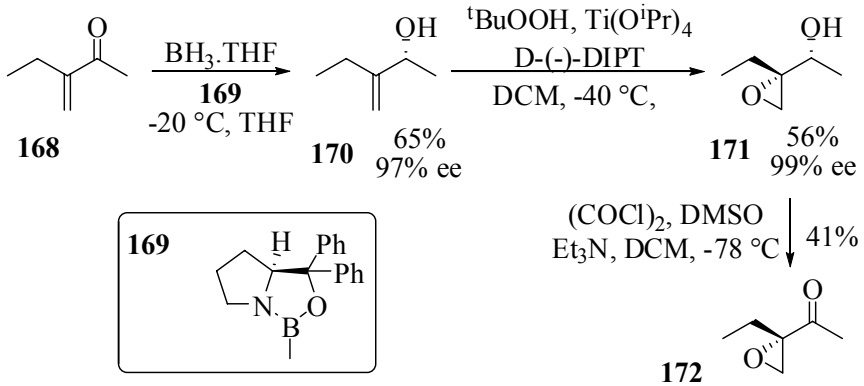


(-)-Mitralactonine
166

(-)-9-Methoxymitralactonine
167

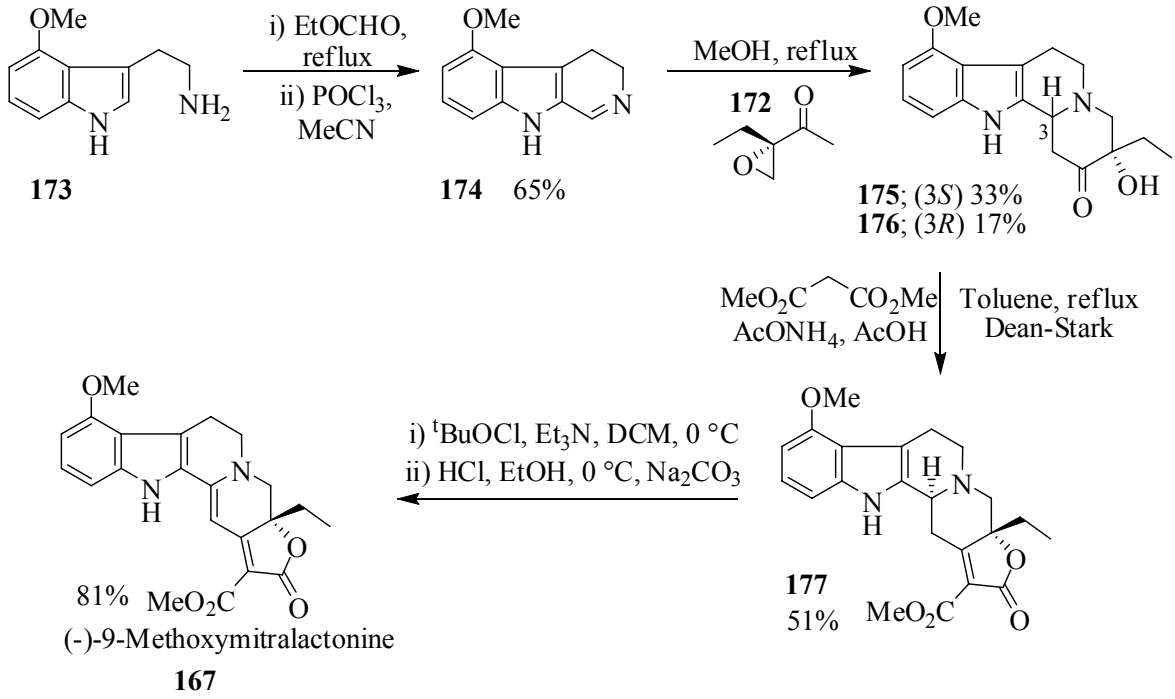
Figure 7

The synthesis of (-)-9-methoxymitralactonine (**167**) started with the preparation of the chiral epoxyketone **1.75** (**Scheme 58**). Initially, a Corey asymmetric reduction of α,β-unsaturated ketone **168** (using an oxazaborolidine catalyst **1.69**) afforded allylic alcohol **170** and a subsequent Sharpless asymmetric epoxidation gave epoxy-alcohol **171**, which on Swern oxidation yielded chiral epoxy-ketone **172**.



Scheme 58

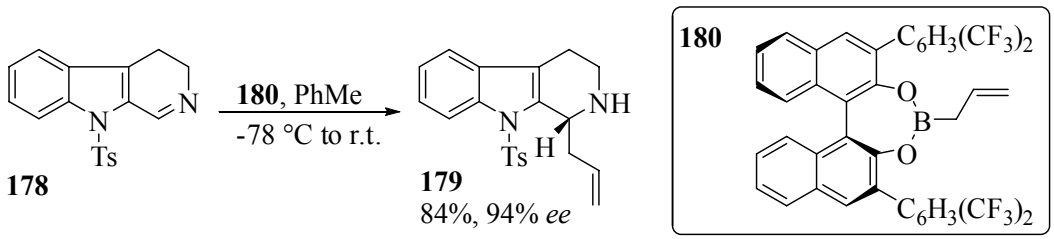
The main core, 5-methoxy-3,4-dihydro-β-carboline (**174**), was prepared from 4-methoxytryptamine (**173**) by *N*-formylation and a subsequent Bischler-Napieralski reaction (**Scheme 59**). The tetracyclic core was prepared by reaction of the imine **174** with chiral epoxy-ketone **172**, to afford two diastereomeric tetracyclic compounds (**175** and **176**) in 33% and 17% yield. The major isomer **175** was subjected to a Knoevenagel condensation with dimethyl malonate in refluxing toluene in the presence of $AcONH_4$ and AcOH to give pentacycle **177** in 51% yield. It is worth pointing out that the same pentacycle (**177**) was obtained from the minor isomer **176**. Finally, the conjugated system was introduced using a two-step process, to furnish (-)-9-methoxymitralactonine (**167**) in 81% yield.



Scheme 59

1.2.3.4.2 - Synthesis of the enantiomer of corynantheidol (183)

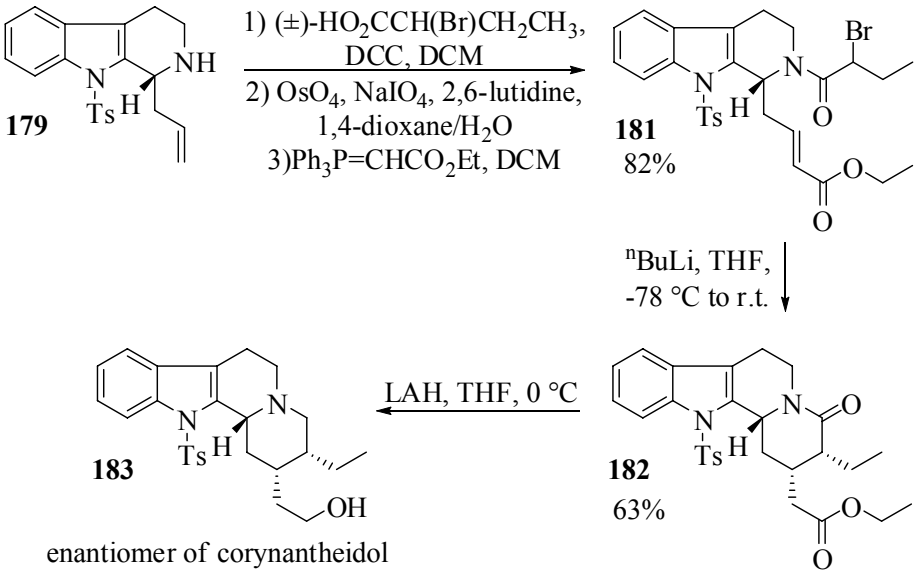
While working on new methods for the enantioselective allylation of cyclic imines Chong has reported the asymmetric synthesis of the enantiomer of corynantheidol (**183**) using an asymmetric allylboration of a cyclic imine in the key synthetic step.[171] Treatment of cyclic imine **178** with the allylboronate **180** in toluene afforded the corresponding homoallylic amine **179** in good yield (71-92% for a range of imines), in excellent enantioselectivity, **Scheme 60**.



Scheme 60

Treatment of the homoallylic amine **179** with bromobutyric acid and DCC afforded the corresponding amide (**Scheme 61**), which was converted into the α,β-unsaturated ester **181**, by a two step procedure involving an osmium tetroxide catalysed oxidation of the alkene and a Wittig reaction on the intermediate aldehyde. An ^{n}BuLi induced intramolecular Michael addition resulted in formation of the *cis* trisubstituted δ-lactam

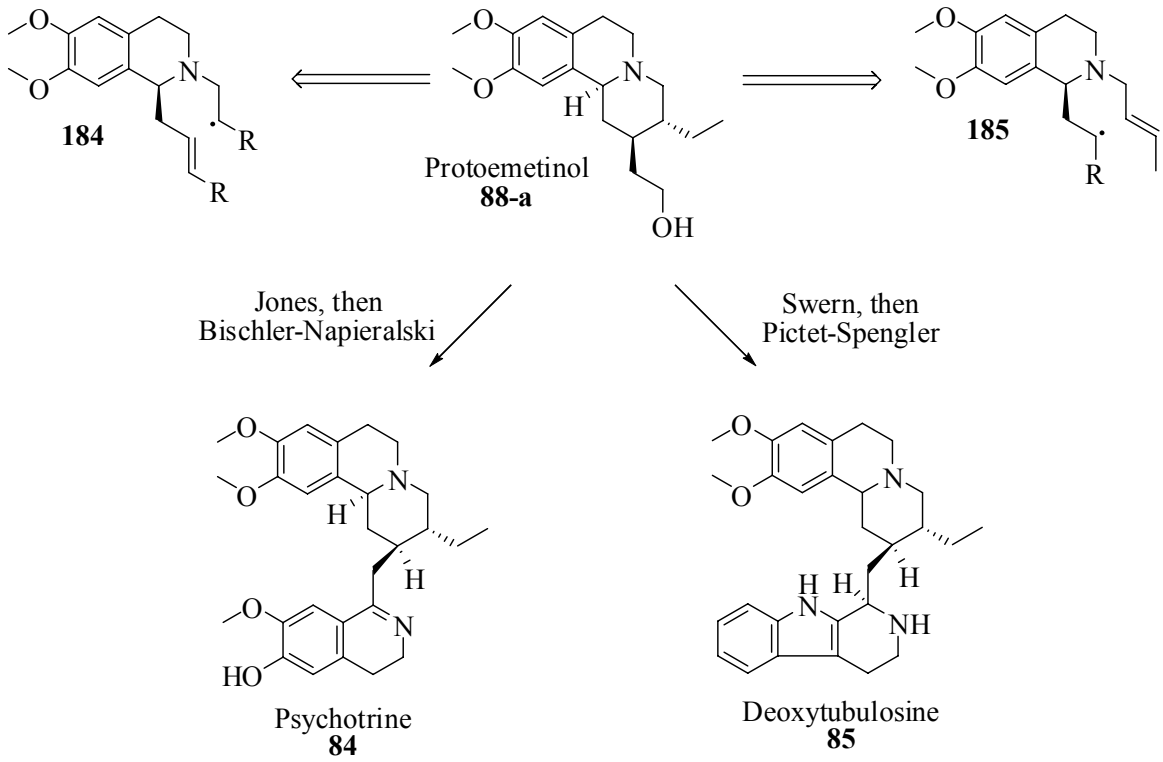
182, as the major diastereomer. Treatment with lithium aluminium hydride resulted in reduction of both the amide and ester to afford the enantiomer of corynantheidol (**183**).[172]



Scheme 61

1.3 Project aims

This project aimed to apply radical cyclisation methodology to the concise syntheses of the *Alangium* and *Mitragyna* alkaloids, which all contain an octahydroquinolizine ring system. It was planned that using a radical promoted cyclisation in the key step would allow a more efficient approach to these structurally complex compounds than existing methods allow. It is known that a range of *Alangium* alkaloids including psychotrine (**84**) and deoxytubulosine (**85**) can be prepared from a common intermediate, protoemetinol (**88**). It was proposed that a radical cyclisation could be used to form protoemetinol (**88**), which could be set-up in one of two ways, either the cyclisation of an alkyl radical onto an *N*-allyl system **185**, or the cyclisation of a radical that is β to nitrogen onto an alkene **184**.



Scheme 62

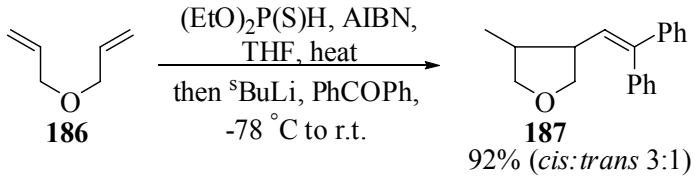
The synthesis of protoemetinol (**88**) and related compounds will be explored using a variety of routes to form radical precursors leading to radicals **184** and **185** (**Scheme 62**). To this end this project will explore the cyclisations using a range of radical mediators, from the cyclisation of vinyl bromides, phenylselenides and acyl halides with tributyltin hydride to the cyclisation of 1,7-dienes using a phosphorus hydride, or a silane. The key aim being to develop an efficient, mild, stereoselective and general synthetic approach to *Alangium* and *Mitragyna* alkaloids.

Chapter 2 – Results and Discussion

Reactions of phosphorus-centred radicals

2.1 Introduction

Previous work within the group had shown that phosphites, thiophosphites and phosphine oxides all add regioselectively to a range of dienes to afford the corresponding cyclic adducts. Subsequent Horner-Wadsworth-Emmons-type (HWE) reactions to form alkenes, in a one-pot reaction, is also possible as exemplified by addition of diethyl thiophosphite to diallyl ether (**186**) and a subsequent reaction with base and benzophenone to afford the substituted alkene **187** (**Scheme 63**).[121, 125, 126] Subsequent work within our group has applied this methodology to the synthesis of the cyclic core of cannabinoids.[173]

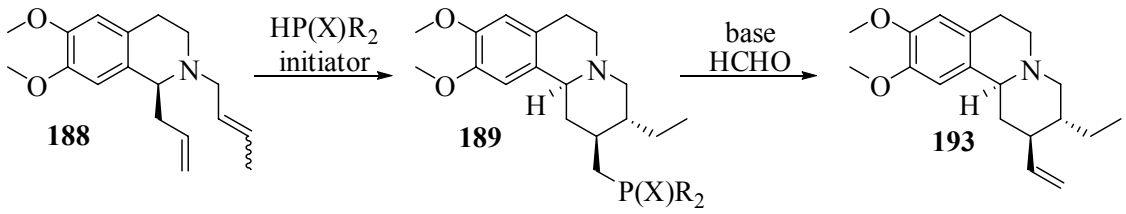


186 **187**

92% (*cis:trans* 3:1)

Scheme 63

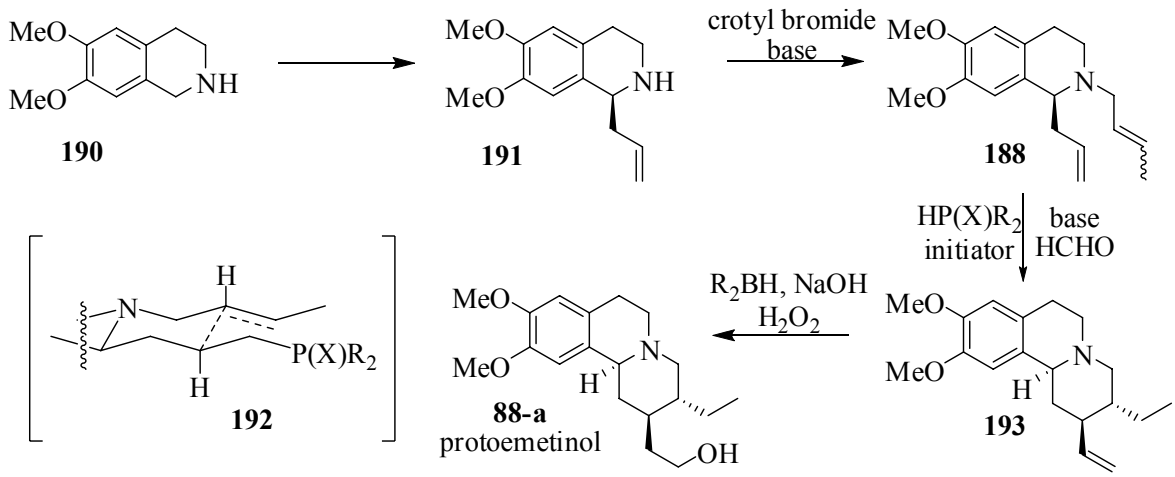
It was postulated that the core of the *Alangium* alkaloids could be prepared by cyclisation of a 1,7-diene, such as **188,** with a phosphorus hydride (**Scheme 64**), followed by a Horner-Wadsworth-Emmons-type reaction of the intermediate phosphonate or phosphonothioate **189** to give tricyclic alkene **193**.



188 **189** **193**

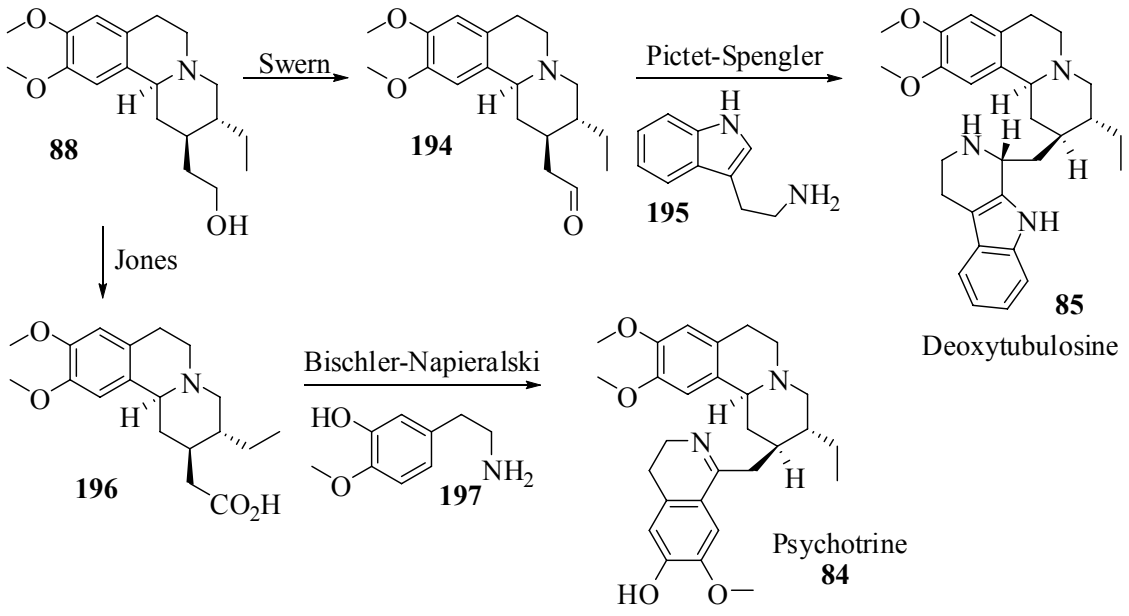
Scheme 64

It was proposed that the synthesis would begin by allylation of tetrahydroisoquinoline **190** to afford dihydroisoquinoline **191**, using one of a number of known approaches (**Scheme 65**). Subsequent *N*-allylation of the secondary amine would afford the 1,7-diene **188**. Reaction of **188** with a phosphorus hydride was expected to result in an 6-*exo*-trig cyclisation (via a chair-like transition state, **192**), and treatment with a base and methanal should afford terminal alkene **193**. Finally, a subsequent oxidative hydroboration[174] is expected to afford protoemetinol (**88**).



Scheme 65

With protoemetinol (**88**) in hand a range of *Alangium* alkaloids could be accessed (**Scheme 66**), for example, psychotrine (**84**) can be accessed by an initial Jones oxidation[175] of protoemetinol (**88**), to afford the carboxylic acid **196**, and then coupling with 5-(2-aminoethyl)-2-methoxyphenol (**197**) (prepared in 3 steps from isovanillin)[176] under Bischler-Napieralski[177] conditions. Alternatively, deoxytubulosine (**85**) could be obtained from protoemetinol (**88**) via oxidation under Swern conditions to afford protoemetine (**194**), which on reaction with tryptamine (**195**) under Pictet-Spengler conditions affords deoxytubulosine (**85**). However, it should be noted that the formation of both deoxytubulosine (**85**) and epideoxytubulosine (the C-1' epimer) is expected.[178]



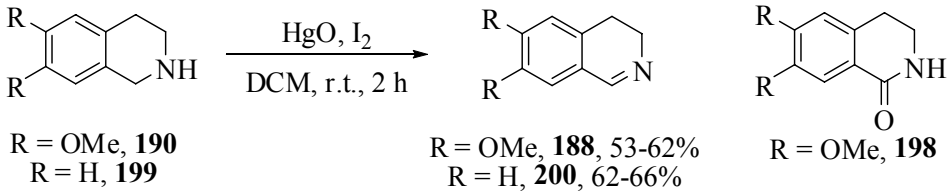
Scheme 66

To investigate the synthetic approach in **Scheme 65**, first, the synthesis of 1,7-diene **188** was developed. This is followed by studies of the phosphorus hydride-mediated radical cyclisation. Although there is literature precedent for the radical cyclisation of 1,7-dienes containing nitrogen, a search of the literature revealed that there are very few examples of phosphorus- or silicon-centred radicals cyclising unsaturated amines.

2.2 Synthesis of the 1,7-diene

2.2.1 Synthesis of imines by oxidation

For the initial route to the substituted-tetrahydroisoquinoline **188**, it was proposed that oxidation of commercially available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**190**), using mercury(II) oxide and iodine according to the literature method,[179] would form dihydroisoquinoline **188** (**Scheme 67**).[180] The desired product was formed although we could not achieve the reported yield of 85%. In addition to **188**, another product, possibly amide **198** (derived from over-oxidation), was observed, along with a black tarry residue, which is likely derived from oxidation of the catechol fragment. Similar oxidation reactions were carried out on 1,2,3,4-tetrahydroisoquinoline (**199**) to yield the corresponding dihydroisoquinoline **200** in higher yields than for the dimethoxy-dihydroisoquinoline **188** (**Scheme 67**).



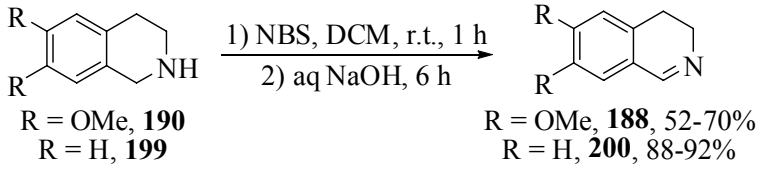
R = OMe, **190**
R = H, **199**

R = OMe, **188**, 53-62%
R = H, **200**, 62-66%

R = OMe, **198**

Scheme 67

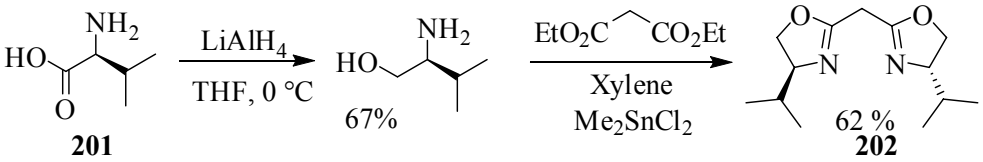
The low yield of imines **188** and **200** led us to try a different oxidation method, involving the use of *N*-bromosuccinimide (NBS) followed by aqueous sodium hydroxide, **Scheme 68**.[181] This method gave a much higher yield of the corresponding imines and so this was adopted as the oxidation method of choice. It is, however, worth noting that for both methods, the yield of the dimethoxy-imine **188** was considerably lower, possibly due to the increased electron density of the dimethoxy-substituted aromatic ring.



Scheme 68

2.2.2 Addition of organometallic reagents to imines

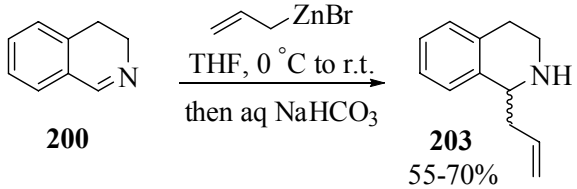
Previous work by Nakamura has shown that organozinc reagents can add efficiently to imines such as **188** and **200**.[182, 183] The addition of allylzinc bromide to imines (prepared in typically 80-90%, based on a Gilman titration)[184-186] can be made enantioselective by using a chiral auxiliary, such as bis-oxazolidine **202**, which can be prepared by reduction of L-valine **(201)** followed by condensation with diethyl malonate (**Scheme 69**).



201 **202**

Scheme 69

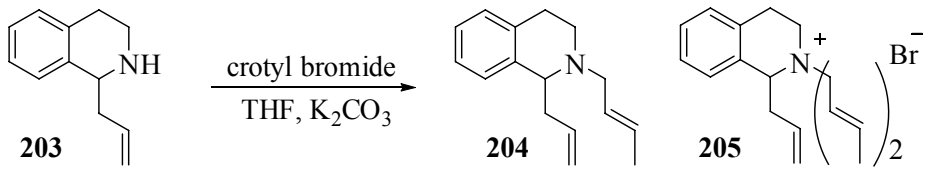
For the initial studies of the radical cyclisation, a racemic synthesis would be sufficient and so addition of allylzinc bromide to imine **200** resulted in the isolation of the desired amine **203** in 55-70% yield after column chromatography, **Scheme 70**. As 1,2,3,4-tetrahydroisoquinoline **199** is significantly cheaper than 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **190**, for optimization of the synthetic approach, we concentrated on the use of this starting material.



200 **203**
55-70%

Scheme 70

It was hoped that *N*-allylation of **203** would proceed following a literature procedure using crotyl bromide (1 equiv.) and K_2CO_3 in MeCN.[187] Unfortunately, this predominantly gave the quaternary ammonium salt **205**, and recovered starting material (**Scheme 71**). It was possible to increase the yield of **204** (to 41%) by using high dilution and slow addition of the crotyl bromide.

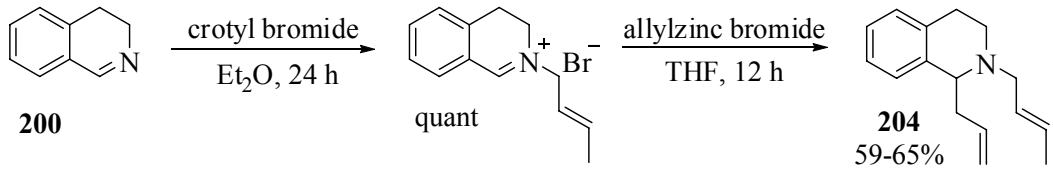


203 204 205

Scheme 71

2.2.3 Addition of organometallic reagents to imine salts

The problems of quaternary ammonium ion formation led us to use a reverse strategy, where dihydroisoquinoline **200** is first *N*-crotylated and then reacted with the organozinc reagent. This method gave the desired adduct **204** in much improved yields over the two steps (**Scheme 72**).



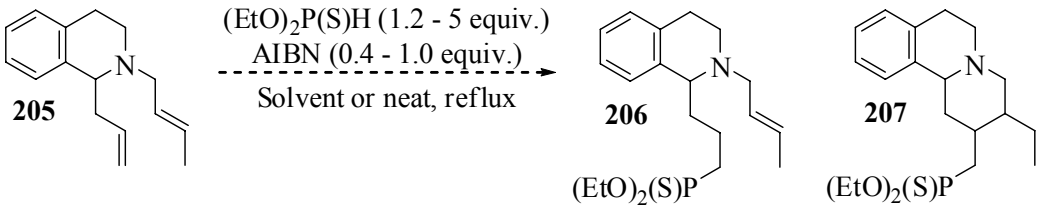
200 quant **204** 59-65%

Scheme 72

2.3 Reaction of phosphorus hydrides

2.3.1 Reaction of phosphorus hydrides with 1,7-diene 188

Radical cyclisation of 1,7-diene **205** using diethyl thiophosphite was then investigated. Initial attempts, using a dilute solution of **205** and diethyl thiophosphite, under a range of conditions resulted in recovered 1,7-diene **205**. Even when the diene, $(EtO)_2P(S)H$ and AIBN were heated at 80 °C in the absence of a solvent, only starting material was recovered (**Scheme 73**).



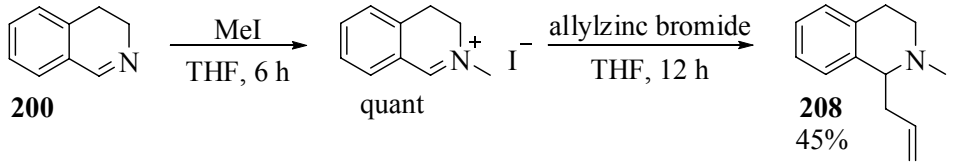
205 **206** **207**

AIBN added portionwise (0.05 or 0.1 equiv. was added every hour)
Solvent = cyclohexane, benzene or THF

Scheme 73

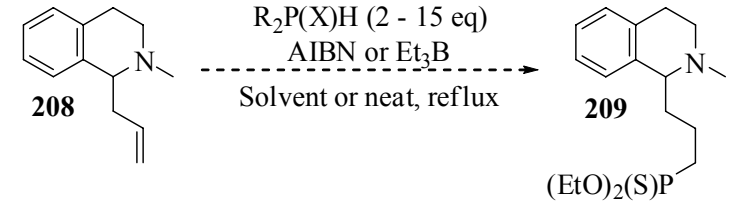
2.3.2 Reaction of phosphorus hydrides with a model system

The inability to cyclise **205** led us to investigate the simple addition of phosphorus hydrides to the allyl bond of the NMe compound **208** (prepared by methylation of **200** using MeI followed by addition of allylzinc bromide, **Scheme 74**).



Scheme 74

Unfortunately, attempted addition of $(EtO)_2P(O)H$, $(EtO)_2P(S)H$ or $Ph_2P(O)H$ to the allyl bond of **208** using AIBN or Et_3B/O_2 as initiator in a range of solvents was unsuccessful, with only starting alkene recovered (**Scheme 75**).

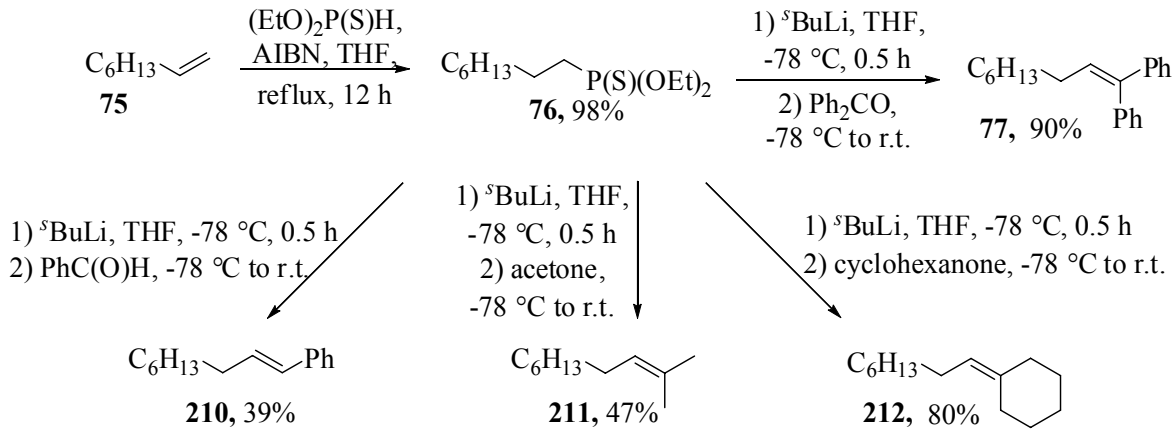


$R_2P(X)H = (EtO)_2P(O)H$, $(EtO)_2P(S)H$ or $Ph_2P(O)H$
AIBN (5 x 0.1 eq) or Et_3B (2 x 1.0 eq)
Solvent = cyclohexane, benzene, THF

Scheme 75

2.3.3 Reaction of phosphorus hydrides with test systems

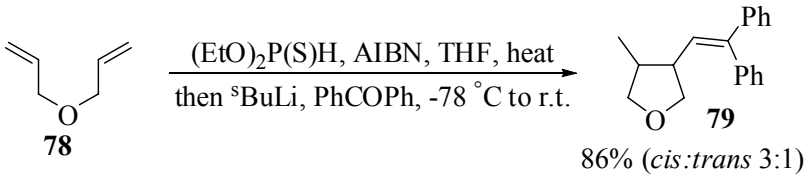
This result contrasts with similar reactions, such as reaction of 1-octene (**75**) with diethyl thiophosphite and AIBN, which, as expected from the literature[121, 125, 126, 173, 188] afforded *O*,*O*-diethyl octylphosphonothioate (**76**) and further Horner-Wadsworth-Emmons-type reactions yielded alkenes **77**, **210**, **211** and **212** in moderate to good yields using benzophenone, benzaldehyde, cyclohexanone or acetone, respectively (**Scheme 76**).



$(EtO)_2P(O)H$ can be used, the yield for the addition to 1-octene is similar (95%), however the yields for the HWE reactions are lower

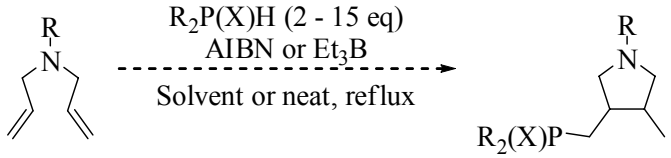
Scheme 76

A consecutive radical addition/cyclisation/Horner-Wadsworth-Emmons type reaction was also tested. Allyl ether (**78**), diethyl thiophosphite and AIBN in dry THF were heated to reflux, after which ^{s}BuLi was added, followed by benzophenone (**Scheme 77**). This resulted in the desired alkene **79** being isolated in 86% yield.



Scheme 77

To test the radical addition and cyclisation of unsaturated amines, the reaction of diallylamine or diallylmethylamine, with a range of phosphorus hydrides, was explored. Unfortunately, under a range of conditions, no cyclisation or addition of the phosphorus hydrides to the allyl amines was observed (**Scheme 78** and **Table 2**). This contrasts with similar reactions of *N*-protected diallylamines with diethyl thiophosphite and AIBN in THF.[121, 173, 188]



R	$R_2P(X)H$	Eq	Initiator	Yield (%)	*cis*	:	*trans*
H	$(EtO)_2P(S)H$	2-6	AIBN or Et_3B	No Reaction			
H	$(EtO)_2P(O)H$	10-15	AIBN or Et_3B	No Reaction			
Me	$(EtO)_2P(S)H$	2-6	AIBN or Et_3B	No Reaction			
Me	$(EtO)_2P(O)H$	10-15	AIBN or Et_3B	No Reaction			
Ts	$(EtO)_2P(O)H$	10	Et_3B	20[188]	3	:	1
Boc	$(EtO)_2P(O)H$	10	Et_3B	80[188]	2.3	:	1
Cbz	$(EtO)_2P(O)H$	10	Et_3B	84[188]	2.1	:	1
Bz	$(EtO)_2P(S)H$	5	AIBN	78	2.2	:	1

Scheme 78 and **Table 2**

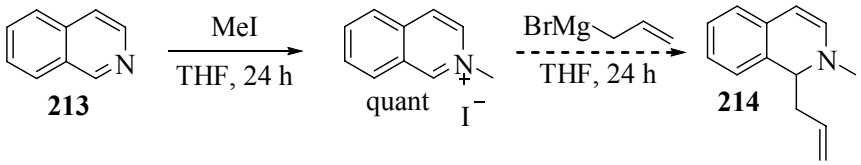
The problematic reactions of diene **205**, alkene **208** and other amines with phosphorus hydrides may be attributed to an electron-transfer process; the intermediate phosphorus-centred radical may accept an electron from the lone pair on nitrogen.[188] Related radical reactions of amines are scarce in the literature, although this contrasts with successful cyclisations of unsaturated precursors containing amide or sulfonamide groups, where the lone pair is resonance-stabilised and less prone to single electron transfer processes. This led us to explore the preparation of related precursors containing enamide and amide groups.

2.4 Reaction of enamines with phosphorus hydrides

2.4.1 Preparation of enamines

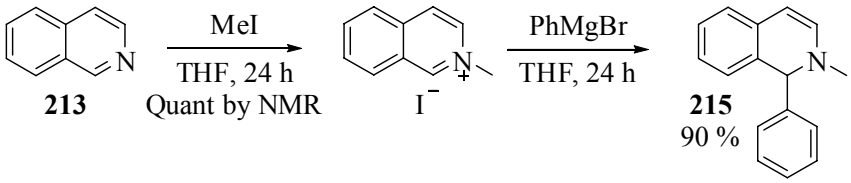
Following a literature procedure, *N*-methylation of **213** proceeded quantitatively (from ^1H NMR spectroscopy) but subsequent addition of allylmagnesium bromide did not proceed smoothly, giving **214** in trace amounts together with unidentified by-products (**Scheme 79**).[c]

[c] It is believed that Grignard formation is occurring, as the reaction mixture starts to reflux, changes colour and the magnesium metal is consumed. However, attempted addition of the Grignard reagent to benzaldehyde, cyclohexanone or 1-tetralone was unsuccessful. In comparison, in-situ formation of PhMgBr and addition to cyclohexanone gave the expected alcohol in 85% yield.



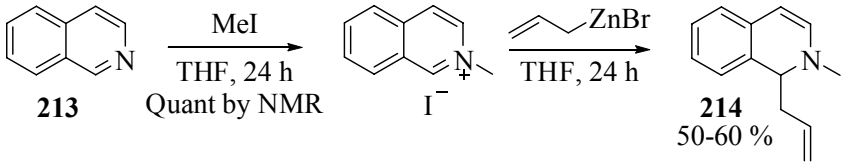
Scheme 79

In comparison, under the same conditions, phenylmagnesium bromide undergoes addition to *N*-methylisoquinoline to give 1,2-dihydro-2-methyl-1-phenylisoquinoline (**215**) in an excellent 90% yield over the two steps (**Scheme 80**).



Scheme 80

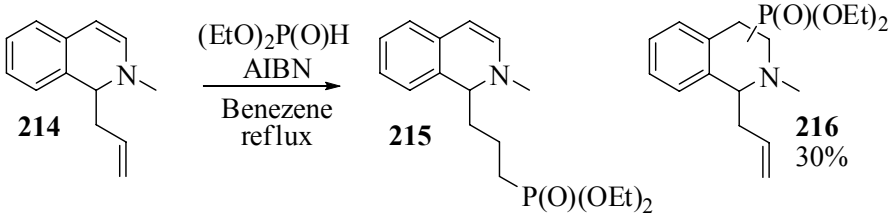
It was pleasingly found that changing the organometallic reagent from allylmagnesium bromide to allylzinc bromide, resulted in a greatly improved yield of the desired 1-allyl-1,2-dihydro-2-methylisoquinoline (**214**) to 50-60% (**Scheme 81**).



Scheme 81

2.4.2 Reactions of enamines with phosphorus hydrides

When the enamine **214** was heated with diethyl phosphite and AIBN in benzene, only addition to the electron rich C=C bond in the ring was indicated from the ^{1}H NMR spectrum, to afford **216** in 30% yield (as a single regioisomer, however the exact structure could not be determined by NMR spectroscopy) along with recovered starting material (40%). None of the expected product **215**, derived from addition to the less substituted C=C bond, was isolated (**Scheme 82**).



Scheme 82

The chemoselective addition to the enamine C=C bond in **214** could be explained by polarity, as the electrophilic phosphorus-centred radical may be expected to add selectively to the most electron-rich C=C bond. With this result in hand, the addition of phosphorus hydrides to a range of enamides was explored. However, disappointingly, under similar conditions only traces of products could be obtained (1-2%, **Figure 8**).

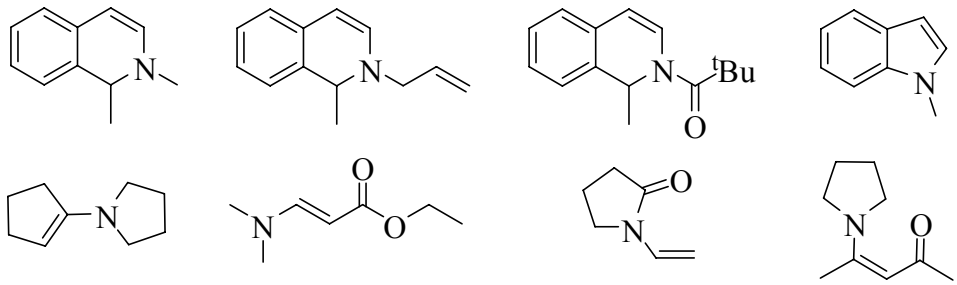
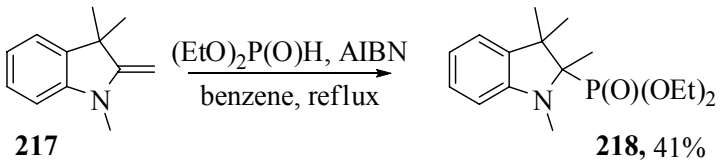


Figure 8

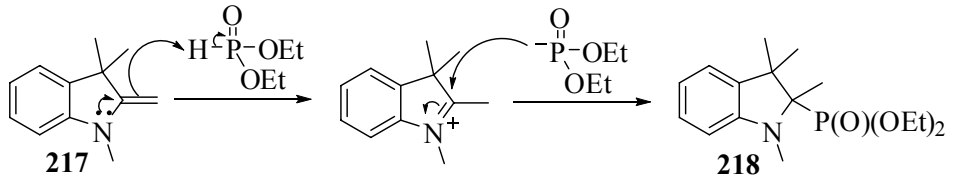
However it was found that the addition of diethyl phosphite to 1,3,3-trimethyl-2-methyleneindoline proceeded well to afford **218** in a reasonable 41% yield, structural assignment was confirmed by comparison with previously reported data.[189]



217 **218,** 41%

Scheme 83

However it was discovered that the group of Tolmachev and Stawinski[190, 191] have previously reported the addition of diethyl phosphite to 1,3,3-trimethyl-2-methyleneindoline (**217**) in the absence of AIBN, or any other radical initiator. It is proposed that the addition of diethyl phosphite to 1,3,3-trimethyl-2-methyleneindoline (or other enamines) occurs via an ionic mechanism as shown in **Scheme 84**.

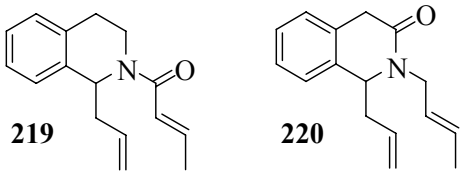


217 **218**

Scheme 84

2.5 Preparation and reactions of amide based 1,7-dienes

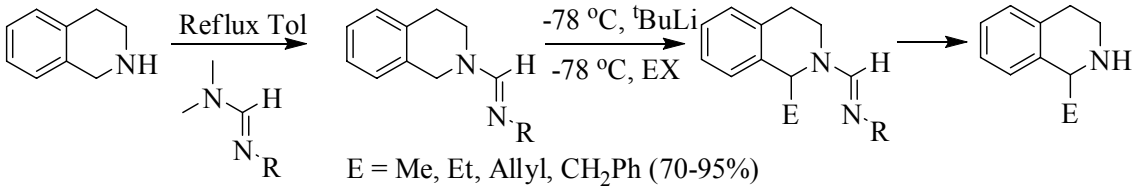
Following the disappointing results with the addition of phosphorus-centred radicals to enamines, it was of interest to see if a 1,7-diene, bearing an amide protecting-group, such as **219** or **220**, **Figure 9**, would undergo radical cyclisation in the presence of a phosphorus hydride.



219 **220**

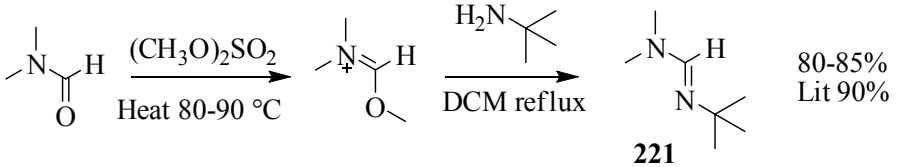
Figure 9

However, the synthesis of **220** would be more complicated, so attention turned to the synthesis of **219**, which could be obtained from **203**. Due to the inefficient routes towards the substituted-tetrahydroisoquinolines **203**, **204** and **208** via the addition of allylmetal reagents to an imine (such as **200**) another synthetic method was explored. Meyers and co-workers have previously shown that tetrahydroisoquinoline can be substituted at the 1-position using the route shown in **Scheme 85**.[151, 192]



Scheme 85

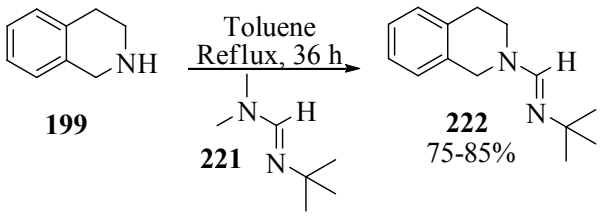
For asymmetric alkylation, Meyers used an L-valinol derived formamide,[152] to give high yields of 1-alkyl tetrahydroisoquinolines in 90-99% enantiomeric excess. To test this route, the racemic derivative *N,N*-dimethyl-*N'*-*tert*-butylformamide (DMBF) **221** was first synthesised (**Scheme 86**).[192]



221

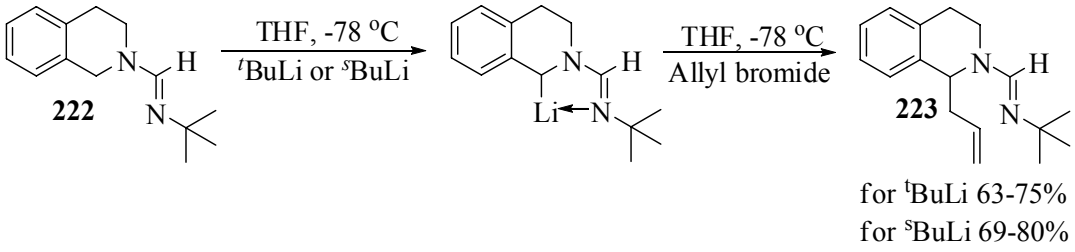
Scheme 86

Reaction of *N,N*-dimethyl-*N'-tert*-butylformamide **221** with 1,2,3,4-tetrahydroisoquinoline **199** subsequently gave the desired 1,2,3,4-tetrahydroisoquinoline formamide **222** in 75-85% yield (**Scheme 87**).



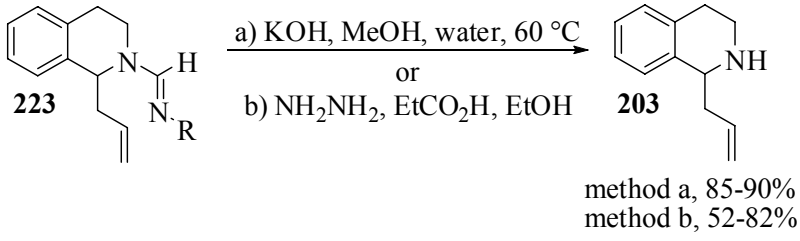
Scheme 87

Metallation-alkylation of formamide **222** was achieved using ^{t}BuLi, although there is some precedent for using ^{s}BuLi. In our hands, reaction of formamide **222** with ^{s}BuLi proceeded to give a cleaner reaction with fewer by-products to afford the allyl substituted butylformamide **223** (**Scheme 88**). However the same reaction with ^{n}BuLi resulted in only recovered starting material.



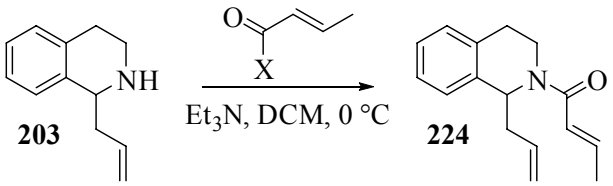
Scheme 88

With substituted-tetrahydroisoquinoline **223** in hand, removal of the formamide fragment was required. There are several possible methods[192] including hydrolysis (KOH, MeOH, water, 60 °C), hydrazinolysis (NH_2NH_2, $EtCO_2H$, EtOH) and reductive cleavage ($LiAlH_4$). It was found that the hydrolysis and hydrazinolysis both worked well, however the hydrolysis resulted in the higher product yields, **Scheme 89**, and slightly cleaner crude reaction mixtures.



Scheme 89

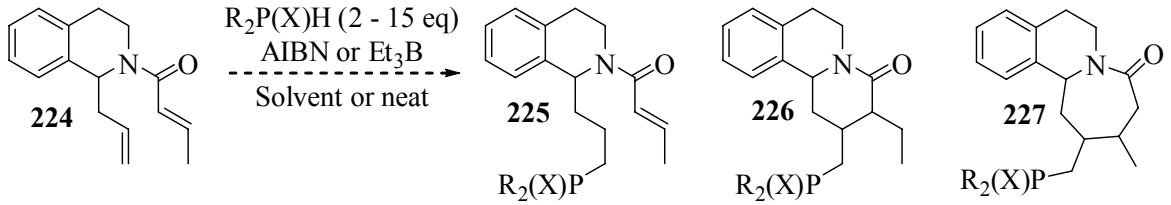
Following isolation of the secondary amine **203**, attention then turned to *N*-acylation using crotonyl chloride or crotonyl anhydride, to afford amide **224** although this did not proceed smoothly, possibly due to a competing 1,4-type addition (**Scheme 90**).



for X = Cl, 35-40%
for X = $OCOCH{=}CHCH_3$, 38-45%

Scheme 90

However, with some of the amine **224** in hand, attempts at the radical mediated addition/cyclisation of a range of phosphorus hydrides ($(EtO)_2P(O)H$, $(EtO)_2P(S)H$ or $Ph_2P(O)H$) were explored (**Scheme 91**). Three possible products were envisaged; the direct addition product **225**, the desired 6-*exo* cyclisation product **226** and the product of 7-*endo* cyclisation **227**.



$R_2P(X)H$ = $(EtO)_2P(O)H$, $(EtO)_2P(S)H$ or $Ph_2P(O)H$
AIBN 5 x 0.1 eq or Et_3B 2 x 1.0 eq
Solvent = cyclohexane, benzene or THF

Scheme 91

Disappointingly only a complex mixture of products was obtained based on TLC analysis and the NMR spectra of the unpurified reaction product. Unfortunately, no isolated products could be assigned and there was no evidence of the direct addition product **225**, 6-*exo* cyclisation product **226**, or 7-*endo* product **227**. It is proposed that some of these problems could be due to restricted bond rotation in the intermediate phosphorus-centred radical, which is discussed further in **Chapter 4**.

2.6 Conclusions

Following previous work within the group it had been hoped that an efficient route towards protoemetinol (**88**), a key intermediate of *Alangium* alkaloids such as psychotrine (**84**) deoxytubulosine (**85**) could be achieved using the phosphorus hydride mediated cyclisation of a 1,7-diene. Unfortunately this was not the case: although the radical addition-cyclisation reaction of simple alkenes and dienes (including 1-octene, 1,6-heptadiene allyl ether, diethyl malonate and a range of amides including *N,N*-diallylbenzamide) with diethyl phosphite proceeds to give adducts in excellent yields, similar reactions of unprotected amines (such as diallylamine and diallylmethylamine) give none of the desired cyclic adducts. This has been attributed to a competing electron-transfer process between the intermediate phosphorus-centred radical and the lone pair of electrons on the amine nitrogen.

Further exploration of the addition of phosphorus hydrides to unsaturated systems was investigated, including addition to an enamine. Reaction of the initial test substrate was promising, with the isolation of the adduct in a 30% yield. However, an investigation of a range of different enamines was disappointing and only the addition of diethyl phosphite to 1,3,3-trimethyl-2-methyleneindoline (**217**) proceeded well. However, it was noted that the group of Tolmachev and Stawinski[190, 191] have reported the same addition occurring under ionic conditions.

Two approaches towards the core allyl-tetrahydroisoquinoline ring system have been explored. The first approach involved the oxidation of an amine (**190** or **199**) to the corresponding imine (**180** or **200**) followed by the addition of an organometallic reagent. This route proved to be very successful when the imine was "activated" by *N*-allylation before addition of the organometallic reagent. However, the addition proved to be more problematic if the addition was attempted on the "unactivated" imine. A second approach towards the allyl-tetrahydroisoquinoline core was achieved using a route previously reported by Meyers and co-workers, involving the deprotonation of an formamide with ^{t}BuLi, followed by quenching with allyl bromide.

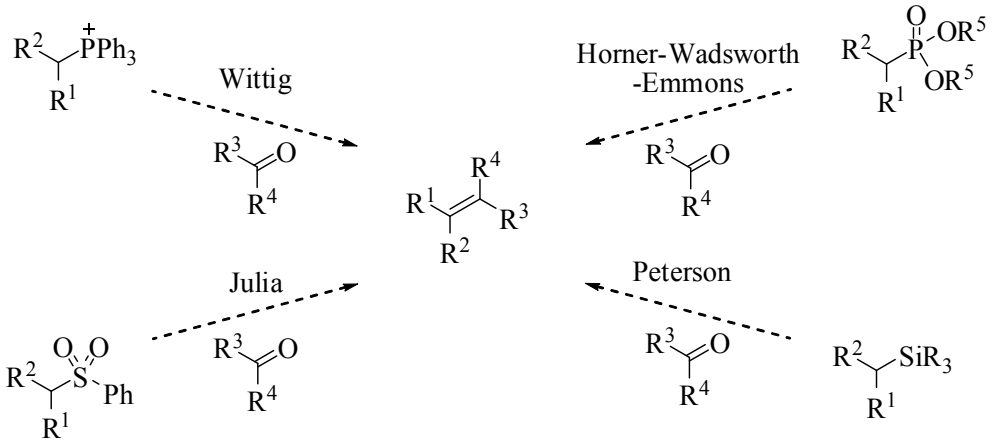
Chapter 3 – Results and Discussion

Addition reactions of silicon-centred radicals

3.1 Introduction

Following the disappointing results on the use of phosphorus-centred radical additions to construct the *Alangium* alkaloids ring system (**Chapter 2**), alternative radical cyclisation methods were explored. As outlined in **Chapter 2**, it was envisaged that addition of a phosphorus-centred radical (generated from a phosphorus hydride) to a diene would form an organophosphorus adduct, which could then undergo a Horner-Wadsworth-Emmons reaction to install the required C=C bond. With this in mind alternative radion methods, combining radical cyclisation with subsequent formation of a C=C bond, were investigated.

Various heteroatom radicals are known to add to a range of alkenes and a number of heteroatom based olefination reactions have been reported. Heteroatom-based olefination reactions are a group of alkene-forming reactions that typically involve the addition of a heteroatom-stabilised carbanion to a C=O bond. For example, silanes can be converted into alkenes by the Peterson reaction,[193, 194] (**Scheme 92**) phenyl sulfones can be converted into alkenes by the Julia olefination,[146, 195, 196] the Wittig reaction typically uses a triphenylphosphonium ylide, while the Horner-Wadsworth-Emmons reaction uses a phosphonate, to form alkenes.[197]



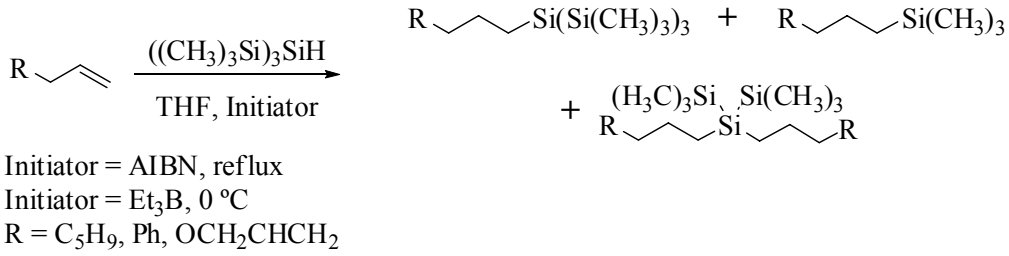
Scheme 92

A variety of work has been reported on the radical addition of silicon hydrides to alkenes,[103, 116, 118] to afford the hydrosilylation products, and so novel radion reactions of silanes was explored. Organosilicon compounds have been exploited in the Peterson

olefination reaction to afford alkenes, and in the Fleming-Tamao oxidation to afford alcohols. However, there are few examples where the radical hydrosilylation of an alkene is combined with subsequent functionalisation of the organosilicon adduct to form, for example, an alkene or an alcohol. Initial studies concentrated on the development of a mild and efficient method of hydrosilylation.

3.2 Reactions of tris(trimethylsilyl)silane

The most widely used silicon hydride, for radical transformations, is tris(trimethylsilyl)silane (Chatgilialoglu's reagent). Previous studies by Chatgilialoglu[116] reported that tris(trimethylsilyl)silane can add to a range of alkenes and dienes, under mild conditions (using AIBN as the initiator) to afford the corresponding organosilicon adducts in high yields. In our hands, addition of tris(trimethylsilyl)silane [$(TMS)_3SiH$] to 1-octene, allylbenzene and diallyl ether, at first glance, appeared to afford the desired adducts in good yields. However on closer inspection of the ^1H NMR, ^{13}C NMR and mass spectra of the unpurified products, it appeared that fragmentation of the silyl radical, $(Me_3Si)_3Si^{\bullet}$, had occurred during the reaction, resulting in a mixture of products. Examination of the NMR spectra of the crude reaction mixtures indicated the absence of any starting alkene, although NMR could not determine the product ratio. After searching the literature, it was found that after the initial work by Chatgilialoglu, the group of Oshima and Utimoto[198, 199] reported that the $(Me_3Si)_3Si^{\bullet}$ radical fragments to form $(Me_3Si)_2Si^{\bullet}$ and $Me_3Si^{\bullet}$ radicals, resulting in a mixture of products, thus supporting our findings.



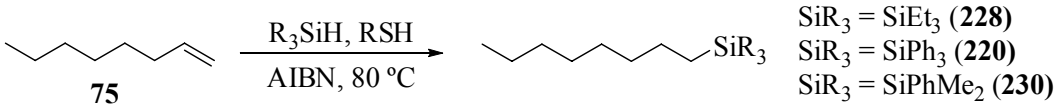
Scheme 93

Another problem with using $(TMS)_3SiH$ in a radion transformation is that there no known methods to convert the $(TMS)_3Si$ group into another functional group. Indeed, in our hands, an attempted Peterson reaction (using NaH, ^{s}BuLi or ^{n}BuLi, and Ph_2CO or PhCHO) or Fleming-Tamao oxidation (using KF, H_2O_2 and $KHCO_3$ in MeOH) failed on the mixture of organosilane adducts from the radical addition reactions, usually resulting in the recovery of the starting material. This led us to study the use of alkyl-, aryl- and chloro-silanes in radical additions.

3.3 Reactions of alkyl- and aryl-silanes

3.3.1 Addition of alkyl- and aryl-silanes at elevated temperature

Previous work by Roberts had shown that, in conjunction with a thiol catalyst, alkyl- or aryl-silanes efficiently add to C=C bonds,[103] although it was necessary to use di-*tert*-butyl hyponitrite (TBHN), as initiator, to obtain good yields in some examples. Our investigations found that treatment of 1-octene (**75**) with a silane and AIBN afforded the desired organosilicon adducts (**Scheme 94** and **Table 3**). The best yields were obtained using triisopropylsilanethiol as the polarity-reversal catalysis and carrying out the reaction neat, in the absence of a solvent.

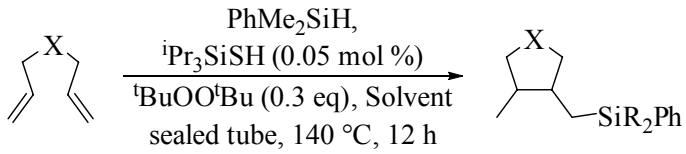


75

R_3SiH (eq)	Thiol	Solvent	Yield (%)	Product
Et_3SiH (2)	None	Hexane	2	**228**
Et_3SiH (2)	PhSH	Hexane	44	**228**
Et_3SiH (2)	Dodecanethiol	Hexane	35	**228**
Et_3SiH (2)	$^{i}Pr_3SiSH$	Hexane	54	**228**
Et_3SiH (4)	$^{i}Pr_3SiSH$	No solvent	65	**228**
Ph_3SiH (1.2)	None	Hexane	2	**229**
Ph_3SiH (1.2)	PhSH	Hexane	54	**229**
Ph_3SiH (1.2)	Dodecanethiol	Hexane	63	**229**
Ph_3SiH (1.2)	$^{i}Pr_3SiSH$	Hexane	86	**229**
Ph_3SiH (1.2)	$^{i}Pr_3SiSH$	No solvent	95	**229**
$PhMe_2SiH$ (1.2)	$^{i}Pr_3SiSH$	Hexane	80	**230**
$PhMe_2SiH$ (1.2)	$^{i}Pr_3SiSH$	No solvent	92	**230**

Scheme 94 and **Table 3**

Unfortunately, attempts at the radical cyclisation of dienes using AIBN or TBHN as initiators were unsuccessful. However, following work by Studer using silylated cyclohexadiene as a source of the phenyldimethylsilane radical, it was noted that an efficient transformation was achieved when using di-*tert*-butyl peroxide in hexane in a sealed tube at 140 °C.[108] This led to an investigation of radical addition-cyclisation reactions of various dienes using similar conditions (**Scheme 95** and **Table 4**).



X	PhR_2SiH		Solvent	Yield	d.r.[a]	Product
	R	equiv		(%)	*trans* :*cis* [b]	
O	Ph	1.1	hexane	32	1 : 2.9	**231**
O	Ph	1.1	benzene	69	1 : 3.0	**231**
O	Me	1.1	hexane	30	1 : 2.0	**232**
O	Me	1.1	benzene	52	1 : 1.9	**232**
O	Me	2.2	benzene	77	1 : 1.9	**232**
CH_2	Me	2.2	benzene	70	1 : 2.0	**233**
$C(CO_2Et)_2$	Me	2.2	benzene	88	1 : 3.8	**234**
$CF_3C(O)N$	Me	2.2	benzene	52 [c]	Note d	**235**
MeC(O)N	Me	2.2	benzene	70	Note d	**236**
^{t}BuC(O)N	Me	2.2	benzene	74	Note d	**237**

a - d.r. determined from the ^{1}H NMR spectrum

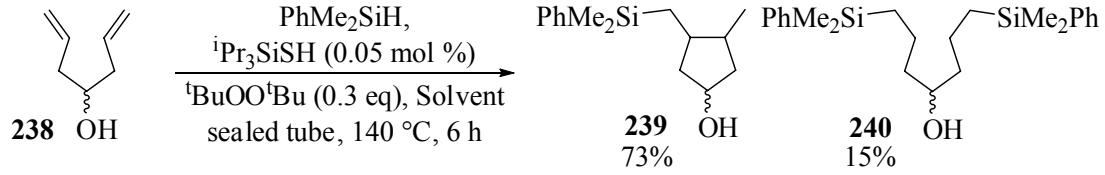
b - assignment based on comparison with literature compounds and NOESY NMRs

c - ^{1}H NMR spectrum shows clean product; product is unstable to silica

d - an accurate dr ratio could not be determined, due to the amide rotamers

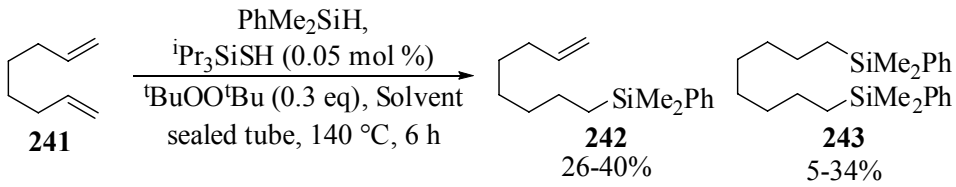
Scheme 95 and **Table 4**

Although in the above case the desired cyclisation proceeded well, extending the method to alternative substrates proved problematic. It was found that under similar conditions, 1,6-heptadien-4-ol (**238**) gave a mixture of products **239** and **240** (**Scheme 96**), derived from addition of the silicon radical, but not cyclisation of the resulting carbon radical. Attempted cyclisation of diallylmethylamine, diallylamine or diallylsulfane were also unsuccessful.



Scheme 96

In a similar approach, it was hoped that cyclisation of 1,7-dienes would afford the corresponding 6-*exo* products, however it is well known that 6-*exo* cyclisation is much more difficult than 5-*exo* cyclisation, due to a slower rate of cyclisation (approx 40 times slower) and competing 1,5-hydrogen atom transfer reactions. So it was not unsurprising to discover that under similar conditions, 1,7-octadiene (**241**) only afforded products of monoaddition **242** and diaddition **243** (**Scheme 97**).

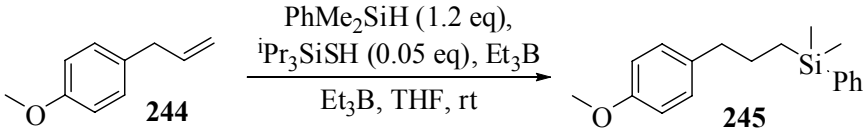


Scheme 97

Although, in some cases, these conditions resulted in the formation of the desired cyclisation products in good yields, the conditions are relatively harsh and are incompatible with the use of polyfunctional precursors. So, it was desirable to find a milder method for the radical addition chemistry.

3.3.2 Addition of alkyl- and aryl-silanes at room temperature

Our investigations moved on to the use of triethylborane, at room temperature, as the radical initiator. It was pleasing to find that addition of phenyldimethylsilane to a C=C bond proceeded very well in the presence of triethylborane and triisopropylsilanethiol as a thiol catalyst (**Scheme 98, Table 5**). It was observed that for efficient high yielding additions, a total of 1 equivalent of triethylborane is required, with addition of two portions of 0.5 equivalents being the most efficient. It was also noted that the thiol catalyst was still required, despite using 1 equivalent of the initiator.



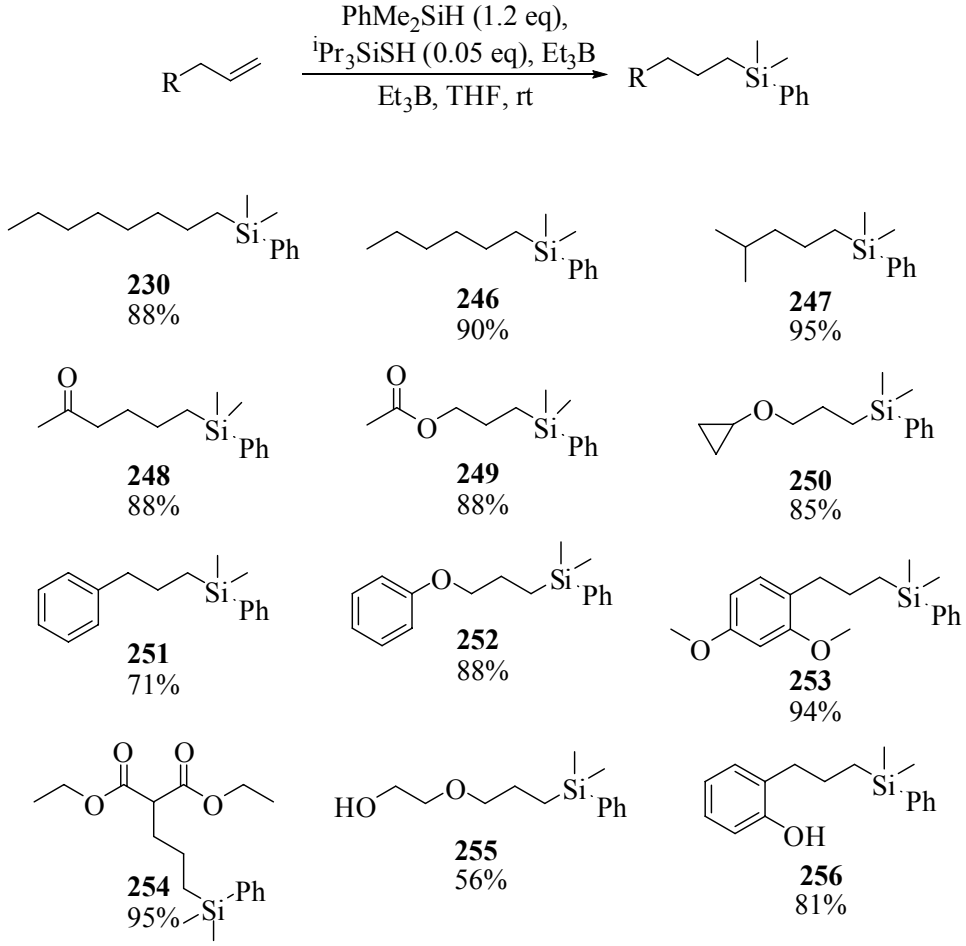
	Et_3B		Ratio[a]			Isolated yield
	portions	equivalents	**244**	:	**245**	(%)
1	2	1	1	:	0.4	27
2	1	0.5	1	:	1.1	52
3	2	0.25	1	:	1.4	58
4	4	0.1	1	:	2.5	71
5	1	1	1	:	7	87
6	2	0.5	1	:	35	97
7 [b]	2	0.5	1	:	0	N/A

a - the ratio was determined by ^{1}H NMR spectroscopy

b - the reaction was attempted in the absence of ^{i}Pr$_3$SiSH

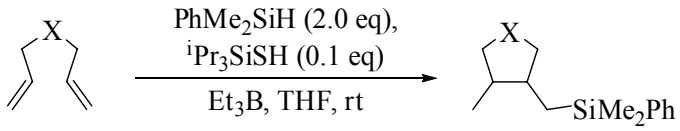
Scheme 98 and **Table 5**

These conditions were then applied to a range of alkenes, where it was found that phenyldimethylsilane efficiently adds to a range of alkenes in the presence of triethylborane and 5 mol% of triisopropylsilanethiol (**Scheme 99** and **Table 6**).



Scheme 99 and Table 6

After the successful addition of dimethylphenylsilane to various terminal alkenes, attempts were made at the cyclisation of a 1,6-diene, however it was found that polymerization occurred under the standard conditions. It was subsequently found that by increasing the dilution, and increasing the amounts of triisopropylsilanethiol and dimethylphenylsilane, clean 5-*exo* cyclisation occurred (**Scheme 100, Table 7**).



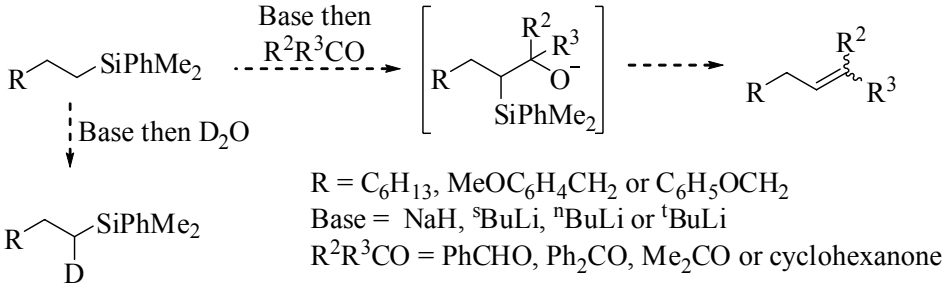
X	Yield (%)	d.r. [a] *trans* :*cis* [b]	Product
O	61	1 : 2.4	**232**
CH_2	70	1 : 2.2	**233**
$C(CO_2Et)_2$	88	1 : 4	**234**
CHOH	73	N/A [c]	**239**

a - d.r. determined from the ^{1}H NMR spectrum
b - assignment based on comparison with literature compounds and NOESY NMRs
c - d.r. could not be determined

Scheme 100 and Table 7

3.3.3 – Ionic reactions of alkyl- and aryl-silanes

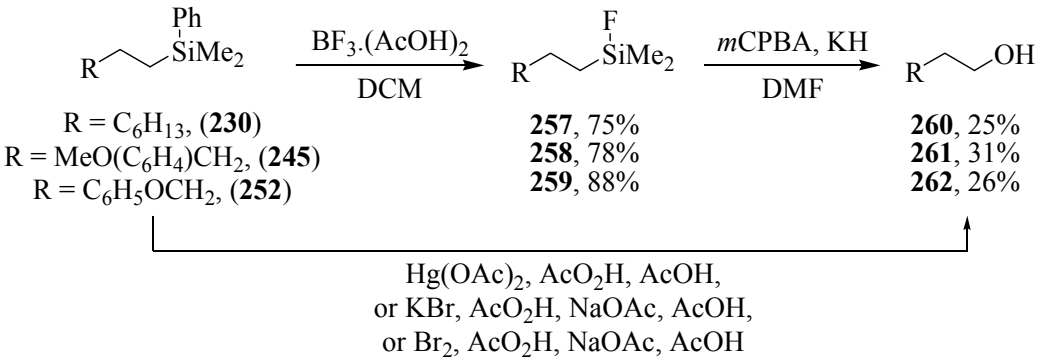
With a range of organosilicon adducts to hand, attention turned to the subsequent ionic tranformations. Initial attempts concentrated on the formation of alkenes using the Peterson reactions. However, treatment of the organosilicon adducts with one of a wide variety of bases (^{s}BuLi, ^{n}BuLi, ^{t}BuLi or NaH) and an aldehyde or ketone (PhCHO, Ph_2CO, acetone or cyclohexanone) (**Scheme 101**) all failed. Subsequent attempts were made to quench the initial anion, formed by deprotonation, by D_2O but again this only resulted in isolation of starting material. It is likely that, with no anion stabilising group alpha to the silicon atom, the organosilicon adducts are not deprotonated.[194]



Scheme 101

Attempts were then made at oxidative removal of the silyl group following the method developed by Fleming,[200, 201] where the phenyldimethylsilyl group is used as a masked hydroxyl group. Cleavage of the Si–Ph bond can be accomplished using boron trifluoride acetic acid complex to form the corresponding fluoro-silane **258, 259** and **260** in 75-88% crude yields (**Scheme 102**). Subsequent oxidation using *meta*-chloroperoxybenzoic acid

and potassium fluoride gave the desired alcohols **261**, **262**, and **263** however in a low yield of 25-31%. The use of various oxidative conditions has been reported in the literature, to give alcohol products in yields of up to 90-95%. Unfortunately, in our hands, when treating the phenyldimethylsilane with *m*CPBA/KF in different solvents or with AcOOH/Et_3N there was no improvement in the yield of the alcohols. Also, a one-pot conversion of the phenyldimethylsilane into the desired alcohol was explored using the conditions developed by Fleming,[200] however these also gave the alcohols in low yield (typically less than 10%).



Scheme 102

3.4 – Reactions of alkoxysilanes

An alternative approach was then explored involving the radical addition of ethoxysilanes and methoxysilanes (including $(EtO)_3SiH$, $(EtO)_2MeSiH$, $(MeO)_3SiH$ and $(MeO)_2MeSiH$) to C=C bonds, to give alkoxysilane adducts, that are precursors of the Tamao oxidation.[202-204] However, it was found that initiation using Et_3B and a thiol catalyst resulted in mainly recovered starting material. Even when using $^tBuOO^tBu$ as initiator, and heating in a sealed tube, only starting alkene was recovered.

3.5 – Reactions of chlorosilanes

3.5.1 – Addition of chlorophenylsilane

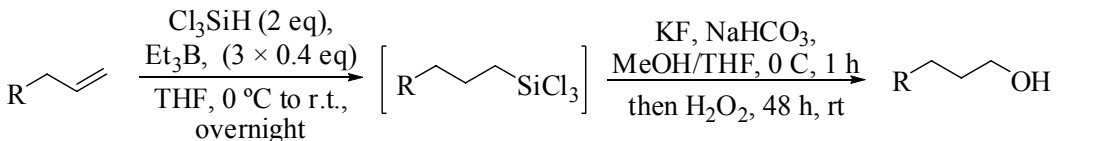
An alternative precursor for the Tamao oxidation are chlorosilanes, particularly trichlorosilanes,[202, 205] and so an investigation of the radical additions of a range of chlorosilanes was explored. Initial attempts concentrated on the radical additions of chlorodimethylsilane or dichloromethylsilane to a range of alkenes (1-octene, 4-allylanisole and 4-allyl-1,2-dimethoxybenzene). Unfortunately no reaction occurred in the presence of 1 equivalent of triethylborane, with no thiol catalyst, despite an exotherm being generated (attempts at cooling the reaction mixture in an ice bath, also proved to be unsuccessful). In the presence of a thiol catalyst the NMR spectra of the unpurified

reaction mixtures were complex, most likely due to formation of products derived from nucleophilic attack of the thiol onto the chlorosilane.

Pleasingly, based on ^{1}H NMR spectra of the crude reaction mixtures, the radical additions of chlorodiphenylsilane or dichlorophenylsilane to 1-octene or 4-allylanisole with 2 portions of 0.5 equivalent of triethylborane, in a ice bath (0-5 °C), with no thiol catalyst, proceeded efficiently. However, isolation of the adducts using column chromatography was not possible, due to the high reactivity of the adduct chlorosilane. It should also be noted that neither chlorodiphenylsilane or dichlorophenylsilane are available pure (from commercial sources), and this, coupled with their relatively high expense, resulted in exploration of alternative chlorosilanes.

3.5.2 – Addition of trichlorosilane

It was then decided to investigate the radical addition of trichlorosilane to C=C bonds using triethylborane as the initiator. Trichlorosilane is commercially available and is relatively inexpensive. Pleasingly it was found that treatment of a terminal alkene with 3 portions of 0.4 equivalent of triethylborane, in an ice bath, with no thiol catalyst, resulted in the reaction proceeding to completion (**Scheme 103**). The ^{1}H and ^{13}C NMR spectra of the reaction mixtures indicated the clean formation of the desired adducts. It is worth noting that although the initial reactions were successful, it was found that, after a while, the reactions stopped working. This was attributed to decomposition of the trichlorosilane, which was overcome by the use of bottles from Aldrich, with a SureSeal™ cap on. Due to the high reactivity of the intermediate organosilicon adduct, isolation and purification was not possible. This resulted in the crude reaction mixtures being taken forward to the subsequent oxidation chemistry. Treatment of the chlorosilane under Tamao oxidation conditions, using potassium fluoride and sodium hydrogen carbonate in THF/MeOH, followed by the addition of hydrogen peroxide proceeded to afford the desired alcohols in good yields (**Scheme 103**).



R = C_5H_{11}, **260**, 39%
R = $MeOC_6H_4$, **261**, 51%

Scheme 103

Following the successful one-pot transformation of the two test alkenes into the corresponding alcohols, the reaction of other alkenes was examined, where for alkenes possessing an alkyl, aryl or ether functionality the reactions proceed well (**Table 8**).

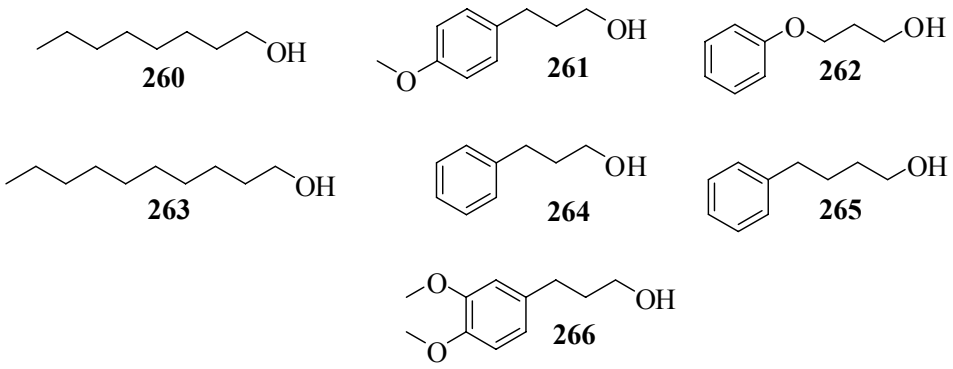
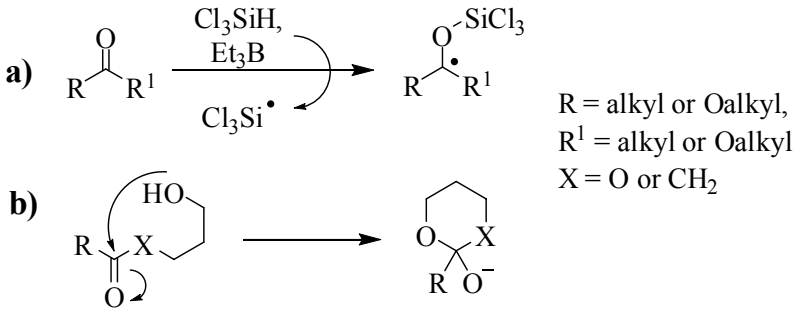


Table 8

However, for alkenes containing a carbonyl group, either an ester or ketone, (**Table 9**) the reaction afforded a complex mixture, possibly due to one of two competing side reactions:

a) the initial silicon radical is able to add to the carbonyl oxygen

b) following the oxidation of the trichlorosilyl group, the resulting alcohol is set up for a 6-*exo* cyclisation on to the carbonyl in all cases, to afford a cyclic ester or lactol (this is supported by the presence of multiple carbonyl peaks in the ^{13}C NMR spectrum, for the product derived from diethyl allylmalonate).



Scheme 104

Attempted addition of trichlorosilane to alkenes bearing an alcohol or amide group was also unsuccessful, (**Table 9**) resulting in complex NMR spectra for the unpurified products (with no evidence of the starting alkenes). This is not unsurprising, due to the potential for ionic reactions between the nucleophilic nitrogen and oxygen atoms and the electrophilic trichlorosilane.

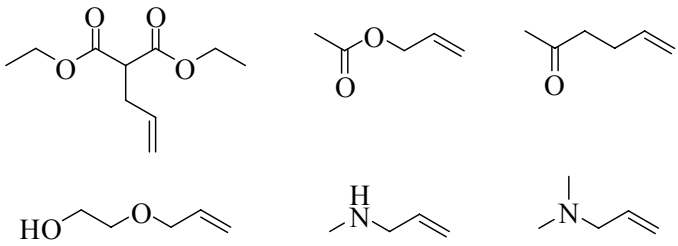
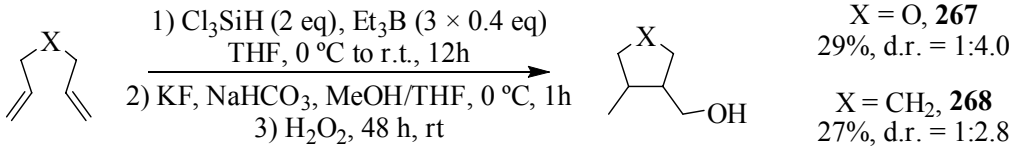


Table 9

Following the successful addition of trichlorosilane to "simple" alkenes, the synthetically more useful cyclisation of dienes, followed by oxidation, was attempted. It was found that under the standard conditions used above, the addition of the trichlorosilane to the dienes resulted in polymerization (based on the broad peaks in the NMR spectrum of the crude reaction mixture). However, efficient cyclisation was found to occur under increased dilution to afford the corresponding cyclic trichlorosilyl products in reasonable yields. Subsequent oxidation of the cyclic trichlorosilyl products, using the above method, resulted in the isolation of the expected cyclic alcohols (**Scheme 105**).



Scheme 105

The addition-cyclisation/oxidation chemistry was also tried using diethyl diallylmalonate, and although the addition-cyclisation step proceeded well, based on the ^{1}H and ^{13}C NMR spectra of the reaction mixture, the oxidation stage resulted in complex NMRs and TLCs of the unpurified reaction mixtures.

3.6 Conclusion

Following the unsuccessful results of the phosphorus hydride mediated cyclisation of dienes (bearing an unprotected nitrogen atom), alternative radical addition methods were explored. Our investigation focused on the radical mediated addition of silanes to alkenes. Several methods for functionalisation of the organosilane adducts are available, including Peterson olefination[193, 194] or the Fleming-Tamao oxidation.[200-204] However, there are few examples where radical hydrosilylation of an alkene is combined with the functionalisation of the adduct.

Our starting point was tris(trimethylsilyl)silane, which was found to add to alkenes. However, fragmentation of the initially formed silicon-centred radical occurred and this gave a mixture of products. This led us to study the use of alkylsilanes and arylsilanes.

Following previous work by Roberts, we have shown that, in conjunction with a thiol catalyst, alkylsilanes and arylsilanes add to simple terminal alkenes using AIBN as the initiator. Unfortunately, attempted addition/cyclisation of 1,5-dienes was unsuccessful. However, it was found that efficient cyclisation of dienes could be achieved using di-*tert*-butyl peroxide as the initiator in hexane in a sealed tube at 140 °C. Due to the harsh reaction conditions it was desirable to find an alternative, milder method for the radical addition chemistry.

Pleasingly, the addition of phenyldimethylsilane to a range of alkenes was achieved by using triethylborane as the radical initiator in the presence of triisopropylsilanethiol. It was also possible to carry out the cyclisation of 1,6-dienes to afford the corresponding pentacycles. However, attempted Peterson reaction of the organosilicon adducts proved unsuccessful. Attempts at the oxidative removal of the phenyldimethylsilyl group were examined, using conditions developed by Fleming, where it was found that efficient conversion to the corresponding fluoro-silanes was possible, however, the subsequent oxidation gave the desired alcohols in disappointing yields.

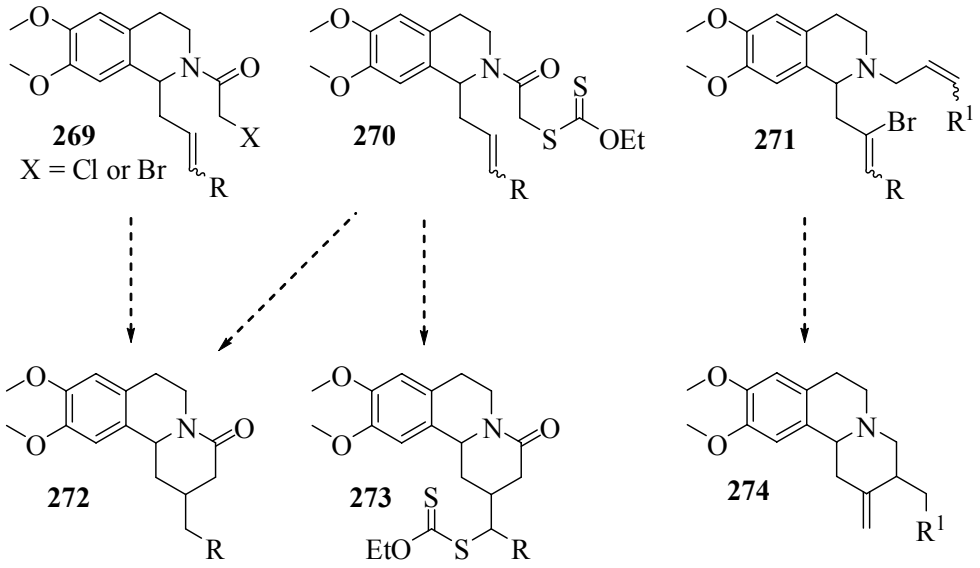
Alternative approaches examined radical additions of various ethoxysilanes and methoxysilanes, however it was found that these were unsuccessful resulting in only starting alkene. Pleasingly, it was found that addition of trichlorosilane to C=C bonds could be achieved in the presence of triethylborane as a radical initiator in the absence of a thiol catalyst. However, isolation of the intermediate adducts was not possible due to the high reactivity of the chlorosilane. The unpurified product was taken forward to the subsequent Tamao oxidation, which gave the desired alcohols in good yields. However this chemistry is limited due to the reactivity of the chlorosilane, for example, reactions with compounds containing an amine or alcohol group fails.

Chapter 4 – Results and Discussion
Tributyltin hydride mediated cyclisation approaches toward protoemetinol (88)

Following the disappointing progress towards *Alangium* alkaloids using a phosphorus hydride mediated radical cyclisation of a 1,7-diene (Chapter 2), and the limitations of the silane radical additions and the subsequent conversion of the silane adducts into useful precursors (Chapter 3), this resulted in a change to our synthetic strategy. Alternative approaches to protoemetinol (**88**), using more classical tributyltin hydride-mediated radical cyclisations, starting from xanthates or organohalides were explored.

4.1 - Synthesis of the allyl-tetrahydroisoquinoline core

Several proposed routes, including the cyclisation of an α-halocarbonyl **269**, a xanthate **270** or vinyl bromide **271**, were predicted to form the alkaloid core ring systems **272**, **273** or **274**, respectively (**Scheme 106**). It was envisaged that each of the resulting cyclic products could subsequently be elaborated into protoemetinol (**88**).

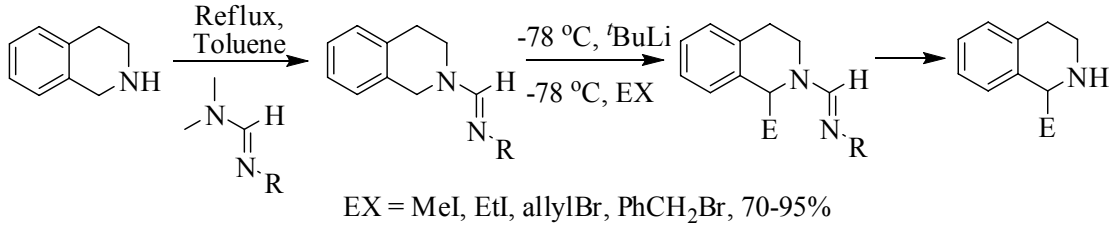


Scheme 106

4.1.1 – Myer's approach to an allyl-tetrahydroisoquinoline core

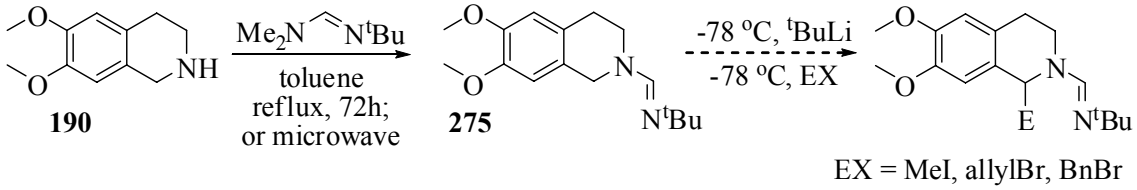
In all cases, a precursor allyl-tetrahydroisoquinoline is required, which could be prepared following previous work by Myers and co-workers. It has been shown that tetrahydroisoquinolines can be substituted at the 1-position by installing an auxiliary on nitrogen, followed by deprotonation of the formamide and quenching with an electrophile

(**Scheme 107**).[151] Asymmetric alkylations are possible when using an L-valinol derived formamide,[152] to give good yields of 1-alkyl tetrahydroisoquinolines in high enantiomeric excess.



Scheme 107

This route allowed for an efficient synthesis of the non-methoxy isoquinoline **203** (**Scheme 89**), suitable for model studies, however, the corresponding 6,7-dimethoxyisoquinoline is required for the synthesis of the *Alangium* alkaloids. This led to attempts at repeating the synthetic sequence starting from 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**190**) (**Scheme 108**). To efficiently prepare the formamide **275** it was found that carrying out the reaction in a sealed reaction tube in a microwave oven at 150 °C, allowed for complete conversion in 2 h as indicated by LCMS and ^{1}H NMR spectroscopy analysis of the reaction mixture. However, purification by silica column chromatography resulted in low yields of isolated formamide **275**, together with unknown by-products that were not present in the reaction mixture. Subsequent attempts to elaborate the unpurified formamide (by deprotonation with ^{s}BuLi or ^{t}BuLi, and quenching with allyl bromide, methyl iodide or benzyl bromide), resulted in complex reaction mixtures, with no clean isolated products after column chromatography on silica. This led to a search for other possible *N*-protecting/activating groups.

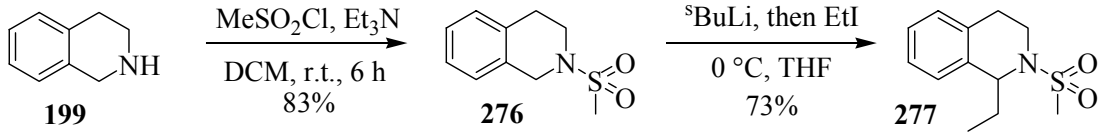


Scheme 108

4.1.2 – Methylsulfonyl approach to an allyl-tetrahydroisoquinoline core

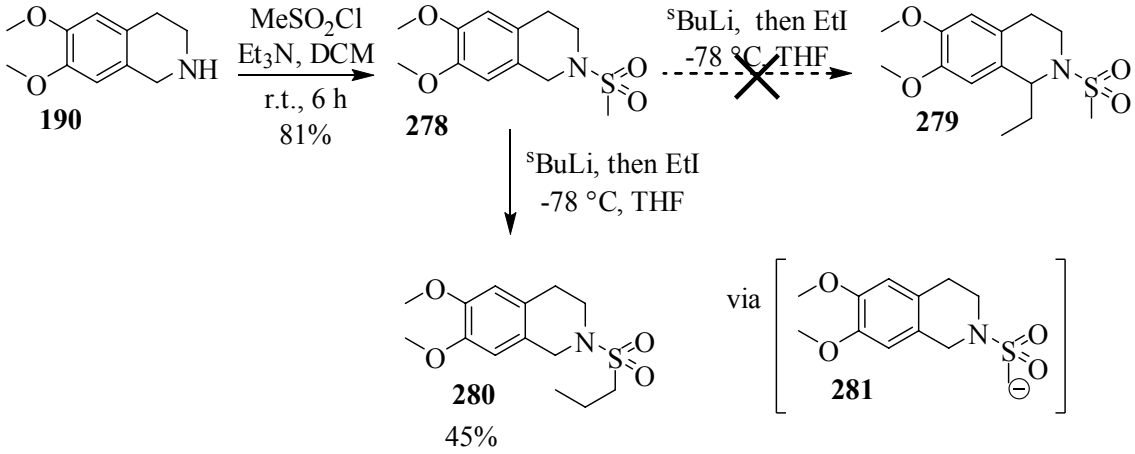
Initially, 2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (**276**) was prepared from the quinoline **199** in 83% yield (**Scheme 109**). The sulfonamide **276** was then treated with

^{s}BuLi, followed by iodoethane, which resulted in the efficient synthesis of the alkylated isoquinoline **277** in 73% yield.



Scheme 109

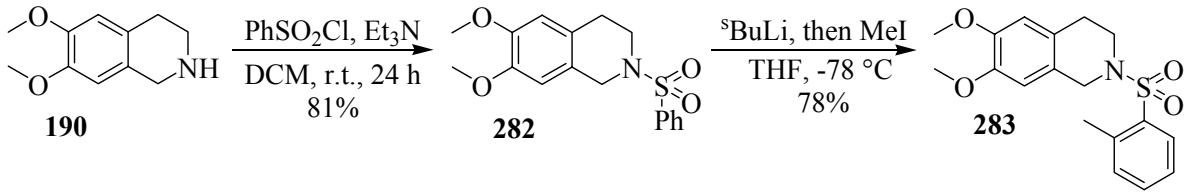
However, when the same procedure was repeated using the dimethoxyisoquinoline **199**, the deprotonation step of the sulfonamide **278** was less successful, with initial attempts resulting in decomposition products, but this could be minimised by maintaining the temperature at –78 °C (**Scheme 110**). However, on reaction with ethyl iodide, the expected product (**279**) was not observed, instead, the ethyl group added to the methylsulfonyl group to yield the propylsulfonyl (**280**), due to deprotonation of the methylsulfonyl group, to afford intermediate **281**.



Scheme 110

4.1.3 – Phenylsulfonyl approach to an allyl-tetrahydroisoquinoline core

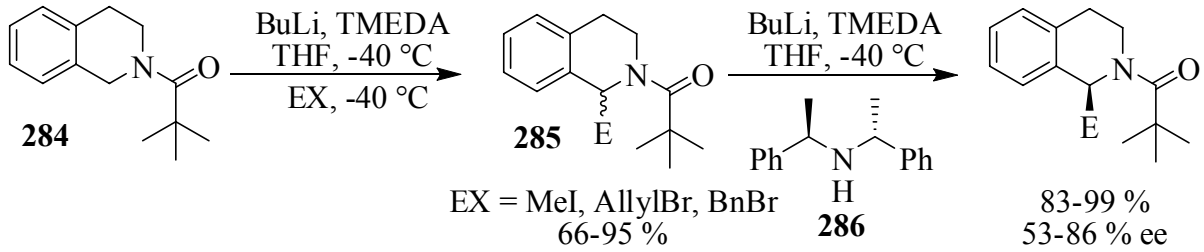
Protection using a phenylsulfonyl group was then explored and the 2-phenylsulfonyl derivative **282** was prepared from isoquinoline **190** in 81% yield (**Scheme 111**). The sulfonamide **282** was then deprotonated at –78 °C followed by the addition of iodomethane. This, however, resulted in *ortho*-lithiation of the phenylsulfonyl group, to afford 6,7-dimethoxy-2-(*o*-tolylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (**283**).



Scheme 111

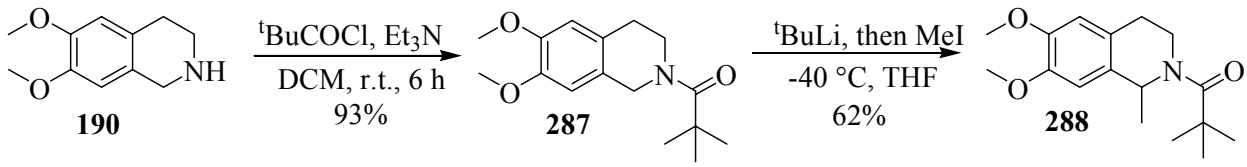
4.1.4 – *N*-Pivaloyl approach to an allyl-tetrahydroisoquinoline core

Work by Simpkins,[206] involving the enantioselective protonation of lithiated tetrahydroisoquinolines (building on previous work by Seebach),[207, 208] established that an *N*-pivaloyl tetrahydroisoquinoline (**284**) could be substituted at the 1-position to give a racemic product (**285**) (**Scheme 112**). However, further metallation followed by reaction with a chiral proton quench (**286**) gave enantiomerically enriched product.



Scheme 112

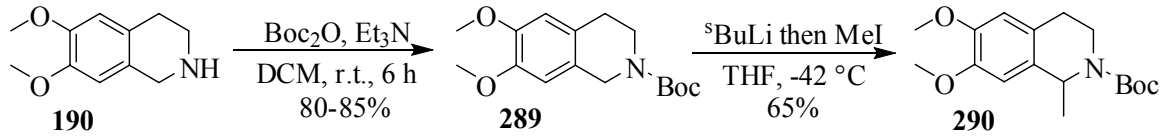
Following this route, the *N*-pivaloyl isoquinoline **287** was prepared (**Scheme 113**). Subsequent deprotonation of a solution of **287** in THF at low temperature, using *tert*-butyllithium, resulted in the solution changing to a deep red colour, which faded to orange on quenching with MeI. On work up, the expected methylated pivaloyl **288** was obtained in 62% yield. However, there were concerns about how easy it would be to cleave the amide group and so an alternative *N*-protecting group was examined.



Scheme 113

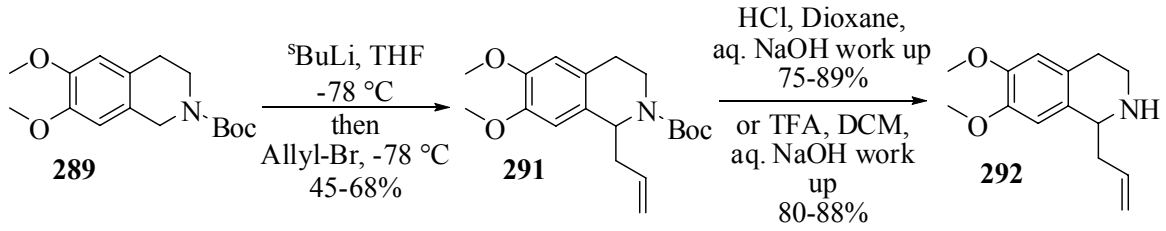
4.1.5 – *N*-Boc approch to allyl-tetrahydroisoquinoline core

The Boc protected isoquinoline **289** was prepared in 80-85% yield and subsequently methylated to give carbamate **290** in 65% yield, along with some decomposition products (**Scheme 114**).



Scheme 114

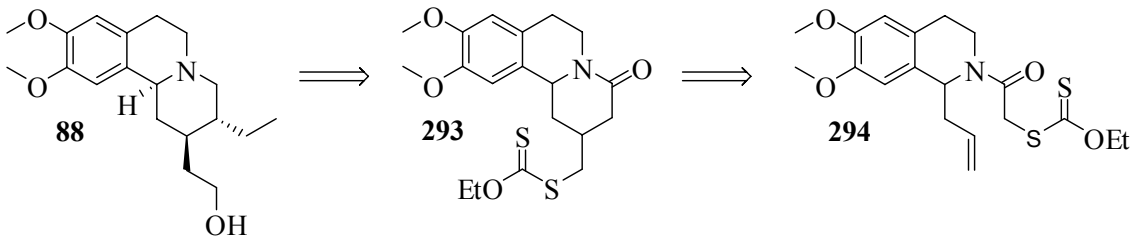
With the success of the metallation, the process was repeated and the desired allyl fragment was introduced (**Scheme 115**). Initially, it was found that low product yields were obtained, but these were improved by carrying out the reactions at –78 °C, although recovered starting material was also obtained. Deprotection of the Boc group, using HCl (10 equiv.) in dioxane, was slow (it required overnight treatment) to give the desired hydrochloride salt, which after aqueous basic work up, afforded the free amine **292** in 75-89% yield. Alternatively, removal of the Boc group could be accomplished by the use of TFA in DCM at rt; after 6 h, following an aqueous basic work up afforded the amine **292** in 80-88% yield.



Scheme 115

4.2 - Synthesis and reaction of a xanthate or alpha-halo amides

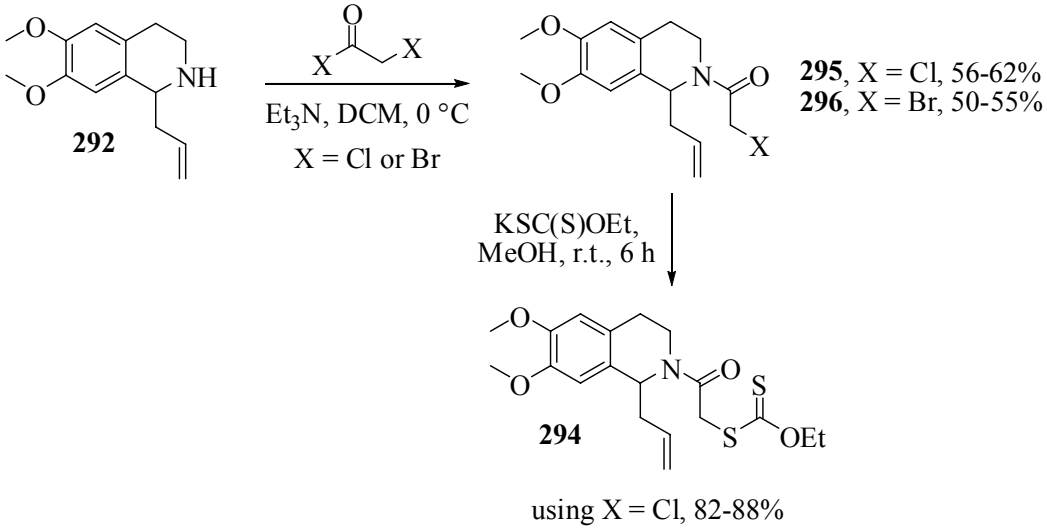
With a robust route to allyl-tetrahydroisoquinoline **292** developed, attention turned to the formation and cyclisation of xanthate **294** (**Scheme 116**). An atom transfer radical cyclisation of xanthate **294** was expected to afford the cyclic xanthate **293**, which could then be elaborated to protoemetinol (**88**) (**Scheme 116**).



Scheme 116

4.2.1 - Synthesis of alpha-halo amides and xanthate

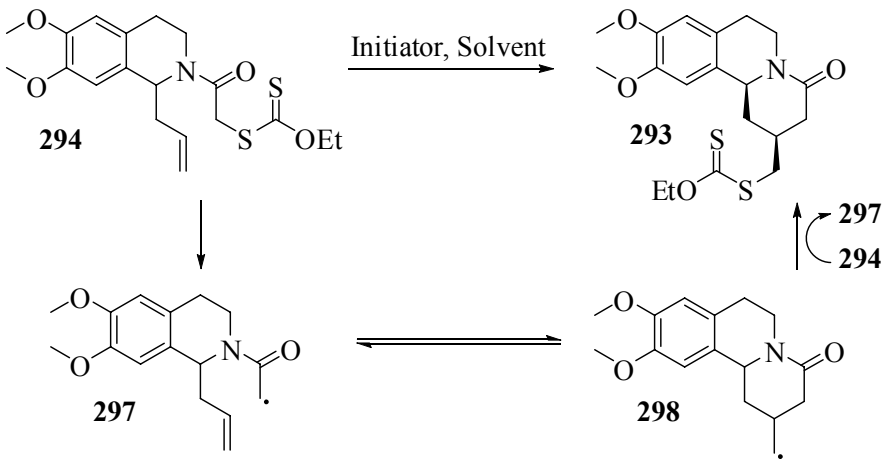
The xanthate **294** was prepared by reaction of the secondary amine **292** with chloroacetyl chloride or bromoacetyl bromide, to form the corresponding halo-amides **295** and **296**, respectively (**Scheme 117**), followed by displacement of the chloride ion using potassium ethyl xanthate. It should be noted, that unsurprisingly **295**, **296** and **294** all occur as slowly interconverting rotamers at room temperature, (with one rotamer prefered over the other). Variable temperature NMR studies were carried out and showed incomplete coalescence of the peaks at 100 ºC in DMSO.



Scheme 117

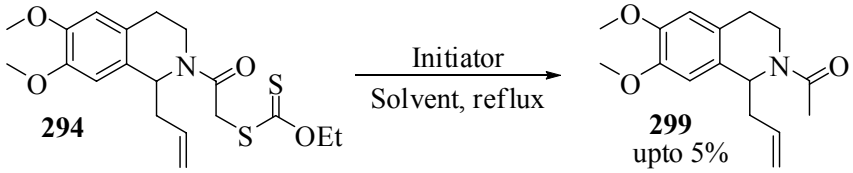
4.2.2 – Radical reactions of xanthate (294)

Treatment of xanthate **294** with a radical initiator was expected to form a resonance-stabilised carbamoyl radical **297**, which after 6-*exo* cyclisation would give a less stable primary radical **298**. Primary radical **298** could then react with a molecule of starting material in a xanthate transfer reaction, to afford the cyclic xanthate **293** (**Scheme 118**).



Scheme 118

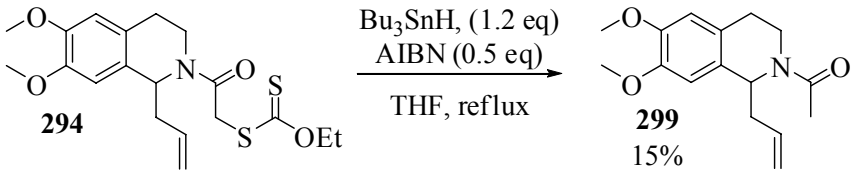
It was with some disappointment that, on treatment of xanthate **294** with dilauroyl peroxide in dichloroethane at reflux,[209-214] no evidence of cyclisation was observed. The major product was recovered starting material, together with a small amount of the direct reduction material **299** (**Scheme 119**) (presumably formed by hydrogen atom abstraction from dichloroethane). Changing the solvent, choice of initiator or equivalents of reagents had little effect, although on increasing the temperature, the NMR spectra of the crude products become more complex.



Initiator = DLP (0.2 - 1 eq), AIBN (0.5 - 1 eq) or Et_3B (4 eq)
Solvent = benzene, DCE, THF, toluene or chlorobenzene

Scheme 119

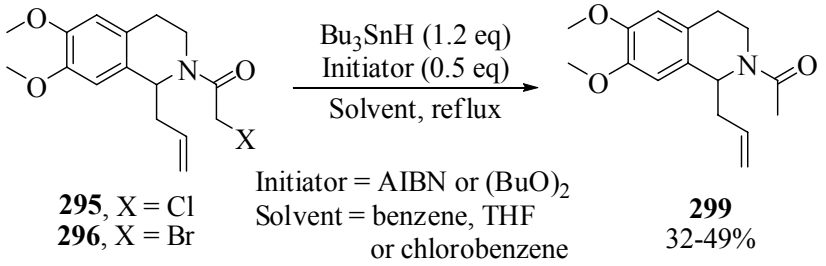
Failure of the xanthate transfer reaction led to treatment of xanthate **294** with tributyltin hydride so as to form the product from reductive cyclisation.[210, 211] However, the NMR spectra of the crude reaction mixture was still complex, and following column chromatography, only the direct reduction product (**299**) was isolated in 15% yield.



Scheme 120

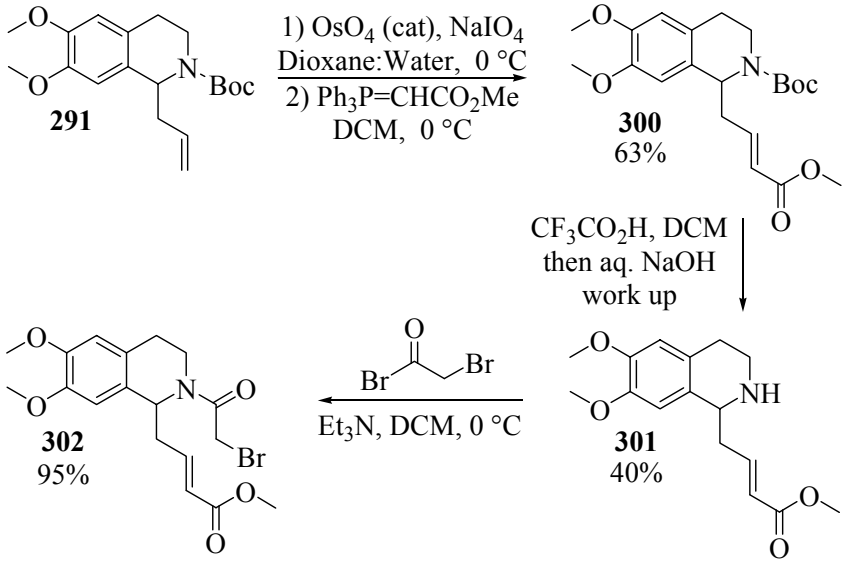
4.2.3 – Radical reactions of alpha-halo amides (295) and (296)

Similarly, attempts to cyclise alpha-chloro or alpha-bromo amides **295** and **296**, using tributyltin hydride under a range of different conditions, were unsuccessful (**Scheme 121**). Only isolation of the direct reduction product (**299**) was observed (in 32-49% yield), with no evidence of the 6-*exo* cyclisation products.



Scheme 121

Previous work has shown that carbamoyl radicals cyclise efficiently onto α,β-unsaturated esters,[215-218] and this led to examining the cyclisation of an α,β-unsaturated ester. Synthesis of the *E*-α,β-unsaturated ester **302** was achieved by an osmium tetroxide catalysed cleavage of the C=C bond in carbamate **291** to give an intermediate aldehyde, which was trapped in-situ by a stabilised phosphorane in a Wittig reaction (**Scheme 122**). The *N*-Boc group was then cleaved using trifluoroacetic acid and formation of the amide was achieved by treatment of the resulting secondary amine with bromoacetyl bromide.



Scheme 122

Subsequent treatment of α,β-unsaturated ester **302** with tributyltin hydride (1.2 equiv) and AIBN (0.5 equiv) in refluxing THF, however, resulted in a complex mixture, with only the

product of direct reduction identified, with no other products isolated. Subsequently it was found that Yamazaki had reported similar attempts to cyclise α,β-unsaturated ester **302**, and in refluxing toluene, they obtained the desired tricyclic ester in only 11% yield.[219] (Yamazaki subsequently showed that the tricyclic core could be accessed by cyclisation of the trichloro-amide **303** using CuCl in acetonitrile at 140 ºC in a sealed tube. Chong has also reported the similar failure of a related α,β-unsaturated ester.[171]) It is proposed that the reason for the poor results of the carbamoyl radicals is due to the slow interconversion of the amide rotamers, where the major conformer has the radical pointing away from the alkene. This is supported by NOESY NMR studies of **299**, **295** and **302**, 25 ºC), which showed no NOESY correlation between the CH_2 or CH_3 of the amide group and the alkene fragment. In addition, the ^{1}H NMR spectra of **294** and **295** in benzene at 70 ºC, showed little change to the NMR spectra run at 25 ºC.

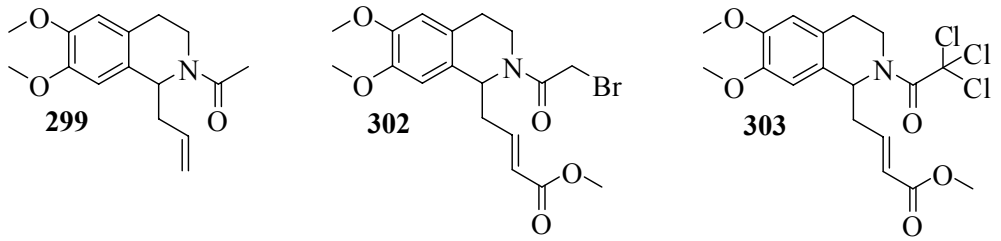
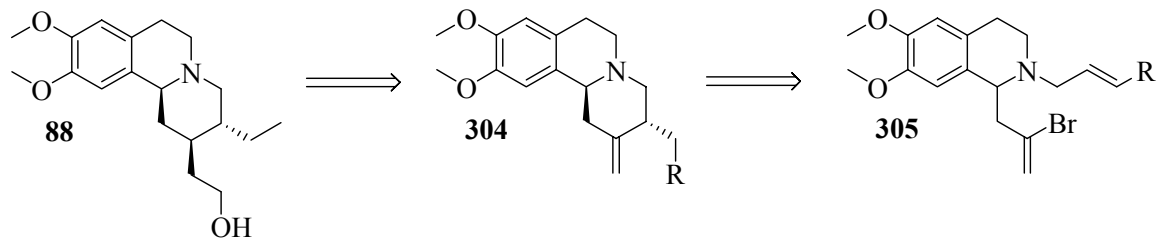


Figure 8

4.3 - Cyclisation of vinyl bromides onto an *N*-allyl fragment

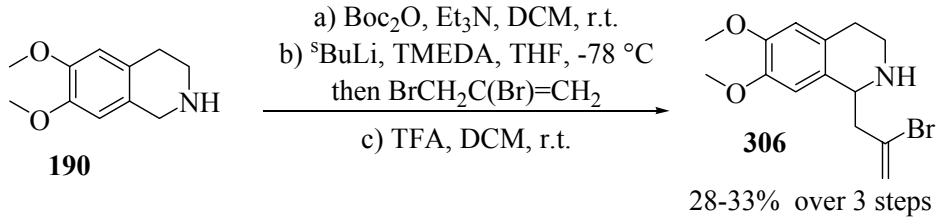
Following the failure of the amide based approach, it was proposed that the tricyclic core of protoemetinol (**88**) could be obtained by cyclisation of vinyl bromide **305** to afford terminal alkene **304** (**Scheme 123**). The C=C bond in **304** could then be functionalised in a cross metathesis reaction (e.g. with methyl acrylate) to afford an α,β-unsaturated ester which on reduction would afford protoemetinol (**88**).



Scheme 123

4.3.1 – Synthesis of vinyl bromide 307

Vinyl bromide **306** was prepared using a similar 4-step procedure to that developed for allyl-isoquinoline **292** (**Scheme 124**). After *N*-protection of 6,7-dimethoxy-isoquinoline (**190**) with a Boc group, deprotonation using *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, then addition of 2,3-dibromopropene, followed by *N*-deprotection, gave secondary amine **306**. Unfortunately, the allylation step proved to be low-yielding (typical 32-39%), perhaps due to the more acidic methylene protons of 2,3-dibromopropene compared to allyl bromide.

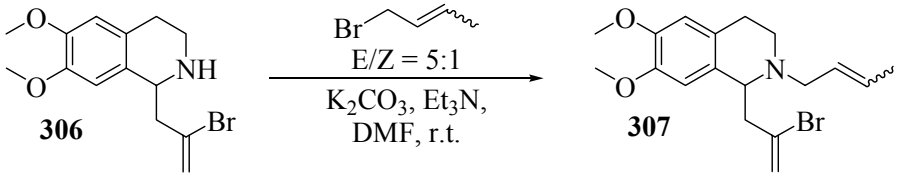


190 **306**

28-33% over 3 steps

Scheme 124

The secondary amine (**306**) was then *N*-crotylated using conditions previously used by Williams,[220] to afford diene **307** in a pleasing yield (**Scheme 125**).



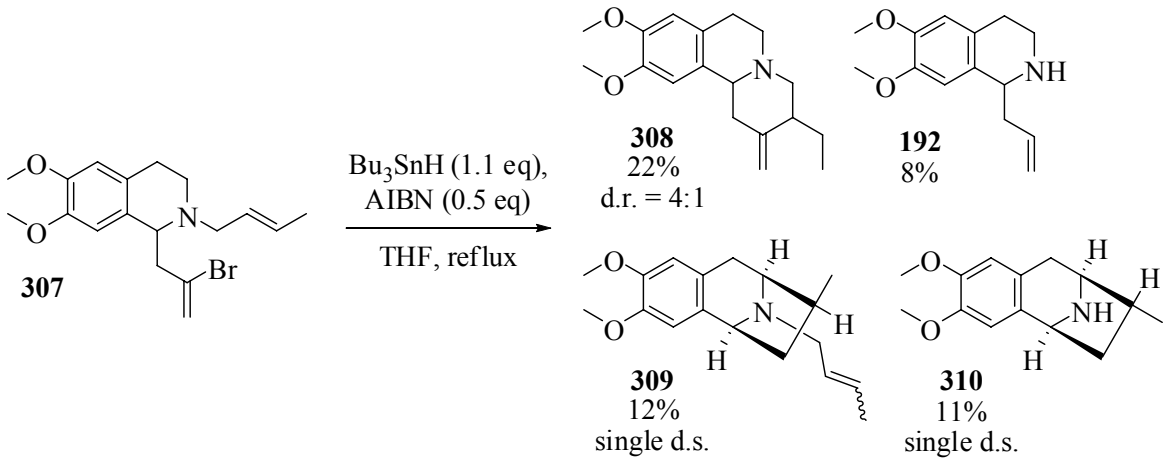
306 **307**

69%, E/Z = 5:1

Scheme 125

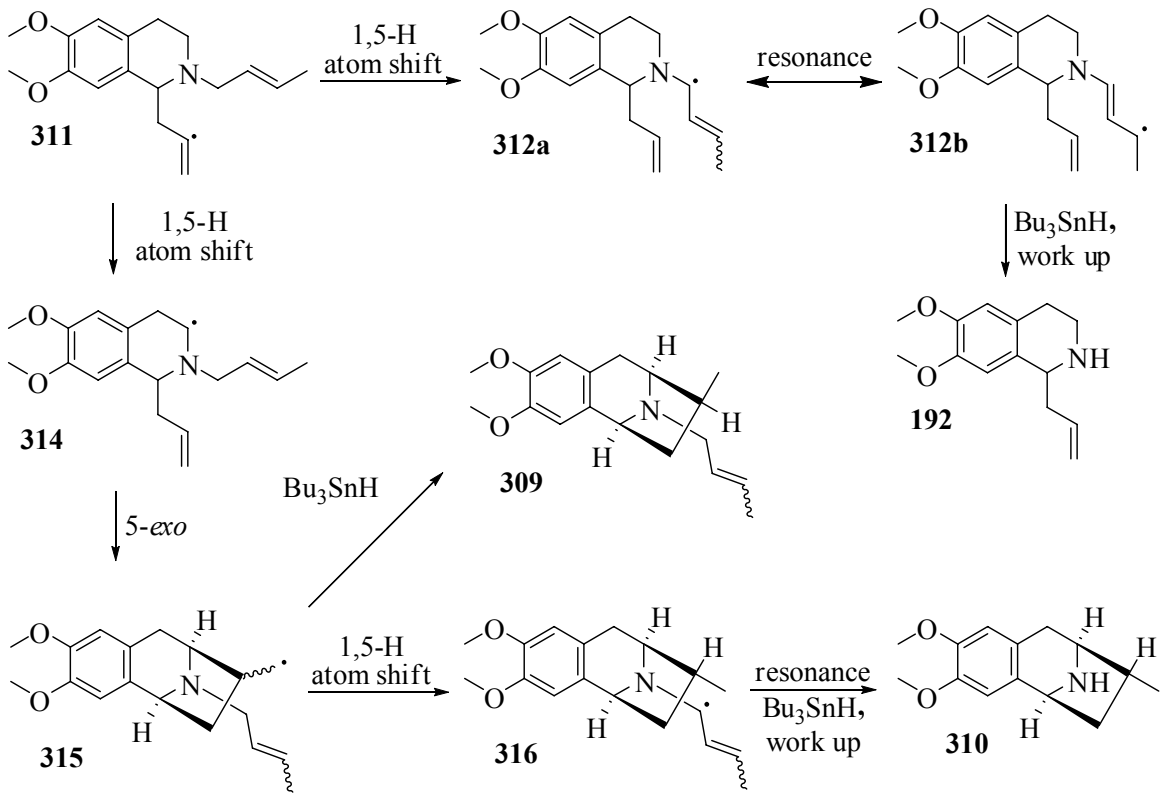
4.3.2 – Radical reaction of vinyl bromide 307

The slow addition of tributyltin hydride and AIBN to a refluxing solution of vinyl bromide **307** in THF afforded a complex mixture of compounds as indicated by TLC and ^{1}H NMR spectroscopy. Following column chromatography, four compounds were isolated: the desired 6,6,6-tricycle **308**; a secondary amine **192**; and two 6,5-fused bicyclic compounds **309** and **310**.



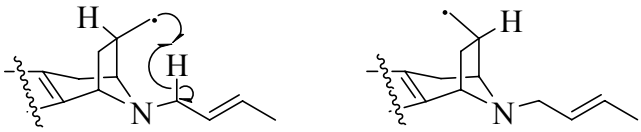
Scheme 126

The desired 6,6,6-tricycle is produced via the expected 6-*exo* cyclisation of the initially formed vinyl radical **311**. Secondary amine **192** could be formed by an initial 1,5-hydrogen atom transfer of vinyl radical **311** to afford resonance-stabilised radical **312a**. Reduction of radical **312b** would form an enamine, which on hydrolysis (on silica column chromatography) gives secondary amine **192**. The 6,5-fused bicyclic compounds **309** and **310** could be formed via an alternative 1,5-hydrogen atom transfer of the initial vinyl radical **311**, followed by 5-*exo* cyclisation to afford the 6,5-bicyclic system **315**. The resulting primary radical could undergo direct reduction to yield **309** or alternatively, another 1,5-hydrogen atom transfer to afford the resonance stabilised radical **316**, which on reduction and hydrolysis (on silica column chromatography) of the resulting enamine gives the bicyclic secondary amine **310**.



Scheme 127

The formation of the single diastereoisomers of **309** and **310**, with opposite stereochemistry for the $CHCH_3$ chiral carbon, can be explained by the stereochemistry of the two diastereoisomers of bicyclic radical **315**. In one diastereoisomer (**315-a**) the primary radical is appropriately positioned to undergo a 1,5-hydrogen atom transfer reaction, however in the alternative diastereoisomer (**315-b**) the radical is unable to undergo a 1,5-hydrogen atom transfer reaction.

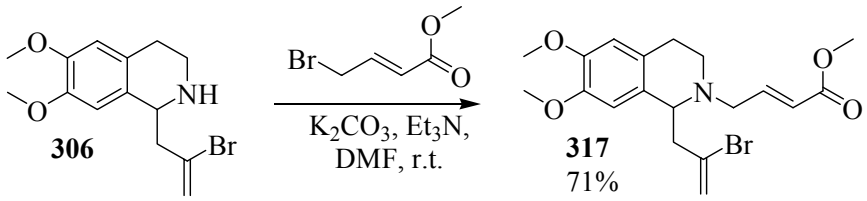


315-a **315-b**

Figure 9

4.3.3 – Synthesis of vinyl bromide 317

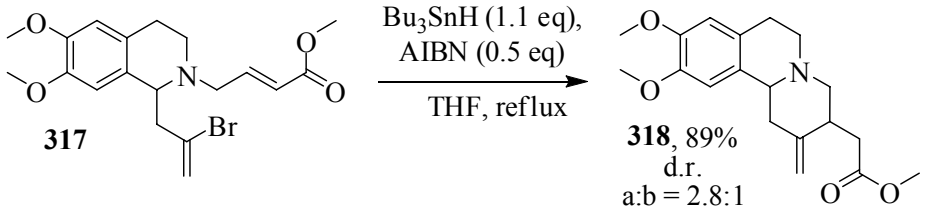
It was envisaged that introducing an ester group onto the acceptor double bond would facilitate the radical cyclisation.[221] This would allow for matching of the polarity of the radical to the acceptor double bond, and should facilitate the cyclisation, and minimise formation of by-products. Hence, α,β-unsaturated ester **317** was prepared from amine **306** in a satisfactory yield (**Scheme 128**).



Scheme 128

4.3.4 – Radical reaction of vinyl bromide 307

Pleasingly, under identical conditions to the reaction of **307** with tributyltin hydride, it was found that α,β-unsaturated ester **317** cleanly afforded the desired tricyclic ester in an excellent 89% yield as a 2.8:1 mixture of partially separable diastereoisomers after column chromatography, with no by-products observed (**Scheme 129**). This crucial, very successful reaction to afford the key tricyclic ester **318**, could be performed on a relatively large scale (3.0 g, 7.5 mmol) with no change in yield or diastereoselectivity.



Scheme 129

The stereochemistry of the two diastereoisomers of **318** was determined from NOESY experiments. The major diastereoisomer is tentatively assigned as having the $CH_2CO_2CH_3$ group in an equatorial arrangement **318-a** (**Figure 10**), which has the desired configuration for proemetinol (**88**). This assignment was based on the presence of a NOESY correlation between the alkene CH=C$\underline{H}_2$ and the C$\underline{H}_2CO_2CH_3$. The minor diastereoisomer was assigned as having the $CH_2CO_2CH_3$ group in an axial arrangement (**318-b**), since the methylene CH=C$\underline{H}_2$ enhances the C$\underline{H}CH_2CO_2CH_3$ signal.

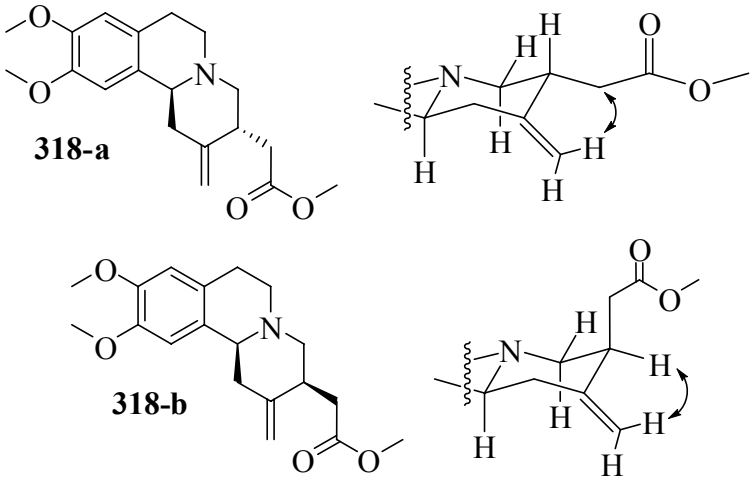
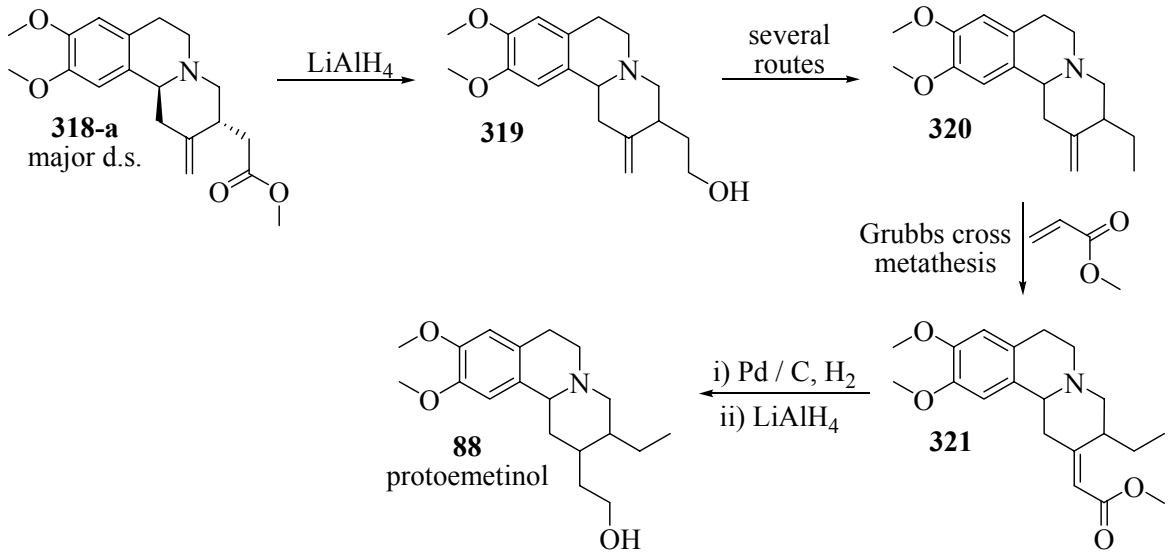


Figure 10

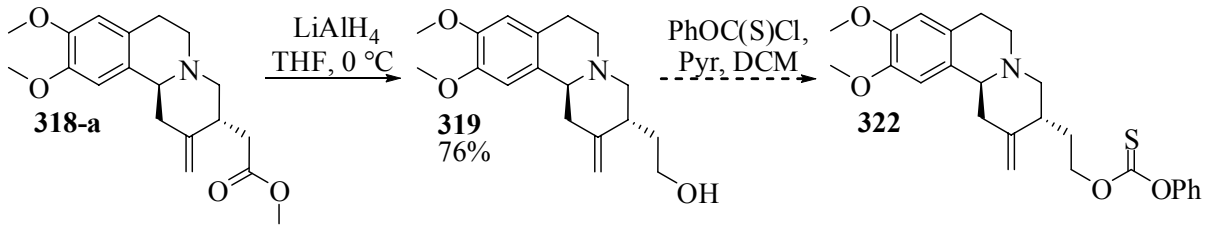
4.3.5 – Approaches to protoemetinol (88) from ester (318-a)

Following the extremely successful cyclisation of vinyl bromide **317** to afford the tricyclic ester **318**, attention then turned to the reduction of the ester side-chain and conversion of the alkene into an alcohol (**Scheme 130**). It was proposed that this could be achieved by an initial lithium aluminium hydride reduction to afford alcohol **319**. There are several strategies to reduce the OH group in **319** including a Barton-McCombie deoxygenation,[46, 222, 223] or conversion of the OH group into a leaving group and a subsequent lithium aluminium hydride reduction. Finally, a Grubbs cross metathesis reaction of the C=C bond in **320** would be expected to afford α,β-unsaturated ester **321**, which could then be reduced to protoemetinol (**88**).



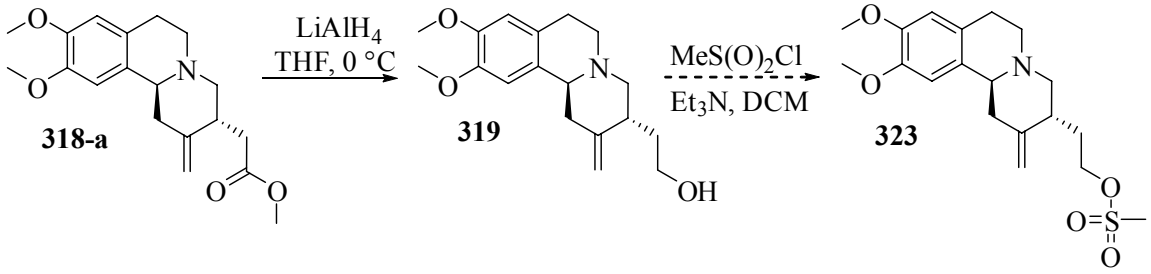
Scheme 130

Gratifyingly, treatment of tricyclic ester **318-a** with lithium aluminium hydride resulted in clean conversion and isolation of the desired alcohol **319**. Unfortunately, subsequent conversion to the Barton ester proved problematic and resulted in decomposition. It was subsequently found that, on standing, alcohol **319** decomposed to give unidentified products.



Scheme 131

Tricyclic ester **318-a** was then treated with lithium aluminium hydride and the unpurified alcohol **319** (^{1}H and ^{13}C NMR spectroscopy confirmed formation of the alcohol) was treated with methanesulfonyl chloride in the hope of forming methanesulfonate (**323**), which could then be treated with a further portion of lithium aluminium hydride**.**[224] Unfortunately, ^{1}H NMR spectroscopy indicated decomposition of the methanesulfonate **323**.

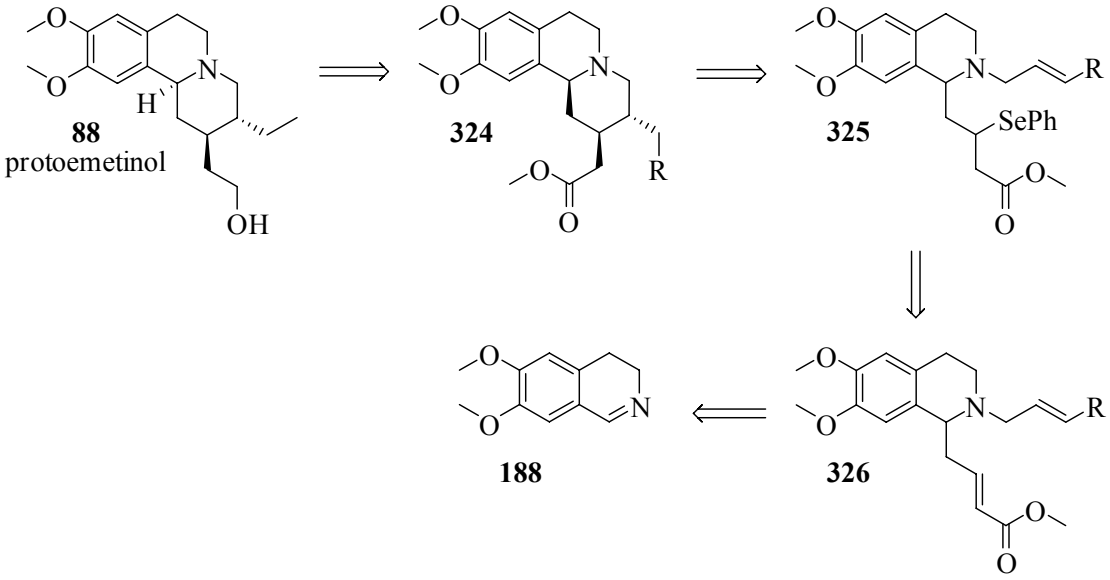


Scheme 132

The decomposition that is observed on converting ester **318-a** into either the Barton ester **322** or methanesulfonate **323**, and the slow decomposition of alcohol **319,** could be explained by nucleophilic attack by the tertiary amine present in the tricyclic core. There are several examples of the relatively facile reactions of related tertiary amines with alkylating agents to afford the quaternary ammonium salts, which are then able to undergo rearrangement or elimination reactions.[225-227]

4.4 Formation and reaction of phenylselenides

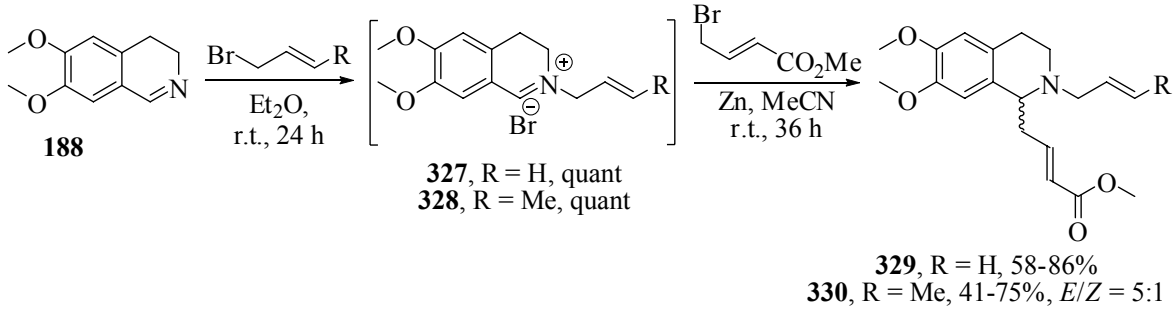
As an alternative route, it was proposed that protoemetinol (**88**) could be accessed from cyclic ester **324**, which in turn, could be prepared by 6-*exo* radical cyclisation of phenylselenide **325** (**Scheme 133**).[228-232] This strategy effectively reverses the order of introduction of the two allylic residues.



Scheme 133

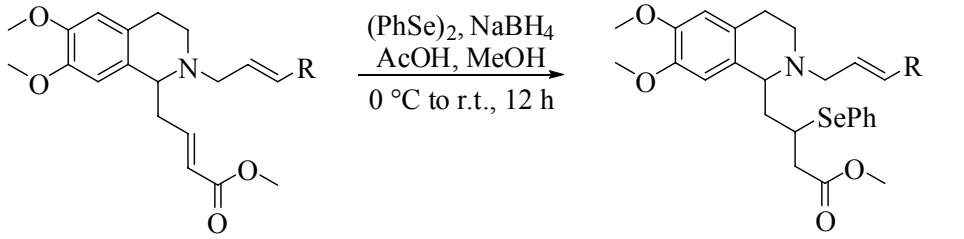
4.4.1 Synthesis of phenylselenides (331) and (332)

The synthesis of phenylselenides **331** and **332** started with the formation of dienes **329** and **330** (**Scheme 134**). The dienes were prepared by treatment of 6,7-dimethoxyisoquinoline **188** with allyl bromide or crotyl bromide to afford the corresponding quaternary salts **327** and **328**, respectively, followed by addition of zinc and methyl (*E*)-4-bromobut-2-enoate to generate an organo-zinc reagent in-situ, which underwent nucleophilic addition to the C=N bonds.



Scheme 134

Treatment of α,β-unsaturated ester **329** and **330** with the sodium salt of phenylselenol (formed by reduction of diphenyl diselenide) yielded only recovered starting material,[233] but it was found that first quenching the sodium salt with acetic acid (to form phenylselenol) resulted in good conversion to the desired selenides **331** and **332** (**Scheme 135**).[234-236]



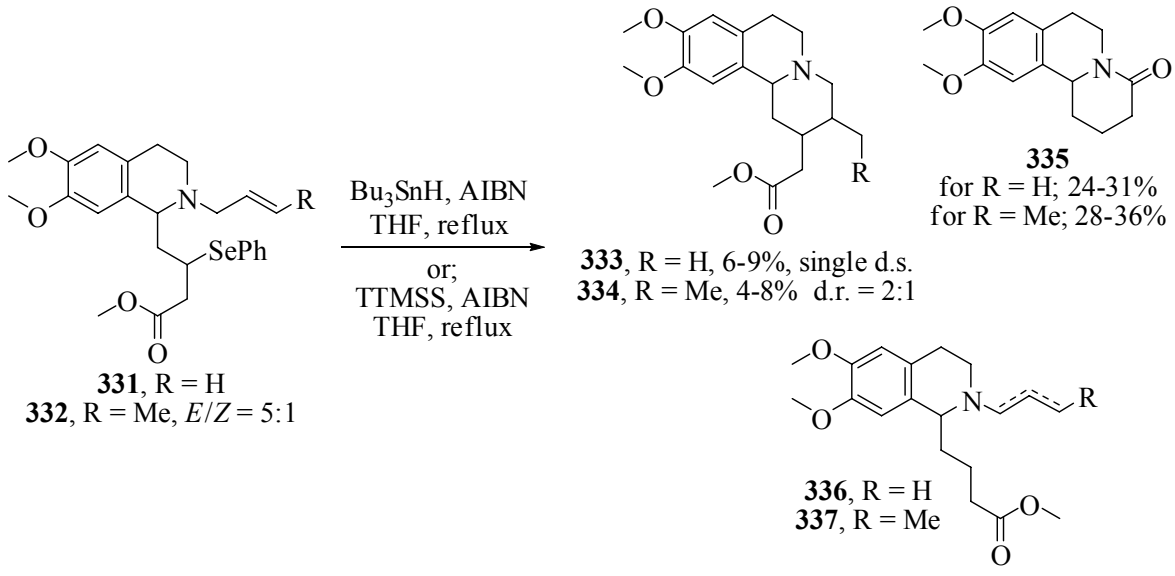
329, R = H
330, R = Me, *E*/*Z* = 5:1

331, R = H, 64-72%
332, R = Me, 66-70%, *E*/*Z* = 5:1

Scheme 135

4.4.2 Radical cyclisation of phenylselenides (331) and (332)

Attention turned to the radical cyclisation of selenides **331** and **332** using tributyltin hydride or tris(trimethylsilyl)silane (TTMSS), which both gave a complex mixture of products, from which two compounds were cleanly isolated (**Scheme 136**). The cyclic amide **335** was isolated as the major compound, while the desired tricyclic ester **333** or **334** was obtained in a disappointingly low yield. From the NMR spectrum of the crude reaction mixture the presence of compounds containing a C=C bond was indicated (such as **336** or **337**), however, these compounds were never isolated.



331, R = H
332, R = Me, *E*/*Z* = 5:1

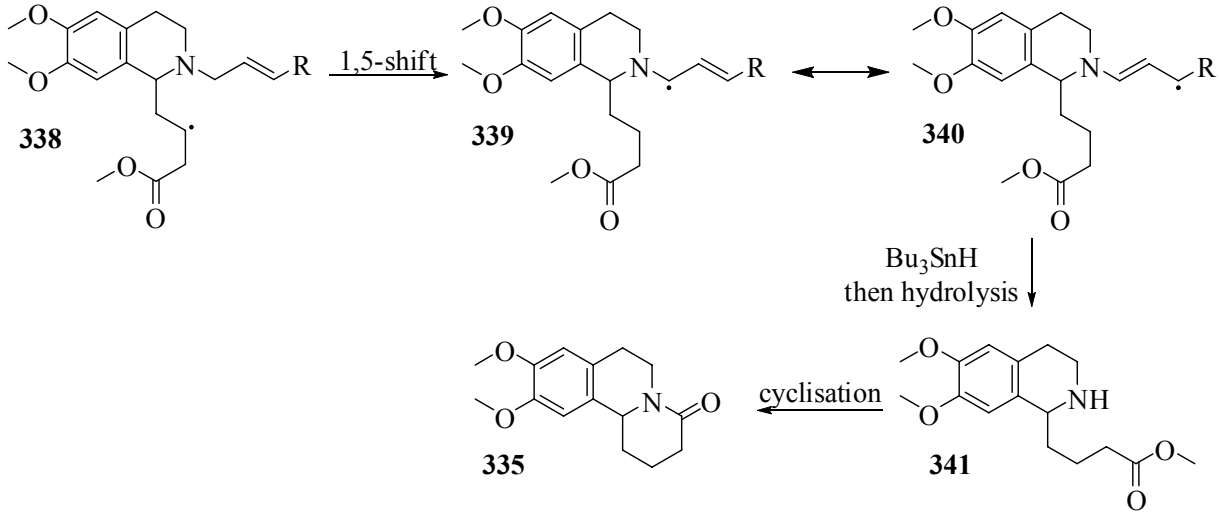
333, R = H, 6-9%, single d.s.
334, R = Me, 4-8% d.r. = 2:1

335
for R = H; 24-31%
for R = Me; 28-36%

336, R = H
337, R = Me

Scheme 136

The formation of the cyclic amide **335** can be explained by a 1,5-hydrogen atom transfer reaction of the initially formed radical **338** (**Scheme 137**), to afford radical **339**, which on reduction of resonance form **340** would afford an enamine – this could explain the presence of compounds containing C=C bonds (**336** and **337**) in the NMR spectra of the crude reaction mixture. Hydrolysis of the enamine would afford the secondary amine **341** that cyclises to form the cyclic amide **335**



Scheme 137

Interestingly the tricyclic ester **333** was isolated as a single diastereoisomer, whereas the tricyclic ester **334** was obtained as a mixture of diastereoisomers, **334-a** and **334-b** as a 2:1 ratio of diastereoisomers. The stereochemistry of **333, 334-a** and **334-b** is tentatively assigned as shown in **Figure 11**, as determined from NOESY experiments.

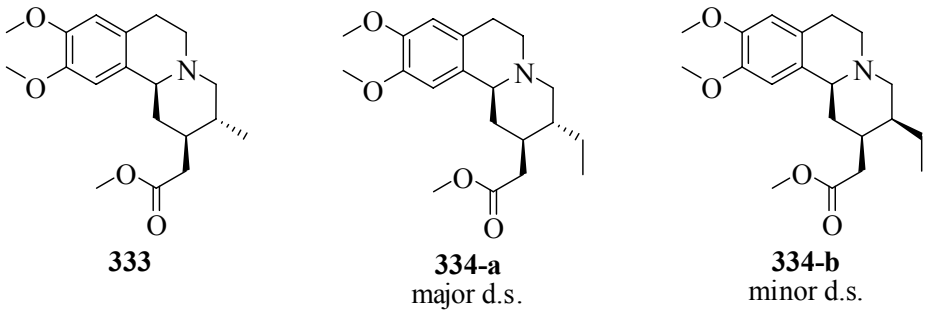
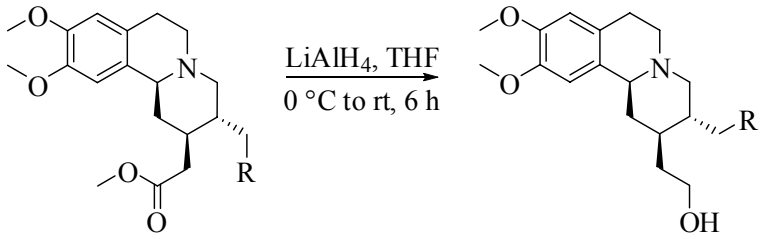


Figure 11

Treatment of the tricyclic ester **333** or **334-a** with lithium aluminium hydride afforded the corresponding alcohols, (±)-des-methyl-protoemetinol (**342**) and (±)-protoemetinol (**88-a)**. Comparison of the ^{1}H and ^{13}C NMR data with published data confirmed the formation of

(±)-protoemetinol (**88-a)**, with the correct stereochemistry. Although (±)-protoemetinol (**88**) was formed using a concise 4-step synthesis, the overall yield (2%) was disappointing.



333, R = H
334-a, R = Me

R = H, **342**, 64-80%
R = Me, **88-a**, 76%

Scheme 138

4.4.3 Synthesis and cyclisation of a vinyl chloride bearing a phenylselenide (343)

To improve the efficiency of the synthesis of protoemetinol (**88**), in particular the radical cyclisation step, the formation and cyclisation of vinyl chloride **343** and α,β-unsaturated ester **344** was explored (**Figure 12**). It was expected that the introduction of an electron-withdrawing Cl or CO_2Me onto the acceptor double bond would increase the rate of 6-*exo* cyclisation, thereby minimizing formation of by-products. For vinyl chloride **343**, it was expected that abstraction of the PhSe group, by a tin-centred radical, would be faster than abstraction of the Cl atom from the C=C bond.

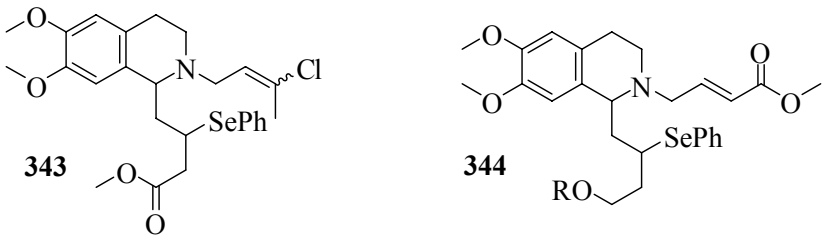
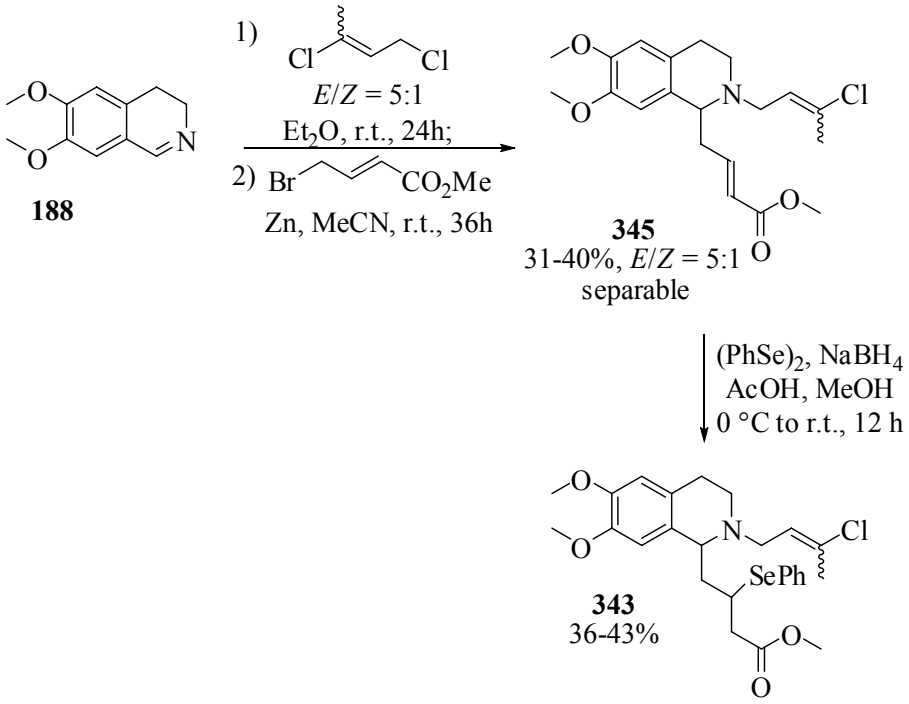


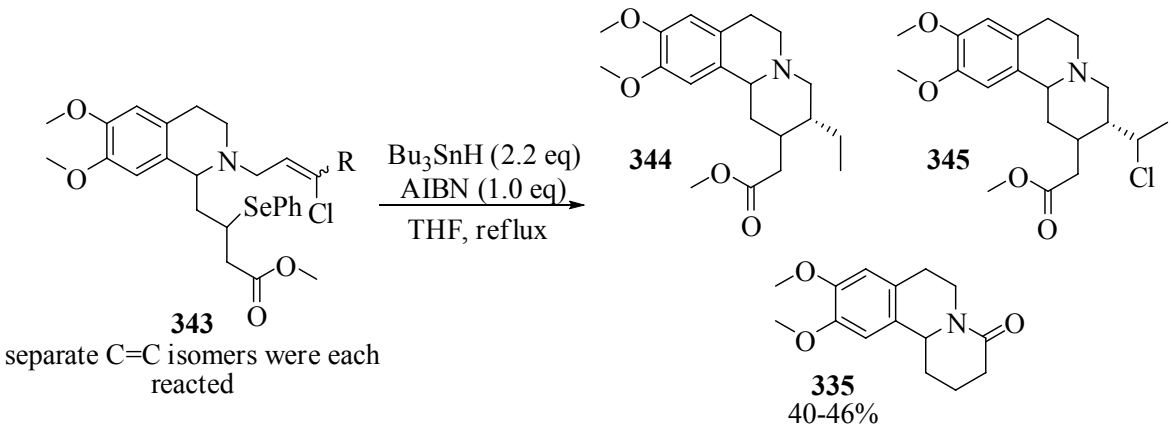
Figure 12

The vinyl chloride **343** was prepared from imine **188** using a familiar two-step sequence, as a separable mixture of *E/Z* isomers, and then converted into phenylselenide **343** (**Scheme 139**).



Scheme 139

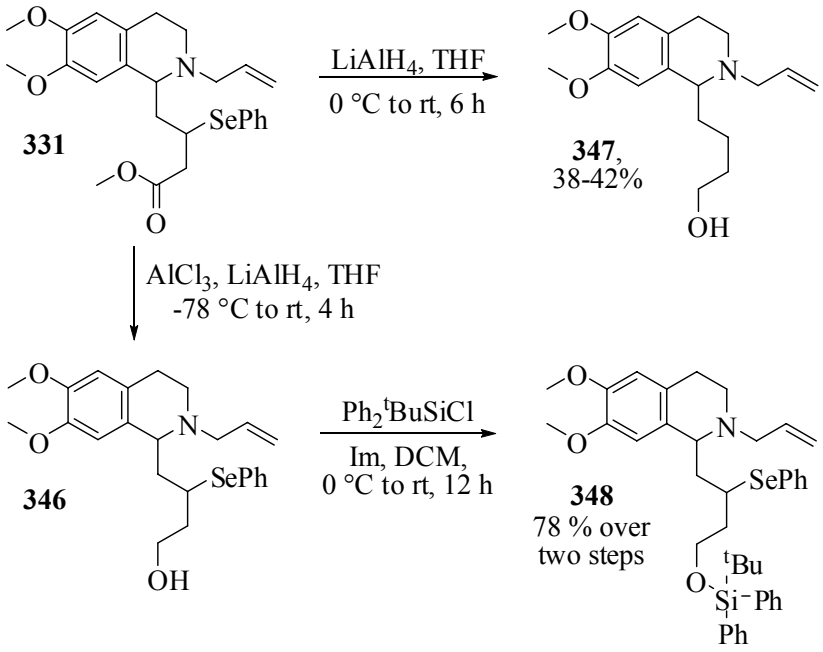
Unfortunately, the attempted radical cyclisation of vinyl chloride **343** using 2.2 equiv. of tributyltin hydride (added slowly to **343**) proved to be disappointing, resulting in a complex mixture of products (**Scheme 140**). The complex mixture contained cyclic products, but reduction of the C–Cl bond was problematic, resulting in a mixture of inseparable chlorinated **345** and non-chlorinated **344** cyclic compounds, with their corresponding diastereoisomers (the yields and diastereoisomer ratios of **344** and **345** could not be calculated, assignment of the structures are tentative based on ^{1}H and ^{13}C NMR and mass spec data, along with comparison with previously made compounds). Unfortunately, the main product isolated was the cyclic amide **335**. This inefficient radical cyclisation route was abandoned due to its limited synthetic use.



Scheme 140

4.4.4 Synthesis of an α,β-unsaturated ester containing a phenylselenide (349)

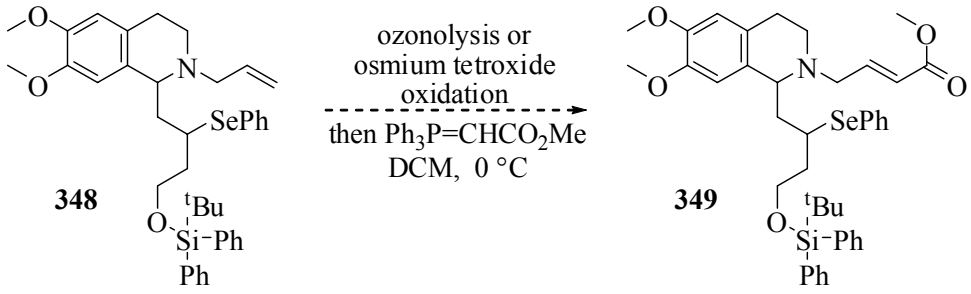
Attention then moved to the preparation and cyclisation of compounds similar to α,β-unsaturated ester **344** (**Figure 12**). It was expected that the α,β-unsaturated ester fragment could be installed by modifying an *N*-allyl group. The synthesis started by lithium aluminium hydride reduction of the previously synthesised phenylselenide **331** (**Scheme 141**). Although this resulted in the reduction of the ester, it was found that the major identifiable product was alcohol **347**, which also had cleavage of the phenylselenide fragment, together with unidentified by-products. However, it was found that treatment of the ester with alane (formed by reduction of aluminum trichloride with lithium aluminium hydride[237]) afforded the desired alcohol **346** cleanly.[238] Attempted purification by column chromatography resulted in decomposition, so the crude alcohol was immediately protected by treatment with *tert*-butyldiphenylsilyl chloride[239-241] to give silyl ether **348** in 78% yield over two steps.



Scheme 141

Attempted incorporation of the α,β-unsaturated ester fragment into **348**, by a Grubbs metathesis using methyl acrylate,[242-245] resulted in recovery of starting material (perhaps due to coordination of the tertiary amine to the ruthenium catalyst[246, 247]) so attempts to carry out the Grubbs metathesis on the protonated amine were attempted, but again this led to predominant recovery of starting material. An alternative approach, involving either an ozonolysis or osmium tetroxide oxidation of the C=C bond to form an aldehyde followed

by a Wittig reaction using methyl (triphenylphosphoranylidene)acetate was also unsuccessful.



Scheme 142

4.5 Conclusion

A robust and efficient synthesis of allyl tetrahydroisoquinoline **292** has been developed, which involves *N*-Boc protection of tetrahydroisoquinoline **190**, allylation and finally, cleavage of the Boc group. Allyl tetrahydroisoquinoline **292** can be converted into alpha-haloamides (**295**) and (**296**) or xanthate **294**, but the attempted radical cyclisation of these precursors proved to be problematic, with only the product of direct reduction or recovered starting material isolated. The inefficient cyclisation was attributed to slow interconversion of the amide rotamers.

This resulted in the exploration of the tributyltin hydride mediated cyclisation of a precursor containing both a vinyl bromide and an *N*-allyl fragment. Vinyl bromides **307** and **317** were synthesised in a similar 4-step procedure to allyl isoquinoline **292**. It was found that attempted cyclisation of the *N*-crotyl compound **307** gave a complex mixture of compounds, including products derived from a range of 1,5-hydrogen atom transfer reactions, such as the secondary amine **192** and the 6,5-fused bicyclic compounds **309** and **310** along with the desired 6-*exo* cyclisation product. However, pleasingly**,** it was found that the corresponding α,β-unsaturated ester **317** cleanly cyclised to afford the desired tricyclic ester **318** in an excellent 89% yield (as a 1:2.8 mixture of diastereoisomers). Unfortunately, subsequent conversion of **318** into protoemetinol (**88**) proved to be problematic.

Finally, the radical cyclisation of phenylselenides **331** and **332** were investigated. The synthesis of the phenylselenides was achieved efficiently by Michael-type addition of phenylselenol to α,β-unsaturated esters **329** and **330**. Subsequent tributyltin hydride-

mediated radical cyclisation afforded a mixture of products, including the desired tricyclic esters **333** or **334-a.** The tricyclic esters could be reduced to the corresponding alcohols, including (±)-protoemetinol (**88**), which was isolated in 2% yield over the 4 steps. Attempts to improve the efficiency of the radical cyclisation by incorporating an electron-withdrawing group onto the acceptor alkene proved to be unsuccessful.

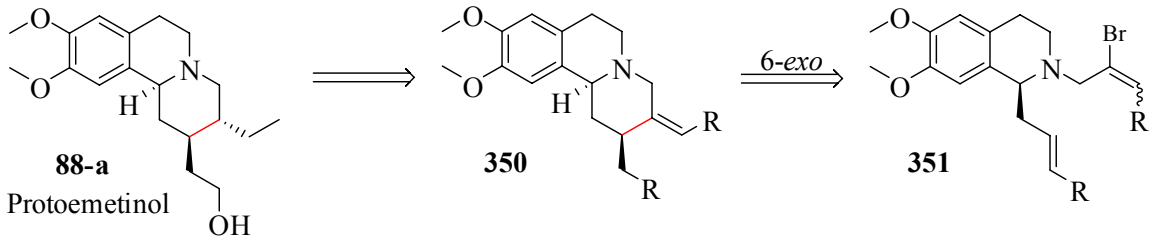
Chapter 5 – Results and Discussion

Vinyl bromide approaches to *Alangium* and *Mitragynine* alkaloids

5.1 - Approaches to (±)-protoemetinol (88a)

Following the generally disappointing progress towards the cyclic core of *Alangium* and *Mitragynine* alkaloids, a revision of the synthetic strategy was made. It was noted that the issues with the amide rotamers would be difficult to overcome, and although the chemistry of the phenylselenides resulted in the synthesis of (±)-protoemetinol (**88a**), the low yields resulted in this route being abandoned. It was however, noted that the radical cyclisations of the vinyl radical derived from the corresponding vinyl bromide onto an α,β-unsaturated ester proceeded extremely well. With this in mind an alternative route for the cyclisation of a vinyl bromide onto an α,β-unsaturated ester were explored.

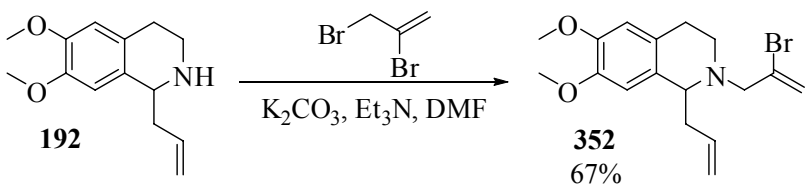
An alternative approach to the synthesis of the tricyclic core of protoemetinol (**88-a**) involves the cyclisation of a vinyl radical β to nitrogen, such as the vinyl bromide of type **351**. It is proposed that the 6-*exo* cyclisation would afford the tricyclic core **350**, which on further functionalisation should furnish protoemetinol (**88-a**) (**Scheme 143**).



Scheme 143

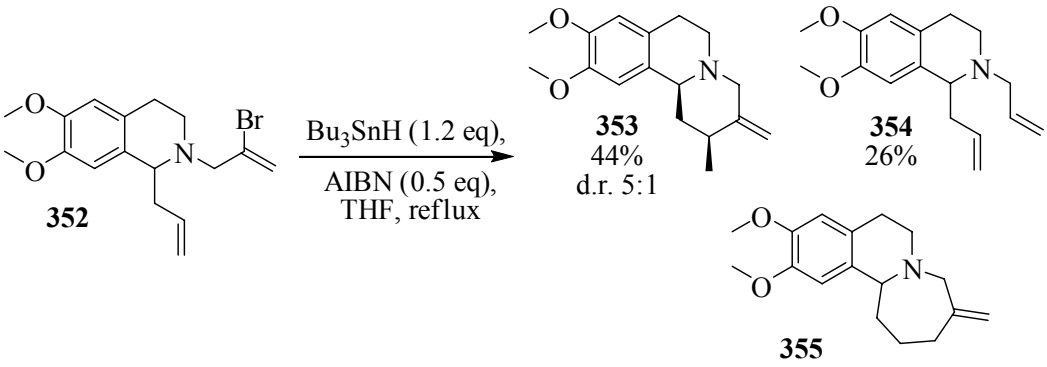
5.1.1 – Synthesis and cyclisation of a model vinyl bromide (352)

To test the proposed cyclisation, a model vinyl bromide system was explored. The synthesis of vinyl bromide **352** was achieved by *N*-allylation of the previously prepared secondary amine **192**, with 2,3-dibromopropene using the conditions previously used, to afford in a pleasing yield the desired vinyl bromide **352**.



Scheme 144

With the model system in hand, the tributyltin hydride mediated radical cyclisation was investigated. Treatment of vinyl bromide **352** in refluxing THF, with the slow addition of 1.2 equivalents of tributyltin hydride afforded in un-optimized conditions the desired 6,6,6-tricycle **353** in 44% yield, as the major compound, as an inseparable mixture of diastereoisomers (**Scheme 145**). Also isolated following column chromatography was the 1,7-diene **354**, derived from simple reduction. Another compound was isolated, possibly the 6,6,7-tricycle **355**, which could be formed by a competing 7-*endo-trig* cyclisation (or from a tandem 6-*exo*/3-*exo* cyclisation followed by fragmentation of the cyclopropane ring), however this compound could not be cleanly isolated, or characterised.



Scheme 145

The relative stereochemistry of the major diastereoisomer of tricycle **353** was determined by a ^{1}H-NOESY experiment and is consistent with that predicted from a 6-*exo*-trig radical cyclisation that proceeds via a chair-like transition state **Figure 13.** The ^{1}H-NOESY spectrum showed correlation between H_a, H_b and H_c. The methyl group showed a correlation to H_f, but no correlation to H_a, indicating that the cyclisation afforded the correct stereochemistry for protoemetinol (**88-a**).

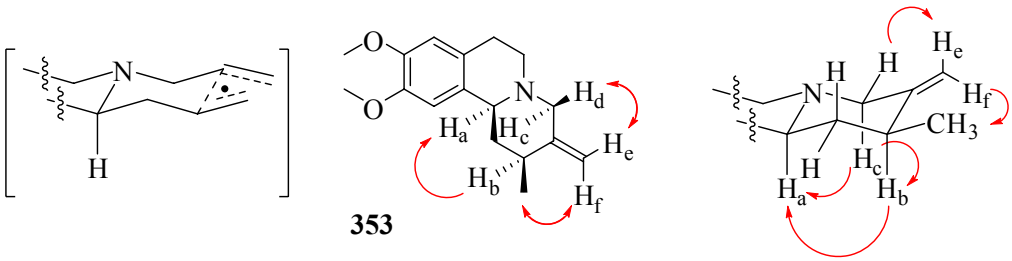
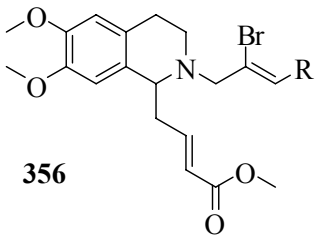


Figure 13 (original in colour)

For the synthesis of protoemetinol (**88-a**), it was envisaged that introducing an ester group at the end of the acceptor alkene (**Figure 14**) would increase the rate of 6-*exo* cyclisation

(by lowering the LUMO) and also reduce the rate of any 7-*endo* cyclisation (for steric reasons). The ester group would also provide a useful synthetic handle for further modification, such as reduction to the required alcohol.

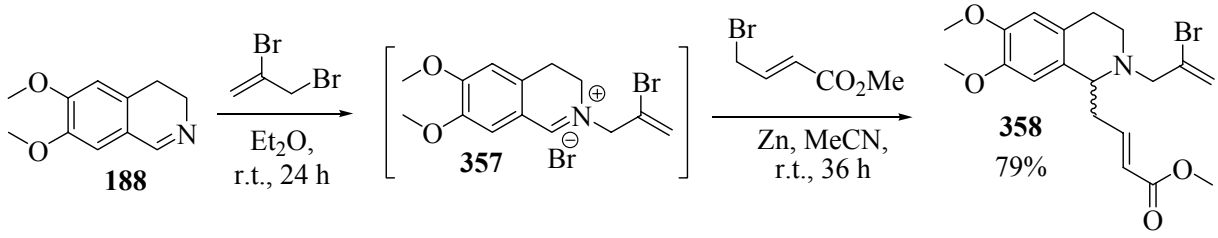


356

Figure 14

5.1.2 - Synthesis (±)-des-methyl protoemetinol (342-a)

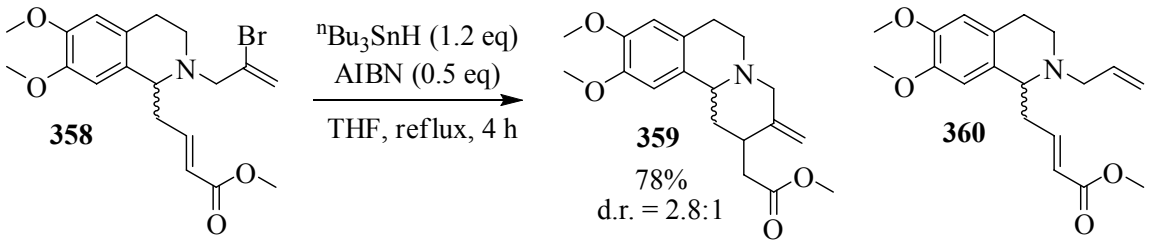
To test the cyclisation of an ester of type **356** (**Figure 14**), the use of a 2-bromoprop-1-ene fragment was explored, due the commercial availability of 2,3-dibromoprop-1-ene, (i.e. R = H in **356**). (It is noted that 1,2-dibromobut-2-ene (ie R = Me in **356**) is required for subsequent conversion into the ethyl group found on the C ring in the target alkaloids). Vinyl bromide **358** was efficiently synthesised from commercially available methyl (*E*)-4-bromobut-2-enoate and 6,7-dimethoxy-3,4-dihydroisoquinoline **(188)** (**Scheme 146**). Formation of the quaternary salt (**357**) with 2,3-dibromoprop-1-ene proceeded quantitatively. This was followed by addition of an organo-zinc reagent generated in-situ (from zinc and methyl (*E*)-4-bromobut-2-enoate), which underwent nucleophilic addition to the C=N bond to give vinyl bromide **358** in an excellent 79% yield.



Scheme 146

Pleasingly, reaction of vinyl bromide **358** in refluxing THF, with the slow addition of tributyltin hydride and AIBN resulted in a clean conversion to the desired tricycle **359**, which was isolated in an excellent 78% yield after column chromatography (as a partially separable 2.8:1 mixture of diastereoisomers) (**Scheme 147**). No evidence of the direct reduction product **360** or other by-products were observed. This very successful reaction to afford the key tricyclic ester **359**, can be preformed on a large scale (up to 7.5 g, 18.3

mmol) with no change in yield or diastereoselectivity. Interestingly, the use of TTMSS (in place of Bu_3SnH) gave a lower yield of the desired 6-*exo* tricycle **359** (42%), although the diastereoselectivity of the cyclisation was improved to 6:1.



Scheme 147

Once again the relative stereochemistry of the major diastereoisomer of tricycle **359-a** was determined by a ^{1}H-NOESY experiment and is consistent with a cyclisation that proceeds via chair-like transition state, **361** (**Figure 15**). The ^{1}H-NOESY spectrum suggested a *cis*-arrangement between H_a and H_b.

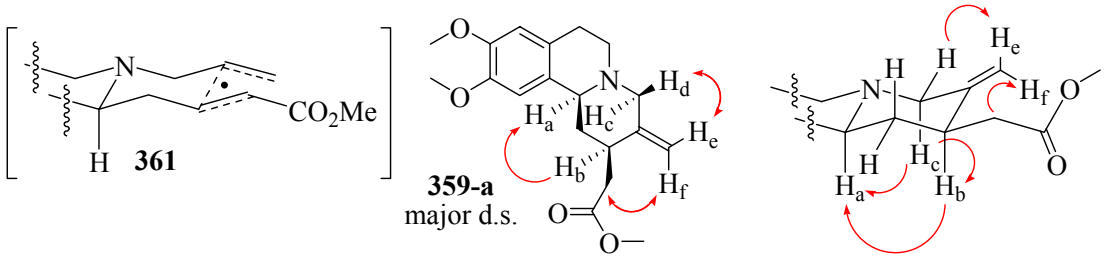
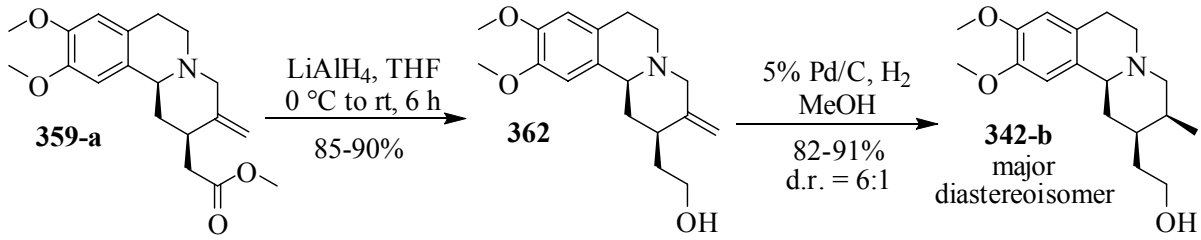


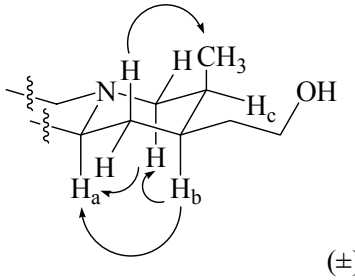
Figure 15 (original in colour)

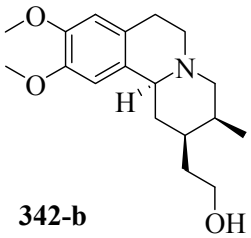
Subsequent reduction of the major diastereoisomer, **359-a**, with lithium aluminium hydride resulted in an excellent yield of the corresponding alcohol **362** (**Scheme 148**). Finally, it was proposed that a palladium on carbon hydrogenation would occur from the top, least hindered face of the C=C bond, to afford des-methyl protoemetinol (**342-a**). However, hydrogenation of **362** using 5% palladium on carbon afforded the reduced compound, as a 10:1 ratio of diastereoisomers, with the major isomer being (±)-des-methyl-epi-protoemetinol (**342-b**).



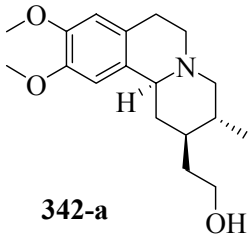
Scheme 148

The predominant formation of (±)-des-methyl-epi-protoemetinol (**342-b**), over diastereoisomer **342-a**, was confirmed by examination of the ^{1}H NOESY correlations of the major diastereoisomer from the hydrogenation reaction (**Figure 16**).





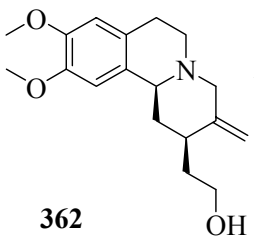
342-b
(±)-des-methyl-epi-protoemetinol
major diastereoisomer



342-a
(±)-des-methyl-protoemetinol
minor diastereoisomer

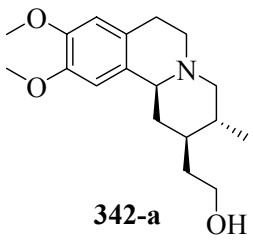
Figure 16

Alternative conditions for the hydrogenation of **362** were then explored. Pleasingly it was found that by changing the catalyst from Pd/C to Crabtree's catalyst,[248-250] a moderate excess of (±)-des-methyl-protoemetinol (**342-a**) was formed (**Scheme 149 and Table 10**). The two diastereoisomers **342-a** and **342-b** can be easily identified using ^{1}H NMR spectroscopy, by examing the signal for the CHC<u>H</u>$_3$ group; **342-a** has the C<u>H</u>$_3$ peak at 0.91 ppm as a doublet with J = 6.5 Hz whereas **342-b** has the C<u>H</u>$_3$ peak at 0.97 ppm as a doublet with J = 6.9 Hz.



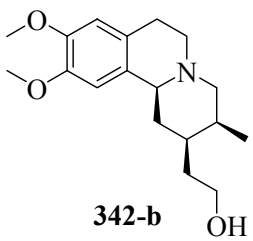
362

Cat, H_2
Solvent



342-a
(±)-des-methyl-protoemetinol

:



342-b
(±)-des-methyl-epi-protoemetinol

Hydrogenation Conditions	Yield (%)	**342-a**	**342-b** (epi)
Pd/C, MeOH, H_2, r.t.	85	1	6
Pd/C, EtOAc, H_2, r.t.	91	1	3
Pd/C, DCM, H_2, r.t.	36	1	2
Crabtree's catalyst, $CHCl_3$, H_2, reflux	60	1	1.2
Crabtree's catalyst, DCM, H_2, r.t.	96	1.4	1

Scheme 149 and Table 10

On storage (with trace amounts of dichloromethane), alcohol **362** slowly crystallised and a subsequent X-ray diffraction of a crystal resulted in an unexpected discovery. Instead of the expected compound **362**, the crystal was in fact the dichloromethane adduct, **363** (**Figure 17**). However it did allow us to confirm the stereochemistry of **362**, which agrees with that assigned from NOESY correlations.

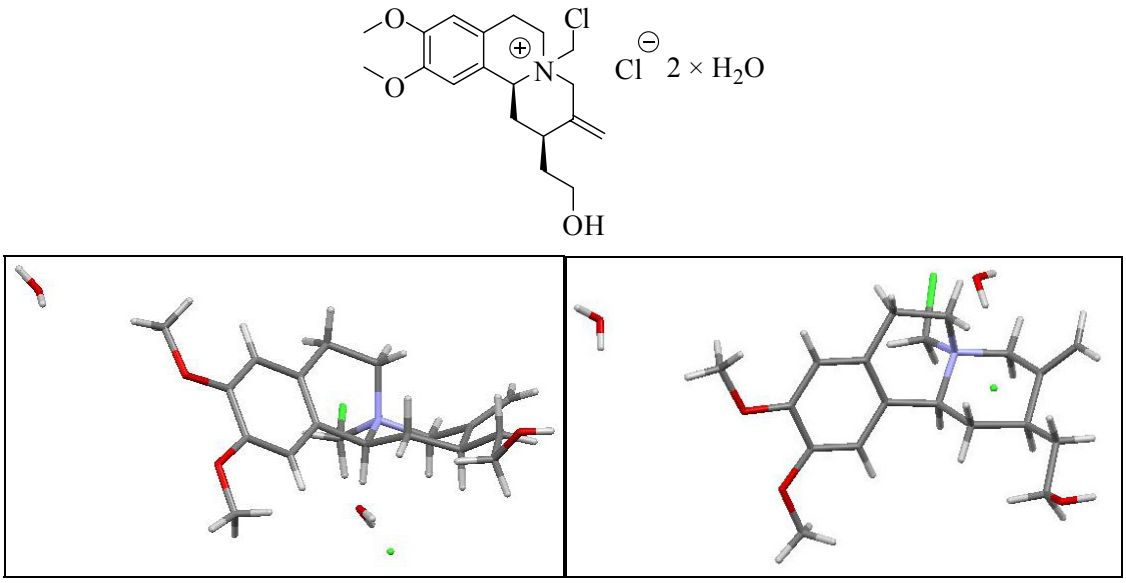
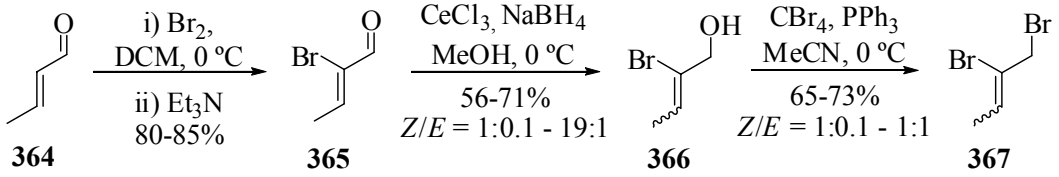


Figure 17 (original in colour)

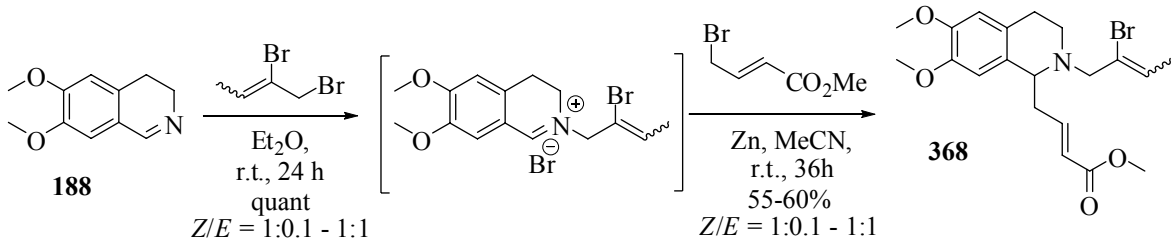
5.1.3 - Synthesis of protoemetinol 88-a

With the preparation of des-methyl-protoemetinol **342-a** in hand, attention turned to the synthesis of protoemetinol **88-a**. To achieve this, 1,2-dibromobut-2-ene (**367**) is required, which could be prepared in 3 steps from crotonaldehyde (**364**) (**Scheme 150**).[251, 252] Bromination of the double bond in **364** is followed by elimination of HBr using triethylamine to give (*Z*)-2-bromobut-2-enal (**365**) (typically in 80-85% yield).[253] A subsequent Leuche[254, 255] reduction using cerium(III) chloride and sodium borohydride yielded 2-bromobut-2-en-1-ol (**366**). In our hands though, the reduction of the alcohol led to isomerisation of the C=C bond, giving **366** as an inseparable mixture of *cis*- and trans-isomers. However, it was found that the extent of isomerisation could be limited by storing 2-bromobut-2-en-1-ol (**366**) at low temperature and by using the crude alcohol in subsequent reactions. Finally, conversion of alcohol **366** into 1,2-dibromobut-2-ene (**367**) was accomplished using carbon tetrabromide and triphenylphosphine.



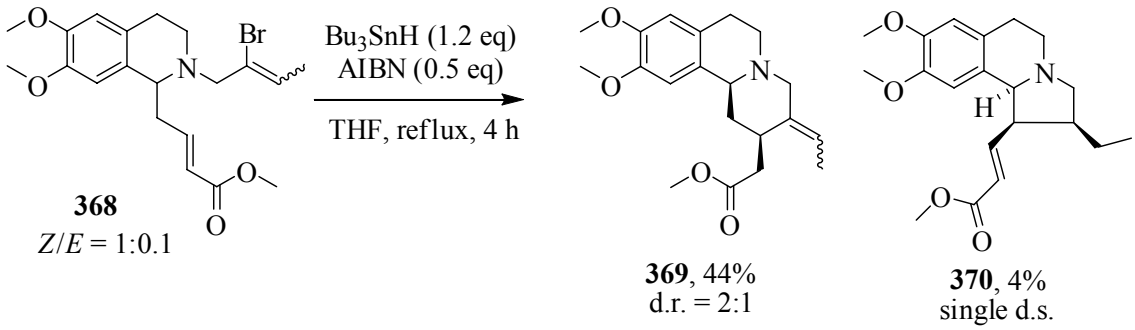
Scheme 150

Vinyl bromide **368** was then synthesised using 1,2-dibromobut-2-ene (**367**), methyl (*E*)-4-bromobut-2-enoate and 6,7-dimethoxy-3,4-dihydroisoquinoline **(188)** (**Scheme 151**). Following the previously developed route, involving formation of the quaternary ammonium salt and then addition of an organo-zinc reagent, gave the desired compound **368**, although in a slightly disappointing yield.



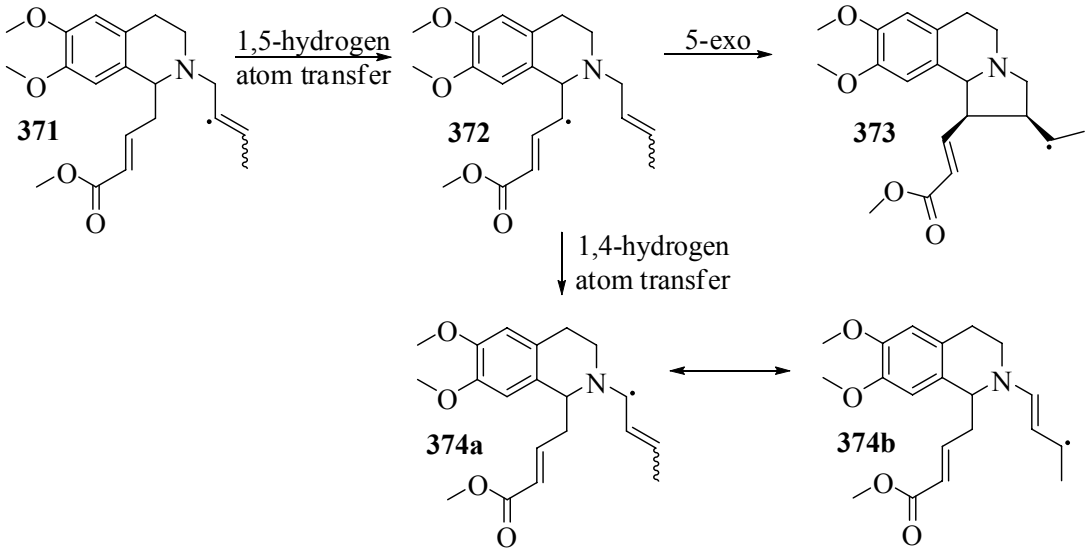
Scheme 151

Attention then turned to the key radical cyclisation step. Treatment of vinyl bromide **368** in refluxing THF, with the slow addition of tributyltin hydride and AIBN resulted in a crude product with a complex ^{1}H NMR spectrum, which indicated a mixture of alkenes. After column chromatography the desired tricycle **369** was isolated in a disappointing yield of 44% (as a partially separable 2:1 mixture of diastereoisomers) (**Scheme 152**). No evidence of the direct reduction product was observed, however a cyclopentane containing tricycle **370** was also obtained in very low yield.



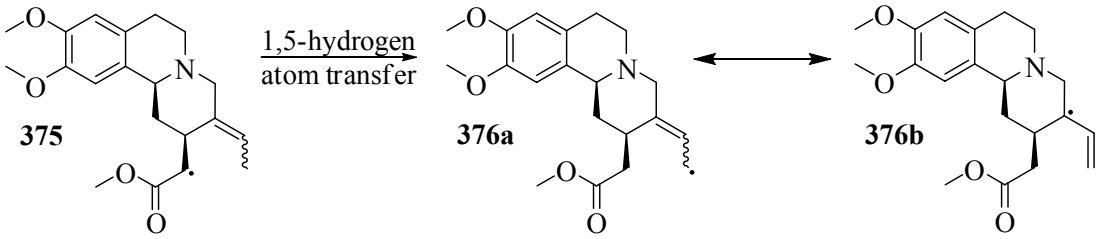
Scheme 152

The cyclopentane containing tricycle **370** is likely formed via a 1,5-hydrogen atom transfer of the initial vinyl radical **371**, to form allyl radical **372**, followed by 5-*exo*-trig cyclisation (affording cyclopentane tricyclic radical **373**) and reaction with tributyltin hydride (**Scheme 153**). It is also proposed that a competing 1,4-hydrogen atom transfer of allyl radical **372** (or a 1,6-hydrogen atom transfer from the alternative resonance form of **372**) to form another allyl radical **374a**, could explain the low yield of this reaction. The alternative resonance form of the allyl radical **374a** is enamine **374b**, which would be unstable to column chromatography, and this could explain some of the alkene signals in the ^{1}H NMR spectrum of the crude product.



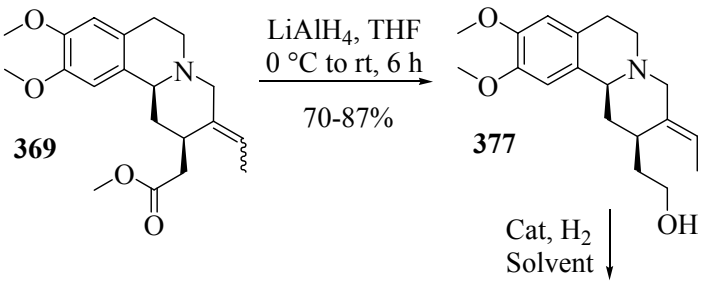
Scheme 153

The formation of additional byproducts could also be explained by a 1,5-hydrogen atom transfer reaction of the initially formed 6-*exo* cyclisation product **375**, which would result in the formation of resonance-stabilised allyl radical **376a** (**Scheme 154**). The presence of signals at 5.01, 5.10 and 5.85 ppm in the ^{1}H NMR spectrum of the crude product provide tentative evidence for the formation of a terminal alkene derived from radical **376b**.

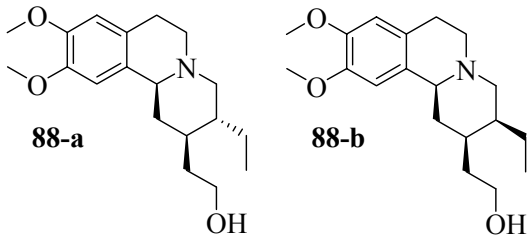


Scheme 154

Subsequent reduction of ester **369** with lithium aluminium hydride resulted in a good yield of the corresponding alcohol **377** (**Scheme 155**). Reduction of the C=C bond by hydrogenation using a palladium on carbon catalyst resulted in isolation of epi-protoemetinol **88-b**, as the major diastereoisomer, with the undesired stereochemistry at C-3. However, once again it was found that the use of Crabtree's catalyst afforded,[248-250] in a moderate excess, (±)-protoemetinol **88-a**.



Hydrogenation Conditions	Yield (%)	d.r. **88-a:88-b**
Pd/C, MeOH, H_2, r.t.	63	**1**:10
Crabtree's Catalyst, DCM, H_2, r.t.	54	**1.1**:1

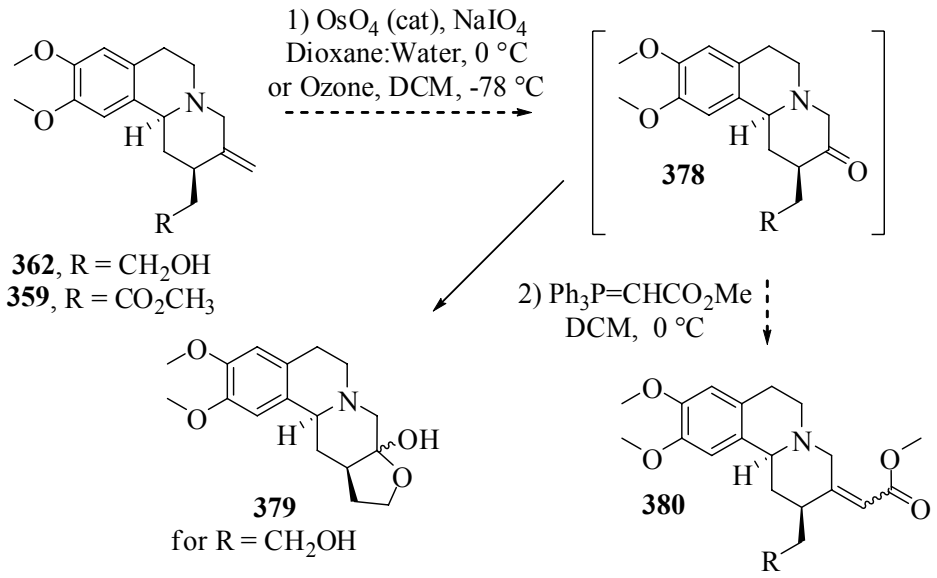


Scheme 155 and Table 11

5.1.4 - Conversion of (±)-des-methyl protoemetinol (343-a) into (±)-protoemetinol (88-a)

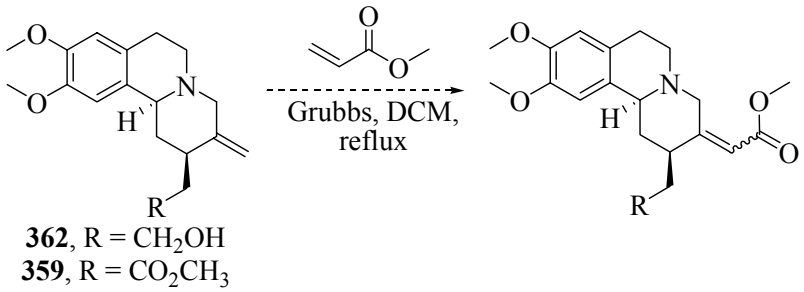
Due to the low yield of (±)-protoemetinol (**88-a**), arising from side reactions during the radical cyclisation of vinyl bromide **368**, methods to convert (±)-des-methyl protoemetinol (**343-a**) into (±)-protoemetinol (**88-a**) were explored.

Initially, an osmium tetroxide catalysed cleavage or ozonolysis of the C=C bond in alcohol **362**, or the related ester **359**, was examined (**Scheme 156**). Examinations of the NMR spectra of the crude products showed no evidence of the expected ketone **378**, or lactol **379**. However, a Wittig reaction was attempted on each of the crude products with methyl (triphenylphosphoranylidene)acetate, which were unsuccessful.



Scheme 156

An alternative approach to functionalise the C=C bond in **359** and **362** involves use of the Grubbs cross metathesis reaction. Unfortunately, treatment of ester **359** or alcohol **362** with Grubbs I or II catalyst along and methyl acrylate (**Scheme 156**)[242-245] resulted in recovery of starting material, with no evidence of cross metathesis products. Attempts to carry out the Grubbs metathesis on the protonated amine of **359** or **362** were attempted, but again, only starting material was recovered.

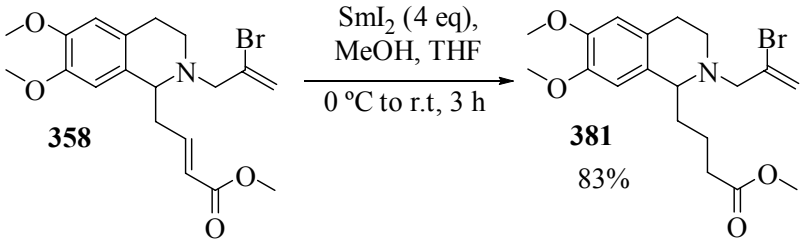


Scheme 157

5.1.5 - Alternative conditions for the cyclisation of the vinyl bromides

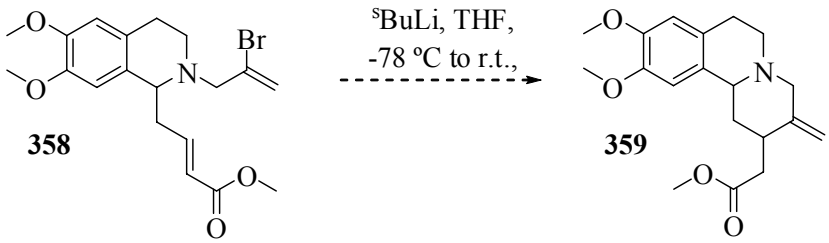
Although vinyl bromides of type **358** and **359** are classically used in tin hydride-mediated reactions they also served as precursors for various alternative cyclisation conditions. With the disappointing results of the cyclisation of vinyl bromide **359**, and the unsuccessful attempts at the conversion of (±)-des-methylprotoemetinol **342-a** derivatives into (±)-protoemetinol **88-a**, alternative cyclisation conditions were explored.

Attempts at the cyclisation of vinyl bromide **358** were made using samarium(II) iodide (**Scheme 158**). It was hoped that samarium(II) iodide would allow for selective reduction of the vinyl bromide group in **358**, [256, 257] in preference to the α,β-unsaturated ester. This, however was not the case, and the reaction resulted in clean reduction of the α,β-unsaturated system to give the ester **381**, in excellent yield**.**



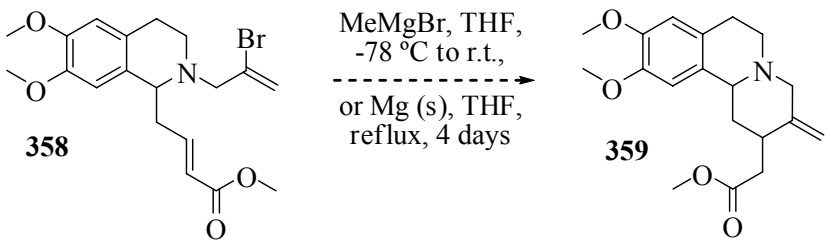
Scheme 158

An alternative cyclisation approach involving halogen-metal exchange was considered. Initial attempts were made using a lithium-bromine exchange,[258-260] but unfortunately this resulted in decomposition of the reaction mixture.



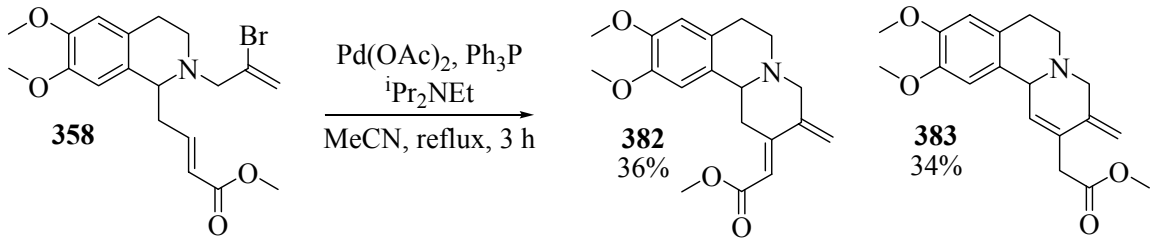
Scheme 159

Subsequent attempts were made using a magnesium-bromine exchange,[261-263] which would afford the corresponding vinyl Grignard reagent, which would hopefully undergo a 1,4-addition to the unsaturated ester, in preference to the 1,2- addition. However the reaction resulted in clean recovery of the starting material, without any addition of any Grignard reagent to the α,β-unsaturated ester. This is perhaps due to the relatively acidic CH_2 group next to the α,β-unsaturated ester, resulting in quenching of the initial Grignard reagent. An alternative approach involved treatment of the vinyl bromide with magnesium metal, in the hope of forming a vinyl Grignard reagent, which could undergo 6-*exo* cyclisation. However, even treatment with a large excess of magnesium in refluxing THF resulted in recovery of clean starting vinyl bromide.



Scheme 160

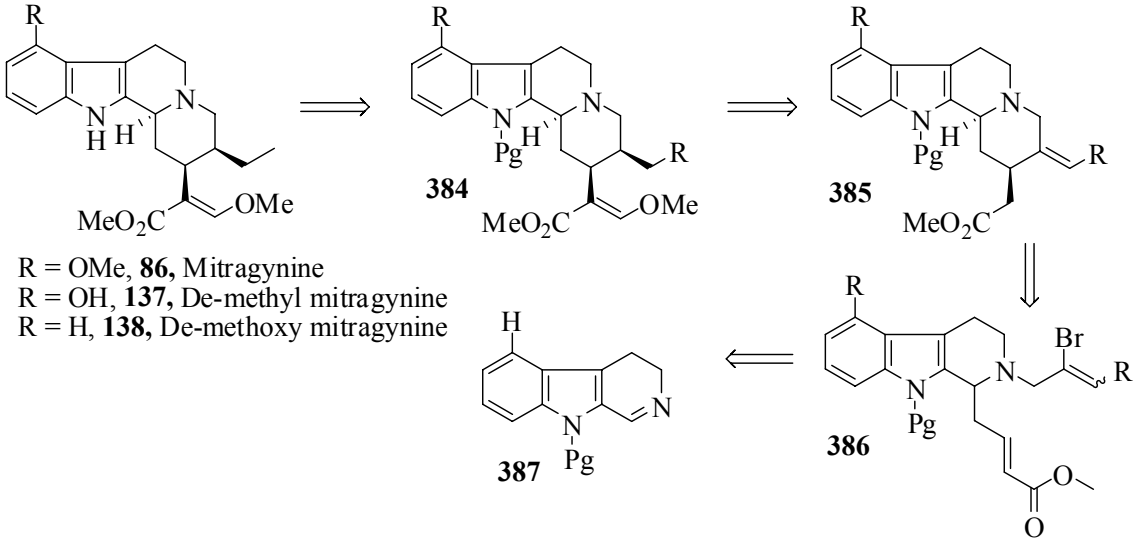
An alternative and synthetically very useful reaction of a vinyl bromide with an alkene is the Heck reaction.[264-266] With this in mind the vinyl bromide **358** was treated with palladium(II) acetate, triphenylphosphine, and an amine base (**Scheme 161**). This resulted in very quick consumption of the starting vinyl bromide which after column chromatography afforded the two conjugated dienes **382** and **383.** The conjugated diene **382**, had the expected NMR spectrum, and H-C connectivity was confirmed by HQSC and HMBC experiments. However the conjugated diene **383** had an unexpected HMBC correlations between δ_C 172.0 ($\underline{C}O_2CH_3$) and δ_H 3.29 + 3.14 ($C\underline{H}_2CO_2CH_3$), and no correlation to alkene H signals. The full connectivity was confirmed by COSY, HQSC and HMBC experiments.



Scheme 161

5.2 - Approaches to mitragynine (86) starting from a vinyl bromide

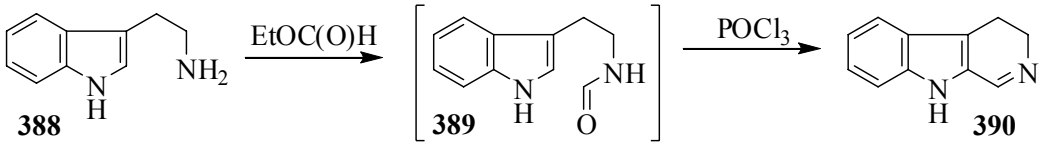
Following the successful synthesis of protoemetinol (**88-a**, Section 5.1), a similar approach should be applicable to the synthesis of mitragynine (**86**), and related compounds (**Figure 6, Chapter 1**). Previous work has shown[164, 167, 267] that installation of the vinyl ether can be accomplished from ester **385**, which could be prepared by radical cyclisation of a vinyl bromide **386** derived from an imine **387** (**Scheme 162**).



Scheme 162

5.2.1 - Synthesis of vinyl bromide 395

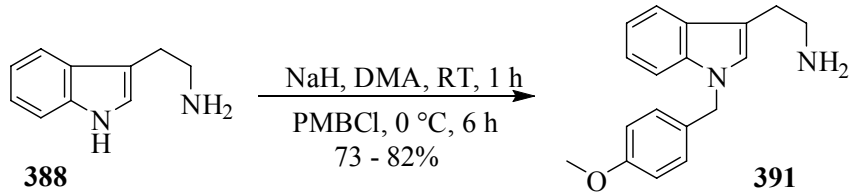
For our model studies, the synthesis of de-methoxy mitragynine (**138,** corynantheidine), was explored due to the lack of commercial availability of 4-methoxytryptophan required for the synthesis of the indole core. Imine (**390**) can be prepared by oxidation of the corresponding amine, 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole under a range of conditions,[180, 181] however this indole is expensive and its availability can be problematic.[d] An alternate and more attractive route to imine **390** is from inexpensive and commercially available tryptamine (**388**),[e] where reaction with ethyl formate is expected to form the intermediate formamide (**389**) (**Scheme 163**), and subsequent cyclisation using phosphoryl trichloride under Bischler-Napieralski conditions should furnish the desired imine **390**.[268]



Scheme 163

[d] The cost of 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole is typically in the region of £35 per gram
[e] Tryptamine typically costs £35 per 50 g, and is available from decarboxylation of the amino acid tryptophan

However, this approach was not successful; analysis of the crude reaction mixture by ^{1}H NMR spectroscopy and LCMS indicated the formation of a range of products and pure 4,9-dihydro-3H-pyrido[3,4-b]indole (**390**) was never isolated. However, installing a protecting group on the indole nitrogen solved this problem. 2-(1-(4-Methoxybenzyl)-1H-(indol-3-yl)ethanamine (**391**) was synthesised by reaction of tryptamine (**388**) with 1.1 equivalents of sodium hydride followed by the slow addition of 1 equivalent of *para*-methoxybenzyl chloride (**Scheme 164**).



388 **391**

Scheme 164

The *para*-methoxybenyl group was chosen due to the mild methods of removal, [269-275] and it is not expected to significantly affect the electronics of the indole ring as, for example, a Boc group would. It is worth noting that benzylic hydrogen atoms are reactive to radical abstraction, however in this system this would require an intramolecular 1,7-H atom abstraction, on a rigid structure, which was thought to be unlikely (**Figure 18**).

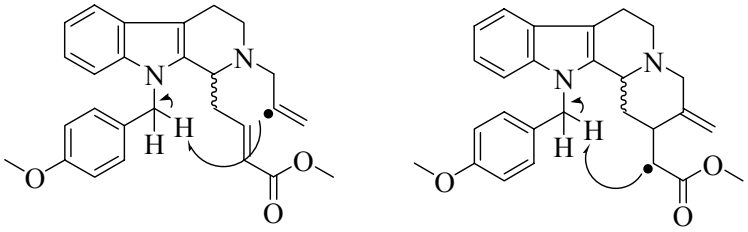
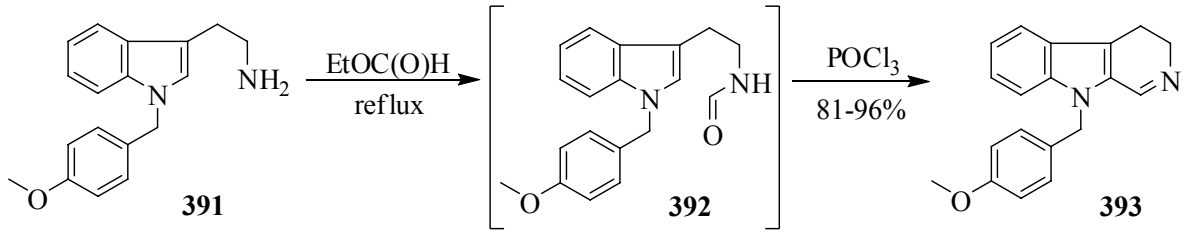


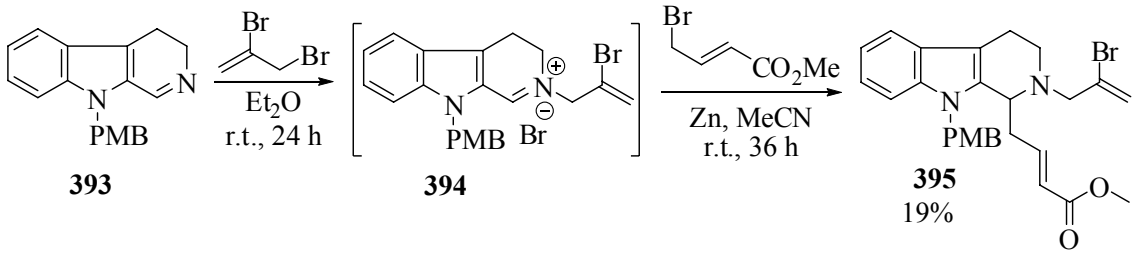
Figure 18

With PMB-tryptamine (**391**) in hand, reaction with ethyl formate formed the intermediate formamide **392** and a subsequent reaction under Bischler-Napieralski[268] conditions (using phosphoryl trichloride) afforded the desired imine **393** in good to excellent yields (**Scheme 165**).



Scheme 165

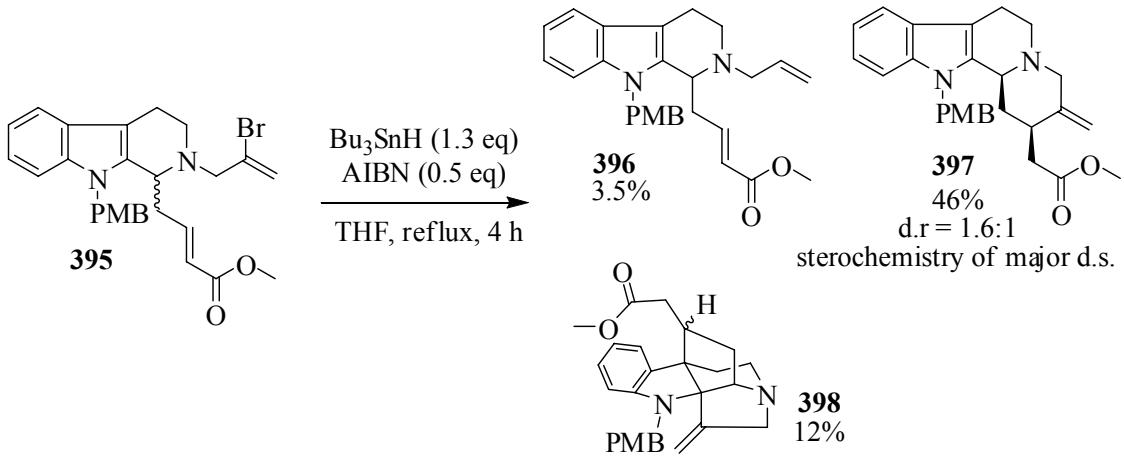
In a similar procedure to that used in the synthesis of protoemetinol (**88**), the imine **393** was stirred with 2,3-dibromoprop-1-ene to form the quaternary salt **394**. Subsequent addition of zinc and methyl (*E*)-4-bromobut-2-enoate generated the organo-zinc reagent in-situ, which reacted with quaternary salt **394** to give but-2-enoate **395** in a low 19% yield (**Scheme 166**).



Scheme 166

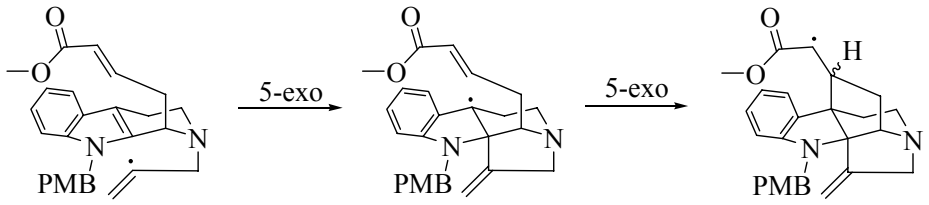
5.2.2 – Radical reactions of vinyl bromide 395

Treatment of the vinyl bromide **395** with the slow addition of tributyltin hydride and AIBN in refluxing THF resulted in the product of direct reduction, diene **396**, the desired cyclised product octahydroquinolizine **397** and a pentacyclic bridged system **398** (**Scheme 167**). Compound **397** was obtained as a mixture of partial separable diastereoisomers on column chromatography.



Scheme 167

The pentacyclic-bridged system **398** was isolated as a 1:1 mixture of partially separable diastereoisomers. The assignment was made initially on the basis of the NMR spectra. For example, a CH_2 peak at 104.1 ppm in the ^{13}C NMR spectrum and signals at 4.89 and 4.43 ppm in the ^{1}H NMR spectrum indicated the presence of a terminal alkene. It is proposed that the ring system is formed by a 5-*exo* cyclisation of the initial vinyl radical onto the indole ring, followed by a second 5-*exo* cyclisation on to the α,β-unsaturated ester (**Scheme 168**).

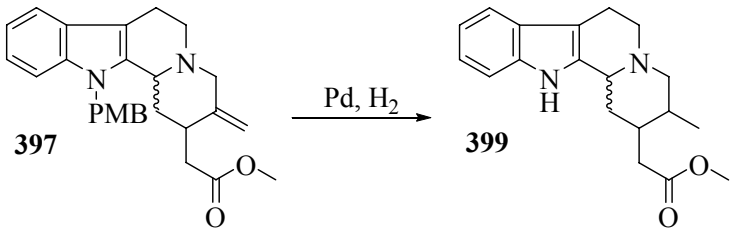


Scheme 168

A similar side reaction has been reported by the group of Takayama,[276, 277] during their attempts at the synthesis of related indole alkaloids using a diester. Interestingly, the group of Cook[167, 267] did not mention the formation of any by-products during their cyclisation of a related α,β-unsaturated ester possessing a vinyl iodide when subjected to a $Ni(COD)_2$-mediated cyclisation (**Scheme 57, Chapter 1**).

5.2.3 –Functionalisation of ester 397

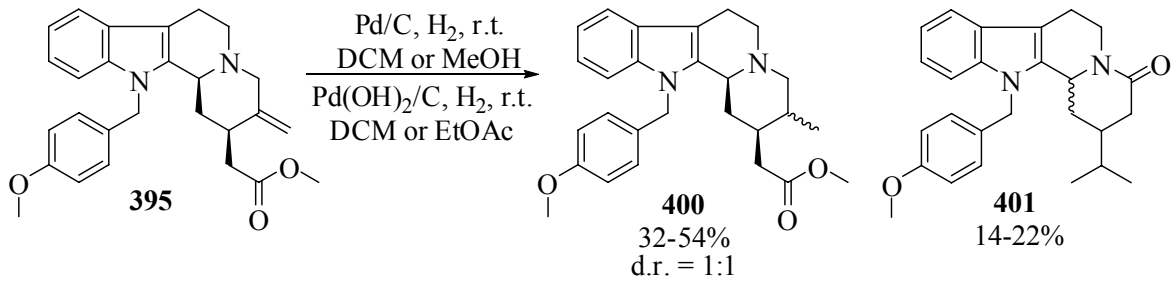
With the desired 6-ring compound **397** in hand, it was envisaged that a palladium-catalysed hydrogenation, or alternatively a palladium hydroxide on carbon-catalysed hydrogenation, would led to hydrogenation of the alkene and also cleave the PMB group[272, 278] to afford ester **399**[273, 279-282] (**Scheme 169**).



Scheme 169

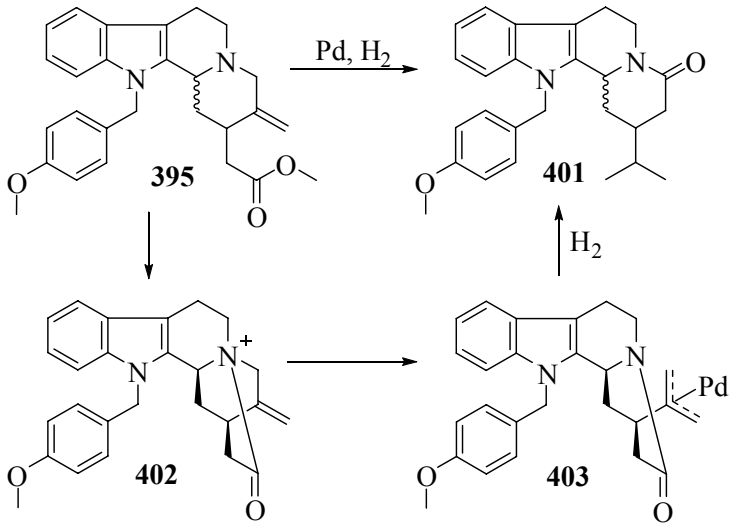
However, hydrogenation of the major diastereoisomer of **397** using either palladium on carbon, or palladium hydroxide on carbon (at standard pressures), resulted in the isolation

of two products, both containing an *N*-PMB group (**Scheme 170**). The direct product of hydrogenation of the alkene, ester (**400**), was obtained as a 1:1 mixture of separable diastereoisomers. The other product was assigned as the cyclic amide **401**.



Scheme 170

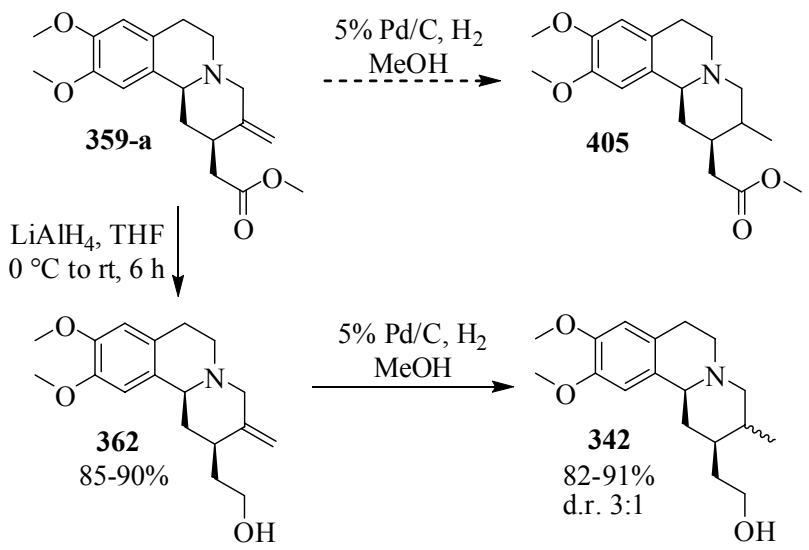
It is tentatively proposed that lactam **401** is formed by initial attack of the nitrogen atom on to the ester, to form amide **402**. The C=C bond in amide **402** can then co-ordinate to palladium and form an η-3 complex **403**, after fragmentation of the positively charged nitrogen. Finally, hydrogenation of the palladium complex results in isolation of the cyclic amide **401** (**Scheme 148**).



Scheme 171

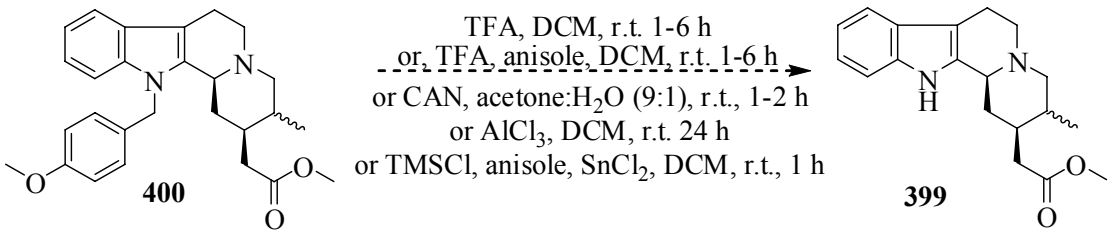
The proposed mechanism is supported by the fact that the palladium-catalysed hydrogenation of the minor cyclic diastereoisomer from the cyclisation (**395**) does not appear to form the cyclic amide **401** (because the ester and amine groups cannot interact). It should be noted, in hindsight, that attempts at the hydrogenation of ester **359-a,** (used in the studies of protoemetinol **88**) did not proceed well, resulting in unidentified side products, whereas the hydrogenation of the corresponding alcohol **362** proceeded well.

(**Scheme 172**) This suggest the presence of the ester is required for the formation of amide **401**.



Scheme 172

It was envisaged that treatment of ester **400** with TFA[274, 275, 283] would allow for cleavage of the PMB group. However, under a range of acidic, oxidative and Lewis acidic conditions, (**Scheme 173**), despite the disappearance of the benzylic signals in the ^{1}H NMR spectra of the crude products, no clean product **399** was obtained, and only apparent decomposition occurred, possibly due to some competing reactions involving the ester group.



Scheme 173

5.3 - Conclusion

Model vinyl bromide **352** was successfully cyclised to afford the desired 6,6,6-tricycle **353** in 44% yield as a 5:1 mixture of diastereoisomers. Attention then turned to the synthesis of des-methyl-protoemetinol (**342**). For this, vinyl bromide **358** was required, which was obtained in an excellent 79% yield from 6,7-dimethoxy-3,4-dihydroisoquinoline **(188)**. The radical cyclisation of vinyl bromide **358** was successful with the desired tricycle **359** isolated in an excellent 78% yield (as a 2.8:1 mixture of diastereoisomers). Subsequent

reduction of the ester group with lithium aluminium hydride afforded the corresponding alcohol **362**. The hydrogenation was however less successful, as a palladium on carbon hydrogenation was found to afford (±)-des-methyl-epi-protoemetinol (**342-b**) in good yield. However, use of Crabtree's catalyst resulted in a moderate excess of the desired (±)-des-methyl-protoemetinol (**342-a**).

Following the synthesis of des-methyl-protoemetinol (**342-a**), attention turned to the synthesis of protoemetinol (**88-a**). To achieve this, 1,2-dibromobut-2-ene (**367**) was required, which was prepared in 3 steps from crotonaldehyde. Following the previously developed route, vinyl bromide **368** was synthesised, although in a slightly disappointing yield. Treatment of vinyl bromide **368** under similar cyclisation conditions to **358**, afforded a complex mixture of alkenes, with the desired tricycle **368** and cyclopentane **369** isolated. A subsequent lithium aluminium hydride-mediated reduction of ester **368**, followed by hydrogenation with Crabtree's catalyst, afforded in a moderate excess (±)-protoemetinol (**88-a**).

Due to the low yield of (±)-protoemetinol (**88-a**), methods for converting advanced intermediates of des-methyl protoemetinol (**343-a**) into protoemetinol (**88-a**) were explored, although these were unsuccessful. Also, alternative conditions for the cyclisation of the vinyl bromides were explored, but these met with limited success.

Subsequent work explored a similar approach towards the synthesis of mitragynine (**86**). This started from PMB-protected tryptamine **391**, which was converted into the desired imine **393** via a Bischler-Napieralski reaction. Formation of the vinyl bromide **395** was achieved via the previously developed one-pot procedure although in a low yield. It was found that treatment of the vinyl bromide **395** with tributyltin hydride resulted in a mixture of products, including the desired product **397**, derived from 6-*exo* cyclisation as a 1.6:1 ratio of diastereoisomers, along with a pentacyclic bridged system **398**, formed via radical cyclisation onto the indole. A subsequent palladium-catalysed hydrogenation of the cyclic ester **397** resulted in hydrogenation of the alkene, and formation of a cyclic amide byproduct, namely **401**, however no cleavage of the PMB group was observed. To date it has not been possible to cleanly remove the PMB protecting group from **398** or **400**.

Chapter 6

Summary, conclusions and future work

6.1 Chapter 2 - Summary, conclusions and future work

Our initial aims were to build on previous work explored within our group which had shown that phosphites, thiophosphites and phosphine oxides all add regioselectively to a range of dienes to afford the corresponding cyclic adducts, and that subsequent Horner-Wadsworth-Emmons-type (HWE) reactions affords the corresponding alkenes, in a one-pot reaction. Our initial approach towards the core of the *Alangium* alkaloids explored the cyclisation of 1,7-dienes**,** with phosphorus hydrides, and it was hoped that following a Horner-Wadsworth-Emmons-type reaction, a tricyclic alkene would be isolated.

Several approaches towards the 1,7-diene were explored. With the required 1,7-diene in hand the addition-cyclisation reaction was explored, however this proved to be problematic and there was no evidence of addition products being formed. This led us to explore the addition of a range of phosphorus hydrides, to a range of alkenes containing either a protected or unprotected nitrogen. It was found that the radical addition of phosphorus hydrides did not proceed in the presence of unsaturated amines, however this contrasts with similar reactions of *N*-protected amines, which proceeds well. This was attributed to an electron-transfer process; the intermediate phosphorus-centred radical may accept an electron from the lone pair on nitrogen. Alternately, an acid/base reaction between the amine and P-H groups is possible. Further work could explore the reaction of various phosphorus hydrides with different amines to determine the reaction mechanism. Also, although the reaction of various phosphorus hydrides was explored, investigations could explore the use of alternative phosphorus hydrides, such as diphenylphosphane (Ph_2PH).

6.2 Chapter 3 - Summary, conclusions and future work

We have shown that phenyldimethylsilane is able to add to a wide range of alkenes in the presence of triethylborane and triisopropylsilanethiol, to give adducts in good to excellent yields (54-95%). Similarly it has been shown that dimethylphenylsilane is able to mediate addition/cyclisation reactions of various 1,6-dienes to afford the corresponding 5-*exo* products. Unfortunately, in our hands, subsequent reactions of the dimethylphenylsilane adducts did not proceed smoothly. The Peterson reactions failed although the oxidative removal of the silyl group, following the method developed by Fleming,[200, 201] proved to be

more promising. The two step procedure, involving cleavage of the Si–Ph bond to afford the corresponding fluoro-silane and subsequent oxidation yielded the desired alcohols, although in low yields (25-31%). A one-pot conversion of the phenyldimethylsilane into the desired alcohol was also explored, however this also gave the alcohols in very low yield (less than 10%).

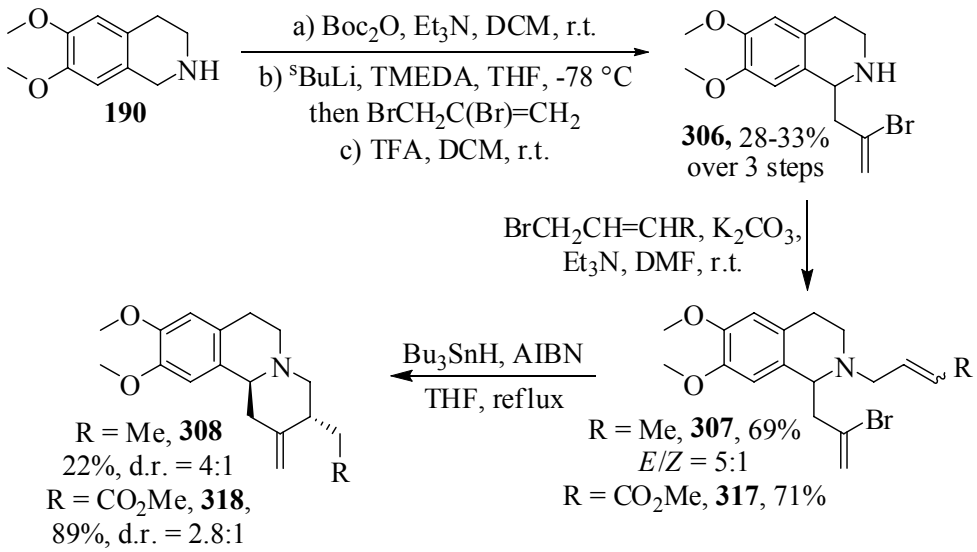
Our studies then investigated the radical addition of trichlorosilane to alkenes, using triethylborane as the initiator. Pleasingly, as evidenced by NMR spectroscopy, it was found that the addition proceeded to completion, but isolation of the trichlorosilane adducts were not possible, due to their high reactivity. Treatment of the unpurified trichlorosilanes under Tamao oxidation conditions, afforded the desired alcohols in good yields (39-70%). However reaction of trichlorosilane with alkenes bearing an alcohol, amide or carbonyl group failed.

The "radion" chemistry of silanes is an area that has not been fully investigated, and is an area that could be developed further. This includes the investigation of other silicon hydrides, possibly hydrides with a fluorine substituent, to form adducts that are more stable than chlorosilanes and are precursors to Fleming type oxidations. Exploration of alternative oxidation methods could also be explored, with a view to increasing the yields of alcohols. In a similar manner, the combined radical addition and subsequent ionic reactions of a range of sulfur hydrides could be investigated. For example, it is known that thiols undergo efficient radical addition to a range of unsaturated systems.[93, 94] The resulting adducts could then be oxidised to sulfones, which could then undergo a Julia type olefination reaction.

6.3 Chapter 4 – Summary, conclusions and future work

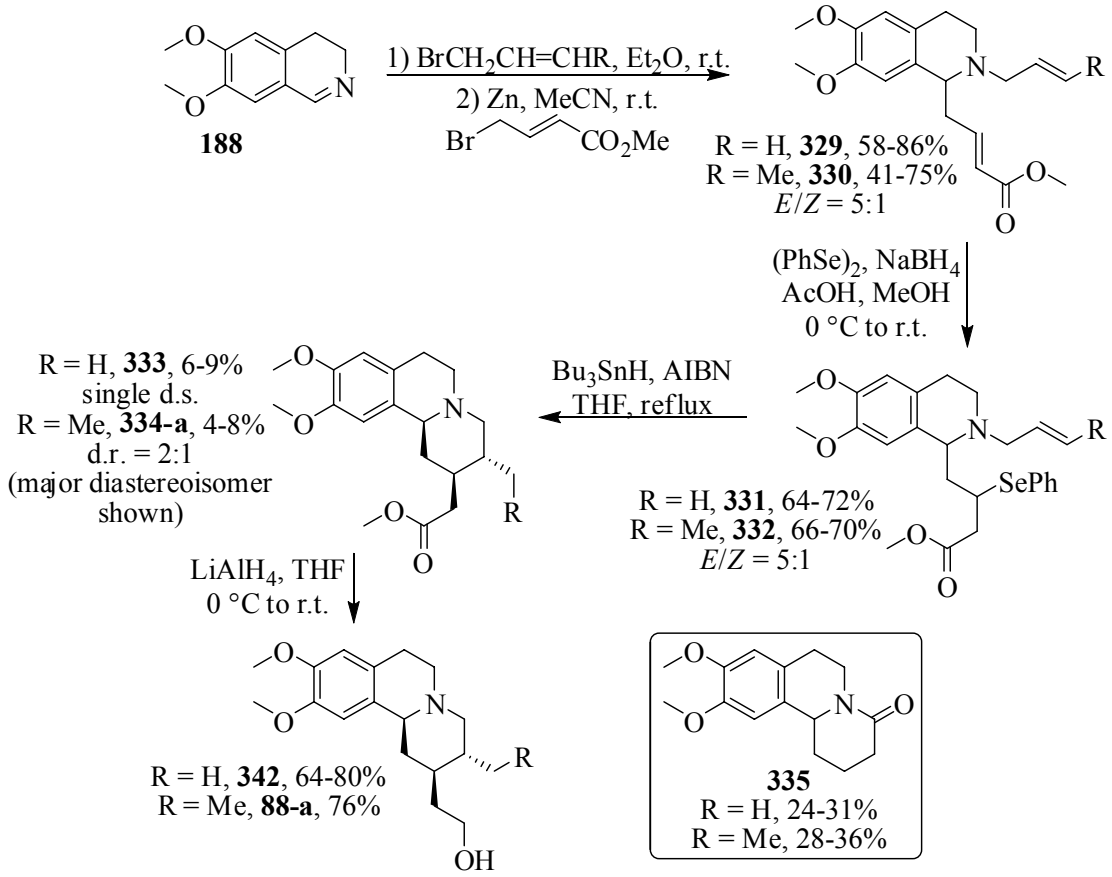
Initial work in Chapter 4 explored the synthesis of a range of unsaturated precursors that, on reaction with tributyltin hydride, would form a radical α to a carbonyl. However, the radical reactions of these precursors proved to give complex reaction mixtures with only the product of direct reduction being isolated. These results led us to explore the radical cyclisation of a vinyl bromide bearing an *N*-allyl system, such as **307** and **317** (**Scheme 174**). Vinyl bromides **307** and **317** were made using a concise 4-step procedure from 6,7-dimethoxy-isoquinoline (**190**). Treatment of vinyl bromide **307** or **317** with tributyltin hydride gave mixed results. Reaction of **307** gave a complex mixture of compounds,

including the desired tricycle **308**, but in a disappointing 22% yield. Whereas under identical conditions compound **317** afforded the desired tricyclic ester in an excellent 89% yield. Unfortunately, subsequent conversion of the tricycle into protoemetinol (**88**) proved to be problematic.



Scheme 174

Chapter 4 then explored the chemistry of phenylselenides **331** and **332**, which were derived from α,β-unsaturated esters **329** and **330**, which in-turn were prepared using an efficient one-pot, two-step procedure (**Scheme 175**). Subsequent reaction of the α,β-unsaturated esters with phenylselenol afforded the desired phenylselenides **331** and **332** in good yields. Treatment of the selenides with tributyltin hydride afforded a complex mixture of products, the desired tricyclic esters **333** or **334** being obtained in a disappointingly low yield. The major product was the cyclic amide **335**. A lithium aluminium hydride reduction of the tricyclic esters **333** and **334-a** afforded the corresponding alcohols, (±)-des-methyl-protoemetinol (**342**) and (±)-protoemetinol (**88-a**).



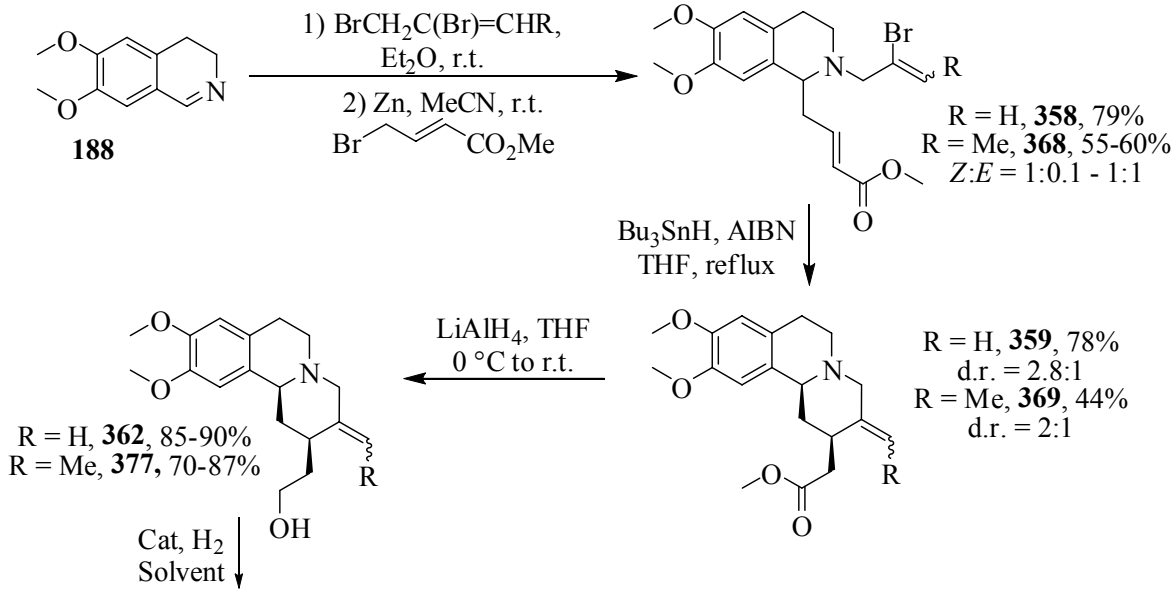
Scheme 175

Attempts were made at improving the efficiency of the radical cyclisation step, by the use of a vinyl chloride, but the radical reaction gave a complex mixture of products, containing an inseparable mixture of chlorinated and non-chlorinated cyclic compounds, along with large amounts of cyclic amide **335**. In an attempt to improve the efficiency of the cyclisation, attempts to change the acceptor C=C bond to an α,β-unsaturated ester were explored, however subsequent functionalisation of the *N*-allyl fragment proved to be unsuccessful. Future work could explore other routes towards phenylselenides containing an α,β-unsaturated ester.

6.4 Chapter 5 - Summary, conclusions and future work

Chapter 5 explored the radical cyclisation of a vinyl bromide bearing an α,β-unsaturated ester. The approach started with the development of an efficient one-pot, two-step route to the α,β-unsaturated esters, **358** and **368**, from imine **118** (**Scheme 176**). Subsequent treatment of the vinyl bromides **358** and **368** with tributyltin hydride afforded the desired tricycles **359** and **369**, respectively, in 44-78% yield as a mixture of diastereoisomers. Unfortunately, for the natural product synthesis (when R = Me) the yield of the desired 6-

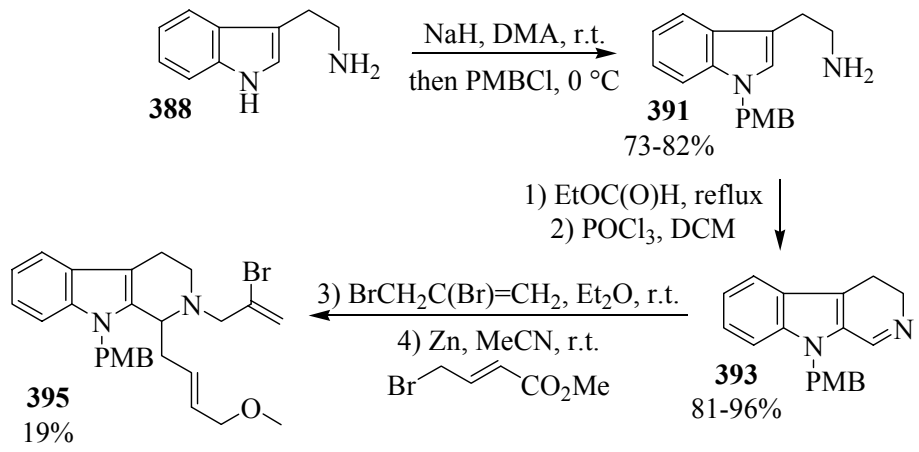
exo cyclisation product was disappointing, with several side reactions taking place. Subsequent reduction of the major diastereoisomers, with lithium aluminium hydride, afforded the expected alcohols in good yields. The final catalytic hydrogenation step proved to be tricky, with a palladium on carbon hydrogenation affording both des-methyl-epi-protoemetinol (**342-b**) and epi-protoemetinol (**88-b**) as the major diastereoisomers. However, the selective synthesis of the desired diastereoisomers could be achieved by using Crabtree's catalyst, to afford in a moderate excess, both (±)-des-methyl-protoemetinol (**342-a**) and protoemetinol (**88-a**).



	R = H, **342**		R = Me, **88**	
Hydrogenation Conditions	Yield (%)	a : b	Yield (%)	a : b
Pd/C, MeOH, H_2, r.t.	85	1.0 : 6.0	63	1.0 : 10.0
Crabtree's Catalyst, DCM, H_2, r.t.	96	1.4 : 1.0	54	1.1 : 1.0

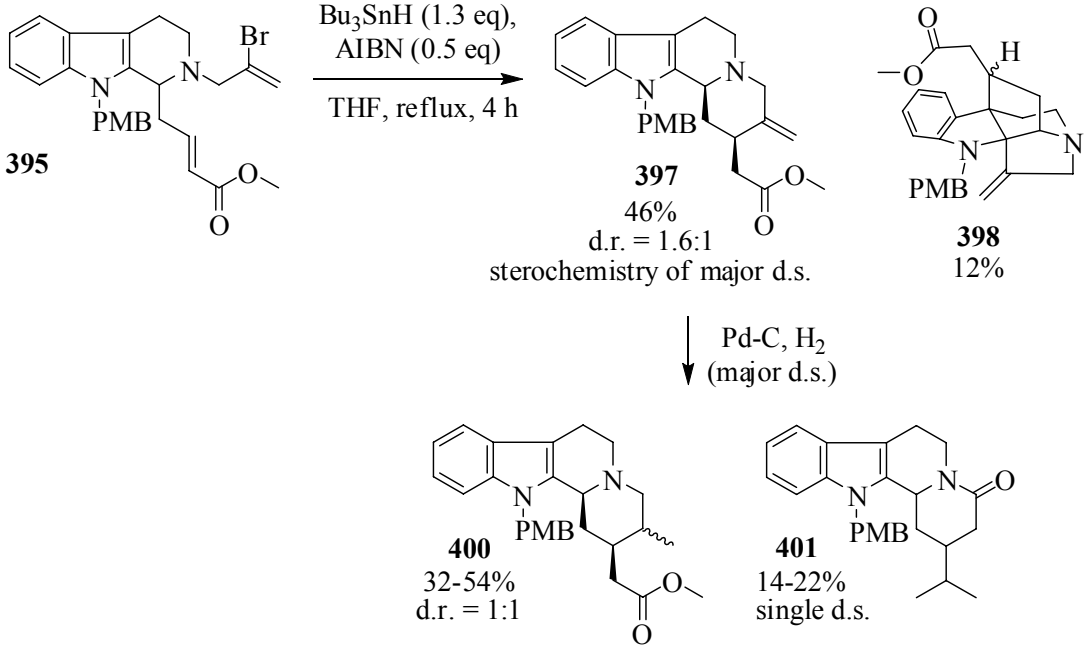
Scheme 176

It was expected that a similar approach should be applicable to the synthesis of mitragynine (**86**) and related compounds. The synthesis of de-methoxy mitragynine (**138**, or corynantheidine) was explored. Our synthesis started by the PMB protection of tryptamine (**388**) (**Scheme 177**) which in hindsight, turned out to be a poor choice of protecting group. Reaction of **391** with ethyl formate formed the intermediate formamide and a subsequent Bischler-Napieralski reaction[268] afforded imine **393**. The synthesis of vinyl bromide **395** from **393** was achieved using a similar procedure to that used earlier, although **395** was isolated in a disappointing yield.



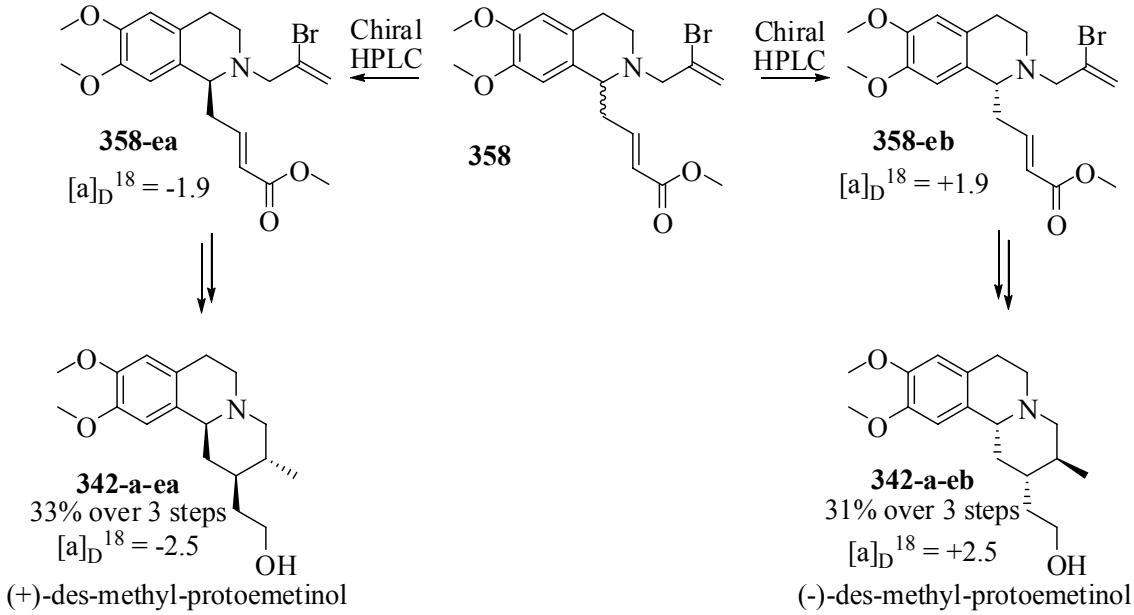
Scheme 177

Treatment of the vinyl bromide **395** with tributyltin hydride and AIBN afforded the desired cyclised product octahydroquinolizine **397** (as a mixture of partially separable diastereoisomers) along with by-products. This included an unexpected pentacyclic bridged system **398**, derived from a 5-*exo* cyclisation of the initial vinyl radical onto the indole ring, followed by a second 5-*exo* cyclisation onto the α,β-unsaturated ester. The major diastereoisomer of octahydroquinolizine **397** was then subjected to a palladium-catalysed hydrogenation, to afford ester **400** (as a 1:1 mixture of diastereoisomers) with retention of the PMB group, along with lactam **401**. Unfortunately, subsequent cleavage of the PMB group proved to be difficult, with apparent decomposition occurring.



Scheme 178

Future work could develop a route to enantiomerically pure protoemetinol (**88**). During time at AstraZeneca, the racemic vinyl bromide **358** was resolved by preparative chiral HPLC, resulting in clean separation of the enantiomers of the vinyl bromide.[f] Each of the enantiomers were elaborated, using the synthetic sequence shown in **Scheme 176**, to give enantiomerically pure (+)-des-methyl protoemetinol (**342**) and (-)-des-methyl protoemetinol (**342**). A similar route could be used to access enantiomerically pure protoemetinol (**88**), or members of the *Mitragyna* alkaloids.



Scheme 179

On this theme, future work could explore the asymmetric synthesis of vinyl bromides **358,** for example, by the asymmetric addition,[182, 183] of an organozinc reagent to imine **188**. Alternatively, an enantioselective synthesis could be achieved using a Myers-type approach,[151, 192] involving an asymmetric allylation of an formamide (see Chapter 2), or a carbamate (see Chapter 4).

6.5 Summary of routes to (±)-des-methyl-protoemetinol (342-a) and (±)-protoemetinol (88-a)

In summary we have explored a range of radical mediated approaches towards the tricyclic core of protoemetinol (**88-a**), and in the process have developed two synthetic routes to both (±)-des-methyl-protoemetinol (**342-a**) and (±)-protoemetinol (**88-a**). Both routes involve 4 steps, and include the use of a powerful one-pot reaction to form the radical

[f] HPLC was carried out at Astrazeneca, Alderly Park, by Michael Hatton on a Rainin prep (200 ml heads) instrument with a Merck 100 mm 20 µm Chiralpak AS column, using IsoHex/IPA/TEA 80/20/0.1 as the mobile phase

precursor. (±)-Des-methyl-protoemetinol (**342-a**) and (±)-protoemetinol (**88-a**) have been isolated in 2-32% overall yield (**Table 12**).

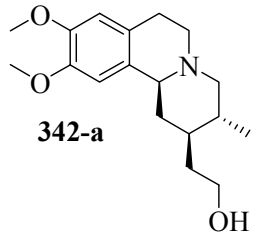
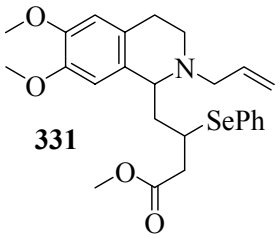
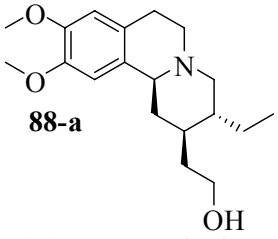
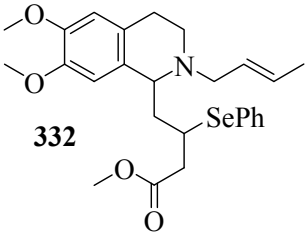
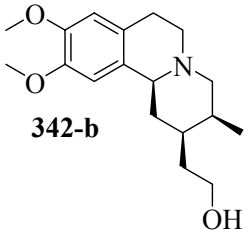
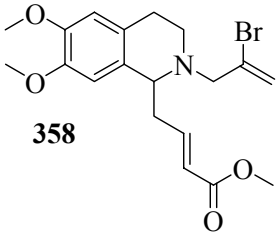
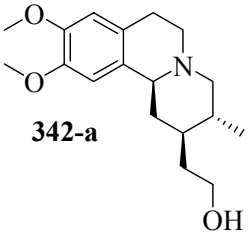
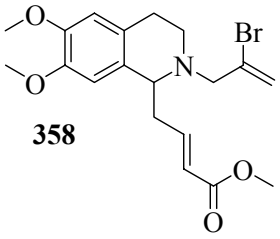
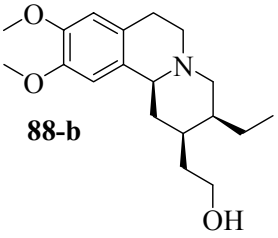
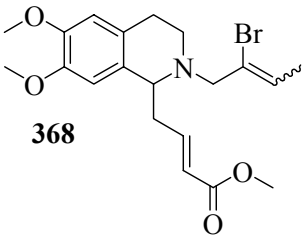
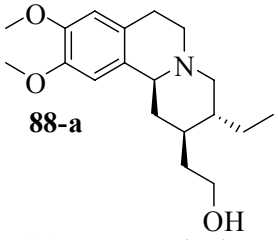
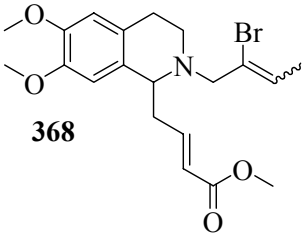
Product	Radical Precursor	Number of Steps	Overall Yield
 **342-a** (±)-des-methyl-protoemetinol	 **331**	4	5%
 **88-a** (±)-protoemetinol	 **332**	4	2%
 **342-b** (±)-des-methyl-epi-protoemetinol	 **358**	4	32%
 **342-a** (±)-des-methyl-protoemetinol	 **358**	4	23%
 **88-b** (±)-epi-protoemetinol	 **368**	4	9%
 **88-a** (±)-protoemetinol	 **368**	4	4%

Table 12

Chapter 7 - Experimental

7.1 General procedures

Solvents and commercially available reagents were either bought from Aldrich or Acros as extra dry solvents, or dried and purified in house before use where appropriate; dichloromethane, toluene, tetrahydrofunan and diethyl ether were dried by passing them through a column of activated alumina according to the procedure outlined by Grubbs.[284] Pyridine was distilled from, and stored over potassium hydroxide. Benzene, toluene and triethylamine were distilled from CaH_2 and stored over 4 Å molecular sieves or KOH as appropriate, for extra dry tetrahydrofunan was distilled from sodium and benzophenone, while dimethylformamide was distilled under reduced pressure from CaH_2.[285] 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 ºC. All non-aqueous experiments were carried out in oven-dried glassware under an argon or nitrogen atmosphere unless otherwise specified. ^{n}BuLi, ^{s}BuLi and ^{t}BuLi were purchased from Aldrich or Acros and stored at 4 ºC and titrated against *N*-benzylbenzamide before use.[286] $LiAlH_4$ was bought as a 2.4 M solution in THF from Acros. Et_3B was bought as a 1 M solution THF from Aldrich or Acros.

Thin layer chromatography was performed using Merck aluminum backed 0.2 mm Kieselgel 60 F_{254} precoated plates. Spots were visualised by the quenching of UV fluorescence (254 nm or 355 nm) and then stained using an aq. alkaline solution of $KMnO_4$, followed by heating. Retention factors (R_f) are reported with the solvent system used in parentheses. Flash column chromatography was performed either on Merck 60 silica gel, with a particle size of 40-63 μm, the solvent system being quoted in parentheses; the column was loaded as a slurry, prepared by pre-mixing silica gel with the eluent,[287] or use of a combiflash companion using pre-sealed cartages ranging from 4 g to 750 g of silica, under a concentration gradient quoted in parentheses.

NMR spectra were recorded on a Jeol EX 270 (^{1}H, 270 MHz; ^{13}C, 67.9 MHz), Jeol ECX400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), Jeol ESX400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), Bruker DPX400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), Bruker DPX500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) or a Bruker AV700 (^{1}H, 700 MHz; ^{13}C, 176 MHz) spectrometer. Chemical shifts (∂_H) are quoted in parts per million (ppm) downfield of tetramethylsilane using residual protonated solvent as an internal standard. Assignments were made on the basis of chemical shift and coupling constants using COSY, TOSCY or NOESY experiments

where appropriate. Abbreviations used in the descriptions of multiplicities are s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintuplet), sept. (septuplet), m (multiplet), br (broad) and app (apparent). Coupling constants (*J*) are quoted to the nearest 0.1 Hz (400, 500 and 700 MHz). Carbon-13 (^{13}C) chemical shifts (∂_C) are quoted in parts per million (ppm) downfield of tetramethylsilane using solvent as an internal standard. Assignments were made on the basis of chemical shift using DEPT, HMQC, HSQC and HMBC where appropriate and by comparison with the data obtained from similar structures. Fluorine-19 (^{19}F) NMR spectra were recorded on a Bruker DPX400 (^{19}F, 376 MHz) or a Jeol ECX400 (^{19}F, 376 MHz) instrument. Chemical shifts (∂_F) are quoted in parts per million (ppm) downfield of trifluoroacetic acid using solvent as an internal standard.

Infrared spectra were recorded as either thin films or as solutions in $CDCl_3$ or CH_2Cl_2 using an ATI Matteson Genesis FT-IR or on a Perkin Elmer Paragon 1000 FT-IR spectrometer. Absorption maxima (ν_{max}) were recorded in wavenumbers (cm^{-1}) and are classified as strong (s), medium (m), weak (w) and broad (br). Melting points (mp) were measured on a Gallenkamp melting point apparatus and are uncorrected.

Mass spectra were recorded on a Brucker Daltronic microOTOF. *m/z* values are reported in Daltons and are followed by their percentage abundances; only peaks with a signal of 10% or greater are included. High resolution mass spectra were recorded using a Bruker Daltronic microOTOF (CI or EI) instrument. Values are calculated from the molecular formula corresponding to the observed signal using the most abundant isotopes of each element, to 4 decimal places.

7.2 - Experimental for chapter 2

General procedures for oxidation of tetrahydroisoquinolines

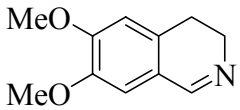
General procedure 1 - Oxidation by mercury(II) oxide and iodine.[180]

To a solution of the 1,2,3,4-tetrahydroisoquinoline (0.5-5 g, 2.2-22 mmol, 1 equiv) in anhydrous DCM (10-150 mL) was added red mercury(II) oxide (0.7-7 g, 3.3-33 mmol, 1.5 equiv) and iodine (0.85-8.5 g, 3.3-33 mmol, 1.5 equiv) the resulting solution was stirred under nitrogen at r.t. for 2 h. The resulting precipitate (HgI_2) was removed by filtration, and the salt washed with a further portion of DCM, the combined DCM fractions were washed with aq. 5% $Na_2S_2O_3$ solution, then water, dried over Na_2SO_4, and evaporated in vacuo to afford the crude product. The crude product was purified by either distillation or flash-chromatography to give the dihydroisoquinoline (0.27-2.2 g, 53-66%).

General procedure 2 - Oxidation by *N*-bromosuccinimide[181]

To a stirred solution of the 1,2,3,4-tetrahydroisoquinoline (0.5-20 g, 2.2-150 mmol, 1 equiv) in DCM (10-400 mL) was added *N*-bromosuccinimide (0.72-29.3 g, 4.1-165 mmol, 1.1 equiv) portionwise over 20 min. After the addition was complete, the mixture was stirred until TLC (CH_3Cl:MeOH = 9:l) indicated that the starting material was consumed (approx 1 h). An excess of sodium hydroxide (30% aqueous solution) was added, and stirring at 25 °C for 1 h. The organic layer was separated and washed with water (100 mL), and the product was extracted with 10% HCl (2 × 100 mL). The combined acidic extracts were washed with DCM (100 mL) and made basic with concentrated ammonia (pH 9). The liberated oil was extracted with DCM (3 × 100 mL), dried over Na_2SO_4, and evaporated in vacuo to afford a light yellow oil which was purified by either distillation or flash chromatography to give the dihydroisoquinoline (0.27-16 g, 51-92%).

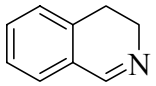
3,4-Dihydro-6,7-dimethoxyisoquinoline (188)[180, 181]



1,2,3,4-Tetrahydro-6,7dimethoxyisoquinoline was oxidised using either **General procedure 1** or **General procedure 2**, the crude product was purified by flash chromatography on silica gel (ethyl acetate:petrol, 1:1), to yield 3,4-dihydro-6,7-dimethoxyisoquinoline **188** as a pale yellow oil which slowly crystallised to give a yellow soft solid; mp 134-138 ºC; ν_{max} (thin film)/cm^{-1} 3643 (m), 3373 (s), 2938 (s), 1695 (w), 1611 (s), 1573 (s), 1516 (s); δ_H (400 MHz, $CDCl_3$) 8.14 (1H, s, NC<u>H</u>), 6.72 (1H, s, ^{Ar}C<u>H</u>),

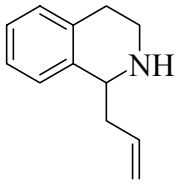
6.58 (1H, s, $^{Ar}C\underline{H}$), 3.82 (6H, s, $OC\underline{H}_3$), 3.65 (2H, t, J = 8.0, $NC\underline{H}_2CH_2Ar$), 2.59 (2H, t, J = 8.0, $NCH_2C\underline{H}_2Ar$); δ_C (100 MHz, $CDCl_3$) 159.4 (N$\underline{C}$H), 150.9 ($^{Ar}\underline{C}OCH_3$), 147.6 ($^{Ar}\underline{C}OCH_3$), 129.6 ($^{Ar}\underline{C}$), 121.3 ($^{Ar}\underline{C}$), 110.1 (2 × $^{Ar}\underline{C}H$), 55.9 (O$\underline{C}H_3$), 55.8 (O$\underline{C}H_3$), 47.0 (N$\underline{C}H_2CH_2Ar$), 24.5 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI) 193 (10%), 192 (MH^+, 100).
The spectroscopic data is in agreement with reported data.[180, 181]

3,4-Dihydroisoquinoline (200)[180, 181]



1,2,3,4-Tetrahydroisoquinoline was oxidised using either **general procedure 1** or **general procedure 2**, the crude product was purified by vacuum distillation (80-85 °C at 5 Torr, lit 60-65 °C at 1 Torr) to yield 3,4-dihydroisoquinoline **200** (62-92 %) as a colourless oil which slowly crystallised to give an off white soft solid; mp 40-42 ºC; ν_{max} (thin film) 3402 (s), 2089 (w), 1642 (s) /cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.28 (1H, s, NC$\underline{H}$), 7.32-7.18 (3H, m, $^{Ar}C\underline{H}$), 7.10 (1H, d, J = 7.3, $^{Ar}C\underline{H}$), 3.72 (2H, app t, J = 7.6, $NC\underline{H}_2CH_2Ar$), 2.69 (2H, t, J = 7.69, $NCH_2C\underline{H}_2Ar$); δ_C (100 MHz, $CDCl_3$) 160.1 (N$\underline{C}$H), 136.0 ($^{Ar}\underline{C}$), 130.8 ($^{Ar}\underline{C}H$), 128.2 ($^{Ar}\underline{C}$), 127.2 ($^{Ar}\underline{C}H$), 126.9 ($^{Ar}\underline{C}H$), 126.8 ($^{Ar}\underline{C}H$), 47.1 ($N\underline{C}H_2CH_2Ar$), 24.8 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI) 133 (15%), 132 (MH^+, 100).
The spectroscopic data is in agreement with reported data.[180, 181]

1-Allyl-1,2,3,4-tetrahydroisoquinoline (203)

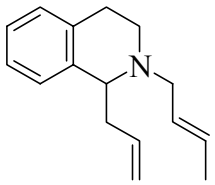


An excess of zinc (5 eq, 3.2-11.2 g, 50-175 mmol) is activated by washing successively with 5% HCl, water, methanol, and diethyl ether and then dried under high vacuum. To a stirred suspension of the activated zinc in dry THF in a two neck round bottom flask fitted with a water condenser under nitrogen was slowly added allyl bromide (2 eq, 20-70 mmol 1.7-6.1 mL), during which time the solution starts to reflux, and turn a pale green-grey colour, following complete addition the solution is stirred for a further 3 h. The greenish supernatuant was then transferred via a cannula, to a stirred solution of the dihydroisoquinoline **200** (1 eq, 1.31-4.59 g, 10-35 mmol) in THF under nitrogen, the resulting solution was left stirring for 12 h. The reaction mixture was quenched by pouring into a saturated solution of aq. $NaHCO_3$ (50-150 mL) and allowed to stir for 30 minutes, the resulting precipitate was removed by filtration, and washed with EtOAc (50-150 mL),

the organic layer was separated and the aqueous layer extracted with EtOAc (2 × 50-150 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered and evaporated to afford a yellow oil. The crude product was purified by flash chromatography on silica gel (triethylamine:hexane, 8:1), to yield 1-allyl-1,2,3,4-tetrahydroisoquinoline **203** as a pale yellow oil (0.96-4.2 g, 55-70%). R_f 0.26 (hexane:triethylamine, 8:1); ν_{max} (thin film) 3318 (m), 3071 (s), 3017 (s), 2921 (s), 2833 (s), 1833 (w), 1668 (s), 1638 (s), 1579 (w) /cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20-7.05 (4H, m, $^{Ar}C\underline{H}$), 5.90-5.78 (1H, m, $CH_2C\underline{H}=CH_2$), 5.21-5.12 (2H, m, $CH_2CH=C\underline{H}_2$), 4.04 (1H, app dd, J = 9.0 and 3.4 $NC\underline{H}$), 3.28 (1H, dt, J = 12.2 and 5.1, $NC\underline{H}_2CH_2Ar$), 3.01-2.93 (1H, m, $NC\underline{H}_2CH_2Ar$), 2.88-2.62 (3H, m, $NCH_2C\underline{H}_2Ar$ and $C\underline{H}_2CH=CH_2$), 2.56-2.48 (1H, m, $C\underline{H}_2CH=CH_2$); δ_C (100 MHz, $CDCl_3$) 138.3 (^{Ar}C), 135.3 ($CH_2\underline{C}H=CH_2$), 135.1 (^{Ar}C), 129.1 (^{Ar}CH), 125.8 (2 × ^{Ar}CH), 125.6 (^{Ar}CH), 117.8 ($CH_2CH=\underline{C}H_2$), 54.8 ($N\underline{C}H$), 40.7 ($N\underline{C}H_2CH_2Ar$), 40.4 ($\underline{C}H_2CH=CH_2$) and 29.7 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI) 175 (15%), 174 (MH^+, 100).

The spectroscopic data is in agreement with reported data.[180, 181]

1-Allyl-2-((*E*)-but-2-enyl)-1,2,3,4-tetrahydroisoquinoline (204)

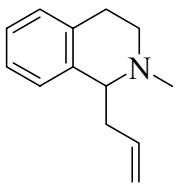


To a stirred solution of 3,4-dihydroisoquinoline (**200**) (2 g, 15.2 mmol) in Et_2O (100 mL) at r.t. under nitrogen was added crotyl bromide (2.0 mL, 85%, 16.3 mmol). The resulting solution was stirred in the dark overnight, during which time a yellow precipitate formed. The crude mixture was evaporated to dryness to afford the bromide salt as an unstable, moisture sensitive yellow power; Major *trans* isomer; δ_H (400 MHz, $CDCl_3$) 10.33 (1H, s, $N\underline{C}H$), 8.11 (1H, d, J = 7.6, $^{Ar}C\underline{H}$), 7.69 (1H, dt, J = 7.6 and 1.2, $^{Ar}C\underline{H}$), 7.44 (1H, t, J = 7.6, $^{Ar}C\underline{H}$), 7.34 (1H, d, J = 7.6, $^{Ar}C\underline{H}$), 6.22-6.14 (1H, m, $NCH_2CH=C\underline{H}CH_3$), 5.74-5.64 (1H, m, $NCH_2C\underline{H}=CHCH_3$), 4.93 (2H, d, J = 7.0, $NC\underline{H}_2CH=CHCH_3$), 4.08 (2H, t, J = 8.0, $NC\underline{H}_2CH_2Ar$), 3.31 (2H, t, J = 8.0, $NCH_2C\underline{H}_2Ar$), 1.78 (3H, app d, J = 6.4, $NCH_2CH=CHC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 166.5 ($N\underline{C}H$), 137.9 ($\underline{C}H=CH$), 137.8 ($CH=\underline{C}H$), 135.9 ($^{Ar}\underline{C}H$), 134.7 ($^{Ar}\underline{C}$), 128.5 ($^{Ar}\underline{C}H$), 128.0 ($^{Ar}\underline{C}H$), 125.0 ($^{Ar}\underline{C}$), 120.7 ($^{Ar}\underline{C}H$), 62.5 ($N\underline{C}H_2CH=CHCH_3$), 48.0 ($N\underline{C}H_2CH_2Ar$), 25.4 ($NCH_2\underline{C}H_2Ar$), 18.0 ($NCH_2CH=CHC\underline{H}_3$); Minor *cis* isomer δ_H (400 MHz, $CDCl_3$) 4.93 (2H, d, J = 7.3, $NC\underline{H}_2CH=CHCH_3$), 1.87 (3H, app dd, J = 7.0 and 1.8, $NCH_2CH=CHC\underline{H}_3$).

To a stirred suspension of the bromide salt in THF (75 mL) under nitrogen at 0 ºC, was added a solution of allyl zinc bromide (30 mmol, prepared as above), following the

complete addition the suspension was warmed to r.t. and stirred for 12 h. The reaction mixture was quenched by pouring into a saturated solution of aq. $NaHCO_3$ (100 mL) and allowed to stir for 30 minutes, the resulting precipitate was removed by filtration, and washed with EtOAc (75 mL), the organic layer was separated and the aqueous layer extracted with EtOAc (2 × 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 2:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound as a pale yellow oil, (1.9 g, 59%); Rf 0.25 (ethyl acetate:petrol, 1:1); ν_{max} (thin film) 3071 (m), 3017 (m), 2915 (s), 1675 (m), 1638 (m), 1490 (s), 1451 (s) /cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.14-7.03 (4H, m, $^{Ar}C\underline{H}$), 5.92-5.80 (1H, m, $CH_2C\underline{H}=CH_2$), 5.60-5.52 (2H, m, $CH_2C\underline{H}=C\underline{H}CH_3$), 5.15-4.95 (2H, m, $CH_2CH=C\underline{H}_2$), 3.75 (1H app t, J = 6.2, $ArC\underline{H}N$), 3.16-3.20 (3H, m, $NC\underline{H}_2CH=CHCH_3$ and $NC\underline{H}_2CH_2Ar$), 2.92-2.80 (2H, m, $NC\underline{H}_2CH_2Ar$ and $NCH_2C\underline{H}_2Ar$), 2.66-2.52 (2H, m, $C\underline{H}_2CH=CH_2$), 2.48-2.40 (1H, m, $NCH_2C\underline{H}_2Ar$), 1.70 (3H, d, J = 4.5, $NCH_2CH=CHC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 138.0 ($^{Ar}\underline{C}$), 136.6 ($\underline{C}H=CH$), 134.5 ($^{Ar}\underline{C}$), 128.7 ($^{Ar}\underline{C}H$), 128.6 ($\underline{C}H=CH$), 128.2 ($^{Ar}\underline{C}H$), 127.8 ($^{Ar}\underline{C}H$), 125.8 ($^{Ar}\underline{C}H$), 125.4 ($^{Ar}\underline{C}H$), 115.7 ($CH=\underline{C}H_2$), 60.1 ($Ar\underline{C}HN$), 55.8 ($N\underline{C}H_2CH=CH$), 43.7 ($N\underline{C}H_2CH_2Ar$), 39.8 ($C\underline{H}_2CH=CH_2$), 25.1 ($NCH_2\underline{C}H_2Ar$), 17.8 (CH_3); *m/z* 228 (17%), 229 (MH^+, 100); HRMS $C_{16}H_{22}N$ (MH^+) requires 228.1752, found 228.1750.

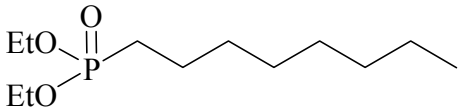
1-Allyl-1,2,3,4-tetrahydro-2-methylisoquinoline (208)



To a stirred solution of 3,4-dihydroisoquinoline **(200)** (1 g, 7.6 mmol), in diethyl ether (75 mL) at r.t. under nitrogen was added methyl iodide (0.54 mL, 8.3 mmol). The resulting solution was stirred in the dark overnight, during which time a yellow precipitate formed. The crude mixture was evaporated to dryness to afford the iodide salt as an unstable, moisture sensitive yellow power; δ_H (400 MHz, $CDCl_3$) 9.96 (1H, s, $NC\underline{H}$), 8.02 (1H, d, J = 7.0, $^{Ar}C\underline{H}$), 7.69 (1H, app t, J = 7.2, $^{Ar}C\underline{H}$), 7.45 (1H, app t, J = 7.0, $^{Ar}C\underline{H}$), 7.37 (1H, d, J = 7.2, $^{Ar}C\underline{H}$), 4.15 (2H, t, J = 8.1, $NC\underline{H}_2CH_2Ar$), 4.01 (3H, s, $NC\underline{H}_3$), 3.41 (2H, t, J = 8.1, $NCH_2C\underline{H}_2Ar$); δ_C (100 MHz, $CDCl_3$) 166.4 ($N\underline{C}H$), 137.9 ($^{Ar}\underline{C}H$), 135.7 ($^{Ar}\underline{C}$), 134.2 ($^{Ar}\underline{C}H$), 128.5 ($^{Ar}\underline{C}H$), 128.3 ($^{Ar}\underline{C}H$), 124.4 ($^{Ar}\underline{C}$), 51.0 ($N\underline{C}H_2CH_2Ar$), 48.7 ($N\underline{C}H_3$), 25.3 ($NCH_2\underline{C}H_2Ar$).

To a stirred suspension of the iodide salt in THF (50 mL) under nitrogen at 0 ºC, was added a solution of allyl zinc bromide (16 mmol, prepared as above), following the complete addition the suspension was warmed to r.t. and stirred for 12 h. The reaction mixture was quenched by pouring into a saturated solution of aq. $NaHCO_3$ (50 mL) and allowed to stir for 30 minutes, the resulting precipitate was removed by filtration, and washed with EtOAc (50 mL), the organic layer was separated and the aqueous layer extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 2:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound as a pale yellow oil (0.65 g, 45%); Rf 0.20 (ethyl acetate:petrol, 1:1); ν_{max} (thin film) 3068 (w), 3024 (m), 2930 (s), 2850 (w), 1661 (m), 1636 (m), 1497 (s) /cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.15-7.05 (4H, m, $^{Ar}C\underline{H}$), 5.82-5.72 (1H, m, $C\underline{H}=CH_2$), 5.07-4.98 (2H, m, $CH=C\underline{H}_2$), 3.56 (1H, t, *J* = 5.5, $NC\underline{H}$), 3.12 (1H, app dt, *J* = 12.2 and 6.1, $NCH_2C\underline{H}_2Ar$), 2.81 (2H, t, *J* = 6.1, $NC\underline{H}_2CH_2Ar$), 2.72-2.54 (3H, m, $NCH_2C\underline{H}_2Ar$ and $C\underline{H}_2CH=CH_2$), 2.47 (3H, s, $NC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 137.5 ($^{Ar}\underline{C}$), 135.7 ($\underline{C}H=CH_2$), 134.6 ($^{Ar}\underline{C}$), 128.6 ($^{Ar}\underline{C}H$), 127.1 ($^{Ar}\underline{C}H$), 125.8 ($^{Ar}\underline{C}H$), 125.6 ($^{Ar}\underline{C}H$), 116.1 ($CH=\underline{C}H_2$), 63.5 ($N\underline{C}H$), 48.5 ($N\underline{C}H_2CH_2Ar$), 42.7 ($N\underline{C}H_3$), 38.8 ($\underline{C}H_2CH=CH_2$), 26.5 ($NCH_2\underline{C}H_2Ar$); *m/z* 189 (14%), 188 (MH^+, 100).
The spectroscopic data is in agreement with reported data.[288]

Diethyl octylphosphonate [121, 125, 188]

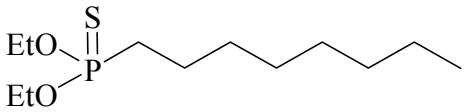


To a stirred solution of 1-octene (1.0 g, 8.18 mmol.) in cyclohexane (20 mL) under nitrogen was added diethyl phosphite (11.3 g, 81.8 mmol) and AIBN (0.24 g, 2.46 mmol). The reaction mixture was heated to 80 ºC, and further portions of AIBN (0.24 g, 2.46 mmol) were added every 1 h, until a total of 5 additions had been made. The solution was stirred at 80 ºC for a further 12 h, after which the reaction mixture was cooled and the solvent removed *in vacuo*. The crude mixture was distilled to remove excess diethyl phosphite, and the resulting residue was purified by column chromatography (silica, petrol/EtOAc, 1:1) to afforded the title compound (1.9 g, 95%) as a colourless oil. R_f 0.3 (EtOAc); ν_{max} (thin film) 2929 (s), 2857 (s), 1466 (m), 1392 (m), 1249 (s), 1164 (s), 1023 (s) cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.16-4.02 (4H, m, 2 × $OC\underline{H}_2CH_3$), 1.78-1.72 (2H, m, $PC\underline{H}_2$), 1.65-1.59 (2H, m, $PCH_2C\underline{H}_2$), 1.41-1.21 (10H, m, 5 × CH_2), 1.32 (6H, t, *J* = 7.0, 2 × $OCH_2C\underline{H}_3$), 0.88 (3H, t, *J* = 7.0, $CH_2CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 61.3 (d, *J* = 7.0, 2

× O<u>C</u>H$_2$CH$_3$), 31.7 and 29.0 (2 × <u>C</u>H$_2$), 30.6 (d, *J* = 17.0, PCH$_2$<u>C</u>H$_2$), 22.6 (CH$_2$<u>C</u>H$_2$CH$_3$), 22.3 (d, *J* = 6.0, PCH$_2$CH$_2$<u>C</u>H$_2$), 25.6 (d, *J* = 140.5, P<u>C</u>H$_2$), 16.4 (d, *J* = 6.0, 2 × OCH$_2$<u>C</u>H$_3$), 14.0 (CH$_2$CH$_2$<u>C</u>H$_3$); *m/z* (CI, NH$_3$) 251 (MH$^+$, 100%); (Found: MH$^+$, 251.1779. $C_{12}H_{27}O_3P$ requires: MH$^+$, 251.1776).

The spectroscopic data is in agreement with reported data.[121, 125, 188]

_O,O_-Diethyl octylphosphonothioate (76) [121, 125, 188]



To a stirred solution of 1-octene (1.0 g, 8.18 mmol.) in cyclohexane (20 mL) under nitrogen was added diethyl thiophosphite (3.793 g, 24.5 mmol) and AIBN (0.24 g, 2.46 mmol). The reaction mixture was heated to 80 ºC, and further portions of AIBN (0.24 g, 2.46 mmol) were added every 1 h, until a total of 5 additions had been made. The solution was stirred at 80 ºC for a further 12 h, after which the reaction mixture was cooled and the solvent removed *in vacuo*. The resulting crude oil was purified by column chromatography (silica, petrol:EtOAc, 19:1) to afforded the title compound (2.15 g, 98%) as a colourless oil. R_f 0.45 (petrol/EtOAc, 9:1); ν_{max} (thin film) 2928 (s), 2954 (s), 2856 (s), 2364 (w), 1465 (m), 1388 (m), 1160 (m), 1097 (s), 1028 (s) cm^{-1}; δ_H (400 MHz; $CDCl_3$) 4.19-3.97 (4H, m, 2 × OC<u>H</u>$_2$CH$_3$), 1.92-1.84 (2H, m, PC<u>H</u>$_2$), 1.63-1.51 (2H, m, PCH$_2$C<u>H</u>$_2$), 1.42-1.14 (10H, m, 5 × C<u>H</u>$_2$), 1.30 (6H, t, *J* = 7.0, 2 × OCH$_2$C<u>H</u>$_3$), 0.84 (3H, t, *J* = 7.0, CH$_2$CH$_2$C<u>H</u>$_3$); δ_C (100 MHz; $CDCl_3$) 62.2 (d, *J* = 7.0, 2 × O<u>C</u>H$_2$CH$_3$), 34.6 (d, *J* = 111.0, P<u>C</u>H$_2$), 31.8 and 29.1 (2 × <u>C</u>H$_2$), 30.3 (d, *J* = 18.5, PCH$_2$<u>C</u>H$_2$), 22.7 (d, *J* = 6.0, PCH$_2$CH$_2$<u>C</u>H$_2$), 22.6 (CH$_2$<u>C</u>H$_2$CH$_3$), 16.2 (d, *J* = 7.0, 2 × OCH$_2$<u>C</u>H$_3$), 14.1 (CH$_2$CH$_2$<u>C</u>H$_3$); *m/z* (CI, NH$_3$) 267 (MH$^+$, 100%); (Found: MH$^+$, 267.1546. $C_{12}H_{27}O_2PS$ requires: MH$^+$, 267.1548).

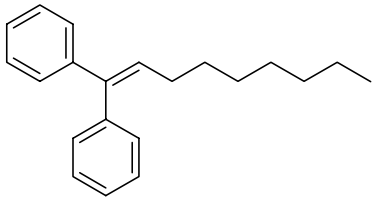
The spectroscopic data is in agreement with reported data.[121, 125, 188]

General procedure 3: HWE reaction of phosphonothioates

A stirred solution of the phosphonothioate (1 equiv, 0.94-2.23 mmol) in dry THF (20 – 40 mL) under nitrogen is cooled to -78 °C, and allowed to achieve thermal equilibrium. ^{s}BuLi (2 equiv, 1.88-4.46 mmol) is added dropwise, following complete addition, the solution is allowed to warm to 0 °C, and stirred for 30 minutes. The resulting solution is then cooled to -78 °C before the addition of the ketone/aldehyde (2 equiv, 1.88-4.46 mmol). The solution is then allowed to warm to rt, and stirred overnight. The crude reaction mixture is then passed through a plug of silica (washed through with EtOAc) and concentrated *in*

vacuo to yield crude product. Purification by column chromatography afforded the desired alkenes (39-85%) as colourless oils.

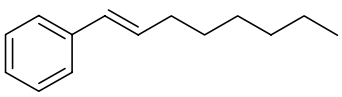
1-(1-Phenyl-1-nonenyl)benzene (77)[121, 125, 188]



O,*O*-Diethyl octylphosphonothioate (0.50 g, 1.82 mmol, 1 eq.), ^{s}BuLi (4.46 mmol) and benzophenone (0.812 g, 4.46 mmol, 2 eq.) were reacted according to **General procedure 3**. Purification by column chromatography (silica, petrol) afforded the title compound **77** (0.57 g, 90%) as a colourless oil. R_f 0.35 (petrol); ν_{max} (thin film) 3081 (m), 3059 (m), 3023 (m), 2957 (s), 2929 (s), 2855 (s), 1598 (m), 1494 (s), 1470 (m), 1443 (s), 1365 (w), 1030 (w) cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.39-7.15 (10H, m, $^{Ar}C\underline{H}$), 6.08 (1H, t, J = 7.5, C=C$\underline{H}$), 2.10 (2H, app. q, J = 7.5, C=CHC$\underline{H}_2$), 1.43 (2H, m, C=CHCH$_2$C$\underline{H}_2$), 1.32-1.20 (8H, m, 4 × C$\underline{H}_2$), 0.87 (3H, t, J = 7.0, C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 142.9, 141.3 and 140.3 (2 × $^{Ar}\underline{C}$, $\underline{C}$=CH), 130.4 (C=$\underline{C}$H), 129.9, 128.1, 128.0, 127.2, 126.8 and 126.7 (10 × ^{Ar}CH), 31.8, 30.0, 29.7, 29.2 and 29.2 (5 × $\underline{C}H_2$), 22.6 ($\underline{C}H_2CH_3$), 14.1 ($\underline{C}H_3$); *m/z* (EI) 278 (M^+, 26%), 193 (Ph_2C=$CHCH_2^+$, 100), 91 ($C_7H_7^+$, 57), 41 ($C_3H_5^+$, 52); (Found: M^+, 180.1028. $C_{20}H_{24}$ requires: M^+, 180.1025).

The spectroscopic data is in agreement with reported data.[121, 125, 188]

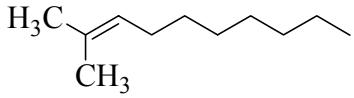
1-[(*E*)-1-Nonenyl]benzene (210)[121, 125, 188]



O,*O*-Diethyl octylphosphonothioate (0.250 g, 0.94 mmol, 1 eq.), ^{s}BuLi (1.88 mmol) and benzaldehyde (0.199 g, 1.88 mmol, 2 eq.) were reacted according to **General procedure 3**. Purification by column chromatography (silica, petrol) afforded the title compound **210** (0.07 g, 39%) as a colourless oil. Only the *E*-isomer was observed in the ^{1}H NMR spectrum. R_f 0.45 (petrol); ν_{max} (thin film) 2927 (s), 2854 (s), 2361 (w), 1667 (w), 1465 (m), 1377 (m) cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.39 (2H, d, J = 7.0, $^{Ar}C\underline{H}$), 7.34 (2H, t, J = 7.0, $^{Ar}C\underline{H}$), 7.23 (1H, t, J = 7.0, $^{Ar}C\underline{H}$), 6.42 (1H, d, J = 16.0, ArC$\underline{H}$=$CHCH_2$), 6.28 (1H, dq, J = 16.0 and 7.0, CH=C$\underline{H}CH_2$), 2.25 (2H, app. q, J = 7.0, CH=CHC$\underline{H}_2$), 1.52 (2H, m, CH=CHCH$_2$C$\underline{H}_2$), 1.44-1.26 (8H, m, C$\underline{H}_2$), 0.88 (3H, t, J = 7.0, $CH_2C\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) 137.9 ($^{Ar}\underline{C}$), 131.3 (CH=*C*HCH_2), 129.6 (*C*H=$CHCH_2$), 128.4 (2 × $^{Ar}\underline{C}$H), 126.7 (2

× ^{Ar}CH), 125.9 (^{Ar}CH), 33.1 (CH$_2$), 31.8 (CH$_2$), 29.7 (*C*H$_2$), 29.4 (CH$_2$), 29.2 (CH$_2$), 22.7 (CH$_2$), 14.1 (CH$_3$); *m/z* (EI) 202 (M$^+$, 21%), 117 (PhCHCHCH$_2^+$, 100); (Found: M$^+$, 202.1730. $C_{15}H_{22}$ requires: M$^+$, 202.1722). The spectroscopic data is in agreement with reported data.[121, 125, 188]

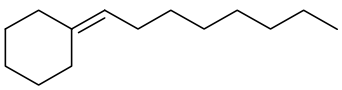
2-Methyl-2-decene (211) [121, 125, 188]



O,*O*-Diethyl octylphosphonothioate (0.250 g, 0.94 mmol, 1 eq.), ^{s}BuLi (1.88 mmol) and acetone (0.109 g, 1.88 mmol, 2 eq.) were reacted according to **General procedure 3**. Purification by column chromatography (silica, petrol) afforded 2-methyl-2-decene **211** (0.065 g, 47%) as a colourless oil. R_f 0.65 (petrol); ν_{max} (thin film) 2957 (s), 2923 (s), 2856 (s), 2729 (w), 2673 (w), 1667 (w), 1465 (s), 1378 (m) cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.15-5.09 (1H, m, C=CH), 2.00-1.92 (2H, m, C=CHCH$_2$), 1.69 (3H, d, *J* = 1.0, CH$_3$C=CH), 1.60 (3H, s, CH$_3$C=CH), 1.45-1.20 (10H, m, 5 × CH$_2$), 0.88 (3H, t, *J* = 7.0, CH$_2$C*H*$_3$); δ_C (100 MHz; $CDCl_3$) 131.1 (C=CH), 125.0 (C=CH), 31.9, 29.9, 29.7, 29.3, 29.3 and 28.1 (5 × CH$_2$), 25.7 (CH$_3$), 22.7 (CH$_2$CH$_3$), 22.7 (CH$_3$), 14.1 (CH$_3$); *m/z* (EI) 154 (M$^+$, 39%), 84 ($C_6H_{12}^+$, 40), 69 ($C_5H_9^+$, 86), 55 ($C_4H_7^+$, 60), 41 ($C_3H_5^+$, 100); (Found: M$^+$, 154.1720. $C_{19}H_{38}$ requires: M$^+$, 154.1722).

The spectroscopic data is in agreement with reported data.[121, 125, 188]

1-Octylidenecyclohexane (212) [121, 125, 188]

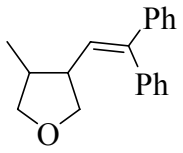


O,*O*-Diethyl octylphosphonothioate (0.250 g, 0.94 mmol, 1 eq.), ^{s}BuLi (1.88 mmol) and cyclohexanone (0.092 g, 1.88 mmol, 2 eq.) were reacted according to **General procedure 3**. Purification by column chromatography (silica, petrol) afforded 1-octylidenecyclohexane **212** (0.15 g, 80%) as a colourless oil. R_f 0.6 (petrol); ν_{max} (thin film) 2930 (s), 2850 (s), 2661 (w), 1447 (m), 1376 (m), 1342 (m), 1306 (m) cm^{-1}; δ_H (400 MHz; $CDCl_3$) 5.06 (1H, t, *J* = 7.0, C=CH), 2.14 (2H, t, *J* = 7.0, CCH$_2$), 2.06 (2H, t, *J* = 7.0, CCH$_2$), 1.96 (2H, app. q, *J* = 7.0, C=CHCH$_2$), 1.58-1.42 (6H, m, 3 × CH$_2$), 1.38-1.20 (10H, m, 5 × CH$_2$), 0.88 (3H, t, *J* = 7.0, CH$_3$); δ_C (100 MHz; $CDCl_3$) 139.7 (C=CH), 121.7 (C=CH), 37.2 (CCH$_2$), 31.7, 30.0 and 29.0 (4 × CH$_2$), 28.5 (CCH$_2$), 28.4, 27.6, 26.7, 26.8 and 22.4 (5 × CH$_2$), 13.8 (CH$_3$); *m/z* (EI) 194 (M$^+$, 58%), 109 ($C_8H_{13}^+$, 66), 96 ($C_7H_{12}^+$,

68), 81 ($C_6H_9^+$, 63), 67 ($C_5H_9^+$, 100), 55 ($C_4H_7^+$, 37), 41 ($C_3H_5^+$, 50); (Found: M^+, 194.2034. $C_{14}H_{26}$ requires: M^+, 194.2035).

The spectroscopic data is in agreement with reported data.[121, 125, 188]

3-(2,2-Diphenylvinyl)-4-methyltetrahydrofuran (79) [121, 125, 188]

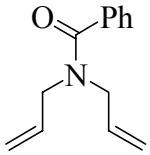


To a stirred solution of allyl ether (1.0 g, 10.2 mmol, 1 eq.) in dry THF (40 mL) under nitrogen was added diethyl thiophosphite (1.9 g, 12.0 mmol, 1.2 eq.) and AIBN (0.405 g, 2.4 mmol, 0.25 eq.). The solution was then heated to reflux for 6 h, after which a further portion of AIBN (0.405 g, 2.4 mmol, 0.25 eq.) was added and reflux maintained overnight. The resulting reaction mixture was then cooled to -78 °C, and allowed to achieve thermal equilibrium. ^{s}BuLi (30.6 mmol, 3 eq.) is added dropwise, following complete addition, the solution is allowed to warm to 0 °C, and stirred for 30 minutes. The resulting solution is then cooled to -78 °C before the addition of benzophenone (3.4 g, 20.1 mmol, 2 eq.). The solution is then allowed to warm to rt, and stirred overnight. The crude reaction mixture is then passed through a plug of silica (washed through with EtOAc) and concentrated *in vacuo* to yield crude product. Purification by column chromatography (silica, petrol/EtOAc, 19:1) affords the title compound **79** (2.3 g, 86%) as an inseparable mixture of *cis*- and *trans*-isomers, (3:1, *cis*:*trans*) as a colourless oil. Rf 0.35 (petrol/EtOAc, 4:1); ν_{max} (thin film) 3081 (m), 3028 (m), 2959 (s), 2933 (s), 2852 (s), 1886 (w), 1809 (w), 1658 (w), 1596 (m), 1575 (w), 1494 (m), 1440 (s) cm^{-1}; δ_H (400 MHz; CDCl3) (*cis*-isomer) 7.40-7.14 (10H, m, ^{Ar}C$\underline{H}$), 6.04 (1H, d, J = 10.5, C=C$\underline{H}$), 3.95-3.87 (2H, m, C$\underline{H}_2$OCH_2), 3.69 (1H, dd, J = 8.0 and 7.0 CHCHC$\underline{H}_2$O), 3.53 (1H, dd, J = 8.0 and 6.0, OC$\underline{H}_2$CHCH_3), 2.99-2.95 (1H, m, CHC$\underline{H}$CH_2O), 2.35-2.29 (1H, m, OCH_2C$\underline{H}$CH_3), 1.08 (3H, d, J = 7.0, C$\underline{H}_3$); δ_C (100 MHz; $CDCl_3$) (*cis*-isomer) 143.7 ($^{Ar}\underline{C}$), 142.3 ($\underline{C}$=CH), 140.0 ($^{Ar}\underline{C}$), 129.8 (4 × $^{Ar}\underline{C}$H), 128.2 (4 × $^{Ar}\underline{C}$H), 127.2 (2 × $^{Ar}\underline{C}$H), 127.0 (C=$\underline{C}$H), 75.1 and 72.9 ($\underline{C}H_2OCH_2$), 43.0 ($\underline{C}$H), 38.2 ($CH_3\underline{C}$H), 13.9 ($\underline{C}H_3$); *m/z* (CI, NH_3) 282 ($M+NH_4^+$, 39%), 265 ($M+H^+$, 100), 207 (46), 180 (56); (Found: MH^+, 265.1589. $C_{19}H_{20}O$ requires: MH^+, 265.1592).

The presence of the *trans*-isomer was indicated by: δ_H (400 MHz; $CDCl_3$) 5.92 (1H, d, J = 10.0, C=C*H*), 4.05-4.01 (1H, m, OC$\underline{H}_2$), 3.95-3.87 (1H, m, OC$\underline{H}_2$), 3.63-3.57 (1H, m, OC$\underline{H}_2$), 3.30-3.25 (1H, m, OC$\underline{H}_2$), 2.59-2.43 (1H, m, C$\underline{H}$), 2.20-2.10 (1H, m, C$\underline{H}$CH_3), 0.94 (3H, d, J = 7.0, C$\underline{H}_3$).

The spectroscopic data is in agreement with reported data.[121, 125, 188]

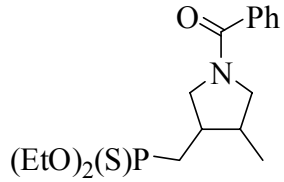
***N,N*-Diallylbenzamide**



To a stirred biphasic mixture of diallylamine (10.0 g, 0.103 mmol) in DCM (150 mL) and NaOH (6.7 g, 0.169 mmol) in water (150 mL) at 0˚C was added dropwise a solution of benzoyl chloride (13.1 mL, 0.113 mmol) in DCM (50 mL) (HCl fumes were observed during the addition). Following the complete addition of the benzoyl chloride solution the reaction mixture was stirred at 0 ˚C for a further 30 minutes, then allowed to warm up to r.t. and left stirring for 6 h. The layers were separated and the aqueous layer was extracted with DCM (2 × 150 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (150 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by vacuum distillation (165 °C at 9 Torr) to yield the title compound as a pale yellow oil (18.5 g, 90%); ν_{max} (thin film)/cm^{-1} 3489 (w), 3080 (m), 3011 (m), 2982 (m), 2921 (m), 1629 (s), 1577 (m), 1494 (m), 1453 (s) 1410 (s); δ_H (400 MHz, $CDCl_3$) 7.42-7.36 (5H, m, 5 × ^{Ar}C<u>H</u>), 5.80 (1H, s, C<u>H</u>=CH_2), 5.65 (1H, s, C<u>H</u>=CH_2), 5.25-5.18 (4H, m, 2 × CH=C<u>H</u>$_2$), 4.06 (2H, s, NC<u>H</u>$_2$) and 3.75 (2H, s, NC<u>H</u>$_2$); δ_C (100 MHz, $CDCl_3$) 171.5 (<u>C</u>=O), 136.1 (^{Ar}<u>C</u>), 132.9 and 132.5 (<u>C</u>H=CH_2), 129.6 (^{Ar}<u>C</u>H), 128.1 (2 x ^{Ar}<u>C</u>H), 126.3 (2 x ^{Ar}<u>C</u>H), 117.6 (2 × CH=<u>C</u>H$_2$), 50.5 (N<u>C</u>H$_2$), 46.9 (N<u>C</u>H$_2$); *m/z* (CI, NH_3) 202 (MNH_4^+, 100%), 105 ($PhC(=O)^+$, 14).

The spectroscopic data is in agreement with reported data.[289]

***O,O*-Diethyl (1-benzoyl-4-methyl-3-pyrrolidinyl)methylphosphonothioate**

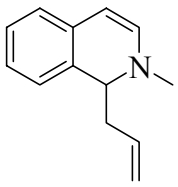


To a stirred solution of *N,N*-diallylbenzamide (0.50 g, 2.5 mmol) and *O,O*-diethyl phosphonothioate (1.92 g, 12.5 mmol) in degassed cyclohexane (30 mL) was added AIBN (0.12 g, 0.70 mmol) under an atmosphere of nitrogen. The solution was heated at 80 ^{o}C for 6 h, then the solution was cooled to r.t. and solvent removed under reduced pressure. Kugelrühr distillation (60 ^{o}C, 1 mmHg) removed excess *O,O*-diethyl phosphonothioate from the mixture affording crude product. The crude product was purified by flash silica chromatography, elution gradient 2:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated

to dryness to afford the title compound (0.72 g, 80%) as a colourless oil, isolated as a 2.2:1 *cis*-:*trans*- mixture of inseparable diastereoisomers. R_f 0.3 (petrol:EtOAc 1:1); ν_{max} (thin film) / cm^{-1} 2979 (s), 1625 (s), 1426 (s), 1047 (s), 1026 (s), 958 (s); major *cis*-diastereoisomer, δ_H (400 MHz, $CDCl_3$) 7.57-7.46 (2H, m, $^{Ar}C\underline{H}$), 7.45-7.32 (3H, m, $^{Ar}C\underline{H}$), 4.30-3.90 (4H, m, $POC\underline{H}_2CH_3$), 3.90-3.05 (4H, m, $NC\underline{H}_2$), 2.83-1.80 (4H, m, C$\underline{H}$ and $PC\underline{H}_2$), 1.40-1.06 (6H, m, $POCH_2C\underline{H}_3$), 1.02 and 0.89 (3H, 2 x d, *J* 7.0 and 7.0, $CHC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 168.7 and 168.6 ($\underline{C}$=O), 136.4, 136.3 ($^{Ar}\underline{C}$), 129.6 (Ar$\underline{C}$H), 128.0, 127.9 (2 x $^{Ar}\underline{C}$H), 126.8 (2 x ^{Ar}CH), 62.0 (d, $^2J_{CP}$ = 7.0, 2 x $PO\underline{C}H_2CH_3$), 56.0 and 53.3 ($N\underline{C}H_2CHCH_3$), 52.4 and 49.3 (2 x d, $^3J_{CP}$ = 7.0 and 10.0, $CH_2CH\underline{C}H_2N$), 37.0 and 35.3 (2 x d, $^2J_{CP}$ = 3 and 4, $PCH_2\underline{C}H$), 35.9 and 34.3 (2 x d, $^3J_{CP}$ = 14.0 and 14.0, $C\underline{H}CH_3$), 33.4 and 32.6 (2 x d, $^1J_{CP}$ = 113.0 and 113.0, $P\underline{C}H_2$), 15.9 and 15.8 (2 x d, $^3J_{CP}$ = 7.0 and 7.0, 2 x $POCH_2\underline{C}H_3$), 13.4, 12.7 ($CH\underline{C}H_3$); *m/z* (CI, NH_3) 356 ($M+H^+$, 100%); (Found: $M+H^+$, 356.1450. $C_{17}H_{27}NO_3PS$ requires 356.1449).

The presence of the minor *trans*- diastereoisomer was indicated by ^1H and ^{13}C NMR spectroscopy; δ_H (270 MHz, $CDCl_3$) (mixture of conformers) 1.11 and 1.00 (3H, 2 x d, *J* 6.5 and 6.5, $CHC\mathit{H}_3$); δ_C (67.9 MHz, $CDCl_3$) (mixture of conformers) 169.2 ($\underline{C}$=O), 61.9 (d, $^2J_{CP}$ 7, 2 x $PO\underline{C}H_2CH_3$), 55.7, 55.0, 52.5, 51.9 (2 x $N\underline{C}H_2$), 40.9, 39.3 (2 x d, $^2J_{CP}$ 4 and 4, $PCH_2\underline{C}H$), 40.1, 38.4 (2 x d, $^3J_{CP}$ 18 and 19, $\underline{C}HCH_3$), 15.1, 14.6 ($CH\underline{C}H_3$).

1-Allyl-1,2-dihydro-2-methylisoquinoline (214)

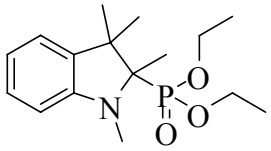


To a stirred solution of isoquinoline (2 g, 15.2 mmol) in diethyl ether (75 mL) at r.t. under nitrogen was added methyl iodide (1.9 mL, 30 mmol). The resulting solution was stirred in the dark at r.t. for 12 h during which time a yellow precipitate formed. The solvent was removed to dryness to afford the iodide salt as an unstable, moisture sensitive yellow power; δ_H (400 MHz, $CDCl_3$) 10.03 (1H, s, C$\underline{N}$H), 8.71 (1H, dd, *J* = 6.7 and 1.2 $^{Ar}C\underline{H}$), 8.57 (1H, d, *J* = 7.1, $^{Ar}C\underline{H}$), 8.47 (1H, d, *J* = 8.2, NC$\underline{H}$CH), 8.34 (1H, d, *J* = 8.2, NCHC$\underline{H}$), 8.26-8.21 (1H, m, $^{Ar}C\underline{H}$), 8.08-8.03 (1H, m, $^{Ar}C\underline{H}$), 4.49 (3H, s, $NC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 152.2 ($^{Ar}\underline{C}$), 150.5 ($^{Ar}\underline{C}$H), 142.7 ($^{Ar}\underline{C}$), 136.6 ($^{Ar}\underline{C}$H), 135.8 ($^{Ar}\underline{C}$H), 130.9 ($^{Ar}\underline{C}$H), 129.9 ($^{Ar}\underline{C}$H), 127.0 ($^{Ar}\underline{C}$H), 125.2 ($^{Ar}\underline{C}$H), 47.8 ($N\underline{C}H_3$).

To a stirred suspension of the iodide salt in THF (50 mL) under nitrogen at 0 ºC, was added a solution of allyl zinc bromide (60 mmol, prepared as above), following the complete addition the suspension was warmed to r.t. and stirred for 12 h. The reaction

mixture was quenched by pouring into a saturated solution of aq. $NaHCO_3$ (100 mL) and allowed to stir for 30 minutes, the resulting precipitate was removed by filtration, and washed with EtOAc (100 mL), the organic layer was separated and the aqueous layer extracted with EtOAc (2 × 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. The crude product was purified by flash chromatography on basic alumina, elution gradient 2:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound as a pale yellow oil (1.8 g, 63%); Rf 0.8 (ethyl acetate:petrol, 1:1); ν_{max} (thin film) 3020 (m), 2905 (s), 1634 (m), 1499 (s) /cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.08 (1H, dt, J = 7.3 and 1.2, $^{Ar}C\underline{H}$), 6.96 (1H, dt, J = 7.3 and 1.2, $^{Ar}C\underline{H}$), 6.89-6.84 (2H, m, $^{Ar}C\underline{H}$), 6.06 (1H, dd, J = 7.3 and 1.5, NCH=C$\underline{H}$), 5.80-5.70 (1H, m, C$\underline{H}$=CH_2), 5.22 (1H, d, J = 7.3, NC$\underline{H}$=CH), 5.00-4.93 (2H, m, CH=C$\underline{H_2}$), 4.32 (1H, app t, J = 5.5, NC$\underline{H}$), 2.95 (3H, s, NC$\underline{H_3}$), 2.49-2.32 (2H, m, C$\underline{H_2}$CH=CH_2); δ_C (100 MHz, $CDCl_3$) 136.6 (N$\underline{C}$H=CH), 135.0 ($\underline{C}$H=CH_2), 132.8 ($^{Ar}\underline{C}$), 128.4 ($^{Ar}\underline{C}$), 127.1 ($^{Ar}\underline{C}$H), 126.1 ($^{Ar}\underline{C}$H), 123.9 ($^{Ar}\underline{C}$H), 122.3 ($^{Ar}\underline{C}$H), 117.2 (CH=$\underline{C}H_2$), 96.1 (N$\underline{C}$H=CH), 62.2 (N$\underline{C}$H), 40.7 (N$\underline{C}H_3$), 36.6 ($\underline{C}H_2$CH=CH_2); *m/z* (CI) 187 (15%), 186 (MH^+, 100).
The spectroscopic data is in agreement with reported data.[290]

1,2,3,3-Tetramethylindolin-2-yl diethyl phosphonate (218) [190, 191]

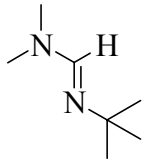


A stirred solution of 1,3,3-trimethyl-2-methyleneindoline (513 mg, 3.0 mmol), and diethyl phosphite (3.9 mL, 30.0 mmol) in THF (20 mL) under an atmosphere of N_2 was heated at reflux for 20 minutes, after which AIBN (74 mg, 0.45 mmol) was added and refluxing maintained, after 1 h, further portions of AIBN (74 mg, 0.45 mmol) were added every 1 h for 2 further portions. The resulting solution was stirred at reflux over night. The excess diethyl phosphite was removed by vacuum distillation (72 °C at 8 mmHg). The resulting crude reaction mixture was purified by flash silica chromatography, elution gradient 10:1 to 2:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound as a pale orange oil (0.38 g, 41%), which on standing changes colour to form a red oil; ν_{max} (thin film) / cm^{-1}) 3019 (m), 2908 (s), 1422 (s), 1049 (s), 1022 (s); δ_H (400 MHz, $CDCl_3$) 7.03 (1H, td, J = 7.6 and 1.2, $^{Ar}C\underline{H}$), 6.91 (1H, dd, J = 7.6 and 0.8, $^{Ar}C\underline{H}$), 6.65 (1H, td, J = 7.6 and 0.8, $^{Ar}C\underline{H}$), 6.34 (1H, d, J = 7.6, $^{Ar}C\underline{H}$), 4.10-3.95 (4H, m, OC$\underline{H_2}CH_3$), 2.87 (3H, d, $^4J_{PH}$ = 1.4, NC$\underline{H_3}$), 1.39 (3H, s, C(C$\underline{H_3}$)$_2$), 1.32 (3H, d, $^3J_{PH}$ = 15.3, PCC$\underline{H_3}$), 1.25 (3H, s, C(C$\underline{H_3}$)$_2$), 1.23 (3H, t, J = 7.0, OCH_2C$\underline{H_3}$), 1.16 (3H, t, J = 7.0,

$OCH_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 149.3 ($^3J_{PC}$ = 7.2, $^{Ar}\underline{C}$), 137.9 ($^3J_{PC}$ = 7.7, $^{Ar}\underline{C}$), 127.4 ($^{Ar}\underline{C}H$), 120.7 ($^{Ar}\underline{C}H$), 117.8 ($^{Ar}\underline{C}H$), 106.2 ($^{Ar}\underline{C}H$), 72.9 ($^1J_{PC}$ = 152.7, N$\underline{C}$P), 62.2 ($^2J_{PC}$ = 7.2, PO$\underline{C}H_2CH_3$), 61.2 ($^2J_{PC}$ = 8.1, PO$\underline{C}H_2CH_3$), 30.9 (N$\underline{C}H_3$), 25.4 ($^3J_{PC}$ =5.0, C($\underline{C}H_3)_2$), 24.0 ($^3J_{PC}$ = 6.9, C($\underline{C}H_3)_2$), 16.5 ($^3J_{PC}$ = 3.2, POCH$_2\underline{C}H_3$), 16.4 ($^3J_{PC}$ = 3.4, POCH$_2\underline{C}H_3$), 13.7 ($^3J_{PC}$ = 13.7, PC$\underline{C}H_3$); *m/z* (CI) 334 (10%), 334 (MNa^+, 95), 313 (10), 312 (MH^+, 100), 310 (70), 174 (40); HRMS $C_{16}H_{27}NO_3P$, (MH^+) requires 312.1723, found 312.1720 and $C_{16}H_{26}NNaO_3P$ (MNa^+) requires 334.1543, found 334.1534.

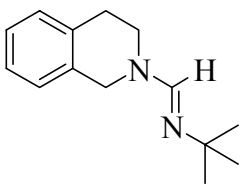
The spectroscopic data is in agreement with reported data [190, 191]

_N_,_N_-Dimethyl-_N'_-_tert_-butylformamidine (221)[151, 152, 192]



To a stirred solution of *N*,*N*-dimethylformamide (155 mL, 2.0 mol) and dimethyl sulfate (190 mL, 2.0 mol) was heated at 80-90 °C for 3 h under nitrogen, then cooled to 0 °C. Then a solution of *tert*-butylamine (231 mL, 2.2 mol) in 400 mL of DCM was slowly added over 45 minutes and the resulting solution was then heated at reflux for 24 h. The reaction mixture was cooled and poured into 2 L of a 20% aq. potassium hydroxide solution. The organic layer was removed and the aqueous layer extracted three times with DCM (200 mL). The combined extracts were washed with brine (300 mL), dried over sodium sulfate, and concentrated by slow distillation at atmospheric pressure. The resulting liquid was fractionally distilled to provide *N*,*N*-dimethyl-*N*'-*tert*-butylformamidine as a colourless liquid, bp 130-134 °C (Lit 132-134 °C); ν_{max} (thin film) 3361 (m), 2963 (s), 1647 (s), 1436 (m), 1369 (s) /cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.15 (1H, s, NC$\underline{H}$=N^{t}Bu), 2.65 (6H, s, N($C\underline{H}_3)_2$), 1.00 (9H, s, NC($C\underline{H}_3)_3$); δ_C (100 MHz, $CDCl_3$) 150.7 (N$\underline{C}$H=N^{t}Bu), 52.6 ($\underline{C}(CH_3)_3$), 36.7 (N($\underline{C}H_3)_2$), 31.2 (($\underline{C}H_3)_3$); *m/z* (CI), 130 (10%), 129 (MH^+, 100), 113 (10). The spectroscopic data is in agreement with reported data [151, 152, 192]

_N_-((3,4-Dihydroisoquinolin-2(1_H_)-yl)methylene)-2-methylpropan-2-amine (222) [151, 152, 192]

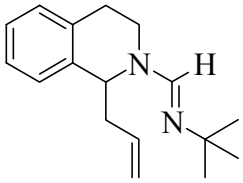


To a stirred solution of the 1,2,3,4-tetrahydroisoquinoline (1 equiv) under an atmosphere of N_2, was added *N*,*N* -dimethyl-*N*'-*tert*-butylformamidine **221** (1.05 equiv), and a catalytic

amount of ammonium sulfate in toluene and heated at reflux for 48-72 h. After consumption of the starting material, the solvent was removed under reduced pressure. The resulting crude oil was purified by flash silica chromatography, elution gradient 12:1 petrol:Et_3N. Pure fractions were evaporated to dryness to afford the title compound as a colourless oil, (75-85%), R_f 0.60 (hexane:triethylamine, 10:1); ν_{max} (thin film) 3276 (w), 3022 (m), 2950 (s), 2820 (s), 1660 (s), 1583 (w) /cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39 (1H, s, NC(N)H), 7.10-6.98 (4H, m, ^{Ar}CH), 4.41 (2H, s, NCH_2Ar), 3.41 (2H, t, *J* = 5.8 NCH_2CH_2Ar), 2.72 (2H, t, *J* = 5.8 NCH_2CH_2Ar), 1.11 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 150.0 (NC(N)H), 134.6 (^{Ar}C), 133.7 (^{Ar}C), 128.7 (^{Ar}CH), 126.4 (^{Ar}CH), 125.9 (2 × ^{Ar}CH), 53.1 ($C(CH_3)_3$), 46.4 (NCH_2CH_2Ar), 44.3 (NCH_2Ar), 31.2 (3 × $C(CH_3)_3$), 29.2 (NCH_2CH_2Ar); *m/z* (CI) 217 (MH^+, 25%), 161 (100); HRMS found 217.1700; $C_{14}H_{21}N_2$ (MH^+) requires 217.1699.

The spectroscopic data is in agreement with reported data [151, 152, 192]

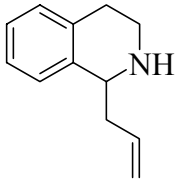
_N_-((1-Allyl-3,4-dihydroisoquinolin-2(1H)-yl)methylene)-2-methylpropan-2-amine (223) [151, 152, 192]



To a stirred solution of *N*-((3,4-dihydroisoquinolin-2(1*H*)-yl)methylene)-2-methylpropan-2-amine (1.0 equiv) in THF under nitrogen at -78 °C (dry ice/acetone), was added ^{s}BuLi (1.1 equiv). The mixture become a yellow colour and was kept at -78 °C for 2 h, before the slow addition of allyl bromide (1.1 equiv), and the mixture slowly warmed to 0 °C over 3 h. The mixture was then partitioned between sat. aq. $NaHCO_3$ and DCM. After an additional extraction with dichloromethane (30 mL), the combined organic layers were washed with brine (30 mL), and dried over K_2CO_3. Concentration *in vacuo* yielded the crude alkylated formamidine. The resulting crude oil was purified by flash silica chromatography, elution gradient 12:1 petrol:Et_3N. Pure fractions were evaporated to dryness to afford the title compound **223** as a pale yellow oil (69-80%), R_f 0.52 (hexane:triethylamine, 10:1); ν_{max} (thin film)/cm^{-1} 3286 (w), 3031 (m), 2934 (s), 2819 (s), 1675 (s), 1642 (m); δ_H (400 MHz, $CDCl_3$) 7.34 (1H, s, NC(H)=N), 7.08-7.0 (4H, m, ^{Ar}CH), 5.80-5.70 (1H, m, $CH=CH_2$), 5.00-4.92 (2H, m, $CH=CH_2$), 4.69-4.60 (1H, m, NCH), 3.91-3.80 (1H, m, NCH_2CH_2Ar), 3.32-3.20 (1H, m, NCH_2CH_2Ar), 2.92-2.81 (1H, m, NCH_2CH_2Ar), 2.68-2.60 (1H, m, NCH_2CH_2Ar), 2.52-2.40 (2H, m, $CH_2CH=CH_2$), 1.07 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 149.9 (NC(H)=N), 137.5 (^{Ar}C), 135.5 ($CH=CH_2$),

134.8 ($^{Ar}\underline{C}$), 128.9 ($^{Ar}\underline{C}H$), 126.9 ($^{Ar}\underline{C}H$), 126.4 ($^{Ar}\underline{C}H$), 125.7 ($^{Ar}\underline{C}H$), 117.2 (CH=$\underline{C}H_2$), 57.8 (N$\underline{C}$H), 52.9 ($\underline{C}(CH_3)_3$), 41.2 (N$\underline{C}H_2CH_2Ar$), 31.5 (C($\underline{C}H_3)_3$), 28.2 (NCH$_2\underline{C}H_2$Ar); *m/z* (CI) 272 (MNH_4^+, 20%) 258 (10), 257 (MH^+, 100), 200 (75).
The spectroscopic data is in agreement with reported data [151, 152, 192]

1-Allyl-1,2,3,4-tetrahydroisoquinoline (203)



Procedure for Hydrolysis of Formamidine 223; A solution containing the formamidine **223** (1 equiv) and KOH (7 equiv) in methanol/water (5/3), was heated at 60 °C under nitrogen for 12 h. The amine was extracted with DCM and the combined extracts dried over sodium sulfate and then concentrated *in vacuo.* The crude amine was purified by flash chromatography on silica gel to afford 1-allyl-1,2,3,4-tetrahydroisoquinoline **203** (85-90%). The spectroscopic data is in agreement with reported data.

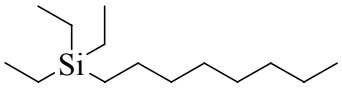
Procedure for Hydrazinolysis of Formamidine 223; A solution of 1 equiv of the formamidine **223**, 4 equiv of hydrazine, and 1 equiv of glacial acetic acid in ethanol was heated at 50 °C under nitrogen for 12 h. Upon cooling, the amine was extracted with DCM (3 × 50 mL), the combined organic layer was washed with a saturated aq. sodium bicarbonate solution and dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The crude amine was purified by flash chromatography on silica gel to afford 1-allyl-1,2,3,4-tetrahydroisoquinoline **203** (52-82%). The spectroscopic data is in agreement with reported data.

7.3 - Experimental for Chapter 3

General procedure 4 - Addition of silanes at elevated temperature

A stirred solution of 1-octene (1.0 g, 9.0 mmol, 1.0 equiv), lauroyl peroxide (99 mg, 0.25 mmol, 0.027 equiv) and the silane (9.8-35.7 mmol, 1.1-4.0 equiv), fitted with a short reflux condenser, was immersed in a preheated oil bath at 80 °C and, after allowing a few minutes for the solution to achieve thermal equilibrium, triisopropylsilane thiol (96 μL, 0.45 mmol, 5 mol%) was added in a single portion. The mixture was heated for 1 h when a further portion of lauroyl peroxide (99 mg, 0.027 equiv, 0.25 mmol) was added and heated for a further 2 h. The crude product was purified by flash silica chromatography (elution gradient petrol). Pure fractions were evaporated to dryness to afford the title compounds (64-95%).

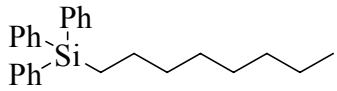
Octyltriethylsilane (228)[103, 104]



1-Octene (1.0 g, 9.0 mmol), lauroyl peroxide (99 mg, 0.25 mmol), triethylsilane (4.15 g, 35.7 mmol), and triisopropylsilane thiol (96 μL, 0.45 mmol, 5 mol%) were reacted according to **general procedure 4**. Purification by column chromatography (silica, petrol) afforded the title compound **228** (1.25 g, 64%) as a colourless oil. Rf 0.85 (petrol); ν_{max} (thin film)/cm^{-1} 2920 (s), 2873 (s), 2853 (s), 1463 (m), 1415 (m), 1237 (w), 1014 (s); δ_H (400 MHz, $CDCl_3$) 1.36-1.24 (12H, m, $SiCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.94 (9H, t, *J* = 7.9, $SiCH_2C\underline{H}_3$), 0.89 (3H, t, *J* = 7.0, $C\underline{H}_3$), 0.54-0.49 (2H, m, $SiC\underline{H}_2$), 0.51 (6H, q, *J* = 7.9, $SiC\underline{H}_2CH_3$); δ_C (100 MHz, $CDCl_3$) 34.0 ($\underline{C}H_2$), 32.0 ($\underline{C}H_2$), 29.4 ($\underline{C}H_2$), 29.3 ($\underline{C}H_2$), 23.9 ($\underline{C}H_2$), 22.7 ($\underline{C}H_2$), 14.1 ($\underline{C}H_3$), 11.3 ($\underline{C}H_2$), 7.4 (3 × $SiCH_2\underline{C}H_3$), 3.3 (3 × $Si\underline{C}H_2CH_3$); *m/z* (ESI) 229 (20%), 228 (100, MH^+), 199 (45).

The spectroscopic data is in agreement with reported data.[103, 104]

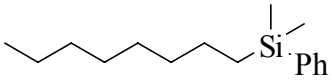
Octyltriphenylsilane (229) [103, 104]



1-Octene (1.00 g, 9.0 mmol), lauroyl peroxide (99 mg, 0.25 mmol), triphenylsilane (3.51 g, 13.7 mmol) and hexane (15 mL) were reacted according to **general procedure 4**. Purification by column chromatography (silica, petrol) afforded the title compound **229** (2.8 g, 86%) as a colourless oil, which forms a soft white wax solid on standing. Rf 0.75

(petrol); ν_{max} (thin film)/cm^{-1} 3066 (w), 3009 (w), 2923 (s), 2854 (s), 1485 (m), 1465 (m), 1427 (s), 1110 (s); δ_H (400 MHz, $CDCl_3$) 7.58-7.54 (2H, m, ^{Ar}CH), 7.45-7.35 (3H, m, ^{Ar}CH), 1.55-1.46 (2H, m, SiC$\underline{H}_2$), 1.44-1.36 (4H, m, 2 × C$\underline{H}_2$), 1.33-1.24 (8H, m, 4 × C$\underline{H}_2$), 0.89 (3H, t, J = 6.8, C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 135.6 (2 × $^{Ar}\underline{C}$H), 135.4 ($^{Ar}\underline{C}$), 129.3 ($^{Ar}\underline{C}$H), 127.8 (2 × $^{Ar}\underline{C}$H), 33.8 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 29.1 ($\underline{C}H_2$), 23.9 ($\underline{C}H_2$), 22.7 ($\underline{C}H_2$), 14.1 ($\underline{C}H_3$) and 13.2 ($\underline{C}H_2$); *m/z* (ESI) 373 (20%), 372 (100, MH$^+$), 295 (20).
The spectroscopic data is in agreement with reported data.[103, 104]

Octyl(dimethyl))(phenyl)silane (230) [103, 104]

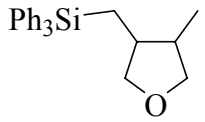


1-Octene (1.00 g, 9.0 mmol), lauroyl peroxide (99 mg, 0.25 mmol), dimethylphenylsilane (1.33 g, 9.8 mmol) and hexane (5 mL) were reacted according to **general procedure 4**. Purification by column chromatography (silica, petrol) afforded the title compound (1.70 g, 80%) as a colourless oil. Rf 0.80 (petrol); ν_{max} (thin film)/cm^{-1} 3058 (w), 2918 (s), 2857 (s), 2120 (w), 1470 (m), 1431 (m); δ_H (400 MHz, $CDCl_3$) 7.55-7.45 (2H, m, ^{Ar}C$\underline{H}$), 7.38-7.30 (3H, m, ^{Ar}C$\underline{H}$), 1.33-1.20 (12H, m, C$\underline{H}_2$), 0.91 (3H, t, J = 7.0, C$\underline{H}_3$), 0.77 (2H, t, J = 8.1, SiC$\underline{H}_2$), 0.29 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 139.7 ($^{Ar}\underline{C}$), 133.5 (2 × $^{Ar}\underline{C}$H), 128.7 ($^{Ar}\underline{C}$H), 127.7 (2 × $^{Ar}\underline{C}$H), 33.6 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 29.3 (2 × $\underline{C}H_2$), 23.8 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2$), 18.2 ($\underline{C}H_2$), 15.7 ($\underline{C}H_2$), 14.1 ($\underline{C}H_3$) and -3.0 (Si($\underline{C}H_3$)$_2$); *m/z* (ESI) 250 (20%), 249 (100, MH$^+$), 233 (30), 171 (20).
The spectroscopic data is in agreement with reported data.[103, 104]

General procedure 5 - Cyclisation of 1,6-dienes using phenylsilanes

A solution of the 1,6-diene (3.8-10.0 mmol, 1.0 equiv), dimethylphenylsilane (7.6-22.0 mmol, 2.2 equiv), or triphenylsilane (2.8 g, 11.0 mmol, 1.1 equiv), triisopropylsilane thiol (42-105 μL, 0.2-0.5 mmol, 5 mol%, care required due to noxious smell) and *tert*-butyl peroxide (0.11-0.30 g, 0.95-2.5 mmol, 0.25 equiv) in benzene (20 mL) were sealed in an Ace pressure tube,[291] and immersed in a preheated oil bath at 140 °C and stirred for 6 h. The reaction mixture was evaporated under reduced pressure, and the resulting crude product was purified by flash silica chromatography, elution gradient petrol to 10:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compounds (52-88%) as a mixture of diastereoisomers.

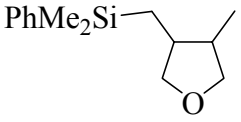
((4-Methyltetrahydrofuran-3-yl)methyl)triphenylsilane (231)



Diallyl ether (1.0 g, 10.0 mmol) was reacted with triphenylsilane (2.8 g, 11.0 mmol) according to **general procedure 5**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 10:1) pure fractions were evaporated to dryness to afford the title product **231** (2.55 g, 69%) as a colourless oil which solidifies to form a white, waxy low melting point solid, MP = 25-30 ºC, Rf 0.51 (petrol:ethyl acetate, 14:1) as an inseparable mixture of diastereoisomers (ratio of *cis*:*trans* = 3:1); ν_{max} (thin film)/cm^{-1} 3070 (m), 3005 (m), 2950 (s), 1429 (s), 1252 (s), 1110 (s); Major (*cis*) diastereoisomer δ_H (400 MHz, $CDCl_3$) 7.70-7.62 (6H, m, $^{Ar}C\underline{H}$), 7.50-7.42 (9H, m, $^{Ar}C\underline{H}$), 3.92 (1H, dd, *J* = 7.9 and 6.1, $C\underline{H}_2O$), 3.70-3.64 (1H, m, $C\underline{H}_2O$), 3.38-3.30 (1H, m, $C\underline{H}_2O$), 2.64-2.54 (1H, m, C<u>H</u>), 2.24-2.06 (1H, m, C<u>H</u>), 1.68 (1H, dd, *J* = 14.9 and 4.2, $SiC\underline{H}_2$), 1.46 (1H, dd, *J* = 14.9 and 10.0, $SiC\underline{H}_2$), 1.03 (3H, d, *J* = 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 135.5 (6 × $^{Ar}\underline{C}H$), 134.7 (3 × $^{Ar}\underline{C}$), 129.4 (3 × $^{Ar}\underline{C}H$), 127.8 (6 × $^{Ar}\underline{C}H$), 74.5 ($O\underline{C}H_2$), 73.0 ($O\underline{C}H_2$), 37.9 ($OCH_2\underline{C}H$), 37.3 ($OCH_2\underline{C}H$), 13.0 ($\underline{C}H_3$), 10.5 ($SiCH_2$); *m/z* (CI) 382 (25%), 381 (100, MNa^+), 377 (10), 376 (MNH_4^+, 30). HRMS $C_{24}H_{26}NaOSi$ (MNa^+) requires 381.1645, found 381.1651.

The minor (*trans*) diastereoisomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 4.04 (1H, t, *J* = 7.6, $C\underline{H}_2O$), 3.70-3.64 (1H, m, $C\underline{H}_2O$), 3.38-3.30 (1H, m, $C\underline{H}_2O$), 3.23 (1H, t, *J* = 8.4, $C\underline{H}_2O$), 1.07 (3H, d, *J* = 6.7, $C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 75.0 ($O\underline{C}H_2$), 74.2 ($O\underline{C}H_2$), 43.4 ($OCH_2\underline{C}H$), 42.8 ($OCH_2\underline{C}H$), 15.7 ($Si\underline{C}H_2$), 15.4 ($\underline{C}H_3$).

((Tetrahydro-4-methylfuran-3-yl)methyl)dimethyl(phenyl)silane (232)

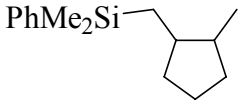


Diallyl ether (1.0 g, 10.0 mmol) was reacted with dimethylphenylsilane (2.6 g, 22.0 mmol), according to **general procedure 5**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 10:1), pure fractions were evaporated to dryness to afford the title product **232** (1.86 g, 52%) as a colourless oil, Rf 0.43 (petrol:ethyl acetate, 10:1), as an inseparable mixture of diastereoisomers (ratio of *cis*:*trans* = 1.9:1); ν_{max} (thin film)/cm^{-1} 3068 (m), 2955 (s), 1426 (s), 1249 (s), 1113 (s); major (*cis*) isomer δ_H (400 MHz, $CDCl_3$) 7.57-7.52 (2H, m, $^{Ar}C\underline{H}$), 7.41-7.36 (3H, m, $^{Ar}C\underline{H}$), 3.89 (1H, dd, *J* = 8.0 and 6.0, $C\underline{H}_2O$), 3.83 (1H, app t, *J* = 7.5,

C$\underline{H}_2$O), 3.49 (1H, dd, *J* = 8.0 and 3.5, C$\underline{H}_2$O), 3.30 (1H, app t, *J* = 8.4, C$\underline{H}_2$O), 2.38-2.26 (1H, m, C*H*$_2$C$\underline{H}_2$O), 2.22-2.12 (1H, m,), 0.97 (1H, app dd, *J* = 14.6 and 5.5, SiC$\underline{H}_2$), 0.93 (3H, d, *J* = 7.0, C$\underline{H}_3$), 0.76 (1H, app dd, *J* = 14.6 and 9.7, SiC$\underline{H}_2$), 0.20 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 138.8 ($^{Ar}\underline{C}$), 133.8 (2 × $^{Ar}\underline{C}$H), 128.9 ($^{Ar}\underline{C}$H), 127.7 (2 × $^{Ar}\underline{C}$H), 74.8 (O$\underline{C}$H$_2$), 73.0 (O$\underline{C}$H$_2$), 38.2 (OCH$_2\underline{C}$H), 37.2 (OCH$_2\underline{C}$H), 13.2 (Si$\underline{C}$H$_2$), 13.0 ($\underline{C}$H$_3$), -2.5 (2 × Si($\underline{C}$H$_3$)$_2$); *m/z* (CI) 257 (40%, MNa^+), 253 (10), 252 (70, MNH_4^+), 174 (15), 157 (100); HRMS $C_{14}H_{22}NaOSi$ (MNa^+) requires 257.1332, found 257.1330.

The spectroscopic data is in agreement with reported data [292]

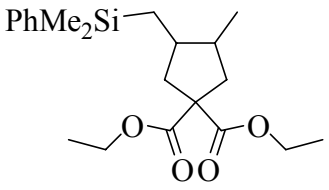
Dimethyl((2-methylcyclopentyl)methyl)(phenyl)silane (233)



1,6-Heptadiene (1.0 g, 10.0 mmol) was reacted with dimethylphenylsilane (2.6 g, 22.0 mmol), according to **general procedure 5**. After removal of the solvent, the crude product was purified by flash silica chromatography (petrol), pure fractions were evaporated to dryness to afford the title product **233** (1.7 g, 68%) as a colourless oil, Rf 0.85 (petrol), as an inseparable mixture of diastereoisomers (*cis*:*trans* = 2:1); ν_{max} (thin film)/cm^{-1} 3062 (w), 2923 (s), 2849 (s), 2131 (w), 1476 (m), 1435 (m); Both diastereoisomers, δ_H (400 MHz, $CDCl_3$) 7.68-7.60 (2H, m, ^{Ar}C$\underline{H}$), 7.47-7.41 (3H, m, ^{Ar}C$\underline{H}$), 2.02-1.83 (2H, m C$\underline{H}_2$), 1.81-1.69 (2H, m, C$\underline{H}_2$), 1.67 (1H, m, C$\underline{H}$), 1.44-1.16 (4H, m, C$\underline{H}$, C$\underline{H}_2$ and SiC$\underline{H}_2$), 1.08-0.74 (4H, m, SiC$\underline{H}_2$ and C$\underline{H}_3$), 0.23 (6H, s, Si(C$\underline{H}_3$)$_2$); Major (*cis*) diastereoisomer, δ_C (100 MHz, $CDCl_3$) 140.1 ($^{Ar}\underline{C}$), 133.5 (2 × $^{Ar}\underline{C}$H), 128.6 ($^{Ar}\underline{C}$H), 127.6 (2 × $^{Ar}\underline{C}$H), 39.1 ($\underline{C}$H), 38.2 ($\underline{C}$H), 32.9 ($\underline{C}$H$_2$), 32.1 ($\underline{C}$H$_2$), 22.5 ($\underline{C}$H$_2$), 16.6 ($\underline{C}$H$_2$), 14.8 ($\underline{C}$H$_3$), -2.26 and -2.33 (2 × Si($\underline{C}$H$_3$)$_2$); Minor (*trans*) diastereoisomer, δ_C (100 MHz, $CDCl_3$) 44.3 ($\underline{C}$H), 43.9 ($\underline{C}$H), 34.7 ($\underline{C}$H$_2$), 33.9 ($\underline{C}$H$_2$), 23.1 ($\underline{C}$H$_2$), 20.6 ($\underline{C}$H$_2$), 18.4 ($\underline{C}$H$_3$), -1.9 and -2.0 (2 × Si($\underline{C}$H$_3$)$_2$); *m/z* (Cl, NH_3) 251 (12%), 250 (MNH_4^+, 60), 233 (MH^+, 30), 151 (100), 136 (40).

The spectroscopic data is in agreement with reported data [292, 293]

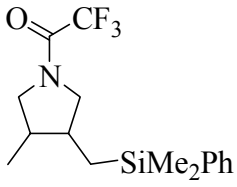
Diethyl 3-((dimethyl(phenyl)silyl)methyl)-4-methylcyclopentane-1,1-dicarboxylate (234)



Diethyl diallyl malonate (2.4 g, 10.0 mmol), was reacted with dimethylphenylsilane (2.6 g, 22.0 mmol), according to **general procedure 5**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 10:1), pure fractions were evaporated to dryness to afford the title product **234** (3.24 g, 88%) as a colourless oil, Rf 0.40 (petrol:ethyl acetate, 10:1), as an inseparable mixture of diastereoisomers (*cis*:*trans* = 3.8:1); ν_{max} (thin film)/cm^{-1} 3068 (m), 2955 (s), 2110 (w), 1728 (s), 1462 (m), 1427 (m), 1365 (m), 1250 (s); Major (*cis*) diastereoisomer, δ_H (400 MHz, $CDCl_3$) 7.43-7.36 (2H, m, $^{Ar}C\underline{H}$), 7.26-7.20 (3H, m, $^{Ar}C\underline{H}$), 4.08-3.98 (4H, m, $OC\underline{H}_2CH_3$), 2.42-2.26 (2H, m, $C\underline{H}_2C(CO_2Et_2)_2C\underline{H}_2$), 2.05-1.88 (2H, m, $C\underline{H}_2C(CO_2Et_2)_2C\underline{H}_2$), 1.82-1.74 (1H, m, C$\underline{H}$), 1.11 (6H app t, *J* = 7.0, $OCH_2C\underline{H}_3$), 1.01 (1H, app d, *J* = 6.1, $C\underline{H}_2Si$), 0.84 (1H, app d, *J* = 6.1, $C\underline{H}_2Si$), 0.80-0.74 (1H, m, C$\underline{H}$), 0.70 (3H, app d, *J* = 5.8, .CH_3), 0.20 (6H, s, $Si(C\underline{H}_3)_2$); δ_C (100 MHz, $CDCl_3$) 172.9 (2 × $\underline{C}$=O), 139.3 ($^{Ar}\underline{C}$), 133.4 (2 × $^{Ar}\underline{C}H$), 128.7 ($^{Ar}\underline{C}H$), 127.8 (2 × $^{Ar}\underline{C}H$), 61.1 (2 × $O\underline{C}H_2CH_3$), 58.8 ($\underline{C}(CO_2Et_2)_2$), 40.9 ($\underline{C}H_2$), 40.3 ($\underline{C}H_2$), 38.7 ($\underline{C}H$), 37.6 ($\underline{C}H$), 15.8 ($Si\underline{C}H_2$), 14.8 ($\underline{C}H_3$), 13.9 (2 × $OCH_2\underline{C}H_3$), -2.2 and -2.5 (2 × $Si(\underline{C}H_3)_2$); *m/z* (Cl) 400 (30%), 399 (MNa^+, 100), 331 (15), 299 (15), 225 (25), 181 (30); HRMS (CI) $C_{21}H_{32}O_4SiNa^+$ (MNa^+) requires 399.1962, found 399.1963.

The spectroscopic data is in agreement with reported data. [292]

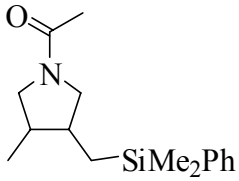
2,2,2-Trifluoro-1-(3-methyl-4-((dimethyl(phenyl)silyl)methyl)pyrrolidin-1-yl)ethanone (235)



N,N-Diallyltrifluoroacetamide (0.75 g, 3.8 mmol), dimethylphenylsilane (0.6 g, 4.4 mmol), triisopropylsilane thiol (0.034 g, 0.3 mmol) and *tert*-butyl peroxide (0.14 g, 1.2 mmol), was reacted, according to **general procedure 5**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 10:1), pure fractions were evaporated to dryness to afford the title product **235** (0.65 g, 52%); Rf 0.55 (petrol:ethyl acetate, 10:1), as an inseparable mixture of diastereoisomers and rotamers; ν_{max} (thin film)/cm^{-1} 3150 (w), 3025 (w), 2976 (w), 1642 (s); both diastereoisomers, δ_H (400 MHz, $CDCl_3$) 7.53-7.48 (2H, m, $^{Ar}C\underline{H}$), 7.41-7.37 (3H, m, $^{Ar}C\underline{H}$), 3.88-3.50 (2H, m, $C\underline{H}_2NC\underline{H}_2$), 3.42-2.90 (2H, m, $C\underline{H}_2NC\underline{H}_2$), 2.34-2.15 (1H, m, C$\underline{H}$), 1.88-1.60 (1H, m, C$\underline{H}$), 1.19-1.12 (2H, app d, *J* = 7.3, $C\underline{H}_2Si$), 0.91 (3H, app d, *J* = 4.0, $CHC\underline{H}_3$), 0.36 (3H, s, $Si(C\underline{H}_3)_2$), 0.32 (3H, s, $Si(C\underline{H}_3)_2$); both diastereoisomers, δ_C

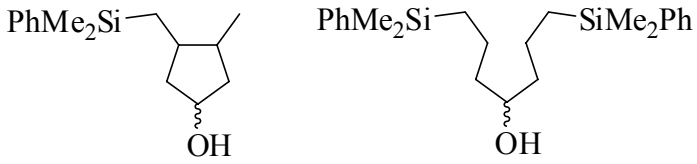
(100 MHz, $CDCl_3$) 155.5 (q, $^2J_{CP}$ = 36.8, N<u>C</u>(O)CF_3), 138.1 (^{Ar}<u>C</u>), 133.3 (2 × ^{Ar}<u>C</u>H), 129.2 (^{Ar}<u>C</u>H), 127.9 (2 × ^{Ar}<u>C</u>H), 116.2 (q, $^1J_{CP}$ = 293, <u>C</u>F_3), 116.1 (q, $^1J_{CP}$ = 293, <u>C</u>F_3), 54.2 (N<u>C</u>H_2), 54.0 (N<u>C</u>H_2), 53.5 (N<u>C</u>H_2), 52.1 (N<u>C</u>H_2), 38.4 (<u>C</u>H), 37.2 (<u>C</u>H), 35.8 (<u>C</u>H), 34.4 (<u>C</u>H), 15.0 (<u>C</u>H_2Si), 14.7 (<u>C</u>H_2Si), 12.9 (CH<u>C</u>H_3), 12.7 (CH<u>C</u>H_3), -2.2 (Si(<u>C</u>H_3)$_2$), -2.4 (Si(<u>C</u>H_3)$_2$), -2.5 (Si(<u>C</u>H_3)$_2$), -2.8 (Si(<u>C</u>H_3)$_2$); *m/z* (CI) 352 (MNa^+, 12%), 331 (10), 330 (MH^+, 55), 293 (12), 252 (95), 203 (12), 202 (100); HRMS $C_{16}H_{23}F_3NOSi$ (MH^+) requires 330.1496, found 330.1508.

1-(3-((Dimethyl(phenyl)silyl)methyl)-4-methylpyrrolidin-1-yl)ethanone (236)



Diethyl *N,N*-diallylacetamide (0.52 g, 3.8 mmol), dimethylphenylsilane (0.6 g, 4.4 mmol), triisopropylsilane thiol (0.034 g, 0.3 mmol) and *tert*-butyl peroxide (0.14 g, 1.2 mmol), was reacted, according to **general procedure 5**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 10:1) pure fractions were evaporated to dryness to afford the title product **236** (0.68 g, 70%) as a colourless oil, Rf 0.60 (petrol:ethyl acetate, 10:1), as an inseparable mixture of diastereoisomers and rotamers; ν_{max} (thin film)/cm^{-1} 3040 (w), 2986 (w), 1652 (s); δ_H (400 MHz, $CDCl_3$) 7.57-7.45 (2H, m, ^{Ar}C<u>H</u>), 7.41-7.30 (3H, m, ^{Ar}C<u>H</u>), 3.82-2.70 (4H, m, NC<u>H</u>$_2$), 2.17-1.50 (5H, NC(O)C<u>H</u>$_3$ and C<u>H</u>C<u>H</u>), 1.20-0.54 (5H, CHC<u>H</u>$_3$ and CHC<u>H</u>$_2$Si), 0.30-0.35 (6H, m, Si(C<u>H</u>$_3$)$_2$); *m/z* (CI) 277 (20%), 276 (MH^+, 100), 232 (40), 140 (10); HRMS $C_{16}H_{26}NOSi$ (MH^+) requires 276.1778, found 275.1780.
The spectroscopic data is in agreement with reported data. [292]

3-((Dimethyl(phenyl)silyl)methyl)-4-methylcyclopentanol (239) and 1,7-bis(dimethyl(phenyl)silyl)heptan-4-ol (240)

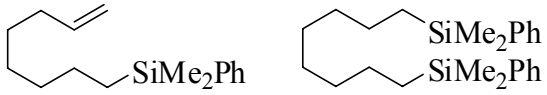


1,6-Heptadien-4-ol (1.0 g, 9.0 mmol) was reacted with dimethylphenylsilane (2.4 g, 20.0 mmol), according to **general procedure 5**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 10:1), pure fractions were evaporated to dryness to afford the title products.

3-((Dimethyl(phenyl)silyl)methyl)-4-methylcyclopentanol (**239**), the 5-*exo* product was obtained as a pale yellow oil, (1.63 g, 73%), Rf 0.40 (petrol:ethyl acetate, 10:1), as an inseparable mixture of 4 diastereoisomers; ν_{max} (thin film)/cm^{-1} 3338 (bs), 3068 (w), 2952 (s), 2868 (m), 1426 (w), 1248 (s), 1112 (s); all diastereoisomers, δ_H (400 MHz, $CDCl_3$) 7.47-7.43 (2H, m, $^{Ar}C\underline{H}$), 7.30-7.25 (3H, m, $^{Ar}C\underline{H}$), 4.23-4.08 (1H, m, C$\underline{H}$OH), 2.21-1.80 (3H, m, CH_2), 1.70-1.40 (2H, m, C$\underline{H}$ and CH_2), 1.30-0.99 (2H, m C$\underline{H_2}$Si), 0.90-0.50 (4H, m, C$\underline{H}$ and CHC$\underline{H_3}$), 0.22 (6H, s, Si(C$\underline{H_3}$)$_2$); all diastereoisomers, δ_C (100 MHz, $CDCl_3$) 139.6 ($^{Ar}\underline{C}$), 133.4 ($^{Ar}\underline{C}$H), 133.3 ($^{Ar}\underline{C}$H), 128.6 ($^{Ar}\underline{C}$H), 127.6 ($^{Ar}\underline{C}$H), 72.6 (C$\underline{H}$(OH)), 72.1 (C$\underline{H}$(OH)), 71.8 (C$\underline{H}$(OH)) and 71.7 (C$\underline{H}$(OH)), 44.9 ($\underline{C}H_2$), 44.2 ($\underline{C}H_2$), 44.1 ($\underline{C}H_2$), 43.7 ($\underline{C}H_2$), 43.2 (C$\underline{H}$), 43.1 ($\underline{C}H_2$), 42.7 (C$\underline{H}$), 42.6 ($\underline{C}H_2$), 41.5 (C$\underline{H}$), 41.3 (C$\underline{H}$), 37.5 (C$\underline{H}$), 36.6 (C$\underline{H}$), 36.5 (2 x C$\underline{H}$), 20.6 ($\underline{C}H_2$Si), 20.3 ($\underline{C}H_2$Si), 18.8 ($\underline{C}H_3$), 17.8 ($\underline{C}H_3$), 16.8 ($\underline{C}H_2$Si), 16.6 ($\underline{C}H_2$Si), 16.0 ($\underline{C}H_3$) and 15.4 ($\underline{C}H_3$), -2.3 (Si($\underline{C}H_3$)$_2$), -2.4 (Si($\underline{C}H_3$)$_2$), -2.5 (Si($\underline{C}H_3$)$_2$), -2.6 (Si($\underline{C}H_3$)$_2$); *m/z* (Cl) 266 (MNH_4^+, 15%), 249 (MH^+, 17), 234 (75), 217 (25), 172 (70), 152 (100).

Bis(dimethyl(phenyl)silyl)heptan-4-ol (**240**), the di-addition product was isolated as a pale yellow oil (0.52 g, 15%); Rf = 0.8 (10:1, petrol:ethyl acetate); ν_{max} (thin film)/cm^{-1} 3339 (bs), 3068 (m), 2952 (s), 1422 (s), 1248 (s), 1112 (s); δ_H (400 MHz, $CDCl_3$) 7.44-7.40 (4H, m, $^{Ar}C\underline{H}$), 7.28-7.24 (6H, m, $^{Ar}C\underline{H}$), 3.50-3.44 (1H, m, C$\underline{H}$OH), 1.42-1.18 (8H, m, 4 × C$\underline{H_2}$), 0.89 (1H, bs, O$\underline{H}$), 0.76-0.56 (4H, m, 2 × SiC$\underline{H_2}$), 0.18 (12H, s, 2 × Si(C$\underline{H_3}$)$_2$); δ_C (100 MHz, $CDCl_3$) 139.4 (2 × $^{Ar}\underline{C}$), 133.5 (4 × $^{Ar}\underline{C}$H), 128.8 (2 × $^{Ar}\underline{C}$H), 127.7 (4 × $^{Ar}\underline{C}$H), 71.2 (C$\underline{H}$OH), 41.4 (2 × $\underline{C}H_2$CHOH), 19.9 (2 × $\underline{C}H_2$), 15.7 (2 × $\underline{C}H_2$), -3.0 (4 × Si($\underline{C}H_3$)$_2$); *m/z* (CI) 387 (10%), 386 (30), 385 (100, MH^+), 250 (20).

Dimethyl(oct-7-enyl)(phenyl)silane (242) and 1,8-bis(dimethyl(phenyl)silyl)octane (243)



1,7-Octadiene (1.0 g, 9.7 mmol) was reacted with dimethylphenylsilane (2.6 g, 22.0 mmol), according to **general procedure 5**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol), pure fractions were evaporated to dryness to afford the title products, dimethyl(oct-7-enyl)(phenyl)silane (**242**), the product of mono-addition (0.6 g, 26%) and 1,8-bis(dimethyl(phenyl)silyl)octane (**243**), the product of di-addition (1.2 g, 34 %).

A solution of 1,7-octadiene (1.0 g, 9.7 mmol), dimethylphenylsilane (1.3 g, 9.7 mmol), triisopropylsilane thiol (86 μL, 0.45 mmol) and *tert*-butyl peroxide (0.30 g, 0.2.5 mmol) in benzene (60 mL) were sealed in a tube and immersed in a preheated oil bath at 140 °C and stirred for 6 h. Removal of the solvent under reduced pressure afforded the crude product. The crude product was purified by flash silica chromatography (elution gradient petrol), pure fractions were evaporated to dryness to afford the title products, dimethyl(oct-7-enyl)(phenyl)silane (**242**) (0.9 g, 40%) and 1,8-bis(dimethyl(phenyl)silyl)octane (**243**) (0.11 g, 5%).

Dimethyl(oct-7-enyl)(phenyl)silane (**242**) was isolated as a colourless oil; Rf = 0.5 (petrol); ν_{max} (thin film)/cm^{-1} 3068 (m), 3050 (w), 2999 (w), 2922 (s), 2853 (s), 1640 (w), 1426 (m), 1247 (s), 1112 (s); δ_H (400 MHz, $CDCl_3$) 7.62-7.58 (2H, m, $^{Ar}C\underline{H}$), 7.45-7.41 (3H, m, $^{Ar}C\underline{H}$), 5.94-5.84 (1H, m, $CH_2{=}C\underline{H}$), 5.11-5.00 (2H, m, $C\underline{H}_2{=}CH$), 2.14-2.08 (2H, m, $C\underline{H}_2CH_2{=}CH$), 1.48-1.38 (8H, 4 × m, $C\underline{H}_2$), 0.87-0.81 (2H, m, $SiC\underline{H}_2$), 0.35 (6H, s, $Si(C\underline{H}_3)_2$); δ_C (100 MHz, $CDCl_3$) 139.6 ($^{Ar}\underline{C}$), 139.1 ($\underline{C}H{=}CH_2$), 133.5 (2 × $^{Ar}\underline{C}H$), 128.7 ($^{Ar}\underline{C}H$), 127.7 (2 × $^{Ar}\underline{C}H$), 114.1 ($CH{=}\underline{C}H_2$), 33.8 ($\underline{C}H_2$), 33.4 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 28.8 ($\underline{C}H_2$), 23.8 ($\underline{C}H_2$), 15.7 ($\underline{C}H_2$), 2.75 (2 × $Si(\underline{C}H_3)_2$); *m/z* (ESI) 247 (15%), 246 (100, M^+), 231 (20), 169 (30).

The spectroscopic data is in agreement with reported data.[293]

1,8-Bis(dimethyl(phenyl)silyl)octane (**243**) was isolated as a colourless oil; Rf 0.58 (petrol); ν_{max} (thin film)/cm^{-1} 3067 (m), 3048 (m), 3020 (w), 2916 (s), 2851 (s), 1461 (w), 1426 (s), 1247 (s), 1181 (w), 1112 (m); δ_H (400 MHz, $CDCl_3$) 7.66-7.61 (4H, m, $^{Ar}C\underline{H}$), 7.47-7.43 (6H, m, $^{Ar}C\underline{H}$), 1.48-1.30 (12H, m, $C\underline{H}_2$), 0.89-0.81 (4H, m, $SiC\underline{H}_2$), 0.38 (12H, s, $Si(C\underline{H}_3)_2$); δ_C (100 MHz, $CDCl_3$) 139.7 (2 × $^{Ar}\underline{C}$), 133.5 (4 × $^{Ar}\underline{C}H$), 128.7 (2 × $^{Ar}\underline{C}H$), 127.6 (4 × $^{Ar}\underline{C}H$), 33.5 (2 × $\underline{C}H_2$), 29.2 (2 × $\underline{C}H_2$), 23.8 (2 × $\underline{C}H_2$), 15.7 (2 × $\underline{C}H_2$), -2.9 (4 × $Si(\underline{C}H_3)_2$); *m/z* (ESI) 383 (30%), 282 (100, M^+), 367 (25), 305 (40).

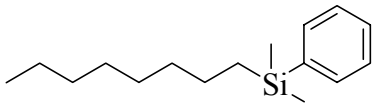
The spectroscopic data is in agreement with reported data.[293]

General procedure 6 - Addition of dimethylphenylsilane to alkenes at room temperature

To a stirred solution of the alkene (10 mmol, 1 equiv.), dimethylphenylsilane (2.0 g, 15 mmol, 1.5 equiv.) in THF (3 mL) was added triethylborane in THF (0.5 mL, 1 M solution, 5 mmol, 0.5 equiv.) and shortly after triisopropylsilane thiol (105 μL, 0.5 mmol, 5 mol%, care required due to noxious smell). After stirring at room temperature for 1 h, a further portion of triethylborane in THF (0.5 mL, 1 M solution 5 mmol, 0.5 equiv.) was added and left stirring overnight. Removal of the solvent under reduced pressure afforded the crude

product. The crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 5:1), pure fractions were evaporated to dryness to afford the silane addition products (56-95%)

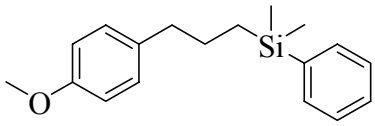
Octyl(dimethyl)(phenyl)silane (230)



1-Octene (1.12 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (petrol), pure fractions were evaporated to dryness to afford the title compound (2.2 g, 88%) as a colourless oil; Rf 0.80 (petrol).

The spectroscopic data matches the sample prepared according to **general procedure 4.**

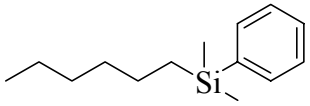
(3-(4-Methoxyphenyl)propyl)dimethyl(phenyl)silane (245)



1-Allyl-4-methoxybenzene (1.48 g, 10 mmol) was reacted according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:EtOAc, 10:1), pure fractions were evaporated to dryness to afford the title compound **245** (2.61 g, 92%) as a colourless oil, Rf = 0.45 (Petrol:EtOAc 10:1); ν_{max} (thin film)/cm^{-1} 3010 (w), 2988 (w), 2959 (w), 2837 (w), 1743 (m), 1503 (w), 1512 (s), 1466 (m); δ_H (400 MHz, $CDCl_3$) 7.57-7.53 (2H, m, $^{Ar}C\underline{H}$), 7.42-7.38 (3H, m, $^{Ar}C\underline{H}$), 7.11 (2H, app dd, J = 8.6 and 2.1, $^{Ar}C\underline{H}$), 6.87 (2H, app dd, J = 8.6 and 2.1, $^{Ar}C\underline{H}$), 3.81 (3H, s, $OC\underline{H}_3$), 2.61 (2H, t, J = 7.7, $^{Ar}C\underline{H}_2$), 1.71-1.63 (2H, m, $C\underline{H}_2$), 0.86-0.79 (2H, m, $SiC\underline{H}_2$), 0.29 (6H, s, $Si(C\underline{H}_3)_2$); δ_C (100 MHz, $CDCl_3$) 157.9 ($^{Ar}\underline{C}O$), 139.6 ($^{Ar}\underline{C}$), 134.4 ($^{Ar}\underline{C}$), 133.7 (2 × $^{Ar}\underline{C}H$), 129.5 (2 × $^{Ar}\underline{C}H$), 128.9 ($^{Ar}\underline{C}H$), 127.9 (2 × $^{Ar}\underline{C}H$), 113.7 (2 × $^{Ar}\underline{C}H$), 55.0 ($O\underline{C}H_3$), 38.5 ($^{Ar}\underline{C}H_2$), 25.8 ($\underline{C}H_2$), 15.0 ($SiCH_2$), -3.5 (2 × $Si(\underline{C}H_3)_2$); *m/z* (ESI) 285 (20%), 284 (100, M^+), 207 (10).

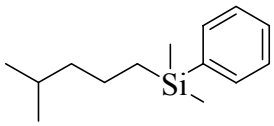
The spectroscopic data is in agreement with reported data**.**[294]

Dimethyl(hexyl)(phenyl)silane (246)



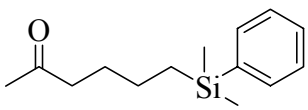
1-Hexene (0.84 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (petrol), pure fractions were evaporated to dryness to afford the title compound **246** (1.97 g, 90%) as a colourless oil; Rf 0.80 (petrol); ν_{max} (thin film)/cm^{-1} 3036 (w), 2940 (s), 2884 (s), 1435 (m), 1269 (s); δ_H (400 MHz, $CDCl_3$) 7.63-7.58 (2H, m, Ar*H*), 7.44-7.41 (3H, m, Ar*H*), 1.43-1.31 (8H, m, 4 × C$\underline{H}_2$), 0.96 (3H, t, *J* = 6.9, C$\underline{H}_3$), 0.87-0.81 (2H, m, SiC$\underline{H}_2$), 0.34 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 139.7 ($^{Ar}\underline{C}$), 133.5 (2 × $^{Ar}\underline{C}$H), 128.7 ($^{Ar}\underline{C}$H), 127.6 (2 × $^{Ar}\underline{C}$H), 33.3 ($\underline{C}H_2$), 31.5 ($\underline{C}H_2$), 23.8 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2$), 15.7 ($\underline{C}H_2$), 14.1 ($\underline{C}H_3$), -3.0 (2 × Si$\underline{C}H_3$); *m/z* (ESI) 221 (20%), 220 (100, M^+), 142 (15).
The spectroscopic data is in agreement with reported data..[103]

Dimethyl(4-methylpentyl)(phenyl)silane (247)



4-Methylpent-1-ene (0.84 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (petrol), pure fractions were evaporated to dryness to afford the title compound **247** (1.8 g, 95%) as a colourless oil; Rf 0.80 (petrol); ν_{max} (thin film)/cm^{-1} 2953 (s), 2919 (m), 2869 (w), 1467 (w), 1426 (m); δ_H (400 MHz, $CDCl_3$) 7.57-7.54 (2H, m, ^{Ar}C$\underline{H}$), 7.40-7.37 (3H, m, ^{Ar}C$\underline{H}$), 1.57 (1H, sept, *J* = 6.6 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.41-1.32 (2H, m, C$\underline{H}_2$), 1.26-1.20 (2H, m, C$\underline{H}_2$), 0.88 (6H, d, *J* = 6.6 Hz, CH(C$\underline{H}_3$)$_2$), 0.79-0.74 (2H, m, SiC$\underline{H}_2$), 0.30 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 139.7 ($^{Ar}\underline{C}$), 133.5 (2 × $^{Ar}\underline{C}$H), 128.7 ($^{Ar}\underline{C}$H), 127.6 (2 × $^{Ar}\underline{C}$H), 43.0 ($\underline{C}H_2$), 27.6 ($\underline{C}$H(CH$_3$)$_2$), 22.6 (2 × CH($\underline{C}H_3$)$_2$), 21.5 ($\underline{C}H_2$), 15.7 (Si$\underline{C}H_2$), -2.9 (2 × Si$\underline{C}H_3$); *m/z* (ESI) 222 (8%), 221 (20), 220 (100, M^+), 142 (15).
The spectroscopic data is in agreement with reported data.[294]

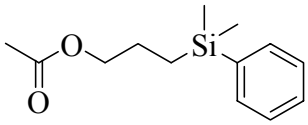
6-(Dimethyl(phenyl)silyl)hexan-2-one (248)



Hex-5-en-2-one (0.98 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:Et_2O, 10:1), pure fractions were evaporated to dryness to afford the title compound **248** (2.06 g, 88%) as a colourless oil; Rf 0.70 (petrol:Et_2O 10:1); ν_{max} (thin film)/cm^{-1} 2952 (m), 2948 (m), 1739 (m), 1715 (s), 1427 (m), 1370 (m), 1246

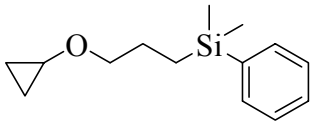
(s); δ_H (400 MHz, $CDCl_3$) 7.54-7.50 (2H, m, $^{Ar}C\underline{H}$), 7.38-7.35 (3H, m, $^{Ar}C\underline{H}$), 2.40 (2H, t, *J* = 7.4, C(O)C$\underline{H}_2$), 2.11 (3H, s, C$\underline{H}_3$C(O)), 1.60 (2H, app quint, *J* = 7.4, C$\underline{H}_2$), 1.39-1.30 (2H, m, C$\underline{H}_2$), 0.81-0.74 (2H, m, SiC$\underline{H}_2$), 0.28 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 209.1 (<u>C</u>=O), 139.1 ($^{Ar}\underline{C}$), 133.4 (2 × $^{Ar}\underline{C}$H), 128.7 ($^{Ar}\underline{C}$H), 127.6 (2 × $^{Ar}\underline{C}$H), 43.3 (<u>C</u>H$_2$), 29.6 (C(O)<u>C</u>H$_3$), 27.4 (<u>C</u>H$_2$), 23.4 (<u>C</u>H$_2$), 15.5 (Si<u>C</u>H$_2$), -2.9 (2 × Si<u>C</u>H$_3$); *m/z* (CI) 258 (15%), 257 (MNa^+, 100); HRMS $C_{14}H_{22}NaOSi$ (MH^+) requires 257.1332, found 257.1327.

3-(Dimethyl(phenyl)silyl)propyl acetate (249)



Allyl acetate (1.0 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:EtOAc, 10:1), pure fractions were evaporated to dryness to afford the title compound **249** (2.07 g, 88%) as a colourless oil; Rf 0.78 (petrol:EtOAc, 10:1); ν_{max} (thin film)/cm^{-1} 3070 (w), 3004 (w), 2953 (m), 1735 (s), 1465 (w), 1427 (m); δ_H (400 MHz, $CDCl_3$) 7.56-7.51 (2H, m, $^{Ar}C\underline{H}$), 7.40-7.31 (3H, m, $^{Ar}C\underline{H}$), 4.03 (2H, t, *J* = 6.9, OC*H*$_2$), 2.05 (3H, s, C$\underline{H}_3$CO), 1.70-1.63 (2H, m, OCH$_2$C$\underline{H}_2$), 0.81-0.75 (2H, m, C$\underline{H}_2$Si), 0.31 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 171.0 (<u>C</u>=O), 138.6 ($^{Ar}\underline{C}$), 133.4 (2 × $^{Ar}\underline{C}$H), 128.9 ($^{Ar}\underline{C}$H), 127.7 (2 × $^{Ar}\underline{C}$H), 66.8 (O<u>C</u>H$_2$), 23.1 (<u>C</u>H$_2$), 20.9 (<u>C</u>H$_3$C(O)), 11.5 (Si<u>C</u>H$_2$), -3.2 (2 × Si<u>C</u>H$_3$); *m/z* (CI) 255 (10%), 254 (MNH_4^+, 60), 238 (15), 237 (MH^+, 100), 159 (45); HRMS $C_{13}H_{21}O_2Si$ (MH^+) requires 237.1305, found 237.1302.

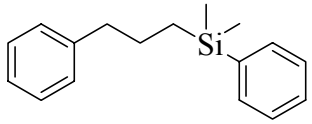
(3-Cyclopropoxypropyl)dimethyl(phenyl)silane (250)



(Allyloxy)cyclopropane (0.98 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:EtOAc, 10:1), pure fractions were evaporated to dryness to afford the title compound **250** (1.95 g, 85%) as a colourless oil, Rf = 0.65 (Petrol:Et_2O 10:1); ν_{max} (thin film)/cm^{-1} 3004 (w), 2953 (w), 2868 (w), 1427 (m), 1336 (w); δ_H (400 MHz, $CDCl_3$) 7.58-7.54 (2H, m, $^{Ar}C\underline{H}$), 7.41-7.37 (3H, m, $^{Ar}C\underline{H}$), 3.70 (1H, dd, *J*=11.5 and 3.0, CH_2), 3.52-3.43 (2H, m, C$\underline{H}_2$O), 3.37 (1H, dd, *J* = 11.5 and 5.8, C$\underline{H}_2$), 3.17-3.13 (1H, m, OC$\underline{H}$), 2.79 (1H, dd, *J* = 4.9 and 4.1, C$\underline{H}_2$), 2.61 (1H, dd, *J* = 4.9 and 2.7, C$\underline{H}_2$), 1.71-1.62 (2H, m, C$\underline{H}_2$), 0.83-0.77 (2H, m, SiC$\underline{H}_2$), 0.32 (6H, s, Si(C$\underline{H}_3$)$_2$);

δ_C (100 MHz, $CDCl_3$) 139.0 ($^{Ar}\underline{C}$), 133.5 (2 × $^{Ar}\underline{C}H$), 128.8 ($^{Ar}\underline{C}H$), 127.7 (2 × $^{Ar}\underline{C}H$), 74.2 ($\underline{C}H_2$), 71.3 ($\underline{C}H_2$), 50.8 (O$\underline{C}$H), 44.2 (O$\underline{C}H_2$), 24.0 ($\underline{C}H_2$), 11.6 (Si$\underline{C}H_2$), -3.15 (2 × Si($\underline{C}H_3$)$_2$); *m/z* (CI, NH_3) 275 ($MMeCN^+$, 30%), 273 (100).

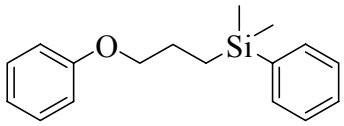
Dimethyl(phenyl)(3-phenylpropyl)silane (251)



1-Allylbenzene (1.18 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:EtOAc, 10:1), pure fractions were evaporated to dryness to afford the title compound **251** (1.79 g, 71%) as a colourless oil, Rf = 0.26 (Petrol); ν_{max} (thin film)/cm^{-1} 3005 (w), 2989 (w), 1559 (w), 1458 (w), 1275 (s), 1260 (s); δ_H (400 MHz, $CDCl_3$) 7.60-7.56 (2H, m, $^{Ar}C\underline{H}$), 7.45-7.41 (3H, m, $^{Ar}C\underline{H}$), 7.35 (2H, app tt, *J* = 7.3 and 1.5, $^{Ar}C\underline{H}$), 7.27 (1H, app dt, *J* = 7.3 and 1.5, $^{Ar}C\underline{H}$), 7.23 (2H, app dd, *J* = 7.3 and 1.5, $^{Ar}C\underline{H}$), 2.70 (2H, t, *J* = 7.6, $^{Ar}C\underline{H}_2$), 1.78-1.69 (2H, m, $C\underline{H}_2$), 0.92-0.84 (2H, m, $SiC\underline{H}_2$), 0.34 (6H, s, Si($C\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 142.8 ($^{Ar}\underline{C}$), 139.6 ($^{Ar}\underline{C}$), 133.8 (2 × $^{Ar}\underline{C}H$), 129.0 ($^{Ar}\underline{C}H$), 128.7 (2 × $^{Ar}\underline{C}H$), 128.4 (2 × $^{Ar}\underline{C}H$), 127.9 (2 × $^{Ar}\underline{C}H$), 125.8 ($^{Ar}\underline{C}H$), 39.5 ($^{Ar}\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 15.2 ($Si\underline{C}H_2$), -3.4 (2 × Si($\underline{C}H_3$)$_2$); *m/z* (ESI) 255 (20%), 254 (100, M^+).

The spectroscopic data is in agreement with reported data.[294]

Dimethyl(3-phenoxypropyl)(phenyl)silane (252)

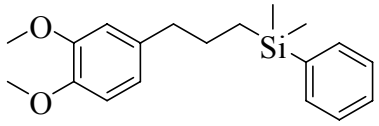


1-(Allyloxy)benzene (1.34 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:EtOAc, 10:1), pure fractions were evaporated to dryness to afford the title compound **252** (2.37 g, 88%) as a colourless oil, Rf = 0.64 (Petrol:EtOAc 10:1); ν_{max} (thin film)/cm^{-1} 3054 (w), 2996 (w), 2972 (w), 2886 (w), 1591 (m), 1479 (m); δ_H (400 MHz, $CDCl_3$) 7.58-7.54 (2H, m, $^{Ar}C\underline{H}$), 7.42-7.36 (3H, m, $^{Ar}C\underline{H}$), 7.32 (2H, t, *J* = 7.3 $^{Ar}C\underline{H}$), 6.95 (1H, app tt, *J* = 7.3 and 1.0, $^{Ar}C\underline{H}$), 6.90 (2H, app dd, *J* = 7.3 and 1.0, $^{Ar}C\underline{H}$), 3.92 (2H, t, *J* = 7.6, O$C\underline{H}_2$), 1.87-1.79 (2H, m, $C\underline{H}_2$), 0.93-0.85 (2H, m, $SiC\underline{H}_2$), 0.32 (6H, s, Si($C\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 159.4 ($^{Ar}\underline{C}O$), 139.2 ($^{Ar}\underline{C}$), 133.5 (2 × $^{Ar}\underline{C}H$), 129.6 (2 × $^{Ar}\underline{C}H$), 129.1 ($^{Ar}\underline{C}H$), 128.0 (2 × $^{Ar}\underline{C}H$), 120.6 ($^{Ar}\underline{C}H$), 114.6

(2 × ^{Ar}CH), 70.2 (OCH$_2$), 23.5 (CH$_2$), 11.3 (SiCH$_2$), -3.5 (2 × Si(CH$_3$)$_2$); *m/z* (ESI) 271 (20%), 270 (100, M$^+$), 193 (30).

The spectroscopic data is in agreement with reported data.[294]

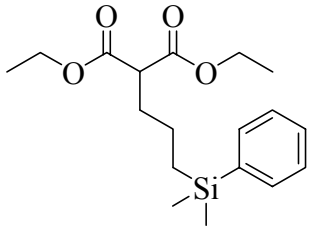
(3-(3,4-Dimethoxyphenyl)propyl)dimethyl(phenyl)silane (253)



1-Allyl-3,4-dimethoxybenzene (1.78 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to Petrol:EtOAc, 10:1), pure fractions were evaporated to dryness to afford the title compound **253** (2.9 g, 94%) as a colourless oil, Rf = 0.30 (Petrol:EtOAc 10:1); ν_{max} (thin film)/cm^{-1} 3004 (w), 2990 (w), 2952 (w), 2929 (w), 2833 (w), 1739 (m), 1509 (w), 1514 (s), 1464 (m); δ_H (400 MHz, CDCl$_3$) 7.53-7.44 (2H, m, ^{Ar}CH), 7.37-7.34 (3H, m, ^{Ar}CH), 6.79 (1H, d, *J* = 8.0, ^{Ar}CH), 6.69 (1H, dd, *J* = 8.0 and 1.9, ^{Ar}CH), 6.66 (1H, d, *J* = 1.9, ^{Ar}CH), 3.86 (6H, s, OCH$_3$), 2.57 (2H, t, *J* = 7.6, ^{Ar}CH$_2$), 1.68-1.56 (2H, m, CH$_2$), 0.83-0.77 (2H, m, SiCH$_2$), 0.26 (6H, s, Si(CH$_3$)$_2$); δ_C (100 MHz, CDCl$_3$) 148.7 (^{Ar}CO), 147.1 (^{Ar}CO), 139.3 (^{Ar}C), 135.3 (^{Ar}C), 133.7 (2 × ^{Ar}CH), 128.9 (^{Ar}CH), 127.8 (2 × ^{Ar}CH), 120.4 (^{Ar}CH), 111.7 (^{Ar}CH), 111.1 (^{Ar}CH), 56.0 (OCH$_3$), 55.9 (OCH$_3$), 39.3 (^{Ar}CH$_2$), 26.1 (CH$_2$), 15.4 (SiCH$_2$), -3.0 (2 × Si(CH$_3$)$_2$); *m/z* (ESI) 315 (20%), 314 (100, M$^+$), 283 (30), 237 (15).

The spectroscopic data is in agreement with reported data.[294]

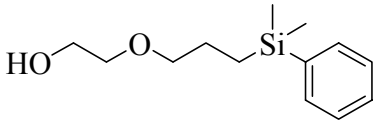
Diethyl 2-(3-(dimethyl(phenyl)silyl)propyl)malonate (254)



Diethyl 2-allylmalonate (2.0 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:EtOAc, 10:1), pure fractions were evaporated to dryness to afford the title compound **254** (3.2 g, 95%) as a colourless oil; Rf = 0.49 (Petrol:EtOAc 10:1); ν_{max} (thin film)/cm^{-1} 2981 (w), 2954 (w), 1748 (m), 1730 (s), 1458 (w), 1427 (w); δ_H (400 MHz, CDCl$_3$) 7.51-7.47 (2H, m, ^{Ar}CH), 7.36-7.33 (3H, m, ^{Ar}CH), 4.17 (4H, qd, *J* = 7.3 and 0.9, 2 x OCH$_2$), 3.33 (1H, t, *J* = 7.6, CH), 1.92 (2H, d, *J* =

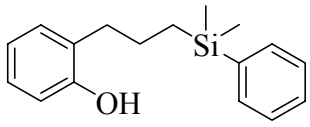
7.6, C$\underline{H}_2$), 1.40-1.32 (2H, m, C$\underline{H}_2$), 1.24 (6H, t, *J* = 7.3, 2 x OCH$_2$C$\underline{H}_3$), 0.78 (2H, app t, *J* = 8.3, SiC$\underline{H}_2$), 0.26 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 169.5 (2 × $\underline{C}$=O), 139.0 ($^{Ar}\underline{C}$), 133.4 (2 × $^{Ar}\underline{C}$H), 128.8 ($^{Ar}\underline{C}$H), 127.7 (2 × $^{Ar}\underline{C}$H), 61.1 (2 × O$\underline{C}$H$_2$), 51.6 (C(O)$\underline{C}$HC(O)), 32.3 ($\underline{C}$H$_2$), 21.7 ($\underline{C}$H$_2$), 15.3 (Si$\underline{C}$H$_2$), 14.0 ($\underline{C}$H$_3$), -3.1 (2 × Si($\underline{C}$H$_3$)$_2$); *m/z* (CI, NH_3) 360 (35%), 359 (MNa^+, 100); Found: 359.1650 (MNa^+), $C_{18}H_{28}NaO_4Si$ requires: 359.1649.

2-(3-(Dimethyl(phenyl)silyl)propoxy)ethanol (255)



2-(Allyloxy)ethanol (1.02 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:EtOAc, 10:1), pure fractions were evaporated to dryness to afford the title compound **255** (1.33 g, 56%) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3370 (b, m), 3068 (w), 2929 (m), 2867 (m), 1458 (w), 1426 (m), 1356 (m); δ_H (400 MHz, $CDCl_3$) 7.55-7.51 (2H, m, ^{Ar}C$\underline{H}$), 7.33-7.29 (3H, m, ^{Ar}C$\underline{H}$), 3.71 (2H, t, *J* = 4.6, OC$\underline{H}_2$), 3.51 (2H, t, *J* = 4.6, OC$\underline{H}_2$), 3.43 (2H, t, *J* = 7.0, OC$\underline{H}_2$), 2.40 (1H, bs, O$\underline{H}$), 1.68-1.57 (2H, m, C$\underline{H}_2$), 0.80-0.73 (2H, m, SiC$\underline{H}_2$), 0.30 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 138.9 ($^{Ar}\underline{C}$), 133.5 (2 × $^{Ar}\underline{C}$H), 128.8 ($^{Ar}\underline{C}$H), 127.7 (2 × $^{Ar}\underline{C}$H), 73.9 (O$\underline{C}$H$_2$), 71.6 (O$\underline{C}$H$_2$), 61.7 (O$\underline{C}$H$_2$), 23.9 ($\underline{C}$H$_2$), 11.6 (Si$\underline{C}$H$_2$), -3.2 (2 × Si($\underline{C}$H$_3$)$_2$); *m/z* (CI) 262 (20%), 261 (MNa^+, 100); Found 261.1281, $C_{13}H_{22}NaO_2Si$ requires 261.1286.

2-(3-(Dimethyl(phenyl)silyl)propyl)phenol (256)



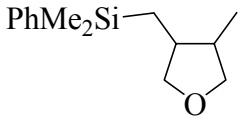
2-Allylphenol (1.34 g, 10 mmol) was reacted, according to **general procedure 6**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:EtOAc, 10:1), pure fractions were evaporated to dryness to afford the title compound **256** (2.1 g, 81%) as a colourless oil; ν_{max} (thin film)/cm^{-1} 3340 (b, w), 3058 (w), 2996 (w), 1495 (w); δ_H (400 MHz, $CDCl_3$) 7.76-7.72 (2H, m, ^{Ar}C$\underline{H}$), 7.58-7.54 (3H, m, ^{Ar}C$\underline{H}$), 7.31 (1H, dd, *J* = 7.4 and 1.6, ^{Ar}C$\underline{H}$), 7.26 (1H, td, *J* = 7.4 and 1.6, ^{Ar}C$\underline{H}$), 7.08 (1H, td, *J* = 7.4 and 1.0, ^{Ar}C$\underline{H}$), 6.90 (1H, dd, *J* = 7.4 and 1.0, ^{Ar}C$\underline{H}$), 5.87 (1H, bs, O$\underline{H}$), 2.86 (2H, t, *J* = 7.6, ^{Ar}C$\underline{H}_2$), 1.94-1.86 (2H, m, C$\underline{H}_2$), 1.09-1.03 (2H, m, SiC$\underline{H}_2$), 0.49 (6H, s, Si(C$\underline{H}_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 153.3 ($^{Ar}\underline{C}$O), 139.3 ($^{Ar}\underline{C}$), 133.5 (2

× ^{Ar}CH), 130.2 (^{Ar}CH), 128.7 (^{Ar}CH), 128.4 (^{Ar}C), 127.6 (2 × ^{Ar}CH), 126.9 (^{Ar}CH), 120.5 (^{Ar}CH), 115.2 (^{Ar}CH), 33.6 ($\underline{C}H_2$), 24.1 ($\underline{C}H_2$), 15.6 ($\underline{C}H_2$), -3.1 (2 × Si($\underline{C}H_3$)$_2$).

General procedure 7 - Cyclisation of 1,6-dienes using dimethylphenylsilane at room temperature

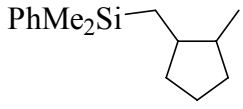
To a stirred solution of the 1,6-diene (3.8-10.0 mmol, 1.0 equiv), dimethylphenylsilane (7.6-22.0 mmol, 2.2 equiv.) in THF (40-100 mL) was added triethylborane in THF (0.5 mL, 1 M solution, 5 mmol, 0.5 equiv.) and shortly after triisopropylsilanethiol (0.4-1.0 mmol, 10 mol%, care required due to noxious smell). After stirring at room temperature for 1 h, a further portion of triethylborane in THF (0.5 mL, 1 M solution 5 mmol, 0.5 equiv.) was added and left stirring overnight. Removal of the solvent under reduced pressure and purification of the resulting reaction mixture by flash chromatography (silica, petrol to petrol:ethyl acetate, 10:1) afforded the title compounds as a mixture of diastereoisomers (61-88 %) as colourless oils.

((Tetrahydro-4-methylfuran-3-yl)methyl)dimethyl(phenyl)silane (232)



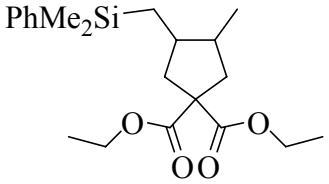
Diallyl ether (1.0 g, 10.0 mmol) was reacted according to **general procedure 7**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 10:1), pure fractions were evaporated to dryness to afford the title product **232** (1.4 g, 61%) as a colourless oil, Rf 0.43 (petrol:ethyl acetate, 10:1), as an inseparable mixture of diastereoisomers (*trans*:*cis* = 1:2.4). The spectroscopic data matches the sample prepared according to **general procedure 5**.

Dimethyl((2-methylcyclopentyl)methyl)(phenyl)silane (233)



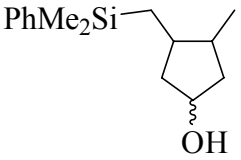
1,6-Heptadiene (1.0 g, 10.0 mmol) was reacted according to **general procedure 7**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol), pure fractions were evaporated to dryness to afford the title product **233** (1.6 g, 70%) as a colourless oil, Rf 0.85 (petrol), as an inseparable mixture of diastereoisomers (*trans*:*cis* = 1:2.2). The spectroscopic data matches the previously made sample according to **general procedure 5.**

Diethyl 3-((dimethyl(phenyl)silyl)methyl)-4-methylcyclopentane-1,1-dicarboxylate (234)



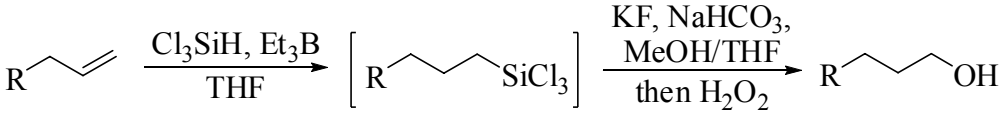
Diethyl diallyl malonate (2.4 g, 10.0 mmol), was reacted according to **general procedure 7**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 10:1), pure fractions were evaporated to dryness to afford the title product **234** (3.3 g, 88%) as a colourless oil, Rf 0.40 (petrol:ethyl acetate, 10:1), as an inseparable mixture of diastereoisomers (*trans*:*cis* = 1:4.0). The spectroscopic data matches the sample prepared according to **general procedure 5.**

3-((Dimethyl(phenyl)silyl)methyl)-4-methylcyclopentanol (239)



1,6-Heptadien-4-ol (1.0 g, 9.0 mmol) was reacted according to **general procedure 7**. After removal of the solvent, the crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 10:1), pure fractions were evaporated to dryness to afford the title compound **239** as a pale yellow oil (1.8 g, 73%), Rf 0.40 (petrol:ethyl acetate, 10:1), as an inseparable mixture of diastereoisomers. The spectroscopic data matches the sample prepared according to **general procedure 5.**

General procedure 8 – Oxidation of dimethylphenylsilanes



General procedure 8.1 – Conversion of dimethylphenylsilanes into dimethylfluorosilanes

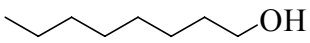
To a stirred solution of the dimethylphenylsilane (5.0 mmol, 1 equiv) in dry dichloromethane (15 mL) at room temperature was added boron trifluoride-acetic acid complex (1.4 mL, 10.0 mmol, 2 equiv), the resulting solution was stirred for 6 h, during

which time the solution turned orange. The reaction mixture was quenched by slowly being poured into a stirred solution of 1 M sodium hydrogen carbonate (100 mL), the aqueous layer was extracted with dichloromethane (2 × 75 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to afford the title compound as a pale yellow oil (0.71-0.93 g, 75-88%). No further purification was carried out, and the resulting oil was subjected to the oxidation conditions.

General procedure 8.2 - Oxidation of dimethylfluorosilanes

To a stirred solution of the unpurified dimethylfluorosilane (3.4-4.0 mmol, 1 equiv) and anhydrous potassium fluoride (0.39-0.46 g, 6.8-8.0 mmol, 2 equiv) in dry DMF (5 mL) at room temperature was added dropwise a solution of *meta*-chloroperoxybenzoic acid (1.38-1.62 g, 85%, 6.8-8.0 mmol, 2 equiv) in dry DMF (10 mL). The resulting solution was stirred for 4 h at room temperature. The reaction mixture was diluted with dichloromethane (75 mL) and washed successively with aqueous sodium thiosulfate (2 × 50 mL), aqueous sodium carbonate (2 × 50 mL), brine (50 mL), and then dried over $MgSO_4$ and purification by flash chromatography (petrol:diethyl ether, 10:1) to afford the title products as colourless oils (0.11-0.18 g, 25-31%).

1-Octanol (260)

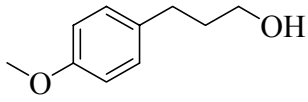


Octyldimethylphenylsilane (1.24, 5.0 mmol) was reacted, according to **general procedure 8.1**. Following the aqueous workup, the solvent was removed under reduced pressure to afford the unpurified octyldimethylfluorosilane as a pale yellow oil (0.71 g, 75%). (No further purification was carried out, and the resulting oil was subjected to the oxidation conditions). δ_H (270 MHz, $CDCl_3$) 1.58-1.42 (2H, m, C<u>H</u>$_2$), 1.38-1.14 (10H, m, 5 × C<u>H</u>$_2$), 0.90 (3H, t, J = 7.0, C<u>H</u>$_3$), 0.76-0.66 (2H, m, C<u>H</u>$_2$Si), 0.17 (6H, d, J = 7.5, Si(C<u>H</u>$_3$)$_2$).

The crude octyldimethylfluorosilane (0.65 g, 3.4 mmol) was reacted, according to **general procedure 8.2.** Following the work up procedure the crude product was purified by flash silica chromatography (petrol:diethyl ether, 10:1) to afford the title product **260** as a colourless oil (0.11 g, 25%); Rf = 0.32 (petrol:diethyl ether, 10:1); ν_{max} (thin film)/cm^{-1} 3332 (m), 2926 (s), 2855 (s), 1465 (w), 1378 (w), 1055 (m); δ_H (400 MHz, $CDCl_3$) 3.60-3.54 (2H, m, C<u>H</u>$_2$OH), 2.60-2.18 (1 H, bs, O<u>H</u>), 1.56-1.46 (2H, m, C<u>H</u>$_2$CH$_2$OH), 1.34-1.16 (10H, m, C<u>H</u>$_2$), 0.84 (3H, t, J = 6.7, C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 62.8 (<u>C</u>H$_2$OH), 32.6 (<u>C</u>H$_2$), 31.7 (<u>C</u>H$_2$), 29.3 (<u>C</u>H$_2$), 29.2 (<u>C</u>H$_2$), 25.7 (<u>C</u>H$_2$), 22.6 (<u>C</u>H$_2$), 13.9 (<u>C</u>H$_3$); *m/z* (Cl) 149 (10%), 148 (MNH_4^+, 100), 131 (MH^+, 30).

The spectroscopic data is in agreement with reported data. (Sigma Aldrich)

3-(4-Methoxyphenyl)propan-1-ol (**261**)

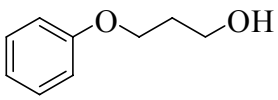


3-(4-Methoxyphenyl)propyl(dimethy)(phenyl)silane (1.42, 5.0 mmol) was reacted, according to **general procedure 8.1**. Following the aqueous workup, the solvent was removed under reduced pressure afford the crude 3-(4-methoxyphenyl)propyl(dimethyl)fluorosilane as a pale yellow oil (0.88 g, 78%). (No further purification was carried out, and the resulting oil was subjected to the oxidation conditions). δ_H (270 MHz, $CDCl_3$) 7.08 (2H, d, J = 9.0, $^{Ar}C\underline{H}$), 6.82 (2H, d, J = 9.0, $^{Ar}C\underline{H}$), 3.78 (3H, s, $^{Ar}OC\underline{H}_3$), 2.58 (2H, t, J = 7.0, $ArC\underline{H}_2$), 1.72-1.60 (2H, m, $CH_2C\underline{H}_2CH_2$), 0.77-0.69 (2H, m, $C\underline{H}_2Si$), 0.19 (6H, d, J = 7.5, $Si(C\underline{H}_3)_2$).

The crude 3-(4-methoxyphenyl)propyldimethylfluorosilane (0.80 g, 3.5 mmol) was reacted, according to **general procedure 8.2.** Following the work-up procedure the crude product was purified by flash silica chromatography (petrol:diethyl ether, 10:1) to afford the title product **261** as a colourless oil (0.18 g, 31%); ν_{max} (thin film)/cm^{-1} 3305 (bs), 3000 (m), 2900 (s), 1610 (s), 1450 (m); δ_H (400 MHz, $CDCl_3$) 7.11 (2H, app dt, J = 8.4 and 2.1, $^{Ar}C\underline{H}$), 6.82 (2H, app dt, J = 8.4 and 2.1, $^{Ar}C\underline{H}$), 3.77 (3H, s, $OC\underline{H}_3$), 3.64 (2H, t, J = 6.4, $OC\underline{H}_2$), 2.64 (2H, t, J = 7.5, $^{Ar}C\underline{H}_2$), 1.85 (2H, app tt, J = 7.5 and 6.4, $CH_2C\underline{H}_2CH_2OH$), 1.75 (1H, bs, $O\underline{H}$); δ_C (100 MHz, $CDCl_3$) 157.6 ($^{Ar}\underline{C}O$), 133.8 ($^{Ar}\underline{C}$), 129.2 (2 × $^{Ar}\underline{C}H$), 113.8 (2 × $^{Ar}\underline{C}H$), 62.1 ($O\underline{C}H_2$), 55.2 ($O\underline{C}H_3$), 34.3 ($^{Ar}\underline{C}H_2$), 31.0 ($CH_2\underline{C}H_2CH_2OH$); *m/z* (CI, NH_3) 167 (10%), 166 (MH^+, 100).

The spectroscopic data is in agreement with reported data. (Sigma Aldrich)

3-Phenoxypropan-1-ol (**262**)

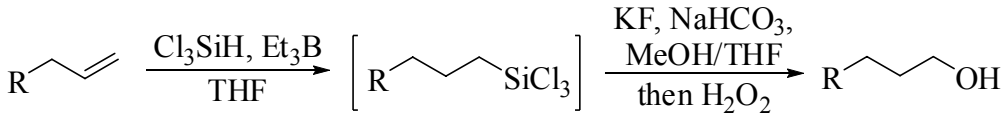


3-Phenoxypropyl(dimethyl)phenylsilane (1.35, 5.0 mmol) was reacted, according to **general procedure 8.1**. Following the aqueous workup, the solvent was removed under reduced pressure afford the crude **3-phenoxypropyldimethylflourosilane** as a pale yellow oil (0.88 g, 78%). No further purification was carried out, and the resulting oil was subjected to the oxidation conditions; δ_H (270 MHz, $CDCl_3$) 7.23-7.10 (2H, m, $^{Ar}C\underline{H}$), 6.88-6.75 (3H, m, $^{Ar}C\underline{H}$), 3.78 (3H, t, J = 7.0, $OC\underline{H}_2$), 1.85-1.70 (2H, m, $CH_2C\underline{H}_2CH_2$), 0.78-0.71 (2H, m, $C\underline{H}_2Si$), 0.17 (6H, d, J = 7.5, $Si(C\underline{H}_3)_2$).

The crude 3-phenoxypropyldimethylfluorosilane (0.85 g, 4.0 mmol) was reacted, according to **general procedure 8.2.** Following the work up procedure the crude product was purified by flash silica chromatography (petrol:diethyl ether, 10:1) to afford the title product **262** as a colourless oil (0.15 g, 26%); ν_{max} (thin film)/cm^{-1} 3390 (bs), 3020 (w), 1610 (m), 1505 (m): δ_H (400 MHz, $CDCl_3$) 7.28 (2H, app t, J = 7.3, $^{Ar}C\underline{H}$), 6.98-6.89 (3H, m, $^{Ar}C\underline{H}$), 4.11 (2H, t, J = 5.9, $OC\underline{H}_2$), 3.86 (2H, t, J = 5.9, $OC\underline{H}_2$), 2.04 (2H, quin, J = 5.9, $OCH_2C\underline{H}_2CH_2OH$), 1.96 (1H, bs, O$\underline{H}$); δ_C (100 MHz, $CDCl_3$) 158.6 ($^{Ar}\underline{C}O$), 129.4 (2 × $^{Ar}\underline{C}H$), 120.8 ($^{Ar}\underline{C}H$), 114.4 (2 × $^{Ar}\underline{C}H$), 65.6 ($\underline{C}H_2$), 60.5 ($\underline{C}H_2$), 31.9 ($OCH_2\underline{C}H_2OCH_2$); *m/z* (CI, NH_3) 153 (10%), 152 (100), 94 (80).

The spectroscopic data is in agreement with reported data.[295]

General procedure 9 – Addition of trichlorosilanes to alkenes followed by oxidation



General procedure 9.1 – Addition of trichlorosilane to alkenes

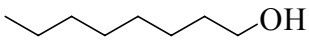
To a stirred solution of the alkene (5.0 mmol, 1 equiv) in THF (5 mL) at 0 ºC, under air, was added trichlorosilane (1.0 mL, 10.0 mmol, 2 equiv) followed by the slow dropwise addition of triethylborane (2.0 mL, 1 M solution in THF, 2.0 mmol, 0.4 equiv). The resulting solution was stirred at 0 ºC for 1 h, after which a further portion of triethylborane (2.0 mL, 1 M solution in THF, 2.0 mmol, 0.4 equiv) was added and the mixture stirred for a further 1 h at 0 ºC followed by addition of a further portion of triethylborane (2.0 mL, 1 M solution in THF, 2.0 mmol, 0.4 equiv). The resulting solution was stirred at 0 ºC for 1 h then warmed to room temperature and stirred for a further 4 h. Removal of the solvent under reduced pressure afforded the crude trichlorosilane addition product, as an oil.

General procedure 9.2 – Oxidation of trichlorosilanes

The crude trichlorosilane addition product was taken up in THF (75 mL) and the solution was stirred at room temperature (under air) while MeOH (75 mL) was slowly added, after which KF (2.6 g, 45.0 mmol, 9 equiv) and $KHCO_3$ (9.00 g, 90.0 mmol 18 equiv) was added and the suspension was stirred for 1 h. To the resulting white suspension was added H_2O_2 (5.1 mL, 30% solution, 45.0 mmol, 9 equiv) and the reaction mixture was vigorously stirred for 24 h. After which sodium thiosulfate pentahydrate (7.4 g, 30.0 mmol, 6 equiv) was added and the mixture stirred for 1 h. The mixture was filtered through a Celite plug, and the filter cake was rinsed with 50 mL of diethyl ether. The filtrate was concentrated

under vacuum and the resulting residue was dissolved in 50 mL of DCM, and dried over $MgSO_4$, the volatiles were removed *in vacuo* to afford the crude product. The crude product was purified by flash silica chromatography (elution gradient petrol to petrol:ethyl acetate, 2:1), and pure fractions were evaporated to dryness to afford the alcohol (39-51%).

1-Octanol (**260**)

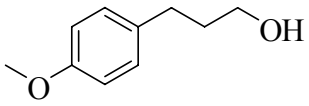


1-Octene (0.56 g, 5.0 mmol) was reacted, according to **general procedure 9.1**. Removal of the solvent under reduced pressure afforded the crude trichlorosilane addition product, as a moisture sensitive oil; δ_H (400 MHz, $CDCl_3$) 1.62-1.54 (2H, m, CH_2), 1.43-1.36 (4H, m, CH_2 and $SiCH_2$), 1.33-1.22 (8H, m, 4 × CH_2), 0.88 (3H, t, J = 6.8, CH_3); δ_C (100 MHz, $CDCl_3$) 31.8 (CH_2), 31.7 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 24.3 (CH_2), 22.6 (CH_2), 22.2 (CH_2), 14.1 (CH_3).

The crude trichlorosilane addition product was reacted, according to **general procedure 9.2**. Following the work-up procedure the crude product was purified by flash silica chromatography (elution gradient petrol:ethyl acetate, 10:1 – 2:1), and pure fractions were evaporated to dryness to afford the title compound **260** as a colourless oil (0.25 g, 39%); Rf = 0.32 (petrol:diethyl ether, 10:1); ν_{max} (thin film)/cm^{-1} 3332 (m), 2926 (s), 2855 (s), 1465 (w), 1378 (w), 1055 (m); δ_H (400 MHz, $CDCl_3$) 3.60-3.54 (2H, m, C$\underline{H}_2$OH), 2.60-2.18 (1H, bs, O$\underline{H}$), 1.56-1.46 (2H, m, C$\underline{H}_2$ CH_2OH), 1.34-1.16 (10H, m, 5 × C$\underline{H}_2$), 0.84 (3H, t, J = 6.7, C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 62.8 ($\underline{C}H_2$OH), 32.6 ($\underline{C}H_2$), 31.7 ($\underline{C}H_2$), 29.3 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 25.7 ($\underline{C}H_2$), 22.6 ($\underline{C}H_2$), 13.9 ($\underline{C}H_3$); *m/z* (Cl) 149 (10%), 148 (MNH_4^+, 100), 131 (MH^+, 30).

The spectroscopic data is in agreement with reported data.[296]

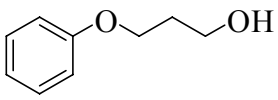
3-(4-Methoxyphenyl)propan-1-ol (**261**)



4-Allylanisole (0.74 g, 5.0 mmol) was reacted, according to **general procedure 9.1**. Removal of the solvent under reduced pressure afforded the crude trichlorosilane addition product as a moisture sensitive oil; δ_H (400 MHz, $CDCl_3$) 7.09 (2H, d, J = 8.7, $^{Ar}C\underline{H}$), 6.84 (2H, d, J = 8.7, $^{Ar}C\underline{H}$), 3.78 (3H, s, OC$\underline{H}_3$), 2.66 (2H, t, J = 7.4, $^{Ar}C\underline{H}_2$), 1.41-1.35 (2H, m, SiC$\underline{H}_2$), 1.27-1.23 (2H, m, $CH_2C\underline{H}_2CH_2Si$); δ_C (100 MHz, $CDCl_3$) 158.1 ($^{Ar}\underline{C}O$), 132.9 ($^{Ar}\underline{C}$), 129.4 (2 × $^{Ar}\underline{C}H$), 113.9 (2 × $^{Ar}\underline{C}H$), 55.3 (O$\underline{C}H_3$), 36.8 ($\underline{C}H_2$), 24.3 ($\underline{C}H_2$), 23.7 ($\underline{C}H_2$).

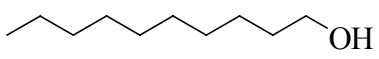
The crude trichlorosilane addition product was reacted, according to **general procedure 9.2**. Following the work-up procedure the crude product was purified by flash silica chromatography (elution gradient petrol:ethyl acetate, 10:1 – 2:1), and pure fractions were evaporated to dryness to afford the title compound **261** as a colourless oil (0.42 g, 51%); ν_{max} (thin film)/cm^{-1} 3305 (bs), 3000 (m), 2900 (s), 1610 (s), 1450 (m); δ_H (400 MHz, $CDCl_3$) 7.11 (2H, app dt, J = 8.4 and 2.1, $^{Ar}C\underline{H}$), 6.82 (2H, app dt, J = 8.4 and 2.1, $^{Ar}C\underline{H}$), 3.77 (3H, s, $OC\underline{H}_3$), 3.64 (2H, t, J = 6.4, $OC\underline{H}_2$), 2.64 (2H, t, J = 7.5, $^{Ar}C\underline{H}_2$), 1.85 (2H, app tt, J = 7.5 and 6.4, $CH_2C\underline{H}_2CH_2OH$), 1.75 (1H, bs, O$\underline{H}$); δ_C (100 MHz, $CDCl_3$) 157.6 ($^{Ar}\underline{C}O$), 133.8 ($^{Ar}\underline{C}$), 129.2 (2 × $^{Ar}\underline{C}H$), 113.8 (2 × $^{Ar}\underline{C}H$), 62.1 ($O\underline{C}H_2$), 55.2 ($O\underline{C}H_3$), 34.3 ($^{Ar}\underline{C}H_2$), 31.0 ($CH_2\underline{C}H_2CH_2OH$); *m/z* (CI, NH_3) 167 (10%), 166 (MH^+, 100).
The spectroscopic data is in agreement with reported data.[296]

3-Phenoxypropan-1-ol (**262**)



Allyl phenyl ether (0.68 mL, 5.0 mmol, 1 equiv) was reacted, according to **general procedure 9.1**. Removal of the solvent under reduced pressure afforded the crude trichlorosilane addition product as a moisture sensitive oil; δ_H (400 MHz, $CDCl_3$) 7.26 (2H, dd, J = 8.8 and 7.7, $^{Ar}C\underline{H}$), 6.93 (1H, td, J = 7.7 and 1.1, $^{Ar}C\underline{H}$), 6.87 (2H, dd, J = 8.8 and 1.1, $^{Ar}C\underline{H}$), 3.98 (2H, t, J = 6.1 $OC\underline{H}_2$), 2.09-2.01 (2H, m, $C\underline{H}_2$), 1.62-1.56 (2H, m, $SiC\underline{H}_2$); δ_C (100 MHz, $CDCl_3$) 157.9 ($^{Ar}\underline{C}OCH_2$), 128.5 (2 × $^{Ar}\underline{C}H$), 120.3 ($^{Ar}\underline{C}H$), 114.1 (2 × $^{Ar}\underline{C}H$), 60.9 ($O\underline{C}H_2$), 34.5 ($\underline{C}H_2$), 22.4 ($\underline{C}H_2$).
The crude trichlorosilane addition product was reacted, according to **general procedure 9.2**. Following the work-up procedure the crude product was purified by flash silica chromatography (elution gradient petrol:ethyl acetate, 10:1 – 2:1), and pure fractions were evaporated to dryness to afford the title compound **262** as a colourless oil (0.36 g, 49%); ν_{max} (thin film)/cm^{-1} 3390 (bs), 3020 (w), 1610 (m), 1505 (m); δ_H (400 MHz, $CDCl_3$) 7.28 (2H, app t, J = 7.3, $^{Ar}C\underline{H}$), 6.98-6.89 (3H, m, $^{Ar}C\underline{H}$), 4.11 (2H, t, J = 5.9, $OC\underline{H}_2$), 3.86 (2H, t, J = 5.9, $OC\underline{H}_2$), 2.04 (2H, quin, J = 5.9, $OCH_2C\underline{H}_2CH_2OH$), 1.96 (1H, bs, O$\underline{H}$); δ_C (100 MHz, $CDCl_3$) 158.6 ($^{Ar}\underline{C}OCH_2$), 129.4 (2 × $^{Ar}\underline{C}H$), 120.8 ($^{Ar}\underline{C}H$), 114.4 (2 × $^{Ar}\underline{C}H$), 65.6 ($\underline{C}H_2$), 60.5 ($\underline{C}H_2$), 31.9 ($OCH_2\underline{C}H_2OCH_2$); *m/z* (CI, NH_3) 153 (10%), 152 (100), 94 (80).
The spectroscopic data is in agreement with reported data.[295]

1-Decanol (263)

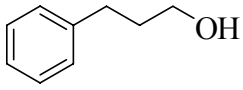


1-Decene (0.70 g, 5.0 mmol) was reacted, according to **general procedure 9.1**. Removal of the solvent under reduced pressure afforded the crude trichlorosilane addition product, as a moisture sensitive oil; δ_H (400 MHz, $CDCl_3$) 1.62-1.54 (2H, m, CH_2), 1.43-1.36 (4H, m, CH_2 and $SiCH_2$), 1.33-1.22 (8H, m, 4 × CH_2), 0.88 (3H, t, J = 6.8, CH_3); δ_C (100 MHz, $CDCl_3$) 31.8 (CH_2), 31.7 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 24.3 (CH_2), 22.6 (CH_2), 22.2 (CH_2), 14.1 (CH_3).

The crude trichlorosilane addition product was reacted, according to **general procedure 9.2**. Following the work-up procedure the crude product was purified by flash silica chromatography (elution gradient petrol:ethyl acetate, 10:1 – 2:1), and pure fractions were evaporated to dryness to afford the title compound **263** as a colourless oil (0.34 g, 43%); ν_{max} (thin film)/cm^{-1} 3232 (m), 2900 (s), 2850 (s), 1470 (w), 1320 (w); δ_H (400 MHz, $CDCl_3$) 3.60 (2H, t, J = 7.3, C$\underline{H}_2$OH), 2.10 (1H, bs, O$\underline{H}$), 1.60-1.46 (2H, m, C$\underline{H}_2$), 1.35-1.20 (14H, m, 7 × C$\underline{H}_2$), 0.90 (3H, t, J = 6.9, C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 63.2 ($\underline{C}H_2$OH), 32.5 ($\underline{C}H_2$), 31.8 ($\underline{C}H_2$), 29.3 (2 × $\underline{C}H_2$), 29.2 (2 × $\underline{C}H_2$), 25.9 ($\underline{C}H_2$), 21.9 ($\underline{C}H_2$), 14.0 ($\underline{C}H_3$); *m/z* (Cl) 160 (10%), 159 (MH^+, 100).

The spectroscopic data is in agreement with reported data.[296]

3-Phenylpropan-1-ol (264)

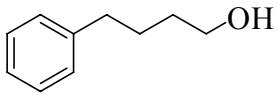


1-Allylbenzene (0.59 g, 5.0 mmol) was reacted, according to **general procedure 9.1**. Removal of the solvent under reduced pressure afforded the crude trichlorosilane addition product, as a moisture sensitive oil; δ_H (400 MHz, $CDCl_3$) 7.25-7.20 (2H, m, $^{Ar}C\underline{H}$), 7.15-7.10 (3H, m, $^{Ar}C\underline{H}$), 2.60 (2H, t, J = 7.5 ArC$\underline{H}_2$), 1.88-1.78 (2H, m, C$\underline{H}_2$), 1.38-1.33 (2H, m, SiC$\underline{H}_2$); δ_C (100 MHz, $CDCl_3$) 140.0 ($^{Ar}\underline{C}$), 128.4 ($^{Ar}\underline{C}H$), 128.3 (2 × $^{Ar}\underline{C}H$), 126.0 (2 × $^{Ar}\underline{C}H$), 37.7 ($\underline{C}H_2$), 23.9 ($\underline{C}H_2$), 23.7 ($\underline{C}H_2$).

The crude trichlorosilane addition product was reacted, according to **general procedure 9.2**. Following the work up procedure the crude product was purified by flash silica chromatography (elution gradient petrol:ethyl acetate, 10:1 – 2:1), and pure fractions were evaporated to dryness to afford the title compound **264** as a colourless oil (0.32 g 47%); ν_{max} (thin film)/cm^{-1} 3300 (m), 3053 (w), 2920 (m), 1602 (m); δ_H (400 MHz, $CDCl_3$) 7.33-7.27 (3H, m, $^{Ar}C\underline{H}$), 7.25-7.17 (2H, m, $^{Ar}C\underline{H}$), 3.68 (2H, t, J = 6.4, C$\underline{H}_2$OH), 2.71 (2H, t, J = 7.7, ArC$\underline{H}_2$), 1.85-1.95 (2H, m, ArCH$_2$C$\underline{H}_2$CH$_2$OH); δ_C (100 MHz, $CDCl_3$) 141.8 ($^{Ar}\underline{C}$), 128.4 (2 × $^{Ar}\underline{C}H$), 128.4 ($^{Ar}\underline{C}H$), 125.8 (2 × $^{Ar}\underline{C}H$), 62.3 ($\underline{C}H_2$OH), 34.3 (CH_2), 32.1 (CH_2); *m/z* (CI) 138 (10%), 137 (MH^+, 100).

The spectroscopic data is in agreement with reported data. (Sigma Aldrich)

4-Phenyl-1-butanol (265)

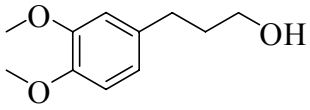


4-Phenyl-1-butene (0.66 g, 5.0 mmol) was reacted, according to **general procedure 9.1**. Removal of the solvent under reduced pressure afforded the crude trichlorosilane addition product, as a moisture sensitive oil; δ_H (400 MHz, $CDCl_3$) 7.24-7.18 (2H, m, $^{Ar}C\underline{H}$), 7.14-7.08 (3H, m, $^{Ar}C\underline{H}$), 2.57 (2H, t, J = 7.4 Ar$C\underline{H}_2$), 1.71-1.63 (2H, m, $C\underline{H}_2$), 1.60-1.54 (2H, m, $C\underline{H}_2$), 1.38-1.33 (2H, m, Si$C\underline{H}_2$); δ_C (100 MHz, $CDCl_3$) 141.7 ($^{Ar}\underline{C}$), 128.5 ($^{Ar}\underline{C}H$), 128.3 (2 × $^{Ar}\underline{C}H$), 125.8 (2 × $^{Ar}\underline{C}H$), 35.3 ($\underline{C}H_2$), 33.5 ($\underline{C}H_2$), 24.1 ($\underline{C}H_2$), 21.9 ($\underline{C}H_2$).

The crude trichlorosilane addition product was reacted, according to **general procedure 9.2**. Following the work up procedure the crude product was purified by flash silica chromatography (elution gradient petrol:ethyl acetate, 10:1 – 2:1), and pure fractions were evaporated to dryness to afford the title compound **265** as a colourless oil (0.34 g, 47%); ν_{max} (thin film)/cm^{-1} 3350 (m), 3020 (w), 2953 (s), 2888 (m), 1499 (m), 1452 (m); δ_H (400 MHz, $CDCl_3$) 7.25-7.19 (2H, m, $^{Ar}C\underline{H}$), 7.15-7.10 (3H, m, $^{Ar}C\underline{H}$), 3.59 (2H, t, J = 7.7, $C\underline{H}_2OH$), 2.60 (2H, t, J = 7.4 Ar$C\underline{H}_2$), 1.75-1.52 (5H, m, $C\underline{H}_2C\underline{H}_2CH_2O\underline{H}$); δ_C (100 MHz, $CDCl_3$) 142.1 ($^{Ar}\underline{C}$), 128.3 ($^{Ar}\underline{C}H$), 128.2 (2 × $^{Ar}\underline{C}H$), 125.7 (2 × $^{Ar}\underline{C}H$), 62.8 ($\underline{C}H_2OH$), 35.5 ($\underline{C}H_2$), 32.1 ($\underline{C}H_2$), 27.4 ($\underline{C}H_2$); *m/z* (CI, NH_3) 168 (MNH_4^+, 45%), 152 (10), 151 (MH^+, 100).

The spectroscopic data is in agreement with reported data.[296]

3-(3,4-Dimethoxyphenyl)-1-propanol (266)



4-Allyl-1,2-dimethoxybenzene (0.86 mL, 5.0 mmol) was reacted, according to **general procedure 9.1**. Removal of the solvent under reduced pressure afforded the crude trichlorosilane addition product as a moisture sensitive oil; δ_H (400 MHz, $CDCl_3$) 6.79 (1H, d, J = 8.0, $^{Ar}C\underline{H}$), 6.70 (1H, dd, J = 8.0 and 1.9, $^{Ar}C\underline{H}$), 6.68 (1H, d, J = 1.9, $^{Ar}C\underline{H}$), 3.87 (3H, s, $OC\underline{H}_3$), 3.85 (3H, s, $OC\underline{H}_3$), 2.66 (1H, t, J = 7.4, $^{Ar}C\underline{H}_2$), 1.43-1.37 (2H, m, Si$C\underline{H}_2$), 1.26-1.24 (2H, m, $C\underline{H}_2$).

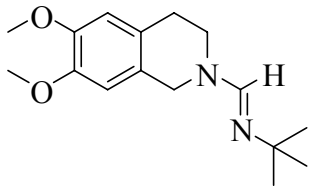
The crude trichlorosilane addition product was reacted, according to **general procedure 9.2**. Following the work-up procedure the crude product was purified by flash silica chromatography (elution gradient petrol:ethyl acetate, 10:1 – 2:1), and pure fractions were

evaporated to dryness to afford the title compound **266** as a colourless oil (0.48 g, 49%); ν_{max} (thin film)/cm^{-1} 3315 (bs), 3010 (w), 2910 (m), 1601 (s), 1450 (m); δ_H (400 MHz, $CDCl_3$) 6.78 (1H, d, *J* = 8.7, $^{Ar}C\underline{H}$), 6.72 (1H, dd, *J* = 8.7 and 1.6, $^{Ar}C\underline{H}$), 6.71 (1H, app d, *J* = 1.6, $^{Ar}C\underline{H}$), 3.85 (3H, s, $OC\underline{H}_3$), 3.84 (3H, s, $OC\underline{H}_3$), 3.66 (2H, t, *J* = 6.4, $OC\underline{H}_2$), 2.64 (1H, t, *J* = 7.4, $^{Ar}C\underline{H}_2$), 1.86 (2H, app tt, *J* = 7.4 and 6.4, $CH_2C\underline{H}_2CH_2OH$); δ_C (100 MHz, $CDCl_3$) 148.7 ($^{Ar}\underline{C}O$), 147.0 ($^{Ar}\underline{C}O$), 134.3 ($^{Ar}\underline{C}$), 120.1 ($^{Ar}\underline{C}H$), 111.6 ($^{Ar}\underline{C}H$), 111.1 ($^{Ar}\underline{C}H$), 62.1 ($O\underline{C}H_3$), 55.8 ($O\underline{C}H_3$), 55.7 ($O\underline{C}H_3$), 34.3 ($CH_2\underline{C}H_2CH_2OH$), 31.6 ($^{Ar}\underline{C}H_2$); *m/z* (CI, NH_3) 197 (10%), 196 (100, MH^+), 181 (30).

The spectroscopic data is in agreement with reported data.[296]

7.4 - Experimental for Chapter 4

_N_-((6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)methylene)-2-methylpropan-2-amine (275) [151, 152, 192]

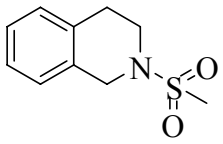


Using conventional heating: To a stirred solution of the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **190** (5 g, 25.87 mmol) under nitrogen was added *N*,*N*-dimethyl-*N*'-*tert*-butylformamidine (4.48 ml, 28.46 mmol), and a catalytic amount of ammonium sulfate (34 mg, 0.26 mmol) in toluene and the mixture was heated at reflux for 4-5 days. After consumption of the starting material, the solvent was removed under reduced pressure. Purification was not possible and the crude material is used in subsequent reactions.

Using microwave heating: A solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **190** (0.25 g, 1.29 mmol), *N*,*N*-dimethyl-*N*'-*tert*-butylformamidine (0.224 ml, 1.42 mmol) and ammonium sulfate (2 mg, 0.01 mmol) were dissolved in toluene (0.65 ml) and sealed into a microwave tube. The reaction was heated to 150 ºC for 2 h in a microwave reactor and cooled to r.t. Further purification was not possible and the crude material was used in subsequent reactions. ν_{max} (thin film) 3279 (w), 3018 (m), 2954 (s) 2816 (s), 1658 (s) /cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39 (1H, s, NC(N)H), 6.55 (1H, s, ^{Ar}CH), 6.51 (1H, s, ^{Ar}CH), 4.33 (2H, s, NCH_2Ar), 3.76 (3H, s, $^{Ar}COCH_3$), 3.74 (3H, s, $^{Ar}COCH_3$), 3.41 (2H, t, J = 6.0, NCH_2CH_2Ar), 2.70 (2H, t, J = 6.0, NCH_2CH_2Ar), 1.10 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 149.9 (NC(N)H), 147.3 ($^{Ar}COCH_3$), 147.1 ($^{Ar}COCH_3$), 126.2 (^{Ar}C), 125.4 (^{Ar}C), 111.2 (^{Ar}CH), 109.0 (^{Ar}CH), 55.7 ($^{Ar}OCH_3$), 55.6 ($^{Ar}OCH_3$), 53.0 ($C(CH_3)_3$), 45.9 (NCH_2Ar), 43.7 (NCH_2CH_2Ar), 31.0 (3 × $C(CH_3)_3$), 28.5 (NCH_2CH_2Ar); *m/z* (CI) 278 (15%), 277 (100, MH^+); HRMS $C_{16}H_{25}N_2O_2$ (MH^+) requires 277.1911, found 277.1920.

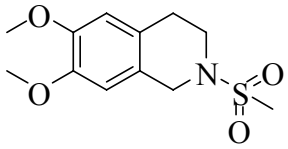
The spectroscopic data is in agreement with reported data. [151, 152, 192]

2-(Methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (276)[297]



To a stirred solution of 1,2,3,4-tetrahydroisoquinoline **188** (1.3 g, 9.76 mmol) and triethylamine (2.72 mL, 19.52 mmol) in DCM (50 mL) at 0 ºC was added methanesulfonyl chloride (0.831 mL, 10.74 mmol) dropwise, and the resulting solution was warmed to r.t. and stirred for 6 h. The reaction mixture was quenched with water (25 mL), and the layers separated, the aqueous layer was extracted with DCM (25 mL), the combined organic layer were dried over Na_2SO_4, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **276** (1.680 g, 83%) as a white crystalline solid, mp 102-106 ºC; ν_{max} (thin film) /cm^{-1} 3015 (w), 2935 (w), 2161 (w), 1317 (s), 1272 (m), 1150 (m), 1136 (s); δ_H (400 MHz, $CDCl_3$) 7.22-7.14 (3H, m, ^{Ar}C$\underline{H}$), 7.11-7.07 (1H, m, ^{Ar}C$\underline{H}$), 4.46 (2H, s, NC$\underline{H}_2$Ar), 3.57 (2H, t, *J*= 6.0, NC$\underline{H}_2$CH$_2$Ar), 2.98 (2H, t, *J*= 6.0, NCH$_2$C$\underline{H}_2$Ar), 2.83 (3H, s, SO$_2$C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 133.2 (^{Ar}C), 131.8 (^{Ar}C), 129.0 (^{Ar}CH), 127.0 (^{Ar}CH), 126.5 (^{Ar}CH), 126.3 (^{Ar}CH), 47.2 (NCH$_2$Ar), 43.4 (NCH$_2$CH$_2$Ar), 36.0 (SO$_2$CH$_3$), 28.7 (NCH$_2$CH$_2$Ar); *m/z* (CI, NH_3) 274 (30%), 252 (100, MMeCN$^+$), 207 (50).
The spectroscopic data is in agreement with reported data.[297]

6,7-Dimethoxy-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (278)[297, 298]

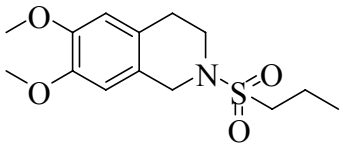


To a stirred solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.5 g, 10.88 mmol) and triethylamine (4.55 mL, 32.65 mmol) in DCM (50 mL) at 0 ºC was added methanesulfonyl chloride (0.831 mL, 10.74 mmol) dropwise, and the resulting solution was warmed to r.t. and stirred for 6 h. The reaction mixture was quenched with water (25 mL), and the layers separated, the aqueous layer was extracted with DCM (2 × 25 mL), the combined organic layer were dried over Na_2SO_4, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 6,7-dimethoxy-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **278** (2.47 g, 84%) as a white crystalline solid, mp 142–144°C; ν_{max} (thin film) /cm^{-1} 2935 (w), 2841 (w), 2160 (w), 2028 (w), 1611 (m), 1518 (s), 1468 (w), 1448 (w); δ_H (400 MHz, $CDCl_3$) 6.63 (1H, s, ^{Ar}C$\underline{H}$), 6.57 (1H, s, ^{Ar}C$\underline{H}$), 4.39 (2H, s, NC$\underline{H}_2$Ar), 3.87 (3H, s, OC$\underline{H}_3$), 3.85 (3H, s, OC$\underline{H}_3$), 3.56 (2H, t, *J*= 6.0, NC$\underline{H}_2$CH$_2$Ar), 2.90 (2H, t, *J*= 6.0, NCH$_2$C$\underline{H}_2$Ar), 2.84 (3H, s, SO$_2$C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 148.2 (^{Ar}COCH$_3$), 148.0 (^{Ar}COCH$_3$), 125.1 (^{Ar}C), 123.5

($^{Ar}\underline{C}$), 111.7 ($^{Ar}\underline{C}H$), 109.1 ($^{Ar}\underline{C}H$), 56.0 ($^{Ar}CO\underline{C}H_3$), 55.9 ($^{Ar}CO\underline{C}H_3$), 47.0 ($N\underline{C}H_2Ar$), 43.5 ($N\underline{C}H_2CH_2Ar$), 36.1 ($SO_2\underline{C}H_3$), 28.1 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI, NH_3) 313 ($MMeCNH^+$, 60%), 272 (MH^+, 100), 193 (29).

The spectroscopic data is in agreement with reported data.[297, 298]

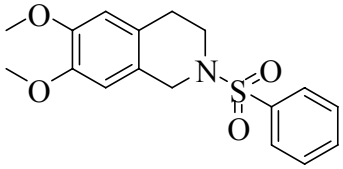
6,7-Dimethoxy-2-(propylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (280)



To a stirred solution of 6,7-dimethoxy-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **278** (0.5 g, 1.84 mmol), in THF (17 mL) under nitrogen at -78 ºC was added a solution of ^{s}BuLi (1.47 mL, 2.21 mmol) dropwise. The resulting solution was stirred for 2 h at -78 ºC. To the resulting dark red solution was added iodoethane (0.3 mL, 2.21 mmol) dropwise, after 5 minutes the dark red colour faded to pale orange, and the reaction mixture was warmed to r.t. and quenched with water (50 mL) and extracted with DCM (3 x 50 mL), the organic layer was dried over Na_2SO_4, filtered and evaporated to afford a colourless oil. The crude product was purified by flash silica chromatography, elution gradient 10 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 6,7-dimethoxy-2-propylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **280** (0.49 g, 89%) as a colourless oil; ν_{max} (thin film) /cm^{-1}; 2930 (w), 2842 (w), 1614 (m), 1513 (s), 1465 (w); δ_H (400 MHz, $CDCl_3$) 6.61 (1H, s, $^{Ar}C\underline{H}$), 6.55 (1H, s, $^{Ar}C\underline{H}$), 4.41 (2H, s, $NC\underline{H}_2Ar$), 3.85 (3H, s, $OC\underline{H}_3$), 3.84 (3H, s, $OC\underline{H}_3$), 3.57 (2H, t, *J*= 5.9, $NC\underline{H}_2CH_2Ar$), 2.96-2.91 (2H, m, $SO_2C\underline{H}_2$), 2.86 (2H, t, *J* = 5.9, $NCH_2C\underline{H}_2Ar$), 1.85 (2H, app sext, *J* = 7.5, $SO_2CH_2C\underline{H}_2$), 1.04 (3H, t, *J* = 7.5, $SO_2CH_2CH_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 148.3 ($^{Ar}\underline{C}OCH_3$), 148.2 ($^{Ar}\underline{C}OCH_3$), 125.3 ($^{Ar}\underline{C}$), 123.3 ($^{Ar}\underline{C}$), 111.5 ($^{Ar}\underline{C}H$), 109.4 ($^{Ar}\underline{C}H$), 55.9 ($^{Ar}CO\underline{C}H_3$), 55.8 ($^{Ar}CO\underline{C}H_3$), 47.9 ($N\underline{C}H_2Ar$), 43.8 ($N\underline{C}H_2CH_2Ar$), 37.6 ($SO_2\underline{C}H_2$), 28.5 ($NCH_2\underline{C}H_2Ar$), 13.5 ($SO_2CH_2\underline{C}H_2$), 12.6 ($SO_2CH_2CH_2\underline{C}H_3$); *m/z* (CI, NH_3) 363 ($MMeCNNa^+$, 60%), 300 (MH^+, 100), 193 (40).

The spectroscopic data is in agreement with reported data.[299, 300]

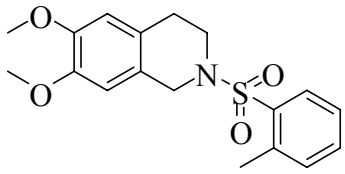
6,7-Dimethoxy-2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (282)[299]



To a stirred solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.5 g, 10.88 mmol) and triethylamine (4.55 mL, 32.65 mmol) in DCM (49 mL) at 0 ºC was added benzenesulfonyl chloride (1.528 mL, 11.97 mmol) dropwise. The resulting solution was stirred at 25 °C for 24 h. The reaction mixture was quenched with water (25 mL), and the layers separated, the aqueous layer was extracted with DCM (2 × 25 mL), the combined organic layer were dried over Na_2SO_4, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% MeOH in DCM. Pure fractions were evaporated to dryness to afford 6,7-dimethoxy-2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **282** (2.95 g, 81 %) as a white solid; mp 156-160 ºC; ν_{max} (thin film) /cm^{-1} 2980 (m), 2970 (m), 1607 (w), 1517 (s), 1463 (w), 1447 (m); δ_H (400 MHz, $CDCl_3$) 7.88-7.84 (2H, m, $PhSO_2C\underline{H}$), 7.61-7.53 (3H, m, $PhSO_2C\underline{H}$), 6.57 (1H, s, $^{Ar}C\underline{H}$), 6.53 (1H, s, $^{Ar}C\underline{H}$), 4.22 (2H, s, $NC\underline{H}_2Ar$), 3.84 (3H, s, $OC\underline{H}_3$), 3.83 (3H, s, $OC\underline{H}_3$), 3.38 (2H, t, J = 5.9, $NC\underline{H}_2CH_2Ar$), 2.85 (2H, t, J = 5.9, $NCH_2C\underline{H}_2Ar$); δ_C (100 MHz, $CDCl_3$) 148.0 ($^{Ar}\underline{C}OCH_3$), 147.8 ($^{Ar}\underline{C}OCH_3$), 136.7 ($PhSO_2\underline{C}$), 132.8 ($PhSO_2\underline{C}H$), 129.1 (2 × $PhSO_2\underline{C}H$), 127.7 (2 × $PhSO_2\underline{C}H$), 125.0 ($^{Ar}\underline{C}$), 123.4 ($^{Ar}\underline{C}$), 111.5 ($^{Ar}\underline{C}H$), 109.1 ($^{Ar}\underline{C}H$), 56.0 ($^{Ar}CO\underline{C}H_3$), 55.9 ($^{Ar}CO\underline{C}H_3$), 47.2 ($N\underline{C}H_2Ar$), 43.8 ($N\underline{C}H_2CH_2Ar$), 28.4 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI, NH_3) 397 (MMeCNNa$^+$, 15%), 334 (MH$^+$, 35), 193 (20), 192 (100).

The spectroscopic data is in agreement with reported data.[299, 300]

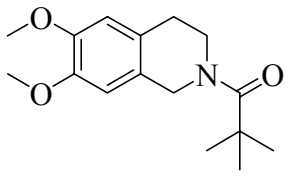
6,7-Dimethoxy-2-(*o*-tolylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (283)



To a stirred solution of 6,7-dimethoxy-2-(phenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **282** (0.613 g, 1.84 mmol), in THF (16.79 mL) at -78 ºC was added of ^{s}BuLi (1.47 mL, 2.21 mmol) dropwise. The resulting solution was stirred for 1 h at -78 ºC. To the resulting dark red solution was added iodomethane (0.138 mL, 2.21 mmol) dropwise, after 5 minutes the dark red colour faded to pale orange. The reaction was warmed to rt and quenched with water (50 mL) then extracted with DCM (3 x 50 mL), the organic layer was dried over Na_2SO_4, filtered and evaporated to afford a colourless oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% MeOH in DCM. Pure fractions were evaporated to dryness to afford 6,7-dimethoxy-2-(*o*-tolylsulfonyl)-1,2,3,4-tetrahydroisoquinoline **283** (0.58 g, 91%) as a colourless gum; ν_{max} (thin film) /cm^{-1} 2980 (m), 2971 (m), 1612 (w), 1517 (s), 1462 (m); δ_H (400 MHz, $CDCl_3$) 7.91 (1H, dd, J = 7.9

and 1.3, TolSO$_2$CH), 7.38 (1H, td, J = 7.5 and 1.3, TolSO$_2$CH), 7.27-7.21 (2H, m, TolSO$_2$CH), 6.50 (1H, s, ^{Ar}CH), 6.44 (1H, s, ^{Ar}CH), 4.24 (2H, s, NCH$_2$Ar), 3.76 (3H, s, OCH$_3$), 3.74 (3H, s, OCH$_3$), 3.43 (2H, t, J = 5.8, NCH$_2$CH$_2$Ar), 2.73 (2H, t, J = 5.8, NCH$_2$CH$_2$Ar), 2.55 (3H, s, TolSO$_2$CH$_3$); δ_C (100 MHz, $CDCl_3$) 147.0 (^{Ar}COCH$_3$), 146.8 (^{Ar}COCH$_3$), 137.1 (^{Ar}C), 135.5 (^{Ar}C), 131.8 (TolSO$_2$CH), 131.7 (TolSO$_2$CH), 129.1 (TolSO$_2$CH), 125.0 (TolSO$_2$CH), 124.2 (TolSO$_2$C), 122.7 (TolSO$_2$C), 110.6 (^{Ar}CH), 108.0 (^{Ar}CH), 55.0 (^{Ar}COCH$_3$), 54.9 (^{Ar}COCH$_3$), 45.2 (NCH$_2$Ar), 41.8 (NCH$_2$CH$_2$Ar), 27.4 (NCH$_2$CH$_2$Ar), 19.5 (TolSO$_2$CH$_3$); *m/z* (CI, NH_3) 370 (MNa^+, 20%), 348 (MH^+, 40), 193 (20), 192 (100).

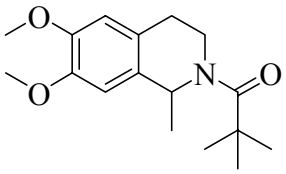
1-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropan-1-one (287)[206]



To a stirred solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.5 g, 10.88 mmol) and triethylamine (4.55 mL, 32.65 mmol) in DCM (50 mL) at 0 ºC was added pivaloyl chloride (1.640 g, 13.60 mmol) dropwise over a period of 5 minutes under nitrogen. The resulting solution was stirred at room temperature for 2 h. The reaction mixture was poured into water (50 mL), extracted with DCM (3 × 50 mL), the organic layer was dried over Na_2SO_4, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropan-1-one **230** (2.82 g, 93%) as a colourless gum; ν_{max} (thin film) /cm^{-1} 3014 (m), 2972 (m), 2954 (m), 2838 (w), 2161 (w), 1615 (s), 1517 (s), 1463 (m), 1449 (w); δ_H (400 MHz, $CDCl_3$) 6.63 (1H, s, ^{Ar}CH), 6.61 (1H, s, ^{Ar}CH), 4.68 (2H, s, NCH$_2$Ar), 3.87 (3H, s, OCH$_3$), 3.86 (3H, s, OCH$_3$), 3.84 (2H, t, J = 5.9, NCH$_2$CH$_2$Ar), 2.81 (2H, t, J = 5.9, NCH$_2$CH$_2$Ar), 1.33 (9H, s, C(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 176.7 (NC(O)C(CH$_3$)$_3$), 147.8 (^{Ar}COCH$_3$), 147.7 (^{Ar}COCH$_3$), 126.2 (^{Ar}C), 125.4 (^{Ar}C), 111.5 (^{Ar}CH), 109.2 (^{Ar}CH), 56.0 (^{Ar}COCH$_3$), 55.9 (^{Ar}COCH$_3$), 47.1 (NCH$_2$Ar), 43.5 (NCH$_2$CH$_2$Ar), 38.6 (C(CH$_3$)$_3$), 28.5 (NCH$_2$CH$_2$Ar), 28.4 (3 × C(CH$_3$)$_3$); *m/z* (CI, NH_3) 279 (10%), 278 (MH^+, 100), 191 (10).

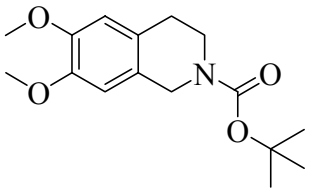
The spectroscopic data is in agreement with reported data.[206]

1-(6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropan-1-one (288)[206]



To a stirred solution of 1-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropan-1-one **287** (0.510 g, 1.84 mmol), in THF (16.79 mL) at -78 ºC was added a solution of ^{t}BuLi (1.47 mL, 2.21 mmol, 1.5 M) in THF dropwise. The resulting solution was stirred for 30 minutes at -78 ºC. Iodomethane (0.138 mL, 2.21 mmol) was added and the resulting solution warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with water (50 mL), extracted with DCM (3 x 50 mL), the organic layer was dried over Na_2SO_4, filtered and evaporated to afford a colourless oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% MeOH in DCM. Pure fractions were evaporated to dryness to afford 1-(6,7-dimethoxy-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropan-1-one **288** (0.32 g, 62%) as a colourless oil, as a mixture of rotamers; δ_H (400 MHz, $CDCl_3$) 6.58 (1H, s, ^{Ar}CH), 6.57 (1H, s, ^{Ar}CH), 5.48 (1H, bs, NC$\underline{H}^{Ar}$), 4.35 (1H, bs, NC$\underline{H}_2$), 3.85 (3H, s, OC$\underline{H}_3$), 3.84 (3H, s, OC$\underline{H}_3$), 3.33 (1H, bs, NC$\underline{H}_2$), 2.92 (1H, ddd, J = 16.0, 12.3 and 5.5, ArC$\underline{H}_2$CH$_2$N), 2.63 (1H, app d, J = 16.0, ArCH$_2$C$\underline{H}_2$N), 1.45 (3H, d, J = 6.6, CHC$\underline{H}_3$), 1.31 (9H, s, C(C$\underline{H}_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 175.6 (N$\underline{C}$(O)C(CH$_3$)$_3$), 147.3 ($^{Ar}\underline{C}$OCH$_3$), 147.2 ($^{Ar}\underline{C}$OCH$_3$), 126.9 ($^{Ar}\underline{C}$), 124.9 ($^{Ar}\underline{C}$), 110.9 ($^{Ar}\underline{C}$H), 109.5 ($^{Ar}\underline{C}$H), 55.9 (^{Ar}CO$\underline{C}$H$_3$), 55.7 (^{Ar}CO$\underline{C}$H$_3$), 49.4 (N$\underline{C}$HAr), 41.0 (N$\underline{C}$H$_2$CH$_2$Ar), 38.4 ($\underline{C}$(CH$_3$)$_3$), 28.4 (NCH$_2\underline{C}$H$_2$Ar), 27.2 (3 × C($\underline{C}$H$_3$)$_3$), 21.0 (CH$\underline{C}$H$_3$); *m/z* (CI, NH_3) 333 (MMeCNH$^+$, 20%), 293 (20), 292 (MH$^+$, 100), 205 (10).
The spectroscopic data is in agreement with reported data.[206]

***tert*-Butyl 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (289)**[301]

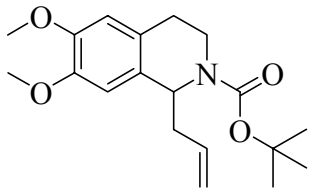


To a stirred solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.5 g, 10.88 mmol) and triethylamine (4.55 mL, 32.65 mmol) in DCM (50 mL) at 0 ºC was added di-*tert*-butyl dicarbonate (3.56 g, 16.33 mmol) portion-wise. The resulting solution was stirred at room temperature for 6 h. The reaction mixture was poured into water (50 mL), extracted with DCM (3 × 50 mL), the combined organic layers were washed with 1 M aq.

NaOH (2 × 50 mL), water (50 mL) and dried over Na_2SO_4, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 20% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford *tert*-butyl 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate **289** (2.55 g, 80%) as a colourless oil, which on standing crystallised to afford a white solid; mp 36-38 ºC; ν_{max} (thin film) /cm^{-1} 3003 (w), 2971 (w), 2929 (w), 2838 (w), 2159 (w), 1701 (s), 1608 (w), 1519 (m); δ_H (400 MHz, $CDCl_3$) 6.63 (1H, s, $^{Ar}C\underline{H}$), 6.60 (1H, s, $^{Ar}C\underline{H}$), 4.51 (2H, s, $NC\underline{H}_2Ar$), 3.88 (3H, s, $OC\underline{H}_3$), 3.87 (3H, s, $OC\underline{H}_3$), 3.64 (2H, t, J = 5.8, $NC\underline{H}_2CH_2Ar$), 2.77 (2H, t, J = 5.8, $NCH_2C\underline{H}_2Ar$), 1.51 (9H, s, $OC(C\underline{H}_3)_3$); δ_C (100 MHz, $CDCl_3$) 154.8 ($N\underline{C}(O)OC(CH_3)_3$), 147.7 ($^{Ar}\underline{C}OCH_3$), 147.5 ($^{Ar}\underline{C}OCH_3$), 127.5 ($^{Ar}\underline{C}$), 125.5 ($^{Ar}\underline{C}$), 111.4 ($^{Ar}\underline{C}H$), 109.4 ($^{Ar}\underline{C}H$), 79.8 ($O\underline{C}(CH_3)_3$), 59.9 ($^{Ar}O\underline{C}H_3$), 59.8 ($^{Ar}O\underline{C}H_3$), 47.6 ($N\underline{C}H_2Ar$), 40.9 ($N\underline{C}H_2CH_2Ar$), 28.4 (3 × $C(C\underline{H}_3)_3$), 28.3 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI) 316 (MNa^+, 45%), 294 (MH^+, 10), 238 (M-$OC(CH_3)_3$+NH_4, 100), 192 (15). HRMS $C_{16}H_{23}NNaO_4$ (MNa^+) requires 316.1519, found 316.1529.

The spectroscopic data is in agreement with reported data.[301]

tert-Butyl 1-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (291)[154]

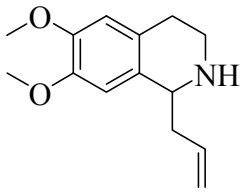


To a stirred solution of *tert*-butyl 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate **289** (12.5 g, 42.61 mmol), in tetrahydrofuran (300 mL) and diethyl ether (100 mL) at -78 ºC, under nitrogen was slowly added a solution of ^tBuLi (31.2 mL, 46.87 mmol, 1.5 M) in hexane. The resulting solution was stirred at -78 ºC, for 1 h during which time the solution turned a dark red. Allyl bromide (4.42 mL, 51.13 mmol) was added dropwise at -78 ºC, and the resulting solution was stirred at -78 ºC for 1 h during which time the solution turned to a light orange colour, after which the solution was allowed to warm to room temperature. The reaction mixture was poured into water (200 mL), and extracted with EtOAc (3 × 250 mL), the combined organic layer was dried over $MgSO_4$, filtered and evaporated to afford a yellow oil, which was used without further purification. Room temperature NMR in $CDCl_3$ show duplication of signals cased by the presence of rotomers, variable temperature NMR showed these peaks to coalesce. δ_H (400 MHz, DMSO, 100 ºC) 6.78 (1H, s, $^{Ar}C\underline{H}$), 6.71 (1H, s, $^{Ar}C\underline{H}$), 5.90-5.79 (1H, m, $C\underline{H}=CH_2$), 5.10-5.00 (2H, m, $CH=C\underline{H}_2$), 4.00-3.90 (1H, m, $NC\underline{H}$), 3.75 (6H, s, 2 × $OC\underline{H}_3$), 3.25-3.00 (3H, m, $NCH_2C\underline{H}_2Ar$ and $NC\underline{H}_2CH_2Ar$), 2.75-2.65 (1H, m, $NCH_2C\underline{H}_2Ar$), 2.60-2.40 (2H, m

$C\underline{H}_2CH=CH_2$), 1.40 (9H, s, $OC(C\underline{H}_3)_3$); δ_C (100 MHz, DMSO, 100 ºC) 156.0 ($N\underline{C}(O)OC(CH_3)$), 150.0 ($^{Ar}\underline{C}OCH_3$), 149.7 ($^{Ar}\underline{C}OCH_3$), 137.5 ($CH_2\underline{C}H=CH_2$), 131.4 ($^{Ar}\underline{C}$), 128.4 ($^{Ar}\underline{C}$), 118.5 ($CH_2CH=\underline{C}H_2$), 115.1 ($^{Ar}\underline{C}H$), 113.8 ($^{Ar}\underline{C}H$), 80.8 ($O\underline{C}(CH_3)_3$), 58.2 ($^{Ar}O\underline{C}H_3$), 58.0 ($^{Ar}O\underline{C}H_3$), 55.4 ($N\underline{C}H$), 41.9 ($N\underline{C}H_2CH_2Ar$), 38.5 ($\underline{C}H_2CH=CH_2$), 30.1 ($OC(\underline{C}H_3)_3$), 29.5 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI, NH_3) 277 (MH^+-^{t}Bu, 20%), 236 (100), 233 (M-Boc$^+$, 40).

The spectroscopic data is in agreement with reported data.[154]

1-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (292) [154]

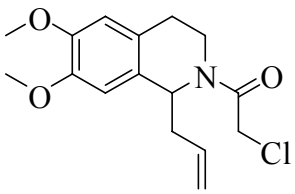


Method A: To a solution of *tert*-butyl 1-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate **291** (17 g, 50.99 mmol) in THF (20 mL) at room temperature was added a solution of hydrochloric acid (102 mL, 407.89 mmol, 4 M in dioxane) the resulting solution was stirred at room temperature for 24 h. The resulting solution was concentrated *in vacuo* to yield the hydrochloride salt as a brown solid, (7.9 g, 80%); δ_H (400 MHz, $CDCl_3$) 6.63 (1H, s, $^{Ar}C\underline{H}$), 6.60 (1H, s, $^{Ar}C\underline{H}$), 6.00-5.90 (1H, m, $C\underline{H}=CH_2$), 5.34 (1H, dd, *J* = 17.0 and 1.3, $CH=C\underline{H}_2$), 5.28 (1H, d, *J* = 10.1, $CH=C\underline{H}_2$), 4.52 (1H, app t, *J* = 5.0, $NC\underline{H}$), 3.86 (3H, s, $OC\underline{H}_3$), 3.83 (3H, s, $OC\underline{H}_3$), 3.69-3.59 (1H, m, $NC\underline{H}_2CH_2Ar$), 3.40-3.32 (1H, m, $NC\underline{H}_2CH_2Ar$), 3.20-3.05 (2H, m, $NCH_2C\underline{H}_2Ar$), 3.00-2.90 (2H, m, $C\underline{H}_2CH=CH_2$), 1.60 (2H, br s, $N\underline{H}_2$); δ_C (100 MHz, $CDCl_3$) 148.9 ($^{Ar}\underline{C}OCH_3$), 148.2 ($^{Ar}\underline{C}OCH_3$), 132.0 ($\underline{C}H=CH_2$), 124.1 ($^{Ar}\underline{C}$), 123.0 ($^{Ar}\underline{C}$), 120.9 ($CH=\underline{C}H_2$), 111.5 ($^{Ar}\underline{C}H$), 109.4 ($^{Ar}\underline{C}H$), 67.1 ($N\underline{C}H$), 56.1 ($O\underline{C}H_3$), 55.9 ($O\underline{C}H_3$), 54.2 ($N\underline{C}H_2CH_2Ar$), 38.8 ($\underline{C}H_2CH=CH_2$), 25.2 ($NCH_2\underline{C}H_2Ar$); The hydrochloride salt was deprotonated using 2 M aq. NaOH solution (200 mL), followed by extraction with DCM (2 x 200 mL). The organic layer was washed with water (200 mL) and dried over $MgSO_4$, and concentrated *in vacuo* to yield 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **292** as a pale yellow oil.

Method B: To a solution of *tert*-butyl 1-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate **291** (4.7 g, 14 mmol) in DCM (20 mL) at room temperature was added trifluoroacetic acid (7.3 mL, 98 mmol) and the resulting solution was stirred at room temperature for 12 h. The resulting solution was concentrated *in vacuo* and the resulting brown oil was taken up in a fresh portion of DCM (100 mL) and stirred with 2 M aq NaOH solution (100 mL) for 15 minutes. The organic layer was separated and the aqueous layer

was extracted with DCM (2 × 50 mL), and the combined organic layers were washed with water (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **292** as a pale yellow oil; ν_{max} (thin film) /cm^{-1} 3332 (bs), 3072 (w), 1637 (m) 1612 (m); δ_H (400 MHz, $CDCl_3$) 6.66 (1H, s, $^{Ar}C\underline{H}$), 6.57 (1H, s, $^{Ar}C\underline{H}$), 5.90-5.80 (1H, m, $C\underline{H}=CH_2$), 5.20-5.13 (2H, m, $CH=C\underline{H_2}$), 3.99 (1H, app dd, *J* = 8.8 and 3.5, $NC\underline{H}$), 3.84 (3H, s, $OC\underline{H_3}$), 3.83 (3H, s, $OC\underline{H_3}$), 3.21 (1H, dt, *J* = 12.3 and 5.3, $NC\underline{H_2}CH_2Ar$), 2.95 (1H, ddd, *J*=12.3, 7.7 and 5.0, $NC\underline{H_2}CH_2Ar$), 2.75-2.60 (2H, m, $NCH_2C\underline{H_2}Ar$ and $CH_2=CHC\underline{H_2}$), 2.52-2.46 (2H, m, $NCH_2C\underline{H_2}Ar$ and $CH_2=CHC\underline{H_2}$), 2.25 (1H, br s, $N\underline{H}$); δ_C (100 MHz, $CDCl_3$) 147.4 ($^{Ar}\underline{C}OCH_3$), 147.2 ($^{Ar}\underline{C}OCH_3$), 135.5 ($\underline{C}H=CH_2$), 129.5 ($^{Ar}\underline{C}$), 127.4 ($^{Ar}\underline{C}$), 117.9 ($CH=\underline{C}H_2$), 112.0 ($^{Ar}\underline{C}H$), 109.0 ($^{Ar}\underline{C}H$), 55.9 ($O\underline{C}H_3$), 55.5 ($O\underline{C}H_3$), 54.7 ($N\underline{C}H$), 42.5 ($N\underline{C}H_2CH_2Ar$), 41.0 ($\underline{C}H_2CH=CH_2$), 29.4 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI, NH_3) 256 (MNa^+, 10%), 234 (MH^+, 100), 205 (35), 189 (10).
The spectroscopic data is in agreement with reported data.[154]

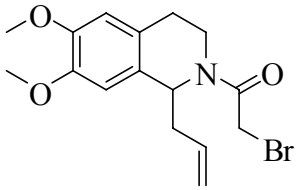
1-(1-Allyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-chloroethanone (295)



To a stirred solution of 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **292** (4.8 g, 21.0 mmol) and triethylamine (7.8 mL, 62.0 mmol) in DCM (100 mL) at 0 ºC was added chloroacetyl chloride (2.0 mL, 25.2 mmol) dropwise. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into water (100 mL), extracted with DCM (2 × 100 mL), the combined organic layer was washed with 1 M aq. NaOH (100 mL), water (100 mL) and dried over Na_2SO_4, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 4:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound **295** as a colourless gum, (4.0 g, 62%); Rf = 0.35 (2:1 petrol:EtOAc); ν_{max} (thin film) /cm^{-1} 2955 (w), 1640 (s), 1453 (m), 1340 (m); Room temperature NMR in $CDCl_3$ show duplication and overlapping of signals cased by the presence of rotomers, variable temperature NMR showed incompleate coalescence of the peaks at 100 ºC in DMSO. δ_H (400 MHz, $CDCl_3$, mixture of rotamers) 6.63 (1H, bs, $^{Ar}C\underline{H}$), 6.59 (1H, bs, $^{Ar}C\underline{H}$), 5.92-5.80 (1H, m, $C\underline{H}=CH_2$), 5.00-4.86 (2H, m, $CH=C\underline{H_2}$), 4.79-4.60 (1H, m, $NC\underline{H}$), 4.20-4.10 (2H, m, $C(O)C\underline{H_2}Cl$), 3.92-3.82 (1H, m, $NCH_2C\underline{H_2}Ar$), 3.85 (3H, bs, $OC\underline{H_3}$), 3.83 (3H, bs, $OC\underline{H_3}$), 3.62-3.56 (1H, m, $NC\underline{H_2}CH_2Ar$), 3.00-2.50 (4H, m, $NCH_2C\underline{H_2}Ar$, $NC\underline{H_2}CH_2Ar$, $CHC\underline{H_2}CH=CH_2$); δ_C (100 MHz, $CDCl_3$, mixture of rotamers)

165.3 (N<u>C</u>(O)CH_2), 165.2 (N<u>C</u>(O)CH_2Cl), 147.9 (^{Ar}<u>C</u>OCH_3), 147.8 (^{Ar}<u>C</u>OCH_3), 147.5 (^{Ar}<u>C</u>OCH_3), 147.4 (^{Ar}<u>C</u>OCH_3), 134.3 (<u>C</u>H=CH_2), 133.5 (<u>C</u>H=CH_2), 128.1 (^{Ar}<u>C</u>), 127.5 (^{Ar}<u>C</u>), 125.8 (^{Ar}<u>C</u>), 124.8 (^{Ar}<u>C</u>), 119.3 (CH=<u>C</u>H_2), 117.5 (CH=<u>C</u>H_2), 111.7 (^{Ar}<u>C</u>H), 111.0 (^{Ar}<u>C</u>H), 109.9 (^{Ar}<u>C</u>H), 109.4 (^{Ar}<u>C</u>H), 56.7 (N<u>C</u>H), 55.9 (2 × O<u>C</u>H_3), 55.8 (O<u>C</u>H_3), 55.7 (O<u>C</u>H_3), 51.9 (N<u>C</u>H), 41.5 (NC(O)<u>C</u>H_2Br), 41.4 (CH_2), 41.3 (CH_2), 40.9 (CH_2), 40.4 (NC(O)<u>C</u>H_2Cl), 36.9 (CH_2), 28.6 (NCH_2<u>C</u>H_2Ar), 27.3 (NCH_2<u>C</u>H_2Ar); *m/z* (CI, NH_3) 312 (M$Cl^{37}H^+$, 35%), 311 (20), 310 (M$Cl^{35}H^+$, 100).

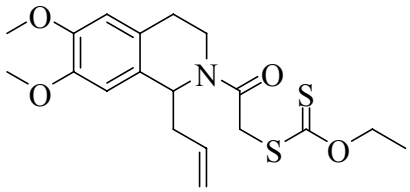
1-(1-Allyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-bromoethanone (296)



To a stirred solution of 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **292** (1.6 g, 7.0 mmol) and triethylamine (2.70 mL, 21.0 mmol) in DCM (50 mL) at 0 ºC was added bromoacetyl bromide (0.92 mL, 10.5 mmol) dropwise. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into water (50 mL), extracted with DCM (2 × 50 mL), the combined organic layer was washed with 1 M aq. NaOH (50 mL), water (50 mL) and dried over Na_2SO_4, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 4:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound **296** as a colourless gum (1.34 g, 55%); Rf = 0.40 (2:1 petrol:EtOAc); ν_{max} (thin film) /cm^{-1} 2944 (w), 1644 (s), 1513 (m), 1360 (m); Room temperature NMR in $CDCl_3$ show duplication and overlapping of signals cased by the presence of rotomers, variable temperature NMR showed incompleate coalescence of the peaks at 100 ºC in DMSO. δ_H (400 MHz, $CDCl_3$, mixture of rotamers) 6.55 (1H, bs, ^{Ar}C<u>H</u>), 6.52 (1H, bs, ^{Ar}C<u>H</u>), 5.80-5.70 (1H, m, C<u>H</u>=CH_2), 5.05-4.90 (2H, m, CH=C<u>H</u>$_2$), 4.75-4.55 (1H, m, NC<u>H</u>), 3.90-3.70 (3H, m, NCH_2C<u>H</u>$_2$Ar, C(O)C<u>H</u>$_2$Br), 3.78 (3H, bs, OC<u>H</u>$_3$), 3.76 (3H, bs, OC<u>H</u>$_3$), 3.58-3.50 (1H, m, NC<u>H</u>$_2$$CH_2$Ar), 3.01-2.48 (4H, m, N$CH_2$C<u>H</u>$_2$Ar, NC<u>H</u>$_2$$CH_2$Ar, CHC<u>H</u>$_2$CH=$CH_2$); δ_C (100 MHz, $CDCl_3$, mixture of rotamers) 165.5 (N<u>C</u>(O)CH_2), 165.4 (N<u>C</u>(O)CH_3), 147.8 (^{Ar}<u>C</u>OCH_3), 147.7 (^{Ar}<u>C</u>OCH_3), 147.6 (^{Ar}<u>C</u>OCH_3), 147.5 (^{Ar}<u>C</u>OCH_3), 134.3 (<u>C</u>H=CH_2), 133.9 (<u>C</u>H=CH_2), 128.1 (^{Ar}<u>C</u>), 127.6 (^{Ar}<u>C</u>), 125.9 (^{Ar}<u>C</u>), 124.9 (^{Ar}<u>C</u>), 119.1 (CH=<u>C</u>H_2), 117.6 (CH=<u>C</u>H_2), 111.5 (^{Ar}<u>C</u>H), 111.0 (^{Ar}<u>C</u>H), 109.9 (^{Ar}<u>C</u>H), 109.4 (^{Ar}<u>C</u>H), 57.5 (N<u>C</u>H), 56.0 (O<u>C</u>H_3), 55.9 (O<u>C</u>H_3), 55.8 (O<u>C</u>H_3), 55.7 (O<u>C</u>H_3), 51.8 (N<u>C</u>H), 41.0 (CH_2), 40.9 (<u>C</u>H_2), 40.6 (<u>C</u>H_2), 34.9 (<u>C</u>H_2), 28.6 (NCH_2<u>C</u>H_2Ar), 28.5 (NCH_2<u>C</u>H_2Ar), 26.6 (NC(O)<u>C</u>H_2Br), 26.3 (NC(O)<u>C</u>H_2Br); *m/z* (CI, NH_3) 378 (M$Br^{81}Na^+$, 50%), 376

($MBr^{79}Na^+$, 50), 357 (18), 356 ($MBr^{81}H^+$, 98), 355 (18), 354 ($MBr^{79}H^+$, 100); HRMS $C_{16}H_{21}BrNO_3$ ($MBr^{79}H^+$) requires 354.0699, found 354.0705.

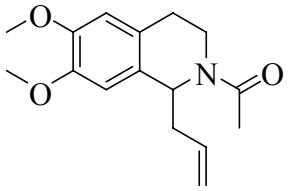
1-[6,7-Dimethoxy-1-(prop-2-en-1-yl)-1,2,3,4-tetrahydroisoquinolin-2-yl]-2-[(ethoxymethanethioyl)sulfanyl]ethan-1-one (294)



To a stirred solution of 1-(1-allyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2-chloroethanone **295** (2.3 g, 7.5 mmol) in MeCN (20 mL) at room temperature was added potassium *O*-ethyl xanthate (1.3 g, 8.25 mmol). The resulting solution was stirred at room temperature for 3 h, during which time a precipitate formed. The reaction mixture was poured into water (50 mL), and extracted with EtOAc (2 × 50 mL), the combined organic layer was washed with 1 M aq. NaOH (50 mL), water (2 × 50 mL), brine (50 mL), and dried over $MgSO_4$, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 9:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound **294** as a colourless gum, (2.6 g, 84%); Rf = 0.55 (1:1 petrol:EtOAc); ν_{max} (thin film) /cm^{-1} 2935 (s), 2834 (w), 1643 (s), 1517 (s), 1443 (s), 1360 (m), 1244 (s), 1224 (s); Room temperature NMR in $CDCl_3$ show duplication and overlapping of signals caused by the presence of rotamers, variable temperature NMR showed incomplete coalescence of the peaks at 90 ºC in DMSO. δ_H (400 MHz, $CDCl_3$, mixture of rotamers) 6.52 (1H, bs, ^{Ar}CH), 6.51 (1H, bs, ^{Ar}CH), 5.85-5.64 (1H, m, $CH{=}CH_2$), 5.44 and 4.84 (1H, t, *J* = 6.5, NCH), 5.10-4.88 (2H, m, $CH{=}CH_2$), 4.52 (2H, q, *J* = 6.5, OCH_2CH_3), 4.06 and 4.04 (2H, s, $C(O)CH_2S$), 3.84-3.76 (1H, m, NCH_2CH_2Ar), 3.72 (3H, bs, 2 × OCH_3), 3.54-3.46 (1H, m, NCH_2CH_2Ar), 3.06-2.38 (4H, m, NCH_2CH_2Ar, NCH_2CH_2Ar and $CHCH_2CH{=}CH_2$); δ_C (100 MHz, $CDCl_3$, major rotamer) 213.6 (SC(S)OEt), 165.1 ($NC(O)CH_2$), 147.8 ($^{Ar}COCH_3$), 147.6 ($^{Ar}COCH_3$), 134.7 ($CH{=}CH_2$), 128.5 (^{Ar}C), 125.2 (^{Ar}C), 117.4 ($CH{=}CH_2$), 111.3 (^{Ar}CH), 110.2 (^{Ar}CH), 70.4 (OCH_2CH_3), 56.0 (OCH_3), 55.9 (OCH_3), 52.4 (NCH), 41.4 (CH_2), 40.6 ($NC(O)CH_2S$), 39.8 (CH_2), 28.7 (NCH_2CH_2Ar), 13.7 (OCH_2CH_3); δ_C (100 MHz, $CDCl_3$, minor rotamer) 213.9 (SC(S)OEt), 165.3 ($NC(O)CH_2$), 148.1 ($^{Ar}COCH_3$), 147.5 ($^{Ar}COCH_3$), 133.8 ($CH{=}CH_2$), 127.8 (^{Ar}C), 126.1 (^{Ar}C), 119.2 ($CH{=}CH_2$), 111.6 (^{Ar}CH), 109.8 (^{Ar}CH), 70.3 (OCH_2CH_3), 56.7 (OCH_3), 56.1 (OCH_3), 52.4 (NCH), 41.0 (CH_2), 40.1 ($NC(O)CH_2S$), 39.9 (CH_2), 27.6 (NCH_2CH_2Ar), 14.2 (OCH_2CH_3); *m/z* (ESI) 459

($M^{32}S_2NaMeCN^+$, 22%), 459 ($M^{32}S_2Na^+$, 25), 398 (10), 397 (20), 396 ($M^{32}S_2H^+$, 100%); HRMS $C_{19}H_{26}{}^{32}S_2NO_3$ ($M^{32}S_2H^+$) requires 396.1298, found 396.1299.

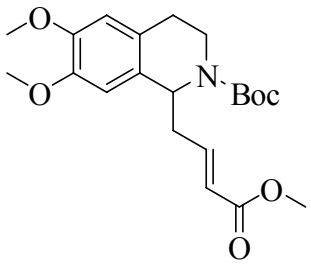
1-(1-Allyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (299)



A solution of **294**, **295** or **296** (1.0-2.5 mmol, 1 equiv.) in THF (50-150 mL) was stirred at reflux for 30 minutes under nitrogen. Then AIBN (0.05-0.12 mmol, 0.05 equiv.) was added, followed by the slow addition of a solution of tributyltin hydride (1.2-3.0 mmol, 1.2 equiv.) and AIBN (0.5-1.25 mmol) in THF (20 mL) by a syringe pump over a period of 1-4 h. Following the completion of the addition of the tributyltin hydride, the solution was maintained at reflux for a further 2 h, after which the solution was cooled to r.t. The reaction mixture was contracted *in vacuo*, until approx 10 ml of solvent was left and this was then stirred with KF/silica for 10 min. The resulting slurry was loaded on to a short KF/silica column, and flushed with petrol then EtOAc, the EtOAc fraction was concentrated *in vacuo* to afford a yellow gum. The gum was purified by flash silica chromatography, elution gradient 5:1 petrol:EtOAc to EtOAc, the pure fractions were concentrated *in vacuo* to afford the title compound as a colourless oil (25-49%); Rf = 0.35 (2:1 petrol:EtOAc); ν_{max} (thin film) /cm^{-1} 2953 (w), 1639 (s), 1516 (m), 1435 (m), 1359 (m); Room temperature NMR in $CDCl_3$ show duplication and overlapping of signals cased by the presence of rotomers, variable temperature NMR showed incompleate coalescence of the peaks at 100 ºC in DMSO. δ_H (400 MHz, $CDCl_3$, mixture of rotamers) 6.59 (1H, bs, $^{Ar}C\underline{H}$), 6.55 (1H, bs, $^{Ar}C\underline{H}$), 5.90-5.78 (1H, m, $C\underline{H}=CH_2$), 5.09-4.95 (2H, m, $C\underline{H}=CH_2$), 4.75-4.65 (1H, m, $NC\underline{H}$), 3.81 (3H, bs, $OC\underline{H_3}$), 3.78 (3H, bs, $OC\underline{H_3}$), 3.77-3.70 (1H, m, $NCH_2C\underline{H_2}Ar$), 3.53-3.48 (1H, m, $NC\underline{H_2}CH_2Ar$), 3.01-2.48 (4H, m, $NCH_2C\underline{H_2}Ar$, $NC\underline{H_2}CH_2Ar$, $CHC\underline{H_2}CH=CH_2$), 2.16 (3H, bs, $NC(O)C\underline{H_3}$); δ_C (100 MHz, $CDCl_3$, mixture of rotamers) 169.2 ($N\underline{C}(O)CH_3$), 169.1 ($N\underline{C}(O)CH_3$), 147.6 ($^{Ar}\underline{C}OCH_3$), 147.5 ($^{Ar}\underline{C}OCH_3$), 147.4 ($^{Ar}\underline{C}OCH_3$), 147.3 ($^{Ar}\underline{C}OCH_3$), 134.9 ($\underline{C}H=CH_2$), 133.8 ($\underline{C}H=CH_2$), 128.9 ($^{Ar}\underline{C}$), 128.1 ($^{Ar}\underline{C}$), 126.4 ($^{Ar}\underline{C}$), 125.1 ($^{Ar}\underline{C}$), 118.6 ($CH=\underline{C}H_2$), 117.0 ($CH=\underline{C}H_2$), 111.5 ($^{Ar}\underline{C}H$), 111.0 ($^{Ar}\underline{C}H$), 110.0 ($^{Ar}\underline{C}H$), 109.5 ($^{Ar}\underline{C}H$), 57.5 ($N\underline{C}H$), 55.9 ($O\underline{C}H_3$), 55.7 ($O\underline{C}H_3$), 51.2 ($N\underline{C}H$), 41.3 ($\underline{C}H_2$), 40.9 ($\underline{C}H_2$), 40.5 ($\underline{C}H_2$), 34.8 ($\underline{C}H_2$), 28.5 ($NCH_2\underline{C}H_2Ar$), 27.6 ($NCH_2\underline{C}H_2Ar$), 21.9 ($NC(O)\underline{C}H_3$), 21.7 ($NC(O)\underline{C}H_3$); *m/z* (CI) 277 (15%), 276 (MH^+, 100), 232 (30).

The spectroscopic data is in agreement with reported data.[302]

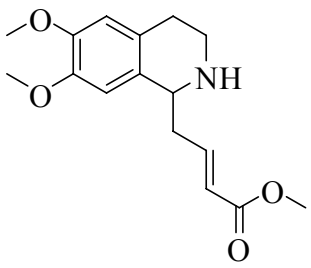
***tert*-Butyl 6,7-dimethoxy-1-[(E)-4-methoxy-4-oxobut-2-en-1-yl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (300)**



To a stirred solution of *tert*-butyl 1-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate **291** (1.1 g, 3.34 mmol) in dioxane:water (8 mL:4 mL) was added a crystal of osmium tetaoxide, followed by the slow portionwise addition of sodium metaperiodate (1.6 g, 7.3 mmol) over 20 minutes. The resulting reaction mixture was stirred for 2 h, after which brine (30 mL) was added and the mixture was extracted with ethyl acetate (3 × 25 mL). The organic layer was dried over $NaSO_4$ and concentrated to afford a light brown oil.

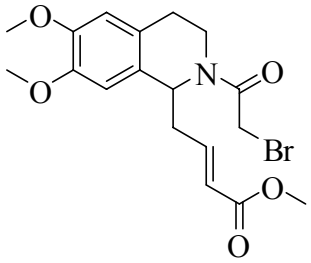
To a stirred solution of the crude aldehyde in DCM (10 mL) was added methoxycarbonylmethylene triphenylphosphorane (1.7 g, 5.0 mmol) and the reaction mixture was stirred for 4 h. The reaction mixture was then concentrated *in vacuo*, then diluted with Et_2O (75 mL), the resulting white precipitate is filtered, and the organic solution washed with water (50 mL), brine (50 mL) and then dried over $MgSO_4$ and concentrated *in vacuo* to afford an brown oil. The resulting oil was purified by flash silica chromatography, elution gradient 5:1 petrol:EtOAc to neat EtOAc. Pure fractions were evaporated to dryness to afford the title compound **300** as a pale yellow oil (0.82 g, 62%), Rf = 0.55 (EtOAc); ν_{max} (thin film) /cm^{-1} 3066 (w), 2905 (w), 1715 (s), 1690 (s), 1630 (m); δ_H (400 MHz, $CDCl_3$) 7.02-6.88 (1H, m, C<u>H</u>=CHCO$_2$CH$_3$), 6.53 (1H, s, ^{Ar}C<u>H</u>), 6.50 (1H, s, ^{Ar}C<u>H</u>), 5.82-5.70 (1H, m, CH=C<u>H</u>CO$_2$CH$_3$), 5.26-5.00 (1H, m, NC<u>H</u>), 4.20-3.92 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 3.78 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.75 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.64 (3H, s, CO$_2$C<u>H</u>$_3$), 3.23-3.01 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 2.84-2.55 (4H, m, NCH$_2$C<u>H</u>$_2$Ar and CHC<u>H</u>$_2$CH); δ_C (100 MHz, $CDCl_3$, major rotamer only) 166.4 (<u>C</u>O$_2$CH$_3$), 154.2 (N<u>C</u>(O)O), 147.4 (^{Ar}<u>C</u>OCH$_3$), 147.3 (^{Ar}<u>C</u>OCH$_3$), 145.5 (<u>C</u>H=CHCO$_2$CH$_3$), 127.9 (^{Ar}<u>C</u>), 126.5 (^{Ar}<u>C</u>), 122.9 (CH=<u>C</u>HCO$_2$CH$_3$), 111.4 (^{Ar}<u>C</u>H), 109.5 (^{Ar}<u>C</u>H), 79.8 (O<u>C</u>(CH$_3$)$_3$), 55.9 (^{Ar}O<u>C</u>H$_3$), 55.8 (^{Ar}O<u>C</u>H$_3$), 53.6 (N<u>C</u>H), 51.3 (CO$_2$<u>C</u>H$_3$), 39.7 (N<u>C</u>H$_2$CH$_2$Ar), 36.6 (<u>C</u>H$_2$CH=CH), 28.3 (3 × OC(<u>C</u>H$_3$)$_3$), 28.2 (NCH$_2$<u>C</u>H$_2$Ar); *m/z* (CI) 393 (10%), 392 (MH^+, 50), 291 (15), 290 (100); HRMS $C_{21}H_{30}NO_6$ (MH^+) requires 392.2067, found 392.2071.

Methyl (*E*)-4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate (301)



To a stirred solution of *tert*-Butyl 6,7-dimethoxy-1-[(E)-4-methoxy-4-oxobut-2-en-1-yl]-1,2,3,4-tetrahydroisoquinoline-2-carboxylate **300** (783 mg, 2 mmol) in DCM (10 mL) at room temperature was added dropwise trifluoroacetic acid (1.9 mL, 25 mmol). Following complete addition the solution was stirred for 12 h at room temperature. The resulting solution was concentrated *in vacuo* and the resulting brown solid was taken up in a fresh portion of DCM (50 mL) and stirred with 2 M aq. NaOH solution (50 mL) for 15 minutes. The organic layer was separated and the aqueous layer was extracted with DCM (2 × 50 mL), and the combined organic layers were washed with water (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown oil. The resulting oil was purified by flash silica chromatography, elution gradient DCM to 10:1 DCM:MeOH. Pure fractions were evaporated to dryness to afford the title compound **301** as a pale yellow oil (0.217 g, 37%), Rf = 0.26 (15:1 DCM:MeOH); ν_{max} (thin film) /cm^{-1} 3340 (bs), 3075 (w), 1712 (s), 1633 (m), 1612 (m); δ_H (400 MHz, $CDCl_3$) 6.92 (1H, dt, *J* = 15.7 and 7.7 C<u>H</u>=CHCO$_2$CH$_3$), 6.52 (1H, s, ^{Ar}C<u>H</u>), 6.51 (1H, s, ^{Ar}C<u>H</u>), 5.85 (1H, dt, *J* = 15.7 and 1.2, CH=C<u>H</u>CO$_2$CH$_3$), 4.10-4.00 (1H, m, NC<u>H</u>), 3.79 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.78 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.66 (3H, s, CO$_2$C<u>H</u>$_3$), 3.18-3.04 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 2.95-2.85 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 2.75-2.50 (4H, m, NCH$_2$C<u>H</u>$_2$Ar and C<u>H</u>$_2$CH=CHCO$_2$CH$_3$), 1.74 (1H, bs, N<u>H</u>); δ_C (100 MHz, $CDCl_3$) 166.2 (<u>C</u>O$_2$CH$_3$), 148.0 (^{Ar}<u>C</u>OCH$_3$), 147.7 (^{Ar}<u>C</u>OCH$_3$), 146.3 (<u>C</u>H=CHCO$_2$CH$_3$), 129.5 (^{Ar}<u>C</u>), 127.5 (^{Ar}<u>C</u>), 123.5 (CH=<u>C</u>HCO$_2$CH$_3$), 111.8 (^{Ar}<u>C</u>H), 108.8 (^{Ar}<u>C</u>H), 55.9 (^{Ar}O<u>C</u>H$_3$), 55.8 (^{Ar}O<u>C</u>H$_3$), 54.5 (N<u>C</u>H), 51.5 (CO$_2$<u>C</u>H$_3$), 40.8 (N<u>C</u>H$_2$CH$_2$Ar), 39.3 (<u>C</u>H$_2$CH=CH), 29.3 (NCH$_2$<u>C</u>H$_2$Ar); *m/z* (CI) 315 (10%), 314 (60, MNa^+), 310 (12), 309 (75, MNH_4^+), 293 (18), 292 (100, MH^+); HRMS $C_{16}H_{22}NO_4$ (MH^+) requires 292.1548, found 292.1545.

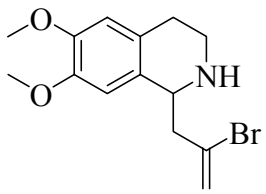
Methyl (*E*)-4-(2-(2-bromoacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate (302)



To a stirred solution of methyl (E)-4-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate **301** (204 mg, 0.7 mmol) and triethylamine (270 µL, 2.1 mmol) in DCM (5 mL) at 0 ºC was added bromoacetyl bromide (92 µL, 1.05 mmol) dropwise. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into water (10 mL), extracted with DCM (2 × 20 mL), the combined organic layers were washed with 1 M aq. NaOH (20 mL), water (20 mL) and dried over Na_2SO_4, filtered and evaporated to afford the crude product. The crude product was purified by a SCX column elution gradient 4:1 DCM:MeOH to 4:1 MeOH/NH_3:DCM to afford the title compound **302** as a yellow gum (273 mg, 95%), as a mixture of rotamers; ν_{max} (thin film) /cm^{-1} 3069 (w), 2912 (w), 1712 (s), 16940 (s); Room temperature NMR in $CDCl_3$ show duplication and overlapping of signals cased by the presence of rotomers, variable temperature NMR showed incompleate coalescence of the peaks at 100 ºC in DMSO. major rotamer, δ_H (400 MHz, $CDCl_3$) 6.90 (1H, dt, *J* = 15.6 and 7.7 C<u>H</u>=CHCO$_2$CH$_3$), 6.59 (1H, s, ^{Ar}C<u>H</u>), 6.58 (1H, s, ^{Ar}C<u>H</u>), 5.80 (1H, dt, *J* = 15.6 and 1.2, CH=C<u>H</u>CO$_2$CH$_3$), 5.59 (1H, t, *J* = 5.5, NC<u>H</u>), 3.92 (2H, s, NC(O)C<u>H$_2$</u>Br), 3.87-3.82 (1H, m, NC<u>H$_2$</u>CH$_2$Ar), 3.85 (3H, s, ^{Ar}OCH$_3$), 3.83 (3H, s, ^{Ar}OCH$_3$), 3.69 (3H, s, CO$_2$CH$_3$), 3.55 (1H, app ddd, *J* = 15.0, 10.6 and 4.2, NC<u>H$_2$</u>CH$_2$Ar), 2.98 (1H, app ddd, *J* = 16.1, 10.6 and 5.4 NCH$_2$C<u>H$_2$</u>Ar), 2.82-2.68 (3H, m, C<u>H$_2$</u>CH=CHCO$_2$CH$_3$ and NCH$_2$C<u>H$_2$</u>Ar); δ_C (100 MHz, $CDCl_3$) 166.5 (<u>C</u>O$_2$CH$_3$), 165.9 (N<u>C</u>(O)CH$_2$Br), 148.1 (^{Ar}<u>C</u>OCH$_3$), 147.8 (^{Ar}<u>C</u>OCH$_3$), 144.3 (<u>C</u>H=CHCO$_2$CH$_3$), 127.1 (^{Ar}<u>C</u>), 125.2 (^{Ar}<u>C</u>), 123.8 (CH=<u>C</u>HCO$_2$CH$_3$), 111.2 (^{Ar}<u>C</u>H), 109.8 (^{Ar}<u>C</u>H), 56.1 (^{Ar}O<u>C</u>H$_3$), 56.0 (^{Ar}O<u>C</u>H$_3$), 51.8 (N<u>C</u>H), 51.6 (CO$_2$<u>C</u>H$_3$), 41.6 (N<u>C</u>H$_2$CH$_2$Ar), 39.1 (<u>C</u>H$_2$CH=CH), 28.6 (NCH$_2$<u>C</u>H$_2$Ar), 26.1 (NC(O)<u>C</u>H$_2$Br); *m/z* (CI) 436 ($MBr^{81}Na^+$, 30%), 434 $MBr^{79}Na^+$, 30), 431 ($MBr^{81}NH_4^+$, 45), 429 (MBr^{79} NH_4^+, 45), 415 (16), 414 ($MBr^{81}H^+$, 98), 413 (18), 412 ($MBr^{79}H^+$, 100); HRMS $C_{18}H_{23}BrNO_5$ (MH^+) requires 412.0754, found 412.0766.

The minor rotamer is identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 6.95 (1H, dt, *J* = 15.6 and 7.7, C<u>H</u>=CHCO$_2$CH$_3$), 6.60 (1H, s, ^{Ar}C<u>H</u>), 5.55 (1H, s, ^{Ar}C<u>H</u>), 5.90 (1H, dt, *J* = 15.6 and 1.2, CH=C<u>H</u>CO$_2$CH$_3$).

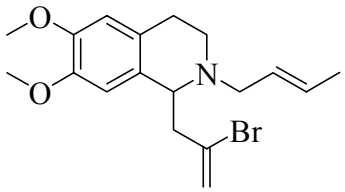
1-(2-Bromoallyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (306)



To a stirred solution of *tert*-butyl 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate **289** (11.7 g, 40.0 mmol), in tetrahydrofuran (300 mL) and diethyl ether (300 mL) at -78 ºC, under nitrogen was slowly added a solution of ^{s}BuLi (40.0 mL, 40 mmol, 1.0 M) in hexane. The resulting solution was stirred at -78 ºC, for 45 minutes, during which time the solution turned a dark red. To the resulting solution was added TMEDA (7.3 mL, 48 mmol), after 15 minutes, 2,3-dibromopropene (4.4 mL, 44 mmol) was added dropwise, and the resulting solution was maintained at -78 ºC for 1 h during which time the solution turned to a light orange colour, after which the solution was allowed to warm to room temperature. The reaction mixture was poured into water (200 mL), and extracted with EtOAc (3 × 250 mL), the combined organic layer was dried over $MgSO_4$, filtered and evaporated to afford yellow oil, which was used without further purification.

To a stirred solution of the crude oil in DCM (50 mL) at room temperature was slowly added trifluoroacetic acid (80 mL, 320 mmol) and the resulting solution was stirred at room temperature for 12 h. After which time the solution was concentrated *in vacuo* and the resulting brown oil was taken up in a fresh portion of DCM (100 mL) and stirred with a 2 M aq. NaOH solution (100 mL) for 15 minutes. The organic layer was separated and the aqueous layer was extracted with DCM (2 × 100 mL), and the combined organic layers were washed with water (2 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The oil was purified by flash silica chromatography, elution gradient 0 to 10% MeOH/NH_3 in DCM. Pure fractions were evaporated to dryness to afford the title compound **306** as a pale yellow oil (3.49 g, 28%); Rf = 0.75 (15:1 DCM:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3335 (sb), 3077 (w), 1633 (m), 1610 (m); δ_H (400 MHz, $CDCl_3$) 6.58 (1H, s, ^{Ar}C<u>H</u>), 6.57 (1H, s, ^{Ar}C<u>H</u>), 5.71 (1H, appt, *J* = 1.1, C(Br)=C<u>H</u>$_2$), 5.57 (1H appd, *J* = 1.3, C(Br)=C<u>H</u>$_2$), 4.24 (1H, dd, *J* = 9.6 and 3.8, NC<u>H</u>), 3.84 (3H, s, OC<u>H</u>$_3$), 3.83 (3H,s, OC<u>H</u>$_3$), 3.16 (1H, app dt, *J* = 12.2 and 5.8, NC<u>H</u>$_2$), 3.00 (1H, app dt, *J* = 12.2 and 5.8, NC<u>H</u>$_2$), 2.86 (1H app ddd, *J* = 14.3, 3.8 and 1.1, C<u>H</u>$_2$CBr), 2.80-2.72 (3H, m, C<u>H</u>$_2$CBr and ^{Ar}C<u>H</u>$_2$), 2.29 (1H, bs, N<u>H</u>); δ_C (100 MHz, $CDCl_3$) 147.5 (^{Ar}<u>C</u>OCH$_3$), 147.1 (^{Ar}<u>C</u>OCH$_3$), 131.4 (C), 129.1 (C), 127.1 (C), 119.7 (=<u>C</u>H$_2$), 111.7 (^{Ar}<u>C</u>H), 109.1 (^{Ar}<u>C</u>H), 55.9 (O<u>C</u>H$_3$), 55.7 (O<u>C</u>H$_3$), 52.8 (N<u>C</u>H), 48.2 (C(Br)=<u>C</u>H$_2$), 40.0 (N<u>C</u>H$_2$), 29.0 (^{Ar}<u>C</u>H$_2$); *m/z* (CI, NH_3) 315 (10%), 314 (MBr^{81}H$^+$, 100), 313 (11), 312 (M Br^{79}H$^+$, 100); HRMS $C_{14}H_{19}BrNO_2$ (MBr^{79}H$^+$) requires 312.0594, found 312.0592.

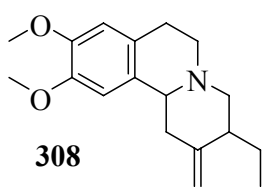
1-(2-Bromoallyl)-2-((*E*)-but-2-enyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (307)

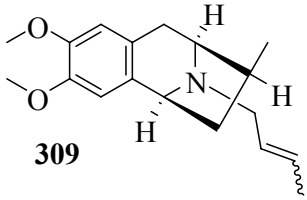


To a stirred solution of 1-(2-bromoallyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **306** (0.75 g, 2.4 mmol) and K_2CO_3 (0.39 g, 2.8 mmol) in DMF (15 mL) under nitrogen at room temperature was added Et_3N (0.39 mL, 2.8 mmol), and crotyl bromide (0.24 mL, 2.8 mmol). After stirring for 24 h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (50 mL) and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with saturated aq. $Na_2S_2O_3$ solution (2 × 30 mL), brine (2 × 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting oil was purified by flash silica chromatography, elution gradient 3:1 to 1:1 Petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound **307** as a yellow gum (0.61 g, 69%) as a 4.8:1 mixture of inseparable *E*:*Z* alkenes; Rf = 0.34 (1:1 Petrol:EtOAc); ν_{max} (thin film) /cm^{-1} 3079 (w), 3033 (w), 1635 (m), 1613 (m); major *E* isomer δ_H (400 MHz, $CDCl_3$) 6.55 (1H, s, ^{Ar}C$\underline{H}$), 6.54 (1H, s, ^{Ar}C$\underline{H}$), 5.57-5.54 (2H, m, C$\underline{H}$=C$\underline{H}$), 5.49 (1H, app d, *J* = 1.4, =C$\underline{H_2}$), 5.44 (1H, app d, *J* = 1.4, =C$\underline{H_2}$), 3.99 (1H, t, *J* = 6.7, NC$\underline{H}$), 3.82 (3H, s, OC$\underline{H_3}$), 3.87 (3H, s, OC$\underline{H_3}$), 3.24-3.01 (3H, m, NC$\underline{H_2}$CH=CH and NC$\underline{H_2}$CH$_2$Ar), 2.95-2.81 (3H, m, NC$\underline{H_2}$CH$_2$Ar, C$\underline{H_2}$CBr and NCH$_2$C$\underline{H_2}$Ar), 2.58 (1H, app dd, *J* = 13.9 and 6.8, C$\underline{H_2}$CBr), 2.48-2.38 (1H, m, NCH$_2$C$\underline{H_2}$Ar), 1.68 (3H, d, *J* = 3.7, C$\underline{H_3}$); δ_C (100 MHz, $CDCl_3$) 147.3 (^{Ar}C$\underline{C}$OCH$_3$), 146.7 (^{Ar}C$\underline{C}$OCH$_3$), 132.4 (C$\underline{C}$(Br)=CH$_2$), 128.8 (^{Ar}C$\underline{C}$), 128.7 (C$\underline{C}$H=CH), 128.2 (C$\underline{C}$H=CH), 125.9 (^{Ar}C), 118.6 (C(Br)=C$\underline{C}$H$_2$), 111.2 (^{Ar}C$\underline{C}$H), 110.7 (^{Ar}C$\underline{C}$H), 57.3 (N$\underline{C}$H), 55.7 (O$\underline{C}$H$_3$), 55.6 (O$\underline{C}$H$_3$), 55.5 (N$\underline{C}$H$_2$CH=), 47.4 (N$\underline{C}$H$_2$CH$_2$Ar), 43.1 (CH$\underline{C}$H$_2$CBr), 23.7 (NCH$_2\underline{C}$H$_2$Ar), 17.7 (C$\underline{H_3}$); *m/z* (CI) 369 (10%), 368 (MBr^{81}H$^+$, 98), 367 (10), 366 (M Br^{79}H$^+$, 100) 268 (30); HRMS $C_{18}H_{25}BrNO_2$ (MBr^{79}H$^+$) requires 366.1063, found 366.1059.

The minor *Z* isomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 1.54 (3H, d, *J* = 5.5 CH$_3$); δ_C (100 MHz, $CDCl_3$) 132.3 (C$\underline{C}$(Br)=CH$_2$), 128.6 (C$\underline{C}$H=CH), 128.0 (C$\underline{C}$H=CH), 126.7 (^{Ar}C$\underline{C}$), 125.8 (^{Ar}C$\underline{C}$), 57.7 (N$\underline{C}$H), 49.4 (N$\underline{C}$H$_2$CH), 47.7 (N$\underline{C}$H$_2$CH$_2$Ar), 43.1 (CH$\underline{C}$H$_2$CBr), 23.6 (NCH$_2\underline{C}$H$_2$Ar), 13.0 (C$\underline{H_3}$).

3-Ethyl-9,10-dimethoxy-2-methylene-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline (308), (1S*,9S*)-12-[but-2-en-1-yl]-4,5-dimethoxy-10-methyl-12-azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6- triene (309), (1S*,9S*)-4,5-dimethoxy-10-methyl-12- azatricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-triene (310) and 1-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (192)


308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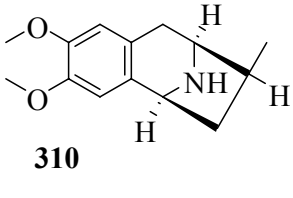
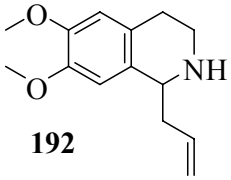

310


192

A solution of 1-(2-bromoallyl)-2-((*E*)-but-2-enyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **307** (0.58 g, 1.60 mmol) in THF (50 mL) was stirred at reflux for 30 minutes under nitrogen. Then AIBN (0.013 g, 0.08 mmol) was added, followed by the slow addition of a solution of tributyltin hydride (0.6 mL, 2.24 mmol) and AIBN (0.12 g, 0.72 mmol) in THF (20 mL) by a syringe pump over a period of 4 h. Following the completion of the addition of the tributyltin hydride, the solution was maintained at reflux for a futher 2 h, after which the solution was cooled to r.t. The crude product was passed thought an SCX column, elution gradient 4:1 DCM:MeOH to 4:1 DCM:MeOH/NH_3, and evaporated to afford a yellow oil. The oil was then purified by flash silica chromatography, elution gradient 6:1 Petrol:EtOAc to 10:10:1 Petrol:EtOAc:MeOH/NH_3, the pure fractions were collected and concentrated *in vacuo* to afford the title compounds.

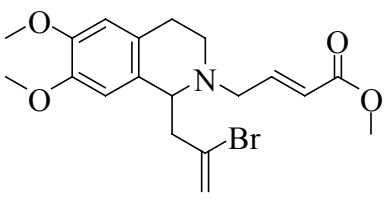
The 6-*exo* cyclisation product, **308** was obtained as a yellow oil (103 mg, 22%) as a 4:1 mixture of partially separable diastereomers; Rf = 0.55 (10:10:1 Petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3205 (w), 3060 (w), 3029 (w), 1632 (m), 1599 (m); major diastereomer, δ_H (400 MHz, $CDCl_3$) 6.68 (1H, s, $^{Ar}C\underline{H}$), 6.58 (1H, s, $^{Ar}C\underline{H}$), 4.90 (1H, d, *J* = 1.2, CH=C$\underline{H}_2$), 4.73 (1H, d, *J* = 1.0, CH=C$\underline{H}_2$), 3.87 (3H, s, OC$\underline{H}_3$), 3.84 (3H, s, OC$\underline{H}_3$), 3.12 (1H, td, *J* = 10.9 and 3.1, NC$\underline{H}_2$CH), 3.12-3.00 (3H, m, NC$\underline{H}$, NC$\underline{H}_2$CH$_2$Ar and NCH$_2$C$\underline{H}_2$Ar), 2.81 (1H, dd, *J* = 12.5 and 2.8, CHC$\underline{H}_2$C=CH$_2$), 2.68-2.63 (1H, m, NCH$_2$C$\underline{H}_2$Ar), 2.50 (1H, td, *J* = 10.9 and 3.6, NC$\underline{H}_2$CH$_2$Ar), 2.29-2.20 (1H, m, C$\underline{H}$CH$_2$CH$_3$), 2.21 (1H, dd, *J* = 12.5, CHC$\underline{H}_2$C=CH$_2$), 1.97 (1H, t, *J* = 11.0, NC$\underline{H}_2$CH), 1.80-1.68 (1H, m, C$\underline{H}_2$CH$_3$), 1.32-1.25 (1H, m, C$\underline{H}_2$CH$_3$), 0.99 (3H, t, *J* = 7.4, CH$_2$C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 149.8 (C=CH$_2$), 147.4 (^{Ar}COCH$_3$), 147.1 (^{Ar}COCH$_3$), 129.7 (^{Ar}C), 126.6 (^{Ar}C), 111.4 (^{Ar}CH), 108.1 (^{Ar}CH), 106.0 (C=CH$_2$), 64.0 (NCH), 62.3 (NCH$_2$CH), 56.0 (OCH$_3$), 55.8 (OCH$_3$), 51.7 (NCH$_2$CHAr), 42.7 (CHCH$_2$CH$_3$), 41.8 (CHCH$_2$C=CH$_2$), 29.2 (NCH$_2$CH$_2$Ar), 22.2 (CH$_2$CH$_3$), 11.7 (CHCH$_3$); *m/z* (CI, NH_3) 289 (15%), 288 (MH$^+$, 100); HRMS $C_{18}H_{26}NO_2$ (MH$^+$) requires 288.1958, found 288.1966.

The 6,5-fused bicyclic compound **309** was obtained as a yellow oil (61 mg, 13%) as a single diastereomer; Rf = 0.15 (10:10:1 Petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3290 (w), 3055 (w), 3015 (w), 1628 (m); δ_H (400 MHz, $CDCl_3$) 6.55 (1H, s, $^{Ar}C\underline{H}$), 6.42 (1H, s, $^{Ar}C\underline{H}$), 5.65-5.45 (2H, m, $CHC\underline{H}=C\underline{H}CH_3$), 3.83 (3H, s, $OC\underline{H}_3$), 3.82 (3H, s, $OC\underline{H}_3$), 3.75 (1H, d, *J* = 6.1, $NC\underline{H}Ar$), 3.40 (1H, t, *J* = 5.4, $NC\underline{H}CH_2Ar$), 3.12-3.07 (2H, m, $NC\underline{H}_2CH=CHCH_3$), 2.91 (1H, dd, *J* = 17.4 and 5.4, $NCHC\underline{H}_2Ar$), 2.60-2.47 (3H, m, $C\underline{H}_2CHCH_3$, $C\underline{H}CH_3$ and $NCHC\underline{H}_2Ar$), 1.66 (3H, d, *J* = 6.1 and 1.1, $CH=CHC\underline{H}_3$), 1.26-1.20 (1H, m, $C\underline{H}_2CHCH_3$), 0.94 (3H, d, *J* = 6.8, $CHC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 147.2 ($^{Ar}\underline{C}OCH_3$), 147.0 ($^{Ar}\underline{C}OCH_3$), 133.6 ($^{Ar}\underline{C}$), 128.6 ($CH=\underline{C}H$), 127.8 ($\underline{C}H=CH$), 124.5 ($^{Ar}\underline{C}$), 111.5 ($^{Ar}\underline{C}H$), 109.2 ($^{Ar}\underline{C}H$), 61.2 ($N\underline{C}HAr$), 59.4 ($N\underline{C}HCH_2Ar$), 55.8 (2 × $OC\underline{H}_3$), 50.7 ($N\underline{C}H_2CH=CHCH_3$), 42.5 ($\underline{C}H_2CHCH_3$), 34.3 ($\underline{C}HCH_3$), 25.0 ($NCH\underline{C}H_2Ar$), 17.8 ($CHCH\underline{C}H_3$), 17.6 ($CH\underline{C}H_3$); *m/z* (CI, NH_3) 289 (15%), 288 (100, MH^+); HRMS $C_{18}H_{26}NO_2$ (MH^+) requires 288.1958, found 288.1961.

The 6,5-fused bicyclic compound **310** was obtained as a yellow oil (46 mg, 12%) as a single diastereomer; Rf = 0.10 (10:10:1 Petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3335 (bs), 3190 (w), 3040 (w), 2995 (w), 1400 (m); δ_H (400 MHz, $CDCl_3$) 6.93 (1H, s, $^{Ar}C\underline{H}$), 6.48 (1H, s, $^{Ar}C\underline{H}$), 4.12 (1H, d, *J* = 5.9, $NC\underline{H}Ar$), 3.82 (3H, s, $OC\underline{H}_3$), 3.81 (3H, s, $OC\underline{H}_3$), 3.33 (1H, d, *J* = 5.0, $NC\underline{H}CH_2Ar$), 3.04 (1H, dd, *J* = 16.5 and 5.0, $NCHC\underline{H}_2Ar$), 2.52 (1H, d, *J* = 16.5, $NCHC\underline{H}_2Ar$), 2.21 (1H, bs, NH), 2.15-2.00 (2H, m, $CHC\underline{H}_2CH$ and $C\underline{H}CH_3$), 1.57 (1H, dt, *J* = 11.4 and 5.9, $CHC\underline{H}_2CH$), 1.12 (3H, d, *J* = 6.7, $C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 147.6 ($^{Ar}\underline{C}OCH_3$), 146.8 ($^{Ar}\underline{C}OCH_3$), 135.8 ($^{Ar}\underline{C}$), 123.8 ($^{Ar}\underline{C}$), 112.5 ($^{Ar}\underline{C}H$), 108.4 ($^{Ar}\underline{C}H$), 61.0 ($N\underline{C}HCH_2Ar$), 59.3 ($N\underline{C}HAr$), 55.9 ($O\underline{C}H_3$), 55.8 ($O\underline{C}H_3$), 46.1 ($CH\underline{C}H_2CH$), 37.2 ($\underline{C}HCH_3$), 37.2 ($NCH\underline{C}H_2Ar$), 22.2 ($CH\underline{C}H_3$); *m/z* (CI, NH_3) 235 (15%), 234 (100, MH^+); HRMS $C_{14}H_{20}NO_2$ (MH^+) requires 234.1489, found 234.1491.

1-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**192**) (31 mg, 8%) was isolated as a pale yellow oil, the spectroscopic data is in agreement with material prepared previously.

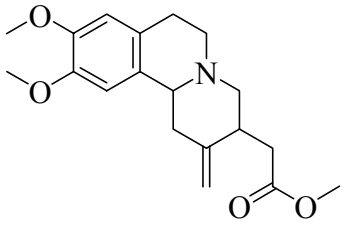
Methyl (*E*)-4-(1-(2-bromoallyl)-3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-yl)but-2-enoate (317)



To a stirred solution of 1-(2-bromoallyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **306** (1.9 g, 6.0 mmol) and K_2CO_3 (0.99 g, 7.2 mmol) in DMF (50 mL) under nitrogen at room

temperature was added Et_3N (0.92 mL, 7.2 mmol), and methyl (E)-4-bromobut-2-enoate (0.70 mL, 7.2 mmol). After stirring for 24 h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (100 mL) the mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ aqueous solution (2 × 50 mL), brine (2 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting oil was purified by flash silica chromatography, elution gradient 4:1 to 1:1 Petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound as a yellow gum (1.73 g, 70%); Rf = 0.4 (1:1 Petrol:EtOAc); ν_{max} (thin film) /cm^{-1} 3100 (w), 3048 (w), 2985 (w), 1712 (s), 1614 (m); δ_H (400 MHz, $CDCl_3$) 7.00 (1H, dt, *J* = 15.7 and 5.8, $NCH_2C\underline{H}$), 6.55 (1H, s, $^{Ar}C\underline{H}$), 6.53 (1H, s, $^{Ar}C\underline{H}$), 6.01 (1H, dt, *J* = 15.7 and 1.6, $C\underline{H}CO_2Me$), 5.52 (1H, d, *J* = 1.1, $C(Br)=C\underline{H}_2$), 5.46 (1H, d, *J* = 1.5 $C(Br)=C\underline{H}_2$), 3.91 (1H, dd, *J* = 7.2 and 6.2, $NC\underline{H}$), 3.82 (3H, s, $^{Ar}OC\underline{H}_3$), 3.81 (3H, s, $^{Ar}OC\underline{H}_3$), 3.72 (3H, s, $CO_2C\underline{H}_3$), 3.38 (2H, ddd, *J* = 15.7, 5.8 and 1.6, $NC\underline{H}_2CH$) 3.15-3.06 (1H, m, $NC\underline{H}_2$), 2.90-2.80 (3H, m, $NC\underline{H}_2$, $C\underline{H}_2CBr$ and $^{Ar}C\underline{H}_2$), 2.61 (1H, dd, *J* = 14.3 and 5.6, $C\underline{H}_2CBr$), 2.50-2.42 (1H, m, $^{Ar}C\underline{H}_2$); δ_C (100 MHz, $CDCl_3$) 166.7 ($\underline{C}$=O), 147.5 ($\underline{C}OCH_3$), 147.0 ($\underline{C}OCH_3$), 146.7 ($CH_2\underline{C}H$), 132.1 ($\underline{C}(Br)=CH_2$), 128.3 ($^{Ar}\underline{C}$), 125.7 ($^{Ar}\underline{C}$), 122.2 ($\underline{C}HCO_2CH_3$), 118.9 ($C(Br)=\underline{C}H_2$), 111.3 ($^{Ar}\underline{C}H$), 110.5 ($^{Ar}\underline{C}H$), 58.7 ($N\underline{C}H$), 55.8 ($O\underline{C}H_3$), 55.7 ($O\underline{C}H_3$), 54.4 ($\underline{C}H_2CBr$), 51.4 ($CO_2\underline{C}H_3$), 48.1 ($N\underline{C}H_2$), 43.2 ($N\underline{C}H_2$), 23.5 ($^{Ar}\underline{C}H_2$); *m/z* (CI, NH_3) 413 (19%), 412 ($MBr^{81}H^+$, 98), 411 (20), 410 ($MBr^{79}H^+$, 100); HRMS $C_{19}H_{25}BrNO_4$ ($MBr^{79}H^+$) requires 410.0961, found 410.0961.

Methyl 2-(2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-methylene-1H-pyrido[2,1-a]isoquinolin-3-yl)acetate (318)



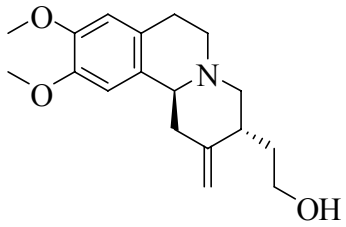
A solution of methyl (*E*)-4-(1-(2-bromoallyl)-3,4-dihydro-6,7-dimethoxyisoquinolin-2(1H)-yl)but-2-enoate **317** (1.50 g, 3.75 mmol) in THF (100 mL) was stirred at reflux for 30 minutes under nitrogen. Then AIBN (31 mg, 0.19 mmol) was added, followed by the slow addition of a solution of tributyltin hydride (1.5 mL, 5.6 mmol) and AIBN (277 mg, 1.69 mmol) in THF (25 mL) by a syringe pump over a period of 5 h. Following the complete addition of the tributyltin hydride solution, the reaction mixture was maintained at reflux for a further 2 h, after which the solution was cooled to r.t. The crude reaction mixture was passed thought a SCX column, elution gradient 4:1 DCM:MeOH to 4:1

DCM:MeOH/NH_3, the DCM:MeOH/NH_3 fractions were evaporated to afford a yellow oil. The oil was purified by flash silica chromatography, elution gradient 16:4:1 petrol:Et_2O:MeOH/NH_3 to 10:10:1 petrol:Et_2O:MeOH/NH_3. Pure fractions were concentrated *in vacuo* to afford the title compound as a yellow oil (1.10 g, 89%) as a 2.6:1 mixture of partially separable diastereomers.

Major diastereoisomer (**318-a**); Rf = 0.20 (16:4:1 petrol:Et_2O:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3043 (w), 2987 (w), 1720 (s), 1610 (m); δ_H (400 MHz, $CDCl_3$) 6.62 (1H, s, $^{Ar}C\underline{H}$), 6.54 (1H, s, $^{Ar}C\underline{H}$), 4.88 (1H, s, C=C$\underline{H}_2$), 4.61 (1H, s, C=C$\underline{H}_2$), 3.82 (3H, s, $^{Ar}OC\underline{H}_3$), 3.79 (3H, s, $^{Ar}OC\underline{H}_3$), 3.65 (3H, s, $CO_2C\underline{H}_3$), 3.14-3.08 (1H, m, NC$\underline{H}$), 3.05 (1H, dd, *J* = 10.9 and 4.6, NC$\underline{H}_2$CH), 3.02-2.94 (2H, m, NC$\underline{H}_2CH_2$Ar and $NCH_2C\underline{H}_2$Ar), 2.90-2.82 (1H, m, $NCH_2C\underline{H}CH_2CO_2CH_3$), 2.77 (1H, dd, *J* = 12.0 and 3.0, NCHC$\underline{H}_2CH=CH_2$), 2.63 (1H, dd, *J* = 15.4 and 6.0, CHC$\underline{H}_2CO_2CH_3$), 2.62-2.57 (1H, m, $NCH_2C\underline{H}_2$Ar), 2.50-2.43 (1H, m, NC$\underline{H}_2CH_2$Ar), 2.24 (1H, dd, *J* = 15.4 and 8.1, CHC$\underline{H}_2CO_2CH_3$), 2.21 (1H, t, *J* = 12.0, NCHC$\underline{H}_2C=CH_2$), 2.07 (1H, t, *J* = 10.9, NC$\underline{H}_2$CH); δ_C (100 MHz, $CDCl_3$) 172.9 ($\underline{C}O_2CH_3$), 148.4 ($\underline{C}=CH_2$), 147.5 ($^{Ar}\underline{C}OCH_3$), 147.2 ($^{Ar}\underline{C}OCH_3$), 129.5 ($^{Ar}\underline{C}$), 126.7 ($^{Ar}\underline{C}$), 111.5 ($^{Ar}\underline{C}H$), 108.2 ($^{Ar}\underline{C}H$), 106.5 (C=$\underline{C}H_2$), 63.6 (N$\underline{C}$H), 62.2 (N$\underline{C}H_2$CH), 56.1 ($^{Ar}O\underline{C}H_3$), 55.8 ($^{Ar}O\underline{C}H_3$), 51.7 ($CO_2\underline{C}H_3$), 51.3 (N$\underline{C}H_2CH_2$Ar), 41.5 (NCH$\underline{C}H_2C=CH_2$), 38.0 ($NCH_2\underline{C}HCH_2CO_2CH_3$), 34.9 (CH$\underline{C}H_2CO_2CH_3$), 29.3 ($NCH_2\underline{C}H_2$Ar); *m/z* (CI) 333 (20%), 332 (100, MH^+); HRMS $C_{19}H_{26}NO_4$ (MH^+) requires 332.1856, found 332.1864.

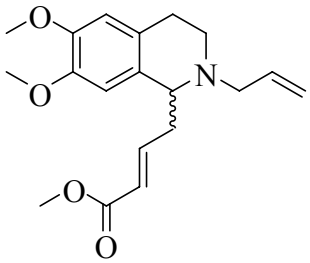
Minor diastereoisomer (**318-b**); Rf = 0.24, (16:4:1 petrol:Et_2O:MeOH/NH_3); δ_H (400 MHz, $CDCl_3$) 6.66 (1H, s, $^{Ar}C\underline{H}$), 6.57 (1H, s, $^{Ar}C\underline{H}$), 4.84 (2H, s, C=C$\underline{H}_2$), 3.85 (3H, s, $^{Ar}OC\underline{H}_3$), 3.83 (3H, s, $^{Ar}OC\underline{H}_3$), 3.63 (3H, s, $CO_2C\underline{H}_3$), 3.12-3.02 (2H, m, NC$\underline{H}$ and $NCH_2C\underline{H}_2$Ar), 2.90-2.74 (4H, m, NC$\underline{H}_2CHCH_2$, NC$\underline{H}_2CH_2$Ar, $NCH_2C\underline{H}CH_2$ and C$\underline{H}CH_2CO_2CH_3$), 2.67 (1H, dd, *J* = 12.0 and 3.0, CHC$\underline{H}_2CH=CH_2$), 2.61 (1H, dd, *J* = 15.3 and 7.3, $NCH_2C\underline{H}_2$Ar), 2.55 (1H, app dd, *J* = 16.0 and 3.0, CHC$\underline{H}_2CO_2CH_3$), 2.52-2.42 (2H, m, NC$\underline{H}_2CH_2$Ar and NC$\underline{H}_2CHCH_2$), 2.26 (1H, app t, *J* = 11.6, CHC$\underline{H}_2C=CH_2$); δ_C (100 MHz, $CDCl_3$) 173.5 ($\underline{C}O_2CH_3$), 147.6 ($\underline{C}=CH_2$), 147.5 ($^{Ar}\underline{C}OCH_3$), 147.3 ($^{Ar}\underline{C}OCH_3$), 129.9 ($^{Ar}\underline{C}$), 127.1 ($^{Ar}\underline{C}$), 111.5 ($^{Ar}\underline{C}H$), 110.3 (C=$\underline{C}H_2$), 108.1 ($^{Ar}\underline{C}H$), 63.7 (N$\underline{C}$H), 60.8 (N$\underline{C}H_2CHCH_2$), 56.1 ($^{Ar}O\underline{C}H_3$), 55.9 ($^{Ar}O\underline{C}H_3$), 52.4 (N$\underline{C}H_2CH_2$Ar), 51.4 ($CO_2\underline{C}H_3$), 40.4 ($NCH_2\underline{C}HCH_2CO_2CH_3$), 37.6 (CH$\underline{C}H_2C=CH_2$), 37.5 (CH$\underline{C}H_2CO_2CH_3$), 29.4 ($NCH_2\underline{C}H_2$Ar).

2-(2,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-2-methylene-1H-pyrido[2,1-a]isoquinolin-3-yl)ethanol (319)



To a stirred solution of methyl 2-(2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-methylene-1H-pyrido[2,1-a]isoquinolin-3-yl)acetate **318-a** (166 mg, 0.5 mmol) in THF (20 mL) at 0 ºC under nitrogen, was slowly added a solution of lithium aluminium hydride in THF (2.3 mL, 2.4 M, 5.5 mmol), the solution was stirred for 15 minutes at 0 ºC, then warmed to r.t. and stirred for 6 h. The stirred reaction mixture was then quenched by the sequential dropwise addition of H_2O (0.21 mL), 15% aqueous NaOH (0.21 mL) and H_2O (0.63 mL), then EtOAc (20 mL) and celite (1.0 g) were added and the mixture was stirred for 1 h. The reaction mixture was filtered through a celite plug, the plug was flushed with EtOAc (2 × 15 mL), evaporation of the solvent afforded the crude product as a yellow oil. The oil was purified by flash silica chromatography, elution gradient 16:4:1 petrol:EtOAc:MeOH/NH_3 to 0:20:1 petrol:EtOAc:MeOH/NH_3. Pure fractions were concentrated *in vacuo* to afford the title compound **319** as a yellow oil (116 mg, 77%); Rf = 0.30 (10:2:1 petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3440 (sb), 3040 (w), 2990 (w), 1610 (m); δ_H (400 MHz, $CDCl_3$) 6.66 (1H, s, ^{Ar}CH), 6.56 (1H, s, ^{Ar}CH), 4.89 (1H, s, C=CH_2), 4.71 (1H, s, C=CH_2), 3.85 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.68 (2H, app t, *J* = 6.7, CH_2OH), 3.19 (1H, d, *J* = 9.5, NCH), 3.10-3.06 (1H, m, NCH_2CH_2Ar), 3.06 (1H, dd, *J* = 10.8 and 4.5, NCH_2CH), 2.98 (1H, ddd, *J* = 11.0, 5.9 and 1.8, NCH_2CH_2Ar), 2.81 (1H, dd, *J* = 12.5 and 2.8, CHCH_2C=CH_2), 2.66-2.59 (1H, m, NCH_2CH_2Ar), 2.49 (1H, td, *J* = 11.0 and 3.9, NCH_2CH_2Ar), 2.47-2.42 (1H, m, CHCH_2CH_2OH), 2.18 (1H, t, *J* = 12.5, CHCH_2C=CH_2), 2.05-1.90 (2H, m, NCH_2CH and CH_2CH_2OH), 1.53-1.43 (1H, m, CH_2CH_2OH); δ_C (100 MHz, $CDCl_3$) 149.0 (C=CH_2), 147.4 (^{Ar}COCH$_3$), 147.0 (^{Ar}COCH$_3$), 129.3 (^{Ar}C), 126.3 (^{Ar}C), 111.2 (^{Ar}CH), 107.9 (^{Ar}CH), 106.4 (C=CH_2), 63.7 (NCH), 62.3 (NCH_2CH), 60.2 (CH_2OH), 55.9 (OCH_3), 55.7 (OCH_3), 51.5 (NCH_2CH_2Ar), 41.4 (CHCH_2C=CH_2), 37.6 (CHCH_2CH_2OH), 32.3 (CH_2CH_2OH), 28.9 (NCH_2CH_2Ar); *m/z* (CI, NH_3) 305 (15%), 304 (100, MH^+); HRMS $C_{18}H_{26}NO_3$ (MH^+) requires 304.1907, found 304.1910.

Methyl (*E*)-4-(2-allyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)but-2-enoate (329)

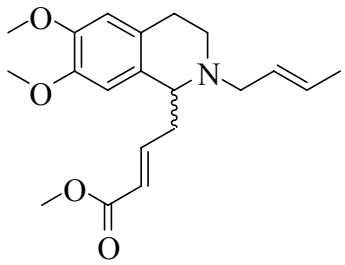


To a stirred solution of 6,7-dimethoxy-3,4-dihydroisoquinoline **188** (2.8 g, 14.6 mmol), in diethyl ether (100 mL) at r.t. under nitrogen was added allyl bromide (1.42 mL, 16.1 mmol). The resulting solution was stirred in the dark overnight, during which time a yellow precipitate formed. The crude mixture was evaporated to dryness to afford the bromide salt as a moisture sensitive yellow power; δ_H (400 MHz, $CDCl_3$) 10.05 (1H, s, NC<u>H</u>), 7.63 (1H, s, ^{Ar}C<u>H</u>), 6.79 (1H, s, ^{Ar}C<u>H</u>), 6.04-5.92 (1H, m, C<u>H</u>=CH_2), 5.57 (1H, dd, *J* = 17.0 and 0.9, CH=C<u>H</u>$_2$), 5.46 (1H, dd, *J* = 10.0 and 0.9, CH=C<u>H</u>$_2$), 4.82 (2H, d, *J* = 6.5, NC<u>H</u>$_2$CH=CH_2), 3.94 (3H, s, OCH_3), 3.92 (2H, t, *J* = 8.2, N<u>C</u>H_2CH_2Ar), 3.85 (3H, s, OC<u>H</u>$_3$), 3.20 (2H, t, *J* = 8.2, NCH_2C<u>H</u>$_2$Ar); δ_C (100 MHz, $CDCl_3$) 165.8 (N<u>C</u>H), 158.0 (^{Ar}<u>C</u>OCH_3), 149.3 (^{Ar}<u>C</u>OCH_3), 132.4 (^{Ar}<u>C</u>), 127.4 (^{Ar}<u>C</u>), 124.6 (CH=<u>C</u>H_2), 117.7 (<u>C</u>H=CH_2), 116.4 (^{Ar}<u>C</u>H), 111.0 (^{Ar}<u>C</u>H), 62.5 (N<u>C</u>H_2CH=CH_2), 57.2 (^{Ar}CO<u>C</u>H_3), 57.1 (^{Ar}CO<u>C</u>H_3), 47.9 (N<u>C</u>H_2CH_2Ar), 26.0 (NCH_2<u>C</u>H_2Ar).

To a stirred suspension of the bromide salt in acetonitrile (100 mL) was added methyl (E)-4-bromobut-2-enoate (2.9 mL, 21.9 mmol) and zinc (2.10 g, 32.2 mmol) and the resulting suspension was stirred at R.T. under nitrogen for 2 days. The reaction mixture was quenched by pouring into a saturated solution of aq. $NaHCO_3$ (150 mL) and allowed to stir for 30 minutes. The resulting precipitate was removed by filtration, and washed with EtOAc (75 mL), the organic layer was separated and the aqueous layer extracted with EtOAc (2 x 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 4:1 to 1:1 isohexane:EtOAc. Pure fractions were evaporated to dryness to afford the title compound (4.10 g, 84%) as a yellow oil which solidified on standing. Rf 0.45 (ethyl acetate:petrol, 1:1); mp 60-64 ºC; ν_{max} (thin film) /cm^{-1} 3007 (w), 2958 (w), 2781 (w), 1706 (s), 1652 (m), 1609 (w), 1514 (m); δ_H (400 MHz, $CDCl_3$) 7.04 (1H, dt, *J* = 15.6 and 7.0, CH_2C<u>H</u>=CHCO_2C<u>H</u>$_3$), 6.57 (1H, s, ^{Ar}C<u>H</u>), 6.48 (1H, s, ^{Ar}C<u>H</u>), 5.95-5.85 (1H, m, CH_2C<u>H</u>=CH_2), 5.81 (1H, app dt, *J* = 15.6 and 1.3, CH_2CH=C<u>H</u>CO_2CH_3), 5.21-5.11 (2H, m, CH_2CH=C<u>H</u>$_2$), 3.84 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.81 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.76 (1H, t, *J* = 6.3, NC<u>H</u>), 3.71 (3H, s, CO_2C<u>H</u>$_3$), 3.23 (2H, d, *J* = 6.3,

$NC\underline{H}_2CH=CH_2$), 3.16-3.08 (1H, m, $NC\underline{H}_2CH_2Ar$), 2.88-2.77 (2H, m, $NC\underline{H}_2CH_2Ar$ and $NCH_2C\underline{H}_2Ar$), 2.66 (1H, app quint d, J = 7.5 and 1.4, $CH=CHC\underline{H}_2$), 2.59-2.47 (2H, m, $NCH_2C\underline{H}_2Ar$ and $CH=CHC\underline{H}_2$); δ_C (100 MHz, $CDCl_3$) 166.9 ($\underline{C}O_2CH_3$), 147.7 ($\underline{C}H=CHCO_2CH_3$), 147.6 ($^{Ar}\underline{C}OCH_3$), 147.2 ($^{Ar}\underline{C}OCH_3$), 136.2 ($\underline{C}H=CH_2$), 128.9 ($^{Ar}\underline{C}$), 126.2 ($^{Ar}\underline{C}$), 122.0 ($CH=\underline{C}HCO_2CH_3$), 117.2 ($CH=\underline{C}H_2$), 111.7 ($^{Ar}\underline{C}H$), 110.6 ($^{Ar}\underline{C}H$), 59.6 ($N\underline{C}H$), 62.0 ($N\underline{C}H_2CH=CH_2$), 55.9 ($^{Ar}CO\underline{C}H_3$), 55.8 ($^{Ar}CO\underline{C}H_3$), 51.3 ($CO_2\underline{C}H_3$), 43.8 ($N\underline{C}H_2CH_2Ar$), 38.4 ($CH\underline{C}H_2CH=CH$), 24.6 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI, NH_3) 333 (20%), 332 (100, MH^+), 232 (15); HRMS $C_{19}H_{26}NO_4$ (MH^+) requires 332.1856 found 332.1852.

Methyl (*E*)-4-(2-((*E*)-but-2-enyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)but-2-enoate (330)



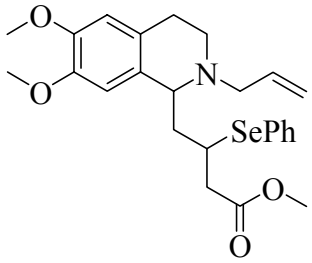
To a stirred solution of 3,4-dihydro-6,7-dimethoxyisoquinoline **188** (2.0 g, 10.5 mmol) in diethyl ether (100 mL) at room temperature under nitrogen was added crotyl bromide (2.5 mL, 21.0 mmol). The resulting solution was stirred in the dark overnight, during which time a yellow precipitate formed. The crude mixture was evaporated to dryness to afford the bromide salt as a moisture sensitive yellow power; δ_H (400 MHz, $CDCl_3$) 9.98 (1H, s, $N\underline{C}H$), 7.63 (1H, s, $^{Ar}\underline{C}H$), 6.81 (1H, s, $^{Ar}\underline{C}H$), 6.12-5.90 (1H, m, $C\underline{H}=CH$), 5.66-5.52 (1H, m, $CH=C\underline{H}$), 4.73 (2H, d, J = 6.9, $NC\underline{H}_2CH=CHCH_3$), 3.94 (3H, s, $OC\underline{H}_3$), 3.90 (2H, app t, J = 8.2, $NC\underline{H}_2CH_2Ar$), 3.86 (3H, s, OCH_3), 3.20 (2H, app t, J = 8.2, $NCH_2C\underline{H}_2Ar$), 1.71 (3H, dd, J = 6.9 and 1.1 $CHC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 164.5 ($N\underline{C}H$), 157.2 ($^{Ar}\underline{C}OCH_3$), 148.6 ($^{Ar}\underline{C}OCH_3$), 137.1 ($C\underline{H}=CH$), 131.8 ($^{Ar}\underline{C}$), 121.1 ($^{Ar}\underline{C}$), 117.1 ($CH=\underline{C}H$), 115.7 ($^{Ar}\underline{C}H$), 110.5 ($^{Ar}\underline{C}H$), 61.5 ($N\underline{C}H_2CH=CH$), 56.6 (OCH_3), 56.5 (OCH_3), 47.1 ($NC\underline{H}_2CH_2Ar$), 25.4 ($NCH_2C\underline{H}_2Ar$), 17.9 ($CHCH_3$); The minor *Z* isomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 4.84 (2H, d, J = 7.3, $N\underline{C}H_2CH=CHCH_3$), 1.80 (3H, dd, J = 7.3 and 1.6, $CHC\underline{H}_3$).

To a stirred suspension of the bromide salt in acetonitrile (100 mL) was added methyl (E)-4-bromobut-2-enoate (2 ml, 16.8 mmol) and zinc dust (1.1 g, 16.8 mmol). The resulting suspension was stirred at r.t. under nitrogen for 2 days. The reaction mixture was quenched by pouring into a saturated solution of aq. $NaHCO_3$ (150 mL) and the mixture was allowed to stir for 30 minutes. The resulting precipitate was removed by filtration, and washed with

EtOAc (75 mL), the organic layer was separated and the aqueous layer extracted with EtOAc (2 x 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 8:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound (2.43 g, 68%) as a yellow oil; Rf 0.55 (ethyl acetate:petrol, 1:1); ν_{max} (thin film) /cm^{-1} 3009 (w), 2948 (w), 1710 (s), 1655 (m), 1605 (w), 1514 (m); δ_H (400 MHz, $CDCl_3$) 6.93 (1H, dt, *J* = 15.6 and 7.3, $CH_2C\underline{H}=CHCO_2CH_3$), 6.47 (1H, s, $^{Ar}\underline{C}H$), 6.39 (1H, s, $^{Ar}\underline{C}H$), 5.71 (1H, d, *J* = 15.6, $C\underline{H}CO_2CH_3$), 5.57-5.40 (2H, m, $NCH_2C\underline{H}=C\underline{H}CH_3$), 3.74 (3H, s, $^{Ar}OC\underline{H}_3$), 3.72 (3H, s, $^{Ar}OC\underline{H}_3$), 3.67 (1H, t, *J* = 6.3, $NC\underline{H}_2CH=CHCH_3$), 3.61 (3H, s, $CO_2C\underline{H}_3$), 3.06 (2H, d, *J* = 6.3, $NC\underline{H}_2CH=CHCH_3$), 3.03-2.96 (1H, m, $NC\underline{H}_2CH_2Ar$), 2.79-2.60 (2H, m, $NC\underline{H}_2CH_2Ar$ and $NCH_2C\underline{H}_2Ar$), 2.62-2.54 (1H, m, $C\underline{H}_2CH=CHCO_2CH_3$), 2.50-2.39 (2H, $NCH_2C\underline{H}_2Ar$ and $C\underline{H}_2CH=CHCO_2CH_3$), 1.61 (3H, d, *J* = 5.9, $CH=CHC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 166.6 ($\underline{C}O_2CH_3$), 147.5 ($\underline{C}H=CHCO_2CH_3$), 147.4 ($^{Ar}\underline{C}OCH_3$), 146.9 ($^{Ar}\underline{C}OCH_3$), 128.8 ($^{Ar}\underline{C}$), 128.5 ($CH=\underline{C}H$), 128.2 ($\underline{C}H=CH$), 126.5 ($^{Ar}\underline{C}$), 121.7 ($CH=\underline{C}HCO_2CH_3$), 111.4 ($^{Ar}\underline{C}H$), 110.4 ($^{Ar}\underline{C}H$), 59.3 ($N\underline{C}H$), 55.8 ($N\underline{C}H_2CH=CH$), 55.7 ($^{Ar}O\underline{C}H_3$), 55.6 ($^{Ar}O\underline{C}H_3$), 51.1 ($CO_2\underline{C}H_3$), 43.5 ($N\underline{C}H_2CH_2Ar$), 38.0 ($\underline{C}H_2CH=CHCO_2CH_3$), 24.5 ($NCH_2\underline{C}H_2Ar$), 17.6 ($CH\underline{C}H_3$); *m/z* (CI, NH_3) 347 (20%), 346 (100, MH^+); HRMS $C_{20}H_{28}NO_4$ (MH^+) requires 346.2018 found 346.2015.

The minor *Z* isomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* = 6.7, $CH=CHC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 147.5 ($\underline{C}H=CHCO_2CH_3$), 147.4 ($^{Ar}\underline{C}OCH_3$), 146.9 ($^{Ar}\underline{C}OCH_3$), 128.7 (Ar$\underline{C}$), 127.8 ($CH=\underline{C}H$), 126.8 ($\underline{C}H=CH$), 126.4 (Ar$\underline{C}$), 59.5 ($N\underline{C}H$), 55.7 ($N\underline{C}H_2CH=CH$), 43.6 ($N\underline{C}H_2CH_2Ar$), 38.2 ($\underline{C}H_2CH=CH$), 24.4 ($NCH_2CH_2Ar$), 12.9 ($CH\underline{C}H_3$).

Methyl 4-(2-[(2E)-3-chlorobut-2-en-1-yl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-(phenylselanyl)butanoate (331)

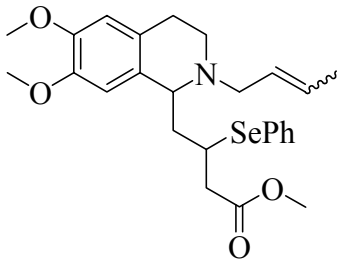


To a stirred suspension of diphenyl diselenide (5.2 g, 18.8 mmol) in degassed EtOH (40 mL) in a 100 mL two-neck round-bottom flask under nitrogen was added sodium borohydride (2.1 g, 56 mmol), until the solution became colourless. The resulting reaction

mixture was then cooled to 0 °C in an ice bath for 5 min. Glacial acetic acid (6.5 mL, 112 mmol) was added dropwise via syringe, and allowed to stir for 5 minutes. Next, the diene **329** (4.6 g, 14.0 mmol) was added in degassed EtOH (10 mL) via cannula, the reaction was stirred for 5 min at 0 ºC, and then allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into H_2O (100 mL) and was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (2 × 75 mL), dried over $MgSO_4$, and concentrated to give a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 8:1 petrol:EtOAc to EtOAc. The pure fractions were concentrated *in vacuo* to afford the title compound **331** as a yellow gum (4.3 g, 64%) as a 5:1 mixture of inseparable diastereomers; Rf 0.45 (2:1, ethyl acetate:petrol); ν_{max} (thin film) /cm^{-1} 3070 (w), 2999 (m), 2948 (s), 2835 (m), 1731 (s), 1609 (w), 1516 (s); major diastereomer, δ_H (400 MHz, $CDCl_3$) 7.68-7.63 (2H, m, $^{Ph}C\underline{H}$), 7.34-7.27 (3H, m, $^{Ph}C\underline{H}$), 6.51 (1H, s, $^{Ar}C\underline{H}$), 6.35 (1H, s, $^{Ar}C\underline{H}$), 5.97-5.84 (1H, m, $C\underline{H}=CH_2$), 5.16-5.07 (2H, m, $CH=C\underline{H_2}$), 3.94-3.85 (2H, m, $NC\underline{H}$ and $C\underline{H}SePh$), 3.82 (3H, s, $^{Ar}OC\underline{H_3}$), 3.79 (3H, s, $^{Ar}OC\underline{H_3}$), 3.63 (3H, s, $CO_2C\underline{H_3}$), 3.25-3.07 (3H, m, $NC\underline{H_2}CH=CH_2$ and $NC\underline{H_2}CH_2Ar$), 2.90 (1H, m, $NC\underline{H_2}CH_2Ar$), 2.86-2.75 (3H, m, $NCH_2C\underline{H_2}Ar$, $C\underline{H_2}CO_2CH$), 2.30 (1H, d, J =11.9 and 4.5, $NCH_2C\underline{H_2}Ar$), 2.00-1.92 (1H, m, $NCHC\underline{H_2}CH$), 1.80-1.73 (1H, m, $NCHC\underline{H_2}CH$); δ_C (100 MHz, $CDCl_3$) 172.3 ($\underline{C}O_2CH_3$), 147.5 ($^{Ar}\underline{C}OCH_3$), 147.4 ($^{Ar}\underline{C}OCH_3$), 138.1 ($\underline{C}H=CH_2$), 135.6 (2 × $^{Ph}\underline{C}H$), 129.0 (2 × $^{Ph}\underline{C}H$), 128.5 ($^{Ph}\underline{C}$), 127.9 ($^{Ph}\underline{C}H$), 127.7 ($^{Ar}\underline{C}$), 126.1 ($^{Ar}\underline{C}$), 116.8 ($CH=\underline{C}H_2$), 111.5 ($^{Ar}\underline{C}H$), 110.4 ($^{Ar}\underline{C}H$), 58.4 ($N\underline{C}H$), 56.4 ($N\underline{C}H_2CH=CH_2$), 56.0 ($^{Ar}OC\underline{H_3}$), 55.9 ($^{Ar}OC\underline{H_3}$), 51.6 ($CO_2C\underline{H_3}$), 42.2 ($N\underline{C}H_2CH_2Ar$), 42.0 ($\underline{C}H_2CO_2CH_3$), 41.4 ($NCH\underline{C}H_2CH$), 37.9 ($\underline{C}HSePh$), 21.7 ($NCH_2C\underline{H_2}Ar$); *m/z* (CI, NH_3) 492 (20%), 491 (23), 490 ($M^{80}SeH^+$, 100), 489 (10), 488 ($M^{78}SeH^+$, 50), 487 (18), 486 ($M^{76}SeH^+$, 18); HRMS $C_{25}H_{32}NO_4Se$ ($M^{80}SeH^+$) requires 490.1491, found 490.1485.

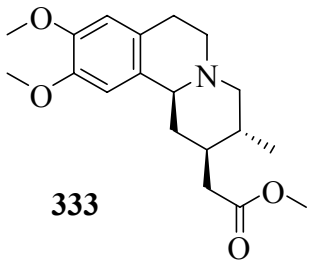
The minor diastereoisomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 7.59-7.55 (2H, m, $^{Ph}C\underline{H}$), 7.27-7.24 (3H, m, $^{Ph}C\underline{H}$), 6.51 (1H, s, ^{Ar}CH), 6.41 (1H, s, ^{Ar}CH).

Methyl 4-(2-[(2E)-but-2-en-1-yl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-(phenylselanyl)butanoate (332)

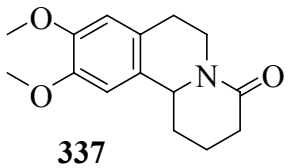


To a stirred suspension of diphenyl diselenide (3.7 g, 12.0 mmol) in degassed EtOH (40 mL) in a 100 mL two-neck round-bottom flask under nitrogen was added sodium borohydride (1.5 g, 40 mmol), until the solution became colourless. The resulting reaction mixture was then cooled to 0 °C in an ice bath for 5 min. Glacial acetic acid (4.6 mL, 80 mmoL) was added dropwise via syringe, and allowed to stir for 5 minutes. Next the diene **330** (3.5 g, 10 mmol) was added in degassed EtOH (10 mL) via cannula, the reaction was stirred for 5 min at 0 °C, and then allowed to warm to room temperature and stirred over night. The reaction mixture was poured into H_2O (50 mL) and was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with brine (2 × 75 mL), dried over $MgSO_4$, and concentrated to give a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 8:1 petrol:EtOAc to EtOAc. The pure fractions were concentrated *in vacuo* to afford the title compound **332** as a yellow gum (3.42 g, 68%); as a mixture of inseparable diastereomers; Rf 0.50 (2:1, ethyl acetate:petrol); ν_{max} (thin film) /cm^{-1} 3053 (w), 2936 (s), 2856 (m), 1736 (s), 1608 (w), 1515 (s); δ_H (400 MHz, $CDCl_3$) 7.62-7.58 (2H, m, $^{Ph}C\underline{H}$), 7.26-7.22 (3H, m, $^{Ph}C\underline{H}$), 6.46 (1H, s, $^{Ar}C\underline{H}$), 6.30 (1H, s, $^{Ar}C\underline{H}$), 5.55-5.45 (2H, m, C$\underline{H}$=C$\underline{H}$), 3.88-3.82 (2H, m, NC$\underline{H}$ and C$\underline{H}$SePh), 3.76 (3H, s, $^{Ar}OC\underline{H}_3$), 3.74 (3H, s, $^{Ar}OC\underline{H}_3$), 3.57 (3H, s, $CO_2C\underline{H}_3$), 3.12-2.96 (3H, m, NC$\underline{H}_2$CH and NC$\underline{H}_2CH_2Ar$), 2.88 (1H, dd, *J* = 13.7 and 5.5, NC$\underline{H}_2$CHAr), 2.82-2.70 (3H, m, $NCH_2C\underline{H}_2Ar$ and C$\underline{H}_2CO_2CH_3$), 2.24 (1H, td, *J* = 16.7 and 4.3, $NCH_2C\underline{H}_2Ar$), 1.98 (1H, dd, *J* = 14.7, 10.9 and 3.5, NCHC$\underline{H}_2$CH), 1.68-1.62 (1H, m, NCHC$\underline{H}_2$CH), 1.64 (3H, d, *J* = 4.9, CHC$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 172.0 ($\underline{C}O_2CH_3$), 147.2 ($^{Ar}\underline{C}OCH_3$), 147.1 ($^{Ar}\underline{C}OCH_3$), 135.4 ($^{Ph}\underline{C}H$), 135.3 (2 x $^{Ph}\underline{C}H$), 129.7 (C$\underline{H}$=C$\underline{C}$H), 128.7 (2 x $^{Ph}\underline{C}H$), 128.4 ($^{Ar}\underline{C}$), 127.6 (CH=C$\underline{H}$), 127.5 ($^{Ph}\underline{C}$), 126.0 ($^{Ar}\underline{C}$), 114.4 ($^{Ar}\underline{C}H$), 110.3 ($^{Ar}\underline{C}H$), 57.8 (N$\underline{C}$H), 55.8 (O$\underline{C}H_3$), 55.6 (O$\underline{C}H_3$), 55.2 (N$\underline{C}H_2$CH=CH), 51.3 ($CO_2\underline{C}H_3$), 41.9 ($\underline{C}H_2CO_2CH_3$), 41.7 (NCH$\underline{C}H_2$CH), 41.4 (N$\underline{C}H_2CH_2Ar$), 37.7 (C$\underline{H}$SePh), 21.6 ($NCH_2\underline{C}H_2Ar$), 17.7 (CH$\underline{C}H_3$); *m/z* (CI), 506 (28%), 505 (30), 504 ($M^{80}SeH^+$, 100), 503 (10), 502 ($M^{78}SeH^+$, 50), 501 (17), 500 ($M^{76}SeH^+$, 20); HRMS $C_{26}H_{34}NO_4Se$ ($M^{80}SeH^+$) requires 504.1648, found 504.1649.

Methyl 2-((2*R,3*R**,11b*S**)-9,10-dimethoxy-3-methyl-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate (333), 9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (337)**



333



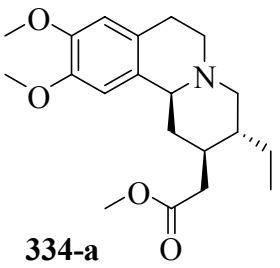
337

A solution of methyl 4-(2-allyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)-3-(phenylselanyl)butanoate (**331**) (2.4 g, 5.0 mmol) in THF (250 mL) was stirred at reflux for 30 minutes under nitrogen. Then AIBN (0.041 g, 0.25 mmol) was added, followed by the slow addition of a solution of tributyltin hydride (2.0 mL, 7.5 mmol) and AIBN (0.41 g, 2.5 mmol) in THF (40 mL) by a syringe pump over a period of 8 h. Following the completion of the addition of the tributyltin hydride, the solution was maintained at reflux for a further 4 h, after which the solution was cooled to r.t. The crude product was passed thought an SCX column, elution gradient 4:1 DCM:MeOH to 4:1 DCM:MeOH/NH_3, and evaporated to afford a yellow oil. The oil was then purified by flash silica chromatography, elution gradient 6:1 petrol:EtOAc to 10:10:1 petrol:EtOAc:MeOH/NH_3. Pure fractions were concentrated *in vacuo* to afford the title compounds **333** and **337**.

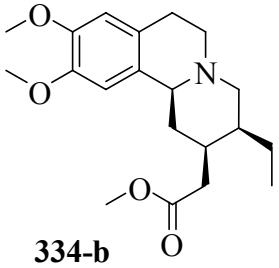
The 6-*exo* cyclisation product, **333**, was obtained as a yellow oil (148 mg, 9%) as a single diastereomer; Rf = 0.85 (10:10:1 petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3215 (w), 3053 (w), 1670 (s), 1432 (m), 1299 (m); δ_H (400 MHz, $CDCl_3$) 6.64 (1H, s, ^{Ar}CH), 6.55 (1H, s, ^{Ar}CH), 3.83 (3H, s, $^{Ar}OCH_3$), 3.82 (3H, s, $^{Ar}OCH_3$), 3.69 (3H, s, CO_2CH_3), 3.11 (1H, d, *J* = 11.6, NCH), 3.04 (1H, dd, *J* = 11.0 and 6.0 NCH_2CH_2Ar), 2.94 (1H, ddd, *J* =11.5, 6.0 and 1.7, NCH_2CH_2Ar), 2.90 (1H, dd *J* = 11.5 and 3.9, NCH_2CHCH_3), 2.65-2.60 (1H, m, NCH_2CH_2Ar), 2.60 (1H, dd, *J* = 15.4 and 4.1, $CHCH_2CO_2CH_3$), 2.46 (1H, td, *J* = 11.5 and 4.0, NCH_2CH_2Ar), 2.31 (1H, dt, *J* = 12.7 and 3.0, $CHCH_2CH$), 2.15 (1H, dd, *J* = 15.4 and 8.6, $CHCH_2CO_2CH_3$), 2.08 (1 H, t, *J* = 11.5, NCH_2CHCH_3), 1.77-1.67 (1H, m, $CHCH_2CO_2CH_3$), 1.65-1.56 (1H, m, $CHCH_3$), 1.24 (1H, dd, *J* = 12.7 and 11.6, $CHCH_2CH$), 0.92 (3H, d, *J* = 6.4, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 173.7 (CO_2CH_3), 147.5 ($^{Ar}COCH_3$), 147.2 ($^{Ar}COCH_3$), 129.7 (^{Ar}C), 126.7 (^{Ar}C), 111.5 (^{Ar}CH), 108.4 (^{Ar}CH), 64.1 (NCH_2CHCH_3), 62.5 ($NCHCH_3$), 56.2 ($^{Ar}OCH_3$), 55.8 ($^{Ar}OCH_3$), 52.1 (NCH_2CH_2Ar), 51.6 (CO_2CH_3), 40.2 ($CHCH_2CO_2CH_3$), 38.5 ($CHCH_2CO_2CH_3$), 37.6 ($CHCH_2CH$), 35.3 ($CHCH_3$), 29.2 (NCH_2CH_2Ar), 16.8 ($CHCH_3$).

The cyclic amide **337** was obtained as a pale yellow oil (401 mg, 31%); Rf = 0.10 (10:10:1 petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3203 (w), 3349 (w), 1658 (s); δ_H (400 MHz, $CDCl_3$) 6.66 (1H, s, $^{Ar}C\underline{H}$), 6.60 (1H, s, $^{Ar}C\underline{H}$), 4.86 (1H, ddd, *J* = 12.0, 4.5 and 3.0, $NC\underline{H}_2CH_2Ar$), 4.59 (1H, dd, *J* = 10.6 and 4.5, $NC\underline{H}$), 3.89 (3H, s, $^{Ar}OC\underline{H}_3$), 3.88 (3H, s, $^{Ar}OC\underline{H}_3$), 2.88 (1H, td, *J* = 15.2 and 4.5, $NCH_2\underline{CH}_2Ar$), 2.75 (1H, td, *J* = 12.0 and 3.0, $NC\underline{H}_2CH_2Ar$), 2.58-2.46 (2H, m, $NCHC\underline{H}_2$ and $NC(O)C\underline{H}_2$), 2.35 (1H, dd, *J* = 17.9 and 6.5, $NC(O)C\underline{H}_2$), 1.98-1.76 (2H, m, $NCHCH_2C\underline{H}_2$), 1.68 (1H, m, $NCHC\underline{H}_2$); δ_C (100 MHz, $CDCl_3$) 169.4 ($NC(O)CH_2$), 147.8 ($^{Ar}\underline{C}OCH_3$), 147.7 ($^{Ar}\underline{C}OCH_3$), 129.2 ($^{Ar}\underline{C}$), 127.3 ($^{Ar}\underline{C}$), 111.6 ($^{Ar}\underline{C}H$), 108.2 ($^{Ar}\underline{C}H$), 56.8 ($N\underline{C}H$), 56.1 ($^{Ar}O\underline{C}H_3$), 55.9 ($^{Ar}O\underline{C}H_3$), 39.7 ($N\underline{C}H_2CH_2Ar$), 32.3 ($NC(O)\underline{CH}_2$), 31.0 ($NCH\underline{C}H_2$), 28.5 ($N\underline{C}H_2CH_2Ar$), 19.7 ($NCHCH_2\underline{C}H_2$); *m/z* (CI, NH_3) 284 (20%, MNa^+), 263 (15), 262 (109, MH^+); HRMS $C_{15}H_{20}NO_3$ (MH^+), requires 262.1438, found 262.1438.

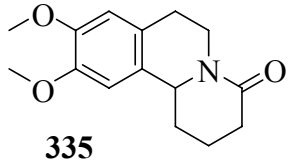
Methyl 2-((2*R,3*R**,11b*S**)-3-ethyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate (334-a) methyl 2-((2*R**,3*S**,11b*S**)-3-ethyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate (334-b) and 9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one**



334-a
major d.s.



334-b
minor d.s.



335

A solution of methyl 4-(2-(but-2-enyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)-3-(phenylselanyl)butanoate (**332**) (1.0 g, 2.0 mmol) in THF (125 mL) was stirred at reflux for 30 minutes under nitrogen. Then AIBN (0.016 g, 0.1 mmol) was added, followed by the slow addition of a solution of tributyltin hydride (0.81 mL, 3.0 mmol) and AIBN (0.15 g, 0.9 mmol) in THF (20 mL) by a syringe pump over a period of 8 h. Following the completion of the addition of the tributyltin hydride, the solution was maintained at reflux for a further 4 h, after which the solution was cooled to r.t. The crude product was passed thought an SCX column, elution gradient 4:1 DCM:MeOH to 4:1 DCM:MeOH/NH_3, and evaporated to afford a yellow oil. The oil was then purified by flash silica chromatography, elution gradient 6:1 petrol:EtOAc to 10:10:1 petrol:EtOAc:MeOH/NH_3. Pure fractions were concentrated *in vacuo*, to afford the title compounds **334a**, **334b** and **335**.

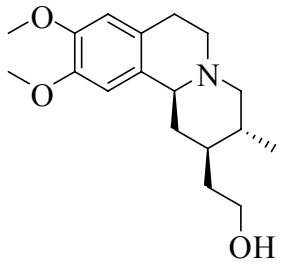
The 6-*exo* cyclisation products were obtained as a 2:1 ratio of diastereomers. The major diastereomer, **334-a** was obtained as a yellow oil, (37 mg, 5.5%); Rf = 0.80 (10:10:1

petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3048 (w), 1668 (s), 1433 (m), 1301 (m); δ_H (400 MHz, $CDCl_3$) 6.64 (1H, s, $^{Ar}C\underline{H}$), 6.55 (1H, s, $^{Ar}C\underline{H}$), 3.83 (3H, s, $^{Ar}OC\underline{H}_3$), 3.82 (3H, s, $^{Ar}OC\underline{H}_3$), 3.69 (3H, s, $CO_2C\underline{H}_3$), 3.13-3.03 (3H, m, NC$\underline{H}$, NC$\underline{H}_2$CH and $NCH_2C\underline{H}_2Ar$), 2.95 (1H, dd, *J* = 11.3 and 4.7, NC$\underline{H}_2CH_2Ar$), 2.67-2.59 (2H, m, CHC$\underline{H}_2CO_2CH_3$ and $NCH_2C\underline{H}_2Ar$), 2.55-2.42 (1H, m, NC$\underline{H}_2CH_2Ar$), 2.36-2.29 (1H, m, CHC$\underline{H}_2$CH), 2.14 (1H, dd, *J* = 15.4 and 8.7, CHC$\underline{H}_2CO_2CH_3$), 2.04 (1H, t, *J* = 11.2, NC$\underline{H}_2$CH), 1.91-1.10 (5H, m, C$\underline{H}CH_2CO_2CH_3$, C$\underline{H}_2CH_3$, C$\underline{H}CH_2CH_3$ and CHC$\underline{H}_2$CH), 0.91 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 173.7 ($\underline{C}O_2CH_3$), 147.4 ($^{Ar}\underline{C}OCH_3$), 147.0 ($^{Ar}\underline{C}OCH_3$), 129.7 ($^{Ar}\underline{C}$), 126.6 ($^{Ar}\underline{C}$), 111.3 ($^{Ar}\underline{C}H$), 108.2 ($^{Ar}\underline{C}H$), 62.4 (N$\underline{C}$H), 61.0 (N$\underline{C}H_2$CH), 56.0 (O$\underline{C}H_3$), 55.7 (O$\underline{C}H_3$), 52.3 (N$\underline{C}H_2CH_2Ar$), 51.5 ($CO_2\underline{C}H_3$), 41.3 ($\underline{C}HCH_2CH_3$), 38.3 (CH$\underline{C}H_2CO_2CH_3$), 37.9 ($\underline{C}HCH_2CO_2CH_3$), 37.7 (CH$\underline{C}H_2$CH), 29.1 ($NCH_2\underline{C}H_2Ar$), 23.5 ($\underline{C}H_2CH_3$), 11.0 ($CH_2\underline{C}H_3$); *m/z* (CI, NH_3) 349 (20%), 348 (MH^+, 100); HRMS $C_{20}H_{30}NO_4$ (MH^+) requires 348.2169, found 348.2171.

The minor diastereomer, **334-b**, was obtained as a yellow oil (18 mg, 2.5%); Rf = 0.85 (10:10:1 petrol:EtOAc:MeOH/NH_3); δ_H (400 MHz, $CDCl_3$) 6.65 (1H, s, $^{Ar}C\underline{H}$), 6.56 (1H, s, $^{Ar}C\underline{H}$), 3.83 (3H, s, $^{Ar}OC\underline{H}_3$), 3.82 (3H, s, $^{Ar}OC\underline{H}_3$), 3.70 (3H, s, $CO_2C\underline{H}_3$), 3.12-3.02 (2H, m, NC$\underline{H}$ and $NCH_2C\underline{H}_2Ar$), 2.96 (1H, dd, *J* = 11.5 and 2.1, NC$\underline{H}_2$CH), 2.83 (1H, dd, *J* = 11.5 and 5.5, NC$\underline{H}_2CH_2Ar$), 2.56 (1H, dd, *J* = 15.5 and 3.1, $NCH_2C\underline{H}_2Ar$), 2.44 (1H, td, *J* = 11.7 and 3.8, NC$\underline{H}_2CH_2Ar$), 2.38-2.25 (4H, m, C$\underline{H}CH_2CO_2CH_3$, NC$\underline{H}_2$CH and CHC$\underline{H}_2CO_2CH_3$), 2.04 (1H, dt, *J* = 12.6 and 2.5, CHC$\underline{H}_2$CH), 1.72-1.57 (1H, m, C$\underline{H}_2CH_3$), 1.54-1.46 (1H, m, C$\underline{H}CH_2CH_3$), 1.36-1.20 (2H, m, CHC$\underline{H}_2$CH and C$\underline{H}_2CH_3$), 0.89 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 173.5 ($\underline{C}O_2CH_3$), 147.2 ($^{Ar}\underline{C}OCH_3$), 147.0 ($^{Ar}\underline{C}OCH_3$), 130.3 ($^{Ar}\underline{C}$), 126.9 ($^{Ar}\underline{C}$), 111.4 ($^{Ar}\underline{C}H$), 108.0 ($^{Ar}\underline{C}H$), 63.0 (N$\underline{C}$H), 58.7 (N$\underline{C}H_2$CH), 56.0 ($^{Ar}O\underline{C}H_3$), 55.7 ($^{Ar}O\underline{C}H_3$), 52.8 (N$\underline{C}H_2CH_2Ar$), 51.5 ($CO_2\underline{C}H_3$), 39.0 ($\underline{C}HCH_2CH_3$), 38.2 (CH$\underline{C}H_2CO_2CH_3$), 37.3 ($\underline{C}HCH_2CO_2CH_3$), 33.5 (CH$\underline{C}H_2$CH), 29.3 ($NCH_2\underline{C}H_2Ar$), 17.7 ($\underline{C}H_2CH_3$), 12.4 ($CH_2\underline{C}H_3$); *m/z* (CI, NH_3) 349 (20%), 348 (MH^+, 100); HRMS $C_{20}H_{30}NO_4$ (MH^+) requires 348.2169, found 348.2160.

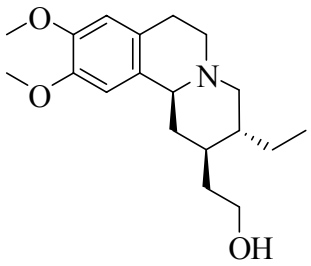
The cyclic amide **337** was obtained as a pale yellow oil (144 mg, 28%); the spectroscopic data is in agreement with material prepared previously.

2-((2*R,3*R**,11b*S**)-9,10-Dimethoxy-3-methyl-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl)ethanol, (±)-des-methyl-protoemetinol (342-a)**



To a stirred solution of methyl 2-((2*R**,3*R**,11b*S**)-9,10-dimethoxy-3-methyl-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate **333** (60 mg, 0.18 mmol) in THF (10 mL) at 0 ºC under nitrogen, was slowly added a solution of lithium aluminium hydride in THF (1.1 mL, 2.4 M, 2.7 mmol). The solution was stirred for 15 minutes at 0 ºC, then warmed to r.t. and stirred for 6 h. The stirred reaction mixture was then quenched by the sequential dropwise addition of H_2O (0.1 mL), 15% aqueous NaOH (0.1 mL) and H_2O (0.33 mL), afterwhich evaporation of the solvent afforded the crude product as a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 10 to 20% MeOH/NH_3 in DCM. Pure fractions were concentrated *in vacuo* to afford the title compound as a yellow oil (45 mg, 80%); Rf = 0.30 (10:2:1 petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1}) 3460 (bs), 3040 (w), 2910 (w), 1422 (m), 1291 (w); δ_H (400 MHz, $CDCl_3$) 6.66 (1H, s, $^{Ar}C\underline{H}$), 6.55 (1H, s, $^{Ar}C\underline{H}$), 3.83 (3H, s, $OC\underline{H}_3$), 3.82 (3H, s, $OC\underline{H}_3$), 3.81-3.70 (2H, m, $OC\underline{H}_2$), 3.14-3.03 (2H, m, $NC\underline{H}$ and $NCH_2C\underline{H}_2Ar$), 2.97-2.92 (1H, m, $NC\underline{H}_2CH_2Ar$), 2.89 (1H, dd, *J* = 11.5 and 4.0, $NC\underline{H}_2CHCH_3$), 2.65-2.56 (1H, m, $NCH_2C\underline{H}_2Ar$), 2.44 (1H, td, *J* = 11.5 and 4.0, $NC\underline{H}_2CH_2Ar$), 2.31 (1H, dt, *J* = 11.5 and 3.0, $CHC\underline{H}_2CH$), 2.02 (1H, t, *J* = 11.2, $NC\underline{H}_2CHCH_3$), 1.97-1.89 (1H, m, $CHC\underline{H}_2CH_2OH$), 1.90 (1H, bs, $CH_2O\underline{H}$), 1.65-1.50 (1H, m, $C\underline{H}CH_3$), 1.45-1.26 (2H, m, $CHC\underline{H}_2CH_2OH$ and $C\underline{H}CH_2CH_2OH$), 1.19 (1H, app q, *J* = 11.5, $CHC\underline{H}_2CH$), 0.91 (3H, d, *J* = 6.5, $CHC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 147.3 ($^{Ar}\underline{C}OCH_3$), 147.0 ($^{Ar}\underline{C}OCH_3$), 129.9 ($^{Ar}\underline{C}$), 126.6 ($^{Ar}\underline{C}$), 111.4 ($^{Ar}\underline{C}H$), 108.2 ($^{Ar}\underline{C}H$), 64.6 ($N\underline{C}H_2CHCH_3$), 62.6 ($N\underline{C}H$), 60.4 ($OC\underline{H}_2$), 56.0 ($^{Ar}OC\underline{H}_3$), 55.7 ($^{Ar}O\underline{C}H_3$), 52.1 ($N\underline{C}H_2CH_2Ar$), 39.8 ($\underline{C}HCH_2CH_2OH$), 36.9 ($CH\underline{C}H_2CH$), 36.0 ($CH\underline{C}H_2CH_2OH$), 35.1 ($\underline{C}HCH_3$), 29.0 ($NCH_2\underline{C}H_2Ar$), 16.8 ($CH\underline{C}H_3$); *m/z* (CI) 307 (15%), 306 (MH^+, 100), 304 (10); HRMS $C_{18}H_{28}NO_3$ (MH^+) requires 306.2064, found 306.2065.

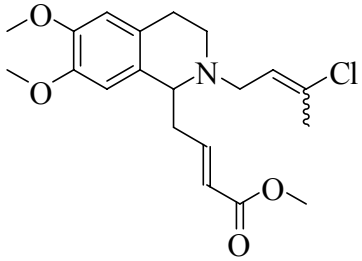
2-((2*R,3*R**,11b*S**)-3-Ethyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl)ethanol, protoemetinol (88-a)**



To a stirred solution of methyl 2-((2*R**,3*R**,11b*S**)-9,10-dimethoxy-3-methyl-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate **334** (31 mg, 0.09 mmol) in THF (5 mL) at 0 ºC under nitrogen, was slowly added a solution of lithium aluminium hydride in THF (0.55 mL, 2.4 M, 1.35 mmol). The solution was stirred for 15 minutes at 0 ºC, then warmed to r.t. and stirred for 6 h. The stirred reaction mixture was then quenched by the sequential dropwise addition of H_2O (0.05 mL), 15% aqueous NaOH (0.05 mL) and H_2O (0.16 mL), afterwhich evaporation of the solvent afforded the crude product as a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 10 to 20% MeOH/NH_3 in DCM. Pure fractions were concentrated *in vacuo* to afford the title compound, protoemetinol (**88-a**) as a yellow oil (21 mg, 76%); Rf = 0.35 (10:2:1 petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 3450 (sb), 2932 (w), 1512 (m), 1426 (m), 1252 (m); δ_H (400 MHz, $CDCl_3$) 6.69 (1H, s, ^{Ar}CH), 6.57 (1H, s, ^{Ar}CH), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.81-3.70 (2H, m, OCH_2), 3.14-3.03 (3H, m, NCH, NCH_2CH_2Ar and CH_2OH), 2.96 (1H, m, NCH_2CHCH_3), 2.61 (1H, dd, *J* = 16.0 and 4.0, NCH_2CH_2Ar), 2.64-2.60 (1H, m, NCH_2CH_2Ar), 2.47 (1H, td, *J* = 11.5 and 4.0, NCH_2CH_2Ar), 2.37-2.30 (1H, app d, *J* = 12.0, $CHCH_2CH$), 2.01 (1H, t, *J* = 11.0, NCH_2CHCH_3), 1.97-1.92 (2H, m, $CHCH_2CH_2OH$ and $CHCH_2CH_3$), 1.70-1.64 (1H, m, $CHCH_2CH_3$), 1.44-1.41 (2H, m, $CHCH_2CH_2OH$ and $CHCH_2CH_3$), 1.28-1.24 (1H, m, $CHCH_2CH_2OH$), 1.10-1.00 (1H, m, $CHCH_2CH$), 0.92 (3H, t, *J* = 7.5, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 147.4 ($^{Ar}COCH_3$), 147.0 ($^{Ar}COCH_3$), 129.4 (^{Ar}C), 126.3 (^{Ar}C), 111.4 (^{Ar}CH), 108.1 (^{Ar}CH), 62.6 (NCH), 61.1 (OCH_2), 60.2 (NCH_2CH), 56.2 ($^{Ar}OCH_3$), 55.7 ($^{Ar}OCH_3$), 52.2 (NCH_2CH_2Ar), 40.8 (CH), 37.4 (CH), 36.9 ($CHCH_2CH$), 35.6 ($CHCH_2CH_2OH$), 29.5 (NCH_2CH_2Ar), 23.3 ($CHCH_2CH_3$), 11.0 ($CHCH_2CH_3$); *m/z* (CI) 321 (20%), 320 (MH^+, 100); HRMS $C_{19}H_{30}NO_3$ (MH^+) requires 320.2220, found 320.2224.

The spectroscopic data is in agreement with reported data.[156, 157]

Methyl (*E*)-4-(2-((*E*/*Z*)-3-chlorobut-2-enyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate (345)

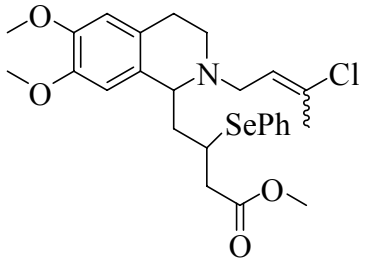


To a stirred solution of 6,7-dimethoxy-3,4-dihydroisoquinoline **188** (4.4 g, 23.0 mmol), in DCM (100 mL) at r.t. under nitrogen was added 1,3-dichloro-2-butene (3.0 mL, 27.6 mmol). The resulting solution was stirred in the dark for 3 days. The crude mixture was evaporated to dryness to afford the salt as a moisture sensitive yellow oil. To a stirred solution of the oil in acetonitrile (100 mL) was added methyl (E)-4-bromobut-2-enoate (4.8 ml, 34.5 mmol) and zinc dust (2.3 g, 34.5 mmol), the resulting suspension was stirred at room temp for 48 h and stirred at r.t. under nitrogen for 2 days. The reaction mixture was quenched by pouring into a saturated solution of aq. $NaHCO_3$ (150 mL) and allowed to stir for 30 minutes. The resulting precipitate was removed by filtration, and washed with EtOAc (100 mL), the organic layer was separated and the aqueous layer extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 4:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compounds as a mixture of separable isomers.

The major isomer, methyl (*E*)-4-(2-((*E*)-3-chlorobut-2-enyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate was isolated as a yellow oil (2.6 g, 31%), Rf = 0.48 (ethyl acetate:petrol, 1:1); ν_{max} (thin film) /cm^{-1} 2995 (w), 2948 (s), 2835 (m), 1722 (s), 1656 (m), 1516 (s); δ_H (400 MHz, $CDCl_3$) 6.96 (1H, dt, *J* = 15.7 and 7.2, C<u>H</u>=CHCO$_2$CH$_3$), 6.53 (1H, s, ^{Ar}C<u>H</u>), 6.45 (1H, s, ^{Ar}C<u>H</u>), 5.77 (1H, dt, *J* = 15.7 and 1.3, CH=C<u>H</u>CO$_2$CH$_3$), 5.57 (1H, app td, *J* = 5.5 and 1.0, NCH$_2$C<u>H</u>=C(Cl)CH$_3$), 3.80 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.77 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.68 (1H, t, *J* = 6.2, NC<u>H</u>), 3.66 (3H, s, CO$_2$C<u>H</u>$_3$), 3.40-3.25 (2H, m, NC<u>H</u>$_2$CH=C(Cl)CH$_3$), 3.10-3.02 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 2.84-2.75 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NCH$_2$C<u>H</u>$_2$Ar), 2.66-2.42 (3H, m, C<u>H</u>$_2$CH=CHCO$_2$CH$_3$ and NCH$_2$C<u>H</u>$_2$^{Ar}), 2.08 (3H, d, *J* = 1.0, NCH$_2$CH=C(Cl)C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 166.9 (<u>C</u>O$_2$CH$_3$), 147.6 (<u>C</u>H=CHCO$_2$CH$_3$), 147.5 (^{Ar}<u>C</u>OCH$_3$), 147.1 (^{Ar}<u>C</u>OCH$_3$), 132.5 (<u>C</u>), 128.7 (<u>C</u>), 126.6 (<u>C</u>), 123.6 (<u>C</u>H=C(Cl)CH$_3$), 122.1 (CH=<u>C</u>HCO$_2$CH$_3$), 111.5 (^{Ar}C<u>H</u>), 110.4 (^{Ar}C<u>H</u>), 60.2 (NC<u>H</u>), 55.9 (^{Ar}O<u>C</u>H$_3$), 55.8 (^{Ar}O<u>C</u>H$_3$), 52.1 (N<u>C</u>H$_2$CH=C(Cl)CH$_3$), 51.4 (CO$_2$<u>C</u>H$_3$), 44.2 (N<u>C</u>H$_2$CH$_2$Ar), 38.2 (<u>C</u>H$_2$CH=CHCO$_2$CH$_3$), 26.4 (CH=C(Cl)<u>C</u>H$_3$), 25.0 (NCH$_2$<u>C</u>H$_2$Ar).

The minor isomer, methyl (*E*)-4-(2-((*Z*)-3-chlorobut-2-enyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate was isolated as a yellow oil (0.52 g, 7%); δ_H (400 MHz, $CDCl_3$) 6.97 (1H, dt, *J* = 15.6 and 7.3, C<u>H</u>=CHCO$_2$CH$_3$), 6.54 (1H, s, ^{Ar}C<u>H</u>), 6.45 (1H, s, ^{Ar}C<u>H</u>), 5.78 (1H, dt, *J* = 15.6 and 1.4, CH=C<u>H</u>CO$_2$CH$_3$), 5.70 (1H, td, *J* = 7.1 and 1.2, C<u>H</u>=C(Cl)CH$_3$), 3.82 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.79 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.72-3.68 (1H, m, NC<u>H</u>), 3.68 (3H, s, CO$_2$C<u>H</u>$_3$), 3.18 (2H, app dd, *J* = 7.3 and 0.8, NC<u>H</u>$_2$CH=C(Cl)CH$_3$), 3.14-3.05 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 2.83-2.72 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NCH$_2$C<u>H</u>$_2$Ar), 2.65-2.47 (3H, m, C<u>H</u>$_2$CH=CHCO$_2$CH$_3$ and NCH$_2$C<u>H</u>$_2$Ar), 1.99 (3H, d, *J* = 0.8, NCH$_2$CH=C(Cl)C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 166.9 (<u>C</u>O$_2$CH$_3$), 147.7 (^{Ar}<u>C</u>OCH$_3$), 147.3 (<u>C</u>H=CHCO$_2$CH$_3$), 147.2 (^{Ar}<u>C</u>OCH$_3$), 132.4 (<u>C</u>), 128.5 (<u>C</u>), 126.3 (<u>C</u>), 125.3 (<u>C</u>H=C(Cl)CH$_3$), 122.2 (CH=<u>C</u>HCO$_2$CH$_3$), 111.5 (^{Ar}<u>C</u>H), 110.4 (^{Ar}<u>C</u>H), 59.8 (N<u>C</u>H), 55.9 (^{Ar}O<u>C</u>H$_3$), 55.8 (^{Ar}O<u>C</u>H$_3$), 51.4 (CO$_2$<u>C</u>H$_3$), 51.3 (N<u>C</u>H$_2$CH=C(Cl)CH$_3$), 43.7 (N<u>C</u>H$_2$CH$_2$Ar), 38.6 (<u>C</u>H$_2$CH=CHCO$_2$CH$_3$), 24.4 (NCH$_2$<u>C</u>H$_2$Ar), 21.3 (CH=C(Cl)<u>C</u>H$_3$).

Methyl 4-(2-[(2E)-3-chlorobut-2-en-1-yl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-(phenylselanyl)butanoate (343)

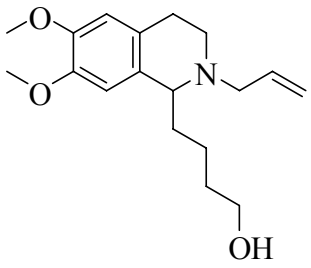


To a stirred suspension of diphenyl diselenide (2.1 g, 6.7 mmol) in degassed EtOH (30 mL) in a 100 mL two-neck round-bottom flask under nitrogen was added sodium borohydride (0.68 g, 18 mmol), until the solution became colourless. The resulting reaction mixture was then cooled to 0 °C in an ice bath for 5 min. Glacial acetic acid (2.1 mL, 36 mmol) was added dropwise via syringe, and the mixture allowed to stir for 5 minutes. Then methyl (*E*)-4-(2-((E)-3-chlorobut-2-enyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate **345** (1.7 g, 4.5 mmol) was added in degassed EtOH (10 mL) via cannula, the reaction was stirred for 5 min at 0 ºC, and then allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into H_2O (50 mL) and was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (2 × 75 mL), dried over $MgSO_4$, and concentrated to give a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 8:1 petrol:EtOAc to EtOAc. The pure fractions were concentrated *in vacuo* to afford the title compound as a yellow gum (1.28 g, 36%) as a 5:1 mixture of inseparable diastereomers; ν_{max} (thin film) /cm^{-1} 2998

(m), 2948 (s), 2837 (m), 1734 (s), 1610 (w), 1511 (s); major diastereomer, δ_H (400 MHz, $CDCl_3$) 7.72-7.67 (2H, m, $^{Ph}C\underline{H}$), 7.33-7.27 (3H, m, $^{Ph}C\underline{H}$), 6.51 (1H, s, $^{Ar}C\underline{H}$), 6.32 (1H, s, $^{Ar}C\underline{H}$), 5.65 (1H, t, *J* = 5.6, $NCH_2C\underline{H}=C(Cl)CH_3$), 3.92-3.84 (2H, m, N$C\underline{H}$ and $C\underline{H}$SePh), 3.82 (3H, s, $^{Ar}OC\underline{H}_3$), 3.78 (3H, s, $^{Ar}OC\underline{H}_3$), 3.63 (3H, s, $CO_2C\underline{H}_3$), 3.38 (1H, dd, *J* = 13.5 and 5.6, $NC\underline{H}_2CH=C(Cl)$), 3.20 (1H, dd, *J* = 13.5 and 5.6, $NC\underline{H}_2CH=C(Cl)$), 3.14-3.08 (1H, m, $NC\underline{H}_2CH_2Ar$), 2.96-2.86 (2H, m, $NC\underline{H}_2CH_2Ar$ and $NCH_2C\underline{H}_2Ar$), 2.80 (1H, dd, *J* = 15.9 and 8.7, $CH(SePh)C\underline{H}_2CO_2CH_3$), 2.72 (1H, dd, *J* = 15.9 and 8.0, $CH(SePh)C\underline{H}_2CO_2CH_3$), 2.38-2.28 (1H, m, $NCH_2C\underline{H}_2Ar$), 2.09 (3H, d, *J* = 1.2, $CH=C(Cl)C\underline{H}_3$), 2.03-1.94 (1H, m, $NCHC\underline{H}_2CHSePh$), 1.64 (1H, ddd, *J* = 14.3, 11.0 and 3.7, N$C\underline{H}CH_2CHSePh$); δ_C (100 MHz, $CDCl_3$) 172.3 ($\underline{C}O_2CH_3$), 147.5 ($^{Ar}\underline{C}OCH_3$), 147.4 ($^{Ar}\underline{C}OCH_3$), 135.7 (2 × $^{Ph}\underline{C}H$), 131.6 ($CH=\underline{C}(Cl)CH_3$), 129.6 ($^{Ar}\underline{C}$), 129.1 (2 × $^{Ph}\underline{C}H$), 127.9 ($^{Ph}\underline{C}H$), 126.1 ($^{Ar}\underline{C}$), 124.9 ($^{Ar}\underline{C}$ and $NCH_2\underline{C}HC(Cl)CH_3$), 111.5 ($^{Ar}\underline{C}H$), 110.4 ($^{Ar}\underline{C}H$), 58.5 (N$\underline{C}H$), 56.0 ($^{Ar}CO\underline{C}H_3$), 55.8 ($^{Ar}CO\underline{C}H_3$), 51.7 ($CO_2\underline{C}H_3$), 51.6 ($N\underline{C}H_2CH=C(Cl)$), 42.2 ($CH(SePh)\underline{C}H_2CO_2CH_3$), 42.1 ($N\underline{C}H_2CH_2Ar$), 41.8 ($NCH\underline{C}H_2CHSePh$), 37.7 ($\underline{C}H$SePh), 26.4 ($CH=C(Cl)\underline{C}H_3$), 22.0 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI), 540 ($M^{80}Se^{37}ClH^+$, 30%), 539 (20), 538 ($M^{80}Se^{35}ClH^+$ and $M^{78}Se^{37}ClH^+$, 100), 537 (10), 536 ($M^{78}Se^{35}ClH^+$ and $M^{76}Se^{37}ClH^+$, 60), 535 (17), 534 ($M^{76}Se\ Se^{35}H^+$, 20); HRMS $C_{26}H_{33}ClNO_4Se$ ($M^{80}Se^{35}ClH^+$) requires 538.1258, found 538.1266.

The minor diastereomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 7.58-7.54 (2H, m, PhSeC$\underline{H}$), 7.30-7.27 (3H, m, PhSeC$\underline{H}$), 6.53 (1H, s, $^{Ar}C\underline{H}$), 6.40 (1H, s, $^{Ar}C\underline{H}$).

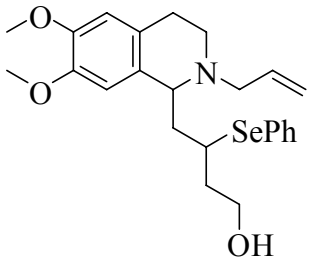
4-(2-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-1-ol (347)



To a stirred solution of methyl 4-(2-[(2*E*)-3-chlorobut-2-en-1-yl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-(phenylselanyl)butanoate (**331**) (1.6 g, 3.2 mmol) in THF (50 mL) at 0 ºC under nitrogen, was slowly added a solution of lithium aluminium hydride in THF (8.0 mL, 2.4 M, 19.2 mmol). The solution was stirred for 15 minutes at 0 ºC, then warmed to r.t. and stirred for 6 h. The stirred reaction mixture was then quenched by the sequential dropwise addition of H_2O (0.72 mL), 15% aqueous NaOH (0.72 mL) and H_2O (2.16 mL). The resulting mixture was stirred for 30 minutes and evaporation of the solvent

afforded the crude product as an oil. The crude oil was purified by flash silica chromatography, elution gradient 1:9 to 2:8 MeOH/NH_3:DCM. Pure fractions were concentrated *in vacuo* to afford the title compound **347**, as a yellow oil (0.38 g, 42%); Rf = 0.35 (1:9 MeOH/NH_3:DCM); ν_{max} (thin film) /cm^{-1} 3400 (sb), 3054 (w), 2920 (w), 1526 (m); δ_H (400 MHz, $CDCl_3$) 6.52 (1H, s, ArC<u>H</u>), 6.49 (1H, s, ArC<u>H</u>), 5.89 (1H, ddt, *J* = 17.0, 10.2 and 6.5, C<u>H</u>=CH_2), 5.16-5.07 (2H, m, CH=C<u>H</u>$_2$), 3.84 (1H, bs, OH), 3.81 (6H, s, 2 × ArOC<u>H</u>$_3$), 3.61 (2H, t, *J* = 6.0, HOC<u>H</u>$_2$), 3.50 (1H, dd, *J* = 8.3 and 4.4, NC<u>H</u>$_2$), 3.17 (2H, d, *J* = 6.5, NC<u>H</u>$_2$CH=CH_2), 3.15 (1H, app q, *J* = 6.9, NC<u>H</u>$_2$), 2.85-2.74 (2H, m, NC<u>H</u>$_2$ and ArC<u>H</u>$_2$), 2.45-2.40 (1H, m, ArC<u>H</u>$_2$), 1.69-1.46 (6H, m, CHC<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$$CH_2$OH); δ_C (100 MHz, $CDCl_3$) 147.2 (Ar<u>C</u>OCH_3), 147.1 (Ar<u>C</u>OCH_3), 136.2 (<u>C</u>H=CH_2), 130.1 (Ar<u>C</u>), 126.0 (ArC), 117.3 (CH=<u>C</u>H_2), 111.2 (Ar<u>C</u>H), 110.6 (Ar<u>C</u>H), 62.2 (<u>C</u>H_2OH), 60.0 (N<u>C</u>H), 56.5 (<u>C</u>H_2), 55.8 (O<u>C</u>H_3), 55.7 (O<u>C</u>H_3), 43.3 (N<u>C</u>H_2), 35.4 (<u>C</u>H_2), 32.2 (<u>C</u>H_2), 23.3 (Ar<u>C</u>H_2), 22.5 (<u>C</u>H_2); *m/z* (CI) 329 (20%), 328 (MNa^+, 100), 306 (45); HRMS $C_{18}H_{27}NNaO_3$ (MNa^+) requires 328.1883, found 328.1885.

4-(2-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-(phenylselanyl)butan-1-ol (346)

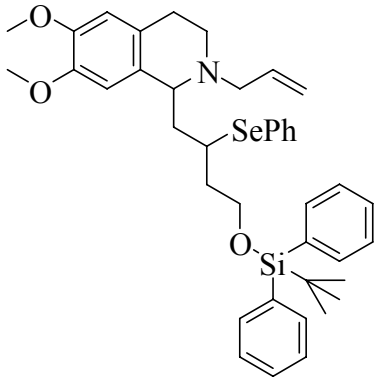


To a stirred suspension of aluminium chloride (0.56 g, 4.2 mmol) in THF (25 mL) at 0 ºC, was slowly added a solution of lithium aluminium hydride in THF (5.2 mL, 2.4 M, 12.6 mmol) and the resulting solution was stirred for 10 minutes, after which the solution was cooled to -78 ºC, and a solution of methyl 4-(2-[(2*E*)-3-chlorobut-2-en-1-yl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-(phenylselanyl)butanoate (**331**) (1.03 g, 2.1 mmol) in THF (10 mL) was added dropwise. The mixture was stirred for 6 h at -78 °C, and then quenched by the sequential dropwise addition of H_2O (0.45 mL), 15% aqueous NaOH (0.45 mL) and H_2O (1.35 mL) at -78 ºC. After 5 min the resulting solution was warmed to r.t., then EtOAc (20 mL) and celite (1.5 g) were added and stirred for 1 h. The reaction mixture was filtered through celite (1 g) and flushed through with EtOAc (2 × 15 mL). Evaporation of the volatile materials *in vacuo* afforded the title compound **346** as a yellow oil (965 mg, 99%), which was used straight away; δ_H (400 MHz, $CDCl_3$) 7.62-7.56 (2H, m, ^{Ph}C<u>H</u>), 7.24-7.18 (3H, m, ^{Ph}C<u>H</u>), 6.44 (1H, s, ^{Ar}C<u>H</u>), 6.19 (1H, s, ^{Ar}C<u>H</u>), 5.92-5.80

(1H, m, C<u>H</u>=CH_2), 5.12-5.03 (2H, m, CH=C<u>H_2</u>), 3.78-3.73 (1H, m, NC<u>H</u>), 3.76 (3H, s, ^{Ar}OC<u>H_3</u>), 3.71 (3H, s, ^{Ar}OC<u>H_3</u>), 3.73-3.66 (2H, m, C<u>H_2</u>OH), 3.62-3.54 (1H, m, C<u>H</u>SePh), 3.22-2.99 (5H, m, NC<u>H_2</u>CH=CH_2, CH_2O<u>H</u> and NC<u>H_2</u>CH_2Ar), 2.92 (1H, dd, *J* = 13.9 and 5.7, NCH_2C<u>H_2</u>Ar), 2.84-2.72 (2H, m, CH(SePh)C<u>H_2</u>CH_2OH), 2.26 (1H, dd, *J* = 16.0 and 4.8, NCH_2C<u>H_2</u>Ar), 2.11-2.02 (1H, m, NCHC<u>H_2</u>CHSePh), 1.80-1.72 (1H, m, NCHC<u>H_2</u>CHSePh); δ_C (100 MHz, $CDCl_3$) 147.6 (^{Ar}<u>C</u>OCH_3), 147.5 (^{Ar}<u>C</u>OCH_3), 135.7 (<u>C</u>H=CH_2), 135.1 (2 × ^{Ph}CH), 134.1 (^{Ph}<u>C</u>H), 129.3 (^{Ph}<u>C</u>), 129.1 (^{Ph}<u>C</u>H), 128.9 (^{Ar}<u>C</u>), 127.7 (^{Ph}<u>C</u>H), 125.5 (^{Ar}<u>C</u>), 118.4 (CH=<u>C</u>H_2), 111.2 (^{Ar}<u>C</u>H), 110.5 (^{Ar}<u>C</u>H), 60.5 (<u>C</u>H_2OH), 59.6 (N<u>C</u>H), 56.3 (N<u>C</u>H_2CH=CH_2), 56.1 (^{Ar}O<u>C</u>H_3), 55.9 (^{Ar}OCH_3), 42.3 (N<u>C</u>$H_2$$CH_2$Ar), 42.2 ($CH_2$CH(SePh)), 40.1 (CHSePh), 39.2 (CH_2CH(SePh)), 21.6 (NCH_2<u>C</u>H_2Ar); *m/z* (CI, NH_3) 464 (20%), 463 (23), 462 ($M^{80}SeH^+$, 100), 461 (10), 460 ($M^{78}SeH^+$, 50), 459 (18), 458 ($M^{76}SeH^+$, 17); HRMS $C_{24}H_{32}NOSe$ ($M^{80}SeH^+$) requires 462.1542, found 462.1541.

The minor diastereoisomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 7.47-7.43 (2H, m, ^{Ph}C<u>H</u>), 7.20-7.17 (3H, m, ^{Ph}C<u>H</u>), 6.43 (1H, s, ^{Ar}CH), 6.41 (1H, s, ^{Ar}CH).

2-Allyl-1-(4-(*tert*-butyldiphenylsilyloxy)-2-((phenylselanyl)butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (348)

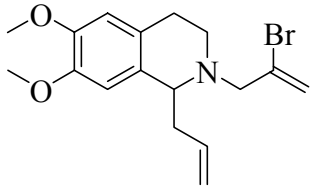


To a stirred solution of the crude 4-(2-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-(phenylselanyl)butan-1-ol **346** (0.96 g, 2.10 mmol) and imidazole (0.34 g, 5.0 mmol) in dichloromethane (50 mL) under nitrogen at 0 ºC was added dropwise *tert*-butyl diphenylchlorosilane (0.65 mL, 2.5 mmol). After 20 min, the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was quenched with brine, and extracted with further portion of DCM, and dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (silica, ethyl acetate:petrol 5:1-2:1) and concentration of the pure fractions afforded the title compound **348** as a yellow oil (1.14 g, 78%); Rf = 0.30 (5:1, EtOAc:Petrol); ν_{max} (thin film) /cm^{-1} 3070 (m), 2997 (m), 2931 (s), 2856 (s), 1515 (s),

1463 (m); δ_H (400 MHz, $CDCl_3$) 7.68-7.59 (5H, m, SiPh), 7.42-7.34 (7H, m, SiPh), 7.26-7.23 (3H, m, SiPh), 6.45 (1H, s, ArCH), 6.30 (1H, s, ArCH), 5.84-5.73 (1H, m, C<u>H</u>=CH_2), 5.06-4.95 (2H, m, CH=C<u>H</u>$_2$), 3.88-3.70 (4H, m, NC<u>H</u>, C<u>H</u>SePh and C<u>H</u>$_2$OSi), 3.76 (3H, s, OC<u>H</u>$_3$), 3.71 (3H, s, OC<u>H</u>$_3$), 3.24 (1H, dd, J = 6.9 and 13.4, NC<u>H</u>$_2$CH=CH_2), 3.16-3.04 (2H, m, NC<u>H</u>$_2$CH=CH_2 and NC<u>H</u>$_2$$CH_2$Ar), 2.97-2.80 (2H, m, NC<u>H</u>$_2$$CH_2$Ar and NCH_2C<u>H</u>$_2$Ar), 2.27 (1H, dd, J = 16.3 and 4.4, NCH_2C<u>H</u>$_2$Ar), 2.09-1.97 (2H, m, C<u>H</u>$_2$CH(SePh)C<u>H</u>$_2$), 1.92 (1H, app q, J = 6.3, CH_2CH(SePh)), 1.69 (1H, app ddd, J = 14.5, 10.7 and 3.2, CH_2CH(SePh)), 1.05 (9H, s, SiC(C<u>H</u>$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 147.4 (^{Ar}<u>C</u>OCH_3), 147.3 (^{Ar}<u>C</u>OCH_3), 137.4 (<u>C</u>H=CH_2), 135.6 (4 × ^{SiPh}CH), 134.6 (2 × ^{SePh}CH), 134.0 (^{SiPh}<u>C</u>H), 139.9 (^{SiPh}<u>C</u>H), 130.5 (^{SePh}<u>C</u>H), 130.0 (^{Ar}<u>C</u>), 129.7 (2 × ^{SiPh}CH), 128.9 (2 × ^{SePh}CH), 127.7 (4 × ^{SePh}CH), 127.1 (^{SePh}<u>C</u>H), 126.1 (^{Ar}<u>C</u>), 116.7 (CH=<u>C</u>H_2), 111.5 (^{Ar}<u>C</u>H), 110.5 (^{Ar}<u>C</u>H), 62.1 (<u>C</u>H_2OSi), 58.7 (N<u>C</u>H), 56.5 (N<u>C</u>H_2CH=CH_2), 56.0 (^{Ar}O<u>C</u>H_3), 55.9 (^{Ar}OCH_3), 43.1 (<u>C</u>H_2CHSePh), 41.3 (N<u>C</u>$H_2$$CH_2$Ar), 40.6 (<u>C</u>HSePh), 40.3 (CH(SePh)<u>C</u>$H_2$$CH_2$OSi), 26.9 (3 × SiC(<u>C</u>H_3)$_3$), 21.6 (NCH_2<u>C</u>H_2Ar), 19.3 (Si<u>C</u>$(CH_3)_3$); *m/z* (CI, NH_3) 702 (30%), 701 (20), 700 (100, $MSe^{80}H^+$), 699 (15), 698 (50, $MSe^{78}H^+$), 697 (15), 696 (15, $MSe^{76}H^+$); HRMS $C_{40}H_{50}NO_3SeSi$ ($MSe^{80}H^+$) requires 700.2720, found 700.2721.

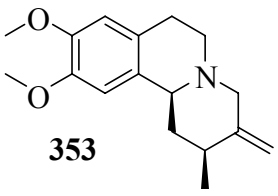
7.5 Experimental for Chapter 5

1-Allyl-2-(2-bromoallyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (352)

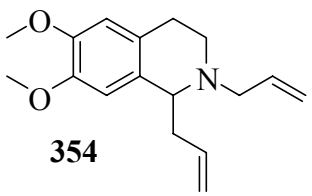


To a stirred solution of 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **192** (1.4 g, 6.0 mmol) and K_2CO_3 (0.99 g, 27.2 mmol) in DMF (30 mL) under nitrogen was added Et_3N (0.93 mL, 7.2 mmol), and 2,3-dibromopropene (1.4 g, 7.2 mmol) at r.t. After stirring for 24 h in the dark, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (100 mL) and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ solution (2 x 50 mL), brine (2 x 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting oil was purified by flash silica chromatography, elution gradient 3:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound as a yellow gum (1.38 g, 66%); Rf = 0.5 (1:1 petrol:EtOAc); ν_{max} (thin film) /cm^{-1} 2932 (w), 2803 (w), 1630 (m), 1511 (s); δ_H (400 MHz, $CDCl_3$) 6.56 (1H, s, ^{Ar}C<u>H</u>), 6.53 (1H, s, ^{Ar}C<u>H</u>), 6.02-5.92 (1H, m, C<u>H</u>=CH$_2$), 5.93 (1H, app d, *J* = 1.0, C(Br)=C<u>H</u>$_2$), 5.57 (1H, app d, *J* = 1.0, C(Br)=C<u>H</u>$_2$), 5.07-5.01 (2H, m, CH=C<u>H</u>$_2$), 3.84 (3H, s, OC<u>H</u>$_3$), 3.83 (3H, s, OC<u>H</u>$_3$), 3.65 (1H, dd, *J* = 7.6 and 5.3, NC<u>H</u>), 3.40 (2H, s, NC<u>H</u>$_2$C(Br)), 3.27-3.20 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 2.87-2.76 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NCH$_2$C<u>H</u>$_2$Ar), 2.59-2.50 (2H, m, NCH$_2$C<u>H</u>$_2$Ar and CHC<u>H</u>$_2$CH=CH$_2$), 2.46-2.39 (1H, m, CHC<u>H</u>$_2$CH=CH$_2$); δ_C (100 MHz, $CDCl_3$) 147.3 (^{Ar}<u>C</u>OCH$_3$), 147.0 (^{Ar}<u>C</u>OCH$_3$), 136.7 (<u>C</u>H=CH$_2$), 132.1 (<u>C</u>(Br)=CH$_2$), 129.5 (^{Ar}<u>C</u>), 126.0 (^{Ar}<u>C</u>), 117.8 (=<u>C</u>H$_2$), 115.9 (=<u>C</u>H$_2$), 111.3 (^{Ar}<u>C</u>H), 110.5 (^{Ar}<u>C</u>H), 61.9 (N<u>C</u>H$_2$C(Br)=CH$_2$), 60.5 (N<u>C</u>H), 55.8 (O<u>C</u>H$_3$), 55.7 (O<u>C</u>H$_3$), 43.6 (N<u>C</u>H$_2$CH$_2$Ar), 40.7 (CHC<u>H</u>$_2$CH=CH$_2$), 24.3 (NCH$_2$<u>C</u>H$_2$Ar); *m/z* (CI, NH_3) (MH^+, 100%), 355 (10), 354 (100), 353 (11), 352 (100); HRMS (ESI) calcd for $C_{17}H_{23}BrNO_2$ 352.0907, found 32.0908.

9,10-Dimethoxy-2-methyl-3-methylene-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline (353) and 1,2-Diallyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (354)



353



354

A solution of 1-allyl-2-(2-bromoallyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline **354** (0.70 g, 2.0 mmol) in THF (25 mL) was stirred at reflux for 30 minutes under nitrogen. Then AIBN (16 mg, 0.10 mmol) was added, followed by the slow addition of a solution of tributyltin hydride (0.75 mL, 2.80 mmol) and AIBN (150 mg, 0.90 mmol) in THF (20 mL) by a syringe pump over a period of 4 h. Following the complete addition of the tributyltin hydride solution, the reaction mixture was maintained at reflux for a further 2 h, after which the solution was cooled to r.t. The reaction mixture was concentrated *in vacuo*, until approx 10 ml of solvent was left, this was then stirred with KF/silica for 10 min. The resulting slurry was loaded on to a short KF/silica column, and flushed with petrol then EtOAc, the EtOAc fraction was concentrated *in vacuo* to afford a yellow gum. The gum was purified by flash silica chromatography, elution gradient 3:1 petrol:EtOAc to EtOAc, pure fractions were concentrated *in vacuo* to afford the title compounds.

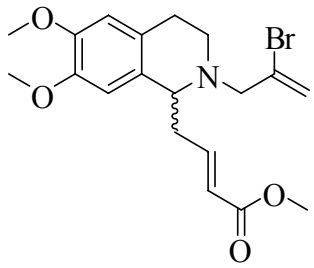
The 6-*exo* cyclisation product, 9,10-dimethoxy-2-methyl-3-methylene-2,3,4,6,7,11b-hexahydro-1H-pyrido[2,1-a]isoquinoline (**353**) was isolated as a yellow gum (0.24 g, 44%), as a 5:1 ratio of diastereoisomers; Rf = 0.16 (EtOAc); ν_{max} (thin film) /cm^{-1} 2995 (s), 2962 (m), 1622 (m), 1518 (m); δ_H (400 MHz, $CDCl_3$) 6.65 (1H, s, $^{Ar}C\underline{H}$), 6.53 (1H, s, $^{Ar}C\underline{H}$), 4.87 (1H, app d, *J* = 0.9, C=C$\underline{H}_2$), 4.76 (1H, s, C=C$\underline{H}_2$), 3.83 (3H, s, OC$\underline{H}_3$), 3.80 (3H, s, OC$\underline{H}_3$), 3.37 (1H, app d, *J* = 11.9, NC$\underline{H}_2$C=CH$_2$), 3.34 (1H, app d, *J* = 11.6, NC$\underline{H}$), 3.08-3.00 (1H, m, NCH$_2$C$\underline{H}_2$Ar), 3.01 (1H, app d, *J* = 11.9, NC$\underline{H}_2$C=CH$_2$), 2.98-2.92 (1H, m, NC$\underline{H}_2$CH$_2$Ar), 2.63 (1H, app dt, *J* = 15.5 and 4.0, NCH$_2$C$\underline{H}_2$Ar), 2.49 (1H, app td, *J* = 15.5 and 4.0, NC$\underline{H}_2$CH$_2$Ar), 2.34-2.24 (2H, m, C$\underline{H}$CH$_3$ and NCHC$\underline{H}_2$), 1.23 (1H, app q, *J* = 11.6, NCHC$\underline{H}_2$), 1.14 (3H, d, *J* = 6.3, CHC$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 147.8 (C=CH$_2$), 147.2 (^{Ar}COCH$_3$), 146.9 (^{Ar}COCH$_3$), 129.6 (^{Ar}C), 126.4 (^{Ar}C), 111.2 (^{Ar}CH), 108.1 (^{Ar}CH), 107.1 (C=CH$_2$), 63.4 (NCH$_2$C=CH$_2$), 62.3 (NCH), 55.8 (OCH$_3$), 55.6 (OCH$_3$), 51.0 (NCH$_2$CH$_2$Ar), 40.7 (NCHCH$_2$), 35.8 (CHCH$_3$), 29.0 (NCH$_2$CH$_2$Ar), 17.5 (CHCH$_3$); *m/z* (CI, NH_3) 275 (20%), 274 (100, MH^+); HRMS $C_{17}H_{24}NO_2$ (MH^+) requires 274.1807, found 274.1805.

The minor diastereoisomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 6.60 (1H, s, $^{Ar}C\underline{H}$), 6.53 (1H, s, $^{Ar}C\underline{H}$), 4.78 (2H, s, C=C$\underline{H}_2$), 3.82 (3H, s, OC$\underline{H}_3$), 3.80 (3H, s, OC$\underline{H}_3$), 1.22 (3H, d, *J* = 7.2, CHC$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 147.9 (C=CH$_2$), 147.2 (^{Ar}COCH$_3$), 146.9 (^{Ar}COCH$_3$), 129.8 (^{Ar}C), 126.7 (^{Ar}C), 111.2 (^{Ar}CH), 108.0 (^{Ar}CH), 108.2 (C=CH$_2$), 57.9 (NCH$_2$C=CH$_2$), 56.4 (NCH), 55.8 (OCH$_3$), 55.6 (OCH$_3$), 51.2 (NCH$_2$CH$_2$Ar), 38.4 (NCHCH$_2$), 35.4 (CHCH$_3$), 28.6 (NCH$_2$CH$_2$Ar), 19.6 (CHCH$_3$).

The simple reduction product **354** was isolated as a yellow gum (0.14 g, 26%); Rf = 0.31 (EtOAc); ν_{max} (thin film) /cm^{-1} 3042 (w), 2928 (w), 1632 (m), 1602 (m), 1516 (s); δ_H

(400 MHz, $CDCl_3$) 6.54 (1H, s, $^{Ar}C\underline{H}$), 6.52 (1H, s, $^{Ar}C\underline{H}$), 5.94-5.82 (2H, m, $CHCH_2C\underline{H}=CH_2$ and $NCH_2C\underline{H}=CH_2$), 5.20-5.00 (4H, m, $CHCH_2CH=C\underline{H_2}$ and $NCH_2CH=C\underline{H_2}$), 3.83 (3H, s, $OC\underline{H_3}$), 3.81 (3H, s, $OC\underline{H_3}$), 3.65 (1H, dd, J = 6.7 and 6.1, $NC\underline{H}$), 3.22 (2H, d, J = 6.4, $NC\underline{H_2}CHCH_2$), 3.20-3.13 (1H, m, $NC\underline{H_2}CH_2Ar$), 2.86-2.76 (2H, m, $NCH_2C\underline{H_2}Ar$ and $NC\underline{H_2}CH_2Ar$), 2.57-2.46 (2H, m, $NCH_2C\underline{H_2}Ar$ and $CHC\underline{H_2}CH=CH_2$), 2.43-2.36 (1H, m, $CHC\underline{H_2}CH=CH_2$); δ_C (100 MHz, $CDCl_3$) 147.2 ($^{Ar}\underline{C}OCH_3$), 146.8 ($^{Ar}\underline{C}OCH_3$), 136.8 ($\underline{C}H=CH_2$), 136.3 ($\underline{C}H=CH_2$), 129.6 ($^{Ar}\underline{C}$), 126.2 ($^{Ar}\underline{C}$), 117.0 ($CH=\underline{C}H_2$), 115.8 ($CH=\underline{C}H_2$), 111.2 ($^{Ar}\underline{C}H$), 110.6 ($^{Ar}\underline{C}H$), 59.8 ($N\underline{C}H$), 56.6 ($N\underline{C}H_2CH=CH$), 55.8 ($O\underline{C}H_3$), 55.7 ($O\underline{C}H_3$), 43.7 ($N\underline{C}H_2CH_2Ar$), 40.0 ($CH\underline{C}H_2CH=CH_2$), 24.3 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI, NH_3) 275 (18%), 274 (100, MH^+); HRMS $C_{17}H_{24}NO_2$ (MH^+) requires 274.1807, found 274.1810.

Methyl (*E*)-4-(2-(2-bromoallyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)but-2-enoate (358)

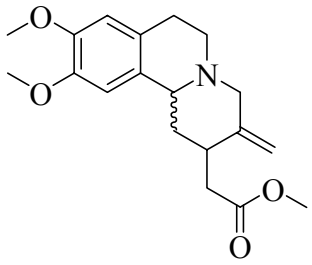


To a stirred solution of 3,4-dihydro-6,7-dimethoxyisoquinoline **188** (7.5 g, 39.22 mmol) in Et_2O (100 mL) at r.t. under nitrogen was added 2,3-dibromoprop-1-ene (8.62 g, 43.14 mmol). The resulting solution was stirred in the dark overnight, during which time a yellow precipitate formed. The crude mixture was evaporated to dryness to afford the bromide salt as an unstable, moisture sensitive yellow power; δ_H (400 MHz, $CDCl_3$) 9.94 (1H, s, $NC\underline{H}$), 7.60 (1H, s, ^{Ar}CH), 6.89 (1H, s, ^{Ar}CH), 6.56 (1H, d, J = 2.1, $C(Br)=C\underline{H_2}$), 5.90 (1H, d, J = 2.1, $C(Br)=C\underline{H_2}$), 5.36 (2H, s, $NC\underline{H_2}C(Br)$), 4.08 (2H, t, J = 8.2, $NC\underline{H_2}CH_2Ar$), 4.02 (3H, s, $OC\underline{H_3}$), 3.94 (3H, s, $OC\underline{H_3}$), 3.29 (2H, t, J = 8.2, $NCH_2C\underline{H_2}Ar$); δ_C (100 MHz, $CDCl_3$) 166.9 ($N\underline{C}H$), 158.5 ($^{Ar}\underline{C}OCH_3$), 149.4 ($^{Ar}\underline{C}OCH_3$), 133.3 ($NCH_2\underline{C}(Br)$), 127.4 ($^{Ar}\underline{C}$), 123.6 ($C(Br)=\underline{C}H_2$), 117.5 ($^{Ar}\underline{C}$), 116.4 ($^{Ar}\underline{C}H$), 111.3 ($^{Ar}\underline{C}H$), 67.0 ($N\underline{C}H_2C(Br)$), 57.2 ($^{Ar}CO\underline{C}H_3$), 57.0 ($^{Ar}CO\underline{C}H_3$), 47.6 ($N\underline{C}H_2CH_2Ar$), 26.0 (($NCH_2\underline{C}H_2Ar$); *m/z* (CI, NH_3) (MH^+, 100%).

To a stirred suspension of the bromide salt in acetonitrile (100 mL) was added methyl (E)-4-bromobut-2-enoate (8.3 mL, 58.8 mmol) and zinc dust (3.8 g, 58.8 mmol), the resulting suspension was stirred at r.t. under nitrogen for 2 days. The reaction mixture was quenched by pouring into a saturated aq. solution of $NaHCO_3$ (250 mL) and allowed to stir for 30

minutes, the resulting precipitate was removed by filtration, and washed with Et_2O (200 mL), the organic layer was separated and the aqueous layer extracted with Et_2O (2 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 10 to 40% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford the title compound **358** as a yellow oil (12.66 g, 79%), which forms a solid on standing. Rf 0.25 (1:1 EtOAc:petrol); mp 55-60 ºC; ν_{max} (thin film) /cm^{-1} 2929 (w), 2909 (w), 2835 (w), 2789 (w), 1712 (s), 1653 (m), 1632 (m), 1608 (m), 1513 (s); δ_H (700 MHz, $CDCl_3$) 7.06 (1H, dt, *J* = 15.6 and 7.4, C<u>H</u>=CHCO$_2$CH$_3$), 6.54 (1H, s, ^{Ar}CH), 6.46 (1H, s, ^{Ar}CH), 5.85 (1H, s, CH$_2$C(Br)=C<u>H</u>$_2$), 5.80 (1H, app dt, *J* = 15.6 and 1.3, CH=C<u>H</u>CO$_2$CH$_3$), 5.55 (1H, s, CH$_2$C(Br)=C<u>H</u>$_2$), 3.82 (3H, s, ^{Ar}COC<u>H</u>$_3$), 3.79 (3H, s, ^{Ar}COC<u>H</u>$_3$), 3.72 (1H, dd, *J* = 7.6 and 5.5, NC<u>H</u>), 3.68 (3H, s, CO$_2$C<u>H</u>$_3$), 3.40 (1H, d, *J* = 15.2, NC<u>H</u>$_2$C(Br)), 3.37 (1H, d, *J* = 15.2, NC<u>H</u>$_2$C(Br)), 3.19-3.14 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 2.84-2.75 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NCH$_2$C<u>H</u>$_2$Ar), 2.64 (1H, app quint d, *J* = 7.0 and 1.3 NCH$_2$C<u>H</u>$_2$Ar) and 2.57-2.49 (2H, m NCHC<u>H</u>$_2$CH); δ_C (176 MHz, $CDCl_3$) 166.8 (<u>C</u>O$_2$CH$_3$), 147.7 (^{Ar}<u>C</u>OCH$_3$), 147.3 (^{Ar}<u>C</u>OCH$_3$), 147.2 (CH=<u>C</u>HCO$_2$CH$_3$), 131.8 (<u>C</u>(Br)=CH$_2$), 128.6 (^{Ar}<u>C</u>), 126.3 (^{Ar}<u>C</u>), 122.2 (<u>C</u>H=CHCO$_2$CH$_3$), 118.0 (C(Br)=<u>C</u>H$_2$), 111.7 (^{Ar}<u>C</u>H), 110.4 (^{Ar}<u>C</u>H), 62.0 (N<u>C</u>H$_2$C(Br)), 60.1 (N<u>C</u>H), 55.9 (^{Ar}CO<u>C</u>H$_3$), 55.8 (^{Ar}CO<u>C</u>H$_3$), 51.3 (CO$_2$<u>C</u>H$_3$), 43.6 (N<u>C</u>H$_2$CH$_2$Ar), 39.0 (NCH$_2$<u>C</u>H$_2$Ar), 24.4 (CH<u>C</u>H$_2$CH); *m/z* (CI, NH_3) 413 (18%) 412 (MH^+Br^{81} 98), 411 (20), 410 (MH^+Br^{79} 100); HRMS $C_{19}H_{25}O_4{}^{79}Br$ (MH^+) requires 410.0967, found 410.0962.

Methyl 2-((2*R,11b*S**)-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-methylene-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate (359)**

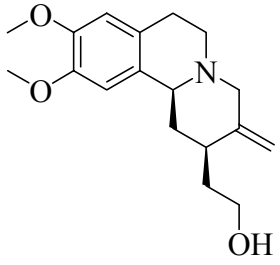


A solution of methyl (*E*)-4-(2-(2-bromoallyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate **358** (2.5 g, 6.09 mmol) in THF (50 mL) was stirred at reflux for 30 minutes under nitrogen. Then AIBN (31 mg, 0.19 mmol) was added, followed by the slow addition of a solution of tributyltin hydride (2.028 mL, 7.31 mmol) and AIBN (0.500 g, 3.05 mmol) in THF (25 mL) by a syringe pump over a period of 3 h. Following the complete addition of the tributyltin hydride solution, the reaction mixture was maintained

at reflux for a further 2 h, after which the solution was cooled to r.t. The crude reaction mixture was passed through a SCX column, elution gradient 4:1 DCM:MeOH to 4:1 DCM:MeOH/NH_3, the DCM:MeOH/NH_3 fractions were evaporated to afford a yellow oil. The oil was purified by flash silica chromatography, elution gradient 16:4 petrol:EtOAc to 8:8:1 petrol:EtOAc:MeOH/NH_3. The pure fractions were concentrated *in vacuo* to afford the title compound **359** as a yellow oil (1.52 g, 75%) as a 2.8:1 mixture of partially separable diastereomers; Rf = 0.33 (8:8:1, petrol:EtOAc:MeOH/NH_3); ν_{max} (thin film) /cm^{-1} 2981 (s), 2971 (m), 1733 (s), 1511 (m); major diastereoisomer; δ_H (700 MHz, $CDCl_3$) 6.63 (1H, s, $^{Ar}C\underline{H}$), 6.55 (1H, s, $^{Ar}C\underline{H}$), 4.92 (1H, s, C=C$\underline{H}_2$), 4.72 (1H, app d, *J* = 0.9, C=C$\underline{H}_2$), 3.83 (3H, s, $^{Ar}OC\underline{H}_3$), 3.82 (3H, s, $^{Ar}OC\underline{H}_3$), 3.71 (3H, s, $CO_2C\underline{H}_3$), 3.45 (1H, app d, *J* = 10.8, NC$\underline{H}$), 3.38 (1H, d, *J* = 12.1, NC$\underline{H}_2$C=CH_2), 3.12 (1H, d, *J* = 12.1, NC$\underline{H}_2$C=CH_2), 3.07-3.01 (1H, m, $NCH_2C\underline{H}_2Ar$), 2.99-2.93 (1H, m, NC$\underline{H}_2CH_2Ar$), 2.83-2.76 (1H, m, $CH_2C\underline{H}CH_2$), 2.73 (1H, dd, *J* = 15.5 and 6.5, C$\underline{H}_2CO_2$Me), 2.67 (1H, app dt, *J* = 15.6 and 3.3 $NCH_2C\underline{H}_2Ar$), 2.54 (1H, app td, *J* = 10.6 and 4.3 NC$\underline{H}_2CH_2Ar$), 2.34 (1H, dd, *J* = 15.5 and 7.2, C$\underline{H}_2CO_2CH_3$), 2.31 (1H, app ddd, *J* = 12.6, 4.3 and 2.9, CHC$\underline{H}_2$CH), 1.29 (1H, app q, *J* = 12.6, CHC$\underline{H}_2$CH); δ_C (100 MHz, $CDCl_3$) 173.5 ($\underline{C}O_2CH_3$), 147.6 ($^{Ar}\underline{C}OCH_3$), 147.2 ($^{Ar}\underline{C}OCH_3$), 145.5 ($\underline{C}$=CH_2), 129.4 ($^{Ar}\underline{C}$), 126.6 ($^{Ar}\underline{C}$), 111.5 ($^{Ar}\underline{C}H$), 108.7 ($^{Ar}\underline{C}H$), 107.6 (C=$\underline{C}H_2$), 63.4 ($N\underline{C}H_2C=CH_2$), 61.9 (N$\underline{C}$H), 56.1 ($^{Ar}CO\underline{C}H_3$), 55.8 ($^{Ar}CO\underline{C}H_3$), 51.6 ($CO_2\underline{C}H_3$), 50.6 ($N\underline{C}H_2CH_2Ar$), 38.4 ($CH\underline{C}H_2CH$), 37.9 ($CH_2\underline{C}HCH_2$), 36.9 ($CH_2CO_2CH_3$), 29.1 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI, NH_3) 333 (20%), 332 (MH^+, 100), 330 (35); Found: MH^+ 332.1855, $C_{19}H_{26}O_4N$ requires: MH^+ 332.1861.

The presence of the minor diastereoisomer was identified by the following key peaks; δ_H (700 MHz, $CDCl_3$) 6.60 (1H, s, $^{Ar}C\underline{H}$), 6.55 (1H, s, $^{Ar}C\underline{H}$), 4.87 (1H, s, C=C$\underline{H}_2$), 4.86 (1H, app d, *J* = 0.9, C=C$\underline{H}_2$), 3.83 (3H, s, $^{Ar}OC\underline{H}_3$), 3.81 (3H, s, $^{Ar}OC\underline{H}_3$), 3.68 (3H, s, $CO_2C\underline{H}_3$), 3.51 (1H, app d, *J* = 11.0, NC$\underline{H}$).

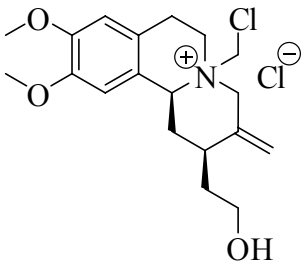
2-((2*R,11b*S**)-2,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-methylene-1H-pyrido[2,1-a]isoquinolin-2-yl)ethanol (362)**



To a stirred solution of methyl 2-((2*R**,11b*S**)-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-methylene-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate **359** (0.30 g, 0.91 mmol), in THF

(10 mL) at 0 ºC under nitrogen, was slowly added a solution of lithium aluminium hydride in THF (1.15 mL, 2.4 M, 2.75 mmol), the solution was stirred for 15 minutes at 0 ºC, then warmed to r.t. and stirred for 6 h. The stirred reaction mixture was then quenched by the sequential dropwise addition of H_2O (0.10 mL), 15% aqueous NaOH (0.10 mL) and H_2O (0.30 mL), then EtOAc (10 mL) and celite (0.5 g) were added and stirred for 1 h. The reaction mixture was filtered through a celite plug, the plug was flushed with EtOAc (2 × 15 mL), evaporation of the solvent afforded the crude product as a yellow oil. The oil was purified by flash silica chromatography, elution gradient 10 to 20% MeOH/NH_3 in DCM. Pure fractions were concentrated *in vacuo* to afford the title compound **363** as a yellow oil (0.24 g, 87%); Rf = 0.52 (10% MeOH/NH_3 in DCM); ν_{max} (thin film) /cm^{-1} 3420 (bs), 3049 (w), 2994 (w), 1608 (m), 1509 (m); δ_H (400 MHz, $CDCl_3$) 6.62 (1H, s, $^{Ar}C\underline{H}$), 6.51 (1H, s, $^{Ar}C\underline{H}$), 4.87 (1H, s, C=C$\underline{H}_2$), 4.72 (1H, app d, *J* = 0.9, C=C$\underline{H}_2$), 3.79 (3H, s, $^{Ar}OC\underline{H}_3$), 3.77 (3H, s, $^{Ar}OC\underline{H}_3$), 3.69 (2H, t, *J* = 6.6, C$\underline{H}_2$OH), 3.36 (1H, app d, *J* = 10.8, $^{Ar}C\underline{H}N$), 3.32 (1H, d, *J* = 12.0, NC$\underline{H}_2$C=CH$_2$), 3.02 (1H, d, *J* = 12.0, NC$\underline{H}_2$C=CH$_2$), 3.01-2.89 (2H, m, NC$\underline{H}_2CH_2{}^{Ar}$ and CH$_2$C$\underline{H}$CH$_2$), 2.69 (1H, bs, CH$_2$O$\underline{H}$), 2.64 (1H, app dt, *J* = 15.7 and 4.0, NCH$_2$C$\underline{H}_2{}^{Ar}$), 2.47 (1H, app td, *J* = 10.2 and 4.0 NC$\underline{H}_2CH_2{}^{Ar}$), 2.37-2.24 (2H, m, CHC$\underline{H}_2$CH and NCH$_2C\underline{H}_2{}^{Ar}$), 1.96 (1H, app td, *J* = 13.0 and 6.6, C$\underline{H}_2$CH$_2$OH), 1.51 (1H, app td, *J*=13.0 and 6.6, C$\underline{H}_2$CH$_2$OH), 1.29 (1H, app q, *J* = 11.7, CHC$\underline{H}_2$CH); δ_C (100 MHz, $CDCl_3$) 147.2 ($^{Ar}\underline{C}OCH_3$), 146.7 ($^{Ar}\underline{C}OCH_3$), 146.1 ($\underline{C}$=CH$_2$), 129.3 ($^{Ar}\underline{C}$), 126.1 ($^{Ar}\underline{C}$), 111.2 ($^{Ar}\underline{C}H$), 108.4 ($^{Ar}\underline{C}H$), 107.2 (C=$\underline{C}$H$_2$), 63.3 (N$\underline{C}$H$_2$C=CH$_2$), 61.9 (Ar$\underline{C}$HN), 59.6 ($\underline{C}$H$_2$OH), 55.7 ($^{Ar}CO\underline{C}H_3$), 55.4 ($^{Ar}CO\underline{C}H_3$), 50.1 (N$\underline{C}$H$_2$CH$_2$Ar), 37.7 (CH$\underline{C}$H$_2$CH), 37.1 (CH$_2\underline{C}$HCH$_2$), 34.3 ($\underline{C}$H$_2$CH$_2$OH), 28.6 (NCH$_2\underline{C}$H$_2$Ar); *m/z* (CI, NH_3) 305 (35%), 304 (MH^+, 100), 302 (25), 274 (10).

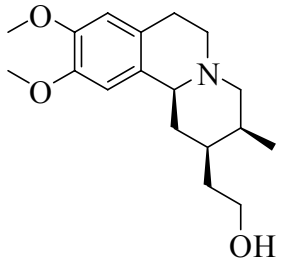
(2*R,11b*S**)-5-(Chloromethyl)-2-(2-hydroxyethyl)-9,10-dimethoxy-3-methylene-1,2,3,4,5,6,7,11b-octahydropyrido[2,1-a]isoquinolinium chloride (363)**



2-((2*R**,11b*S**)-2,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-methylene-1H-pyrido[2,1-a]isoquinolin-2-yl)ethanol (**362**) was stored with trace amounts of DCM, after 6 months a small amount of crystalline material was formed, which turned out to be the DCM salt, (**363**); δ_H (400 MHz, $CDCl_3$) 6.95 (1H, s, ArCH), 6.83 (1H, s, ArCH), 5.49 (1H, d, *J* =

10.2, NCH_2Cl), 5.44 (1H, s, $=CH_2$), 5.27 (1H, d, J = 10.2, NCH_2C1), 5.22 (1H, s, $=CH_2$), 4.89 (1H, dd, J = 11.7 and 3.2, NCHAr), 4.67 (1H, t, J = 5.3, $NC\underline{H}_2CH_2Ar$), 4.40 (1H, d, J = 12.5, $NC\underline{H}_2C=CH_2$), 4.27 (1H, d, J = 12.5, $NC\underline{H}_2C=CH_2$), 3.94-3.84 (1H, m, $NCH_2C\underline{H}_2Ar$), 3.75 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.58-3.54, (1H, m $NC\underline{H}_2CH_2Ar$), 3.52 (1H, app d, J = 6.0, $C\underline{H}_2OH$), 3.49 (1H, app d, J = 6.0, $C\underline{H}_2OH$), 3.32 (1H, bs, OH), 3.12-2.94 (1H, m, $CH_2C\underline{H}CH_2$), 3.05 (1H, app, d, J = 6.1, $NCH_2C\underline{H}_2Ar$), 2.62-2.54 (1H, m, $CHC\underline{H}_2CH$), 1.91-1.81 (1H, m, $C\underline{H}_2CH_2OH$), 1.65 (1H, app, dd, J = 14.2 and 12.3, $C\underline{H}_2CH_2OH$), 1.46-1.36 (1H, m, $CHC\underline{H}_2CH$), δ_C (100 MHz, $CDCl_3$) 149.3 ($^{Ar}\underline{C}OCH_3$), 148.5 ($^{Ar}\underline{C}OCH_3$), 138.5 ($\underline{C}$), 123.0 ($\underline{C}$), 120.9 ($\underline{C}$), 117.5 ($=\underline{C}H_2$), 112.2 ($^{Ar}\underline{C}H$), 110.8 ($^{Ar}\underline{C}H$), 66.6 (Ar$\underline{C}$HN), 66.5 ($\underline{C}H_2$), 65.6 ($\underline{C}H_2$), 58.1 ($\underline{C}H_2$), 56.2 ($O\underline{C}H_3$), 56.1 ($O\underline{C}H_3$), 47.5 ($\underline{C}H_2$), 38.5 ($\underline{C}H_2$), 35.6 ($\underline{C}H$), 33.8 ($\underline{C}H_2$), 22.9 ($\underline{C}H_2$); *m/z* (ESI) 354 (MCl^{37}-Cl, 33%), 353 (20), 352 (MCl^{35}-Cl, 100).

2-((2*R,3*S**,11b*S**)-2,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-methyl-1H-pyrido[2,1-a]isoquinolin-2-yl) (342-b) or (±)-des-methyl-epi-protoemetinol**



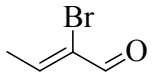
A stirred solution of 2-((2*R**,11b*S**)-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-3-methylene-1H-pyrido[2,1-a]isoquinolin-2-yl)ethanol **362** (303 mg, 1.0 mmol) and 5% Pd/C (30 mg) in MeOH (10 mL) was evacuated and back-filled with nitrogen (×3) then hydrogen (×2). The solution was then stirred under 1 bar hydrogen at r.t. for 6 h, after which time the reaction mixture was filtered through a plug of Celite (EtOAc) and the solvent was evaporated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 10 to 20% MeOH/NH_3 in DCM. Pure fractions were evaporated to dryness to afford the title compound **342-b** (273 mg, 91%) as a yellow oil, as a 3:1 mixture of diastereoisomers.

Major diastereoisomer, (±)-des-methyl-epi-protoemetinol (**342-b**); ν_{max} (thin film) /cm^{-1} 3460 (bs), 3040 (w), 2910 (w), 1422 (m) 1291 (w); δ_H (400 MHz, $CDCl_3$) 6.68 (1H, s, $^{Ar}C\underline{H}$), 6.65 (1H, s, $^{Ar}C\underline{H}$), 3.84 (3H, s, $OC\underline{H}_3$), 3.82 (3H, s, $OC\underline{H}_3$), 3.70 (2H, app td, J = 6.7 and 3.0, $C\underline{H}_2OH$), 3.12-3.02 (1H, m, $NCH_2C\underline{H}_2Ar$), 2.97 (1H, d, J = 11.0, $NC\underline{H}$), 2.81 (1H, ddd, J = 11.0, 6.9 and 1.2, $NC\underline{H}_2CH_2Ar$), 2.74 (1H, dd, J = 11.1 and 2.2, $NC\underline{H}_2CH$), 2.55 (1H, dd, J = 15.9 and 3.5, $NCH_2C\underline{H}_2Ar$), 2.43 (1H, dd, J = 11.1 and 3.5, $NC\underline{H}_2CH$),

2.38 (1H, td, J = 11.0 and 3.5, NC$\underline{H}_2$CH$_2$Ar), 2.01 (1H, bs, CH$_2$O$\underline{H}$), 1.98 (1H, dt, J = 12.5 and 3.0, CHC$\underline{H}_2$CH), 1.90-1.75 (2H, m, C$\underline{H}$CH$_2$CH$_2$OH and C$\underline{H}$CH$_3$), 1.60-1.50 (2H, m, C$\underline{H}_2$CH$_2$OH), 1.31 (1H, app dd, J = 12.5 and 11.0, CHC$\underline{H}_2$CH), 0.97 (3H, d, J = 6.9, CHC$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 147.1 ($^{Ar}\underline{C}OCH_3$), 146.9 ($^{Ar}\underline{C}OCH_3$), 130.4 ($^{Ar}\underline{C}$), 126.9 ($^{Ar}\underline{C}$), 111.3 ($^{Ar}\underline{C}$H), 107.9 ($^{Ar}\underline{C}$H), 63.6 (N$\underline{C}$H$_2$CH), 63.3 (N$\underline{C}$H), 60.4 ($\underline{C}$H$_2$OH), 56.0 (O$\underline{C}$H$_3$), 55.7 (O$\underline{C}$H$_3$), 52.8 (N$\underline{C}$H$_2$CH$_2$Ar), 36.5 ($\underline{C}$H$_2$CH$_2$OH), 35.7 ($\underline{C}$HCH$_2$CH$_2$OH), 32.9 (CH$\underline{C}$H$_2$CH), 31.4 ($\underline{C}$HCH$_3$), 29.2 (NCH$_2\underline{C}$H$_2$Ar), 12.5 (CH$\underline{C}$H$_3$); *m/z* (CI) 307 (15%), 306 (MH^+, 100), 304 (10); HRMS $C_{18}H_{28}NO_3$ (MH^+) requires 306.2064, found 306.2063.

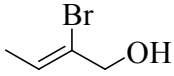
The minor diastereoisomer, (±)-des-methyl-protoemetinol (**342-a**), has spectroscopic data that is in agreement with the previously prepared material.

(*Z*)-2-Bromobut-2-enal (365)[251]



To a stirred solution of crotonaldehyde (12.5 mL, 150 mmol) in anhydrous DCM (400 mL) at 0 ºC was slowly added a solution of bromine (7.7 mL, 150 mmol) in DCM (75 mL). The resulting dark red solution was stirred at 0 °C for 10 minutes, during this time the red colour was replaced with a golden yellow colour. Triethylamine (41.8 mL, 300 mmol) was added and the reaction stirred for a further 1 h. The reaction mixture was diluted with DCM (200 mL), and washed with 10% aq HCl (2 × 250 mL), and brine (250 mL). The organic layer was dried over $MgSO_4$, followed by concentrated *in vacuo*. The resulting oil was purified by Kugelrohr distillation to afford (*Z*)-2-bromobut-2-enal (**365)** as a pale yellow oil; b.p 68-74 °C at 17 mmHg, (lit b.p 65 °C at 15 mmHg); ν_{max} (thin film) /cm^{-1} 1690 (s), 1605 (s); δ_H (400 MHz, $CDCl_3$) 9.12 (1H, s, C(O)$\underline{H}$), 7.17 (1H, q, J = 6.8, CH$_3$C$\underline{H}$), 2.05 (3H, t, J = 6.8, C$\underline{H}_3$CH); δ_C (100 MHz, $CDCl_3$) 186.3 ($\underline{C}$(O)H), 151.2 (CH$_3\underline{C}$HCBr), 130.5 (CH$_3$CH$\underline{C}$Br), 18.3 (C$\underline{H}_3$CH); *m/z* (CI, NH_3) 262 ($^{81Br}M_2$MeCNH-Br$^+$, 100%), 260 ($^{79Br}M_2$MeCNH-Br$^+$, 99), 192 (^{81Br}MMeCNH$^+$, 10), 190 (^{79Br}MMeCNH$^+$, 10). The spectroscopic data is in agreement with reported data.[251]

***(Z)*-2-Bromobut-2-en-1-ol (366)[251]**



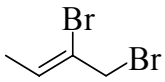
To a stirred solution of (*Z*)-2-bromobut-2-enal **365** (14.9 g, 100 mmol) in MeOH (200 mL), was added cerium(III) chloride heptahydrate (41.0 g, 110 mmol). The reaction was cooled to 0 ºC and stirred until all the solid had dissolved. Sodium borohydride (4.2 g, 110

mmol) was then added to the reaction portionwise over a period of 10 mim, to control the vigorous evolution of gas. Once the evolution of gas had ceased (30 min) the resulting solution was concentrated *in vacuo*. The resulting white suspension was partitioned between Et_2O (300 mL) and saturated aqueous ammonium chloride solution (300 mL). The organic layer was separated and the aqueous layer re-extracted with a further portions of Et_2O (2 × 250 mL). The combined organic layers were washed with water (300 mL), brine (300 mL) and dried over Na_2SO_4, and the solvent removed *in vacuo* to yield the crude product **366** (14.9 g) (no purification was carried out); ν_{max} (thin film) /cm^{-1} 3330 (bs), 2850 (m), 1630 (w), 1420 (m); major isomer; δ_H (400 MHz, $CDCl_3$) 5.98 (1H, qt, *J* = 6.5 and 1.2, $CH_3C\underline{H}$), 4.12 (2H, t, *J* = 1.2, $BrCC\underline{H}_2OH$), 2.60 (1H, bs, $CH_2O\underline{H}$), 1.64 (3H, dt, *J* = 6.5 and 1.2, $C\underline{H}_3CH$); δ_C (100 MHz, $CDCl_3$) 128.4 ($\underline{C}HCH_3$), 124.7 ($\underline{C}Br$), 77.1 ($\underline{C}H_2OH$), 16.5 ($\underline{C}H_3$).

The minor (*E*)-isomer is indicated by; δ_H (400 MHz, $CDCl_3$) 6.22 (1H, qd, *J* = 6.6 and 0.8, $CH_3C\underline{H}$), 4.58 (2H, t, *J* = 0.8, $BrCC\underline{H}_2OH$), 1.72 (3H, dd, *J* = 6.6 and 0.8, $C\underline{H}_3CH$); δ_C (100 MHz, $CDCl_3$) 128.3 ($\underline{C}HCH_3$), 124.4 ($\underline{C}Br$), 68.4 ($\underline{C}H_2OH$), 16.4 ($\underline{C}H_3$).

The spectroscopic data is in agreement with reported data.[251]

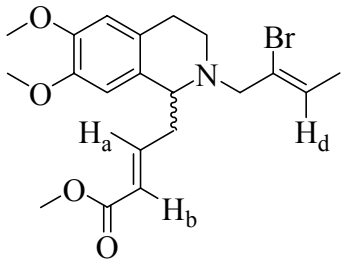
(*Z*)-1,2-Dibromobut-2-ene (367)[251]



To a stirred solution of the crude 2-bromobut-2-en-1-ol (100 mmol) and carbon tetrabromide (39.3 g, 120 mmol) in acetonitrile (250 mL) at 0 ºC was added triphenylphosphine (31.5 g, 120 mmol) portionwise. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 h, the solution was evaporated to dryness. The crude product was purified by flash silica chromatography, elution gradient 2:1 petrol:Et_2O. Subsequent vacuum distillation (50-52 °C at 15 mbar) resulted in a 1:1 mixture of the title compound and bromoform (24.1 g, 73%); ν_{max} (thin film) /cm^{-1} 3019 (s), 1721 (m), 11211 (m), 1143 (s); δ_H (400 MHz, $CDCl_3$) 6.17 (1H, qt, *J* = 6.6 and 0.6, $CH_3C\underline{H}CBr$), 4.23 (2H, t, *J* =0.6, $CBrC\underline{H}_2Br$), 1.76 (3H, d, *J* = 6.6, $C\underline{H}_3CH$); δ_C (100 MHz, $CDCl_3$) 129.7 ($CH_3\underline{C}H$), 123.6 ($\underline{C}Br$), 39.0 ($CBr\underline{C}H_2Br$), 17.4 ($\underline{C}H_3CH$); *m/z* (CI, NH_3) (MH^+, 100%), 216 ($MBr^{81}Br^{81}$, 48), 214 ($MBr^{81}Br^{79}$, 100), 212 ($MBr^{79}Br^{79}$, 50); HRMS (ESI) calcd for $C_4H_6Br_2$ 211.8836, found 211.8843.

The spectroscopic data is in agreement with reported data.[251]

Methyl (*E*) 4-(2-((*Z*)-2-bromobut-2-enyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)but-2-enoate (368)

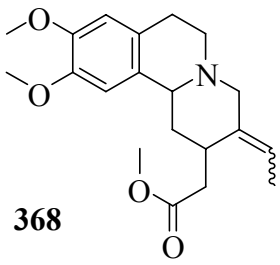


To a stirred solution of 3,4-dihydro-6,7-dimethoxyisoquinoline (2.8 g, 14.5 mmol) in Et_2O (100 mL) at r.t. under nitrogen was added the dibromoalkene (a 1:1 mixture of 1,2-dibromobut-2-ene and $CHBr_3$, 12 g, 29 mmol). The resulting solution was stirred in the dark overnight, during which time a yellow precipitate formed. The crude mixture was evaporated to dryness to afford the bromide salt as an unstable, moisture sensitive yellow power; δ_H (400 MHz, $CDCl_3$) 9.83 (1H, s, NC<u>H</u>), 7.60 (1H, s, ^{Ar}C<u>H</u>), 6.88 (1H, s, ^{Ar}C<u>H</u>), 6.72 (1H, q, *J* = 6.3, C<u>H</u>CH$_3$), 5.26 (2H, s, NC<u>H</u>$_2$CBr), 4.09-3.96 (2H, m, NCH$_2$), 3.98 (3H, s, OCH$_3$), 3.87 (3H, s, OCH$_3$), 3.21 (2H, t, *J*= 8.0, ^{Ar}CH$_2$), 1.74 (3H, d, *J* = 6.5, CHC<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 165.6 (N<u>C</u>H), 155.6 (^{Ar}<u>C</u>OCH$_3$), 148.5 (^{Ar}<u>C</u>OCH$_3$), 135.3 (CBr=<u>C</u>H), 132.6 (<u>C</u>Br) 117.7 (^{Ar}<u>C</u>), 116.8 (^{Ar}<u>C</u>), 115.6 (^{Ar}<u>C</u>H), 110.6 (^{Ar}<u>C</u>H), 66.9 (N<u>C</u>H$_2$CBr), 56.7 (^{Ar}CO<u>C</u>H$_3$), 56.4 (^{Ar}CO<u>C</u>H$_3$), 46.7 (N<u>C</u>H$_2$), 25.3 (^{Ar}<u>C</u>H$_2$), 17.0 (<u>C</u>H$_3$).

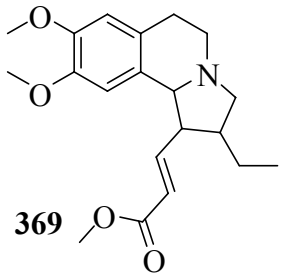
To a stirred suspension of the bromide salt in acetonitrile (100 mL) was added methyl (E)-4-bromobut-2-enoate (3.4 mL, 29.0 mmol) and zinc dust (1.9 g, 29.0 mmol), and the resulting suspension was stirred at r.t. under nitrogen for 2 days. The reaction mixture was quenched by pouring into a saturated aqueous solution of $NaHCO_3$ (150 mL) and allowed to stir for 30 minutes, the resulting precipitate was removed by filtration, and washed with Et_2O (200 mL), the organic layer was separated and the aqueous layer extracted with Et_2O (2 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford a yellow oil. The crude product was purified by flash silica chromatography, elution gradient 8:1 to 1:1 petrol:EtOAc. Pure fractions were evaporated to dryness to afford the title compound **368** as a yellow oil (5.77 g, 55%); Rf 0.27 (1:1, ethyl acetate:petrol); ν_{max} (thin film) /cm^{-1} 2997 (w), 2947 (m), 2834 (w), 1722 (s), 1657 (m), 1516 (s); δ_H (400 MHz, $CDCl_3$) 7.08 (1H, dt, *J* = 15.7 and 7.3, C<u>H</u>=CHCO$_2$CH$_3$), 6.54 (1H, s, ^{Ar}CH), 6.45 (1H, s, ^{Ar}CH), 5.95 (1H, q, *J* = 6.5, C<u>H</u>CH$_3$), 5.80 (1H, dt, *J* = 15.7 and 1.4, CH=C<u>H</u>CO$_2$CH$_3$), 3.82 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.80 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.72-3.68 (1H, m, NC<u>H</u>), 3.69 (3H, s, CO$_2$C<u>H</u>$_3$), 3.39 (2H, s, NC<u>H</u>$_2$CBr), 3.20-3.10 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 2.84-2.72 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NCH$_2$C<u>H</u>$_2$Ar), 2.65-2.45 (3H, m, NCH$_2$C<u>H</u>$_2$Ar and CHC<u>H</u>$_2$CH=), 1.75 (3H, d, *J* = 6.5, CHC<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 166.8 (<u>C</u>O$_2$CH$_3$), 147.5

(C̲H=CHCO$_2$CH$_3$), 147.4 (^{Ar}C̲OCH$_3$), 147.1 (^{Ar}C̲OCH$_3$), 128.5 (C̲(Br)=CH), 126.6 (^{Ar}C̲), 126.3 (^{Ar}C̲), 125.7 (C̲HCH$_3$), 121.9 (CH=C̲HCO$_2$CH$_3$), 111.3 (^{Ar}C̲H), 110.2 (^{Ar}C̲H), 62.3 (C̲H$_2$CBr), 59.5 (NC̲H), 55.8 (^{Ar}CO C̲H$_3$), 55.7 (^{Ar}CO C̲H$_3$), 51.2 (CO$_2$C̲H$_3$), 43.3 (NC̲H$_2$CH$_2$Ar), 38.9 (C̲H$_2$CHCH), 24.1 (NCH$_2$C̲H$_2$Ar), 16.5 (CHC̲H$_3$); *m/z* (CI, NH$_3$) 427 (20%), 426 (MBr^{81}H, 100), 425 (20), 424 (MBr^{79}H, 100); HRMS (ESI, MBr^{79}H$^+$) calcd for $C_{20}H_{27}BrNO_4$ 424.1118, found 424.1114.

Methyl 2-(3-ethylidene-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate (368) and **methyl (*E*)-3-(2-ethyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxypyrrolo[2,1-a]isoquinolin-1-yl)acrylate (369)**



368



369

A solution of methyl (*E*) 4-(2-((*Z*)-2-bromobut-2-enyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)but-2-enoate **(368)** (1.8 g, 4.25 mmol) in THF (100 mL) was stirred at reflux for 30 minutes under a flow of nitrogen. Then AIBN (0.035 g, 0.21 mmol) was added, followed by the slow addition of a solution of tributyltin hydride (1.5 mL, 5.5 mmol) and AIBN (0.314 g, 1.91 mmol) in THF (20 mL) by a syringe pump over a period of 4 h. Following the complete addition of the tributyltin hydride, the solution was maintained at reflux for a further 4 h, after which the solution was cooled to r.t The reaction mixture was concentrated *in vacuo*, until approx 20 ml of solvent was left. This was stirred with a 1:4 mixture of KF/Silica for 10 min. The resulting slurry was then loaded on to a KF/silica column and washed with approximately 400 mL of petrol, followed by flushing the column with EtOAc (approximately 300 mL). The resulting oil/gum was purified by flash silica chromatography, elution gradient 6:1 petrol:EtOAc to EtOAc. The pure fractions were concentrated *in vacuo* to afford the title compounds.

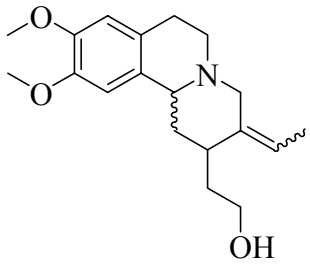
The 6-*exo* cyclisation product **368** was isolated as a yellow gum (0.64 g, 44%), as a 2:1 mixture of partially separable diastereoisomers; ν_{max} (thin film) /cm^{-1} 2948 (m), 1730 (s), 1613 (w), 1520 (s); δ_H (400 MHz, CDCl$_3$) (major isomer) 6.62 (1H, s, ^{Ar}C̲H), 6.54 (1H, s, ^{Ar}C̲H), 5.19 (1H, q, *J* = 6.5, C=C̲HCH$_3$), 3.82 (3H, s, ^{Ar}OC̲H$_3$), 3.81 (3H, s, ^{Ar}OC̲H$_3$), 3.72 (1H, d, *J* = 13.2, NC̲H$_2$C=CH), 3.70 (3H, s, CO$_2$C̲H$_3$), 3.43 (1H, app d, *J* = 8.9, NC̲H), 3.08-2.98 (2H, m, NCH$_2$C̲H$_2$Ar and NC̲H$_2$CH$_2$Ar), 2.80-2.62 (4H, m, NC̲H$_2$C=CH, CH$_2$C̲HCH$_2$, C̲H$_2$CO$_2$Me, NCH$_2$C̲H$_2$Ar), 2.58-2.52 (1H, m, NC̲H$_2$CH$_2$Ar), 1.68 (3H, d, *J* =

6.5, C=CHC$\underline{H}_3$), 1.27 (1H, app dd, J = 12.2 and 10.5, CHC$\underline{H}_2$CH); δ_C (100 MHz, $CDCl_3$) 173.4 ($\underline{C}O_2CH_3$), 147.4 ($^{Ar}\underline{C}OCH_3$), 147.0 ($^{Ar}\underline{C}OCH_3$), 136.0 ($\underline{C}$=CHCH$_3$), 129.5 ($^{Ar}\underline{C}$), 126.4 ($^{Ar}\underline{C}$), 115.8 (C=$\underline{C}$HCH$_3$), 111.3 ($^{Ar}\underline{C}$H), 108.3 ($^{Ar}\underline{C}$H), 62.1 (N$\underline{C}$H), 56.1 (N$\underline{C}$H$_2$C=CH), 56.0 (^{Ar}CO$\underline{C}$H$_3$), 55.7 (^{Ar}CO$\underline{C}$H$_3$), 51.6 (CO$_2\underline{C}$H$_3$), 51.1 (N$\underline{C}$H$_2$CH$_2$Ar), 38.7 (CH$\underline{C}$H$_2$CH), 38.5 (CH$_2\underline{C}$HCH$_2$), 36.9 ($\underline{C}$H$_2$CO$_2$CH$_3$), 29.1 (NCH$_2\underline{C}$H$_2$Ar), 13.0 (CH$\underline{C}$H$_3$); *m/z* (CI, NH_3) 347 (20%), 346 (MH^+, 100); HRMS $C_{20}H_{28}NO_4$ (MH^+) requires 346.2013, found 346.2018.

The presence of the minor diastereoisomer was identified by the following key peaks; δ_C (100 MHz, $CDCl_3$) 172.5 ($\underline{C}O_2CH_3$), 147.2 ($^{Ar}\underline{C}OCH_3$), 146.8 ($^{Ar}\underline{C}OCH_3$), 134.8 ($\underline{C}$=CHCH$_3$), 126.6 ($^{Ar}\underline{C}$), 126.3 ($^{Ar}\underline{C}$), 115.8 (C=$\underline{C}$HCH$_3$), 111.4 ($^{Ar}\underline{C}$H), 108.4 ($^{Ar}\underline{C}$H), 60.2 (N$\underline{C}$H$_2$C=CH), 57.1 (N$\underline{C}$H), 55.8 (^{Ar}CO$\underline{C}$H$_3$), 55.6 (^{Ar}CO$\underline{C}$H$_3$), 51.5 (CO$_2\underline{C}$H$_3$), 51.3 (N$\underline{C}$H$_2$CH$_2$Ar), 38.6 (CH$\underline{C}$H$_2$CH), 38.4 (CH$_2\underline{C}$HCH$_2$), 31.5 ($\underline{C}$H$_2$CO$_2$CH$_3$), 29.8 (NCH$_2\underline{C}$H$_2$Ar), 12.4 (CH$\underline{C}$H$_3$).

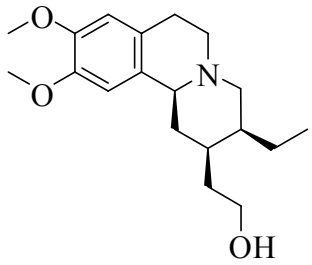
The 5-*exo* cyclisation product **369** was isolated as a yellow gum (58 mg, 4%); ν_{max} (thin film) /cm^{-1} 3030 (m), 2945 (m), 1721 (s), 1608 (m); δ_H (400 MHz, $CDCl_3$) 7.13 (1H, dd, J = 15.5 and 9.0, CHC$\underline{H}$=CHCO$_2$CH$_3$), 6.57 (1H, s, ^{Ar}CH), 6.56 (1H, s, ^{Ar}CH), 5.90 (1H, d, J = 15.5, CHCH=C$\underline{H}$CO$_2$CH$_3$), 3.82 (1H, s, ^{Ar}OCH$_3$), 3.76-3.70 (1H, m, NC$\underline{H}$), 3.74 (3H, s, CO$_2$CH$_3$), 3.71 (1H, s, ^{Ar}OCH$_3$), 3.10 (1H, app dq, J = 11.8 and 3.3, NC$\underline{H}_2$CH$_2$Ar), 2.97-2.88 (2H, m, NC$\underline{H}_2$CH and NCH$_2$C$\underline{H}_2$Ar), 2.79-2.70 (2H, m, NC$\underline{H}_2$CH and NC$\underline{H}_2$CH$_2$Ar), 2.57 (1H, dt, J = 15.8 and 3.3, NCH$_2$C$\underline{H}_2$Ar), 2.34 (1H, app q, J = 9.0, C$\underline{H}$CH=CHCO$_2$CH$_3$), 2.03-1.94 (1H, m, C$\underline{H}$CH$_2$CH$_3$), 1.57-1.46 (1H, m, CHC$\underline{H}_2$CH$_3$), 1.35-1.21 (1H, m, CHC$\underline{H}_2$CH$_3$), 0.88 (3H, t, J = 7.0, CH$_2$C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 166.8 ($\underline{C}O_2CH_3$), 152.8 (CH$\underline{C}$H=CHCO$_2$CH$_3$), 147.4 ($^{Ar}\underline{C}OCH_3$), 147.1 ($^{Ar}\underline{C}OCH_3$), 129.9 ($^{Ar}\underline{C}$), 126.6 ($^{Ar}\underline{C}$), 121.8 (CHCH=$\underline{C}$HCO$_2$CH$_3$), 111.4 ($^{Ar}\underline{C}$H), 108.8 ($^{Ar}\underline{C}$H), 66.4 (N$\underline{C}$H), 57.4 (N$\underline{C}$H$_2$CH), 56.7 ($\underline{C}$HCH=CHCO$_2$CH$_3$), 55.9 (^{Ar}O$\underline{C}$H$_3$), 55.8 (^{Ar}O$\underline{C}$H$_3$), 51.7 (CO$_2\underline{C}$H$_3$), 48.0 (N$\underline{C}$H$_2$CH$_2$Ar), 46.0 ($\underline{C}$HCH$_2$CH$_3$), 26.6 (CH$\underline{C}$H$_2$CH$_3$), 26.4 (NCH$_2\underline{C}$H$_2$Ar), 12.8 (CH$_2\underline{C}$H$_3$); *m/z* (CI, NH_3) 347 (20%), 346 (MH^+, 100), 344 (10); HRMS $C_{20}H_{28}NO_4$ (MH^+) requires 346.2013, found 346.2025.

2-(3-Ethylidene-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-1H-pyrido[2,1-a]isoquinolin-2-yl)ethanol (378)



To a stirred solution of methyl 2-(3-ethylidene-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-1H-pyrido[2,1-a]isoquinolin-2-yl)acetate **368** (185 mg, 0.55 mmol), in THF (10 mL) at 0 ºC under nitrogen, was slowly added a solution of lithium aluminium hydride in THF (2.3 mL, 2.4 M, 5.5 mmol), the solution was stirred for 15 minutes at 0 ºC, then warmed to r.t. and stirred for 6 h. The stirred reaction mixture was then quenched by the sequential dropwise addition of H_2O (0.20 mL), 15% aqueous NaOH (0.20 mL) and H_2O (0.60 mL), then EtOAc (10 mL) and celite (0.5 g) were added and stirred for 1 h. The reaction mixture was filtered through a celite plug, the plug was flushed with EtOAc (2 × 25 mL), and evaporation of the solvent afforded the crude product as a yellow oil. The oil was purified by flash silica chromatography, elution gradient 10 to 20% MeOH/NH_3 in DCM. Pure fractions were concentrated *in vacuo* to afford the title compound **378** as a yellow oil (146 mg, 84%); Rf = 0.50 (10% MeOH/NH_3 in DCM); ν_{max} (thin film) /cm^{-1} 3400 (sb), 2995 (w), 1612 (m), 1510 (m); δ_H (400 MHz, $CDCl_3$) 6.61 (1H, s, $^{Ar}C\underline{H}$), 6.52 (1H, s, $^{Ar}C\underline{H}$), 5.22 (1H, q, J = 6.5, C=C$\underline{H}CH_3$), 3.79 (3H, s, $^{Ar}OC\underline{H}_3$), 3.78 (3H, s, $^{Ar}OC\underline{H}_3$), 3.73 (2H, t, J = 6.5, C$\underline{H}_2$OH), 3.56-3.48 (1H, m, NC$\underline{H}_2$C=CH_2), 3.39 (1H, app d, J = 10.5, NC$\underline{H}$), 3.08-2.90 (3H, m, NC$\underline{H}_2$C=CH_2, NC$\underline{H}_2CH_2$Ar and $NCH_2C\underline{H}_2$Ar), 2.76-2.52 (4H, m, $CH_2C\underline{H}CH_2$, $NCH_2C\underline{H}_2$Ar, NC$\underline{H}_2CH_2$Ar and $CH_2O\underline{H}$), 2.28-2.20 (1H, m, CHC$\underline{H}_2$CH), 1.84-1.78 (1H, m, C$\underline{H}_2CH_2$OH), 1.68 (3H, d, J = 6.5, C=CHC$\underline{H}_3$), 1.56-1.48 (1H, m, C$\underline{H}_2CH_2$OH), 1.27 (1H, app q, J = 11.5, CHC$\underline{H}_2$CH); δ_C (100 MHz, $CDCl_3$) 147.2 ($^{Ar}\underline{C}OCH_3$), 146.8 ($^{Ar}\underline{C}OCH_3$), 136.6 ($\underline{C}$=$CHCH_3$), 129.7 ($^{Ar}\underline{C}$), 126.2 ($^{Ar}\underline{C}$), 115.6 (C=$\underline{C}HCH_3$), 111.1 ($^{Ar}\underline{C}$H), 108.2 ($^{Ar}\underline{C}$H), 62.0 (N$\underline{C}$H), 60.2 (N$\underline{C}H_2$C=CH), 56.1 ($\underline{C}H_2$OH), 55.8 ($^{Ar}CO\underline{C}H_3$), 55.7 ($^{Ar}CO\underline{C}H_3$), 50.6 (N$\underline{C}H_2CH_2$Ar), 38.3 (CH$\underline{C}H_2$CH), 37.8 ($CH_2\underline{C}HCH_2$), 34.4 ($\underline{C}H_2CH_2$OH), 28.8 ($NCH_2\underline{C}H_2$Ar), 12.9 (C=$CHCH_3$); *m/z* (CI) 319 (20%), 318 (100, MH^+); HRMS $C_{19}H_{28}NO_3$ (MH^+) requires 318.2064, found 318.2075.

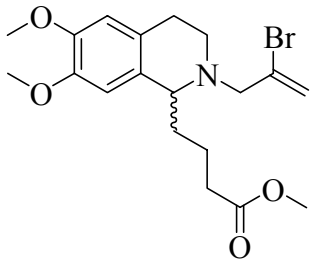
2-((2*R,3*S**,11b*S**)-3-Ethyl-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-1H-pyrido[2,1-a]isoquinolin-2-yl)ethanol or epi-protoemetinol (88-b)**



A stirred solution of 2-(3-ethylidene-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-1H-pyrido[2,1-a]isoquinolin-2-yl)ethanol **378** (75 mg, 0.26 mmol) and 5% Pd/C (10 mg) in MeOH (10 mL) was evacuated and back-filled with nitrogen (×3) then hydrogen (×2). The solution was then stirred under 1 bar hydrogen at r.t. for 6 h, after which the reaction mixture was filtered through a plug of Celite (EtOAc) and the solvent was evaporated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 10 to 20% MeOH/NH_3 in DCM. Pure fractions were evaporated to dryness to afford the title compound **88-b** (47 mg, 63%) as a yellow oil, as a 10:1 mixture of diastereoisomers.

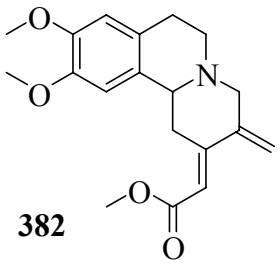
Major diastereoisomer (epi-protoemetinol (**88-b**)) was isolated as a pale yellow oil; ν_{max} (thin film) /cm^{-1} 3448 (b), 2930 (w), 1510 (m), 1428 (m), 1252 (m); δ_H (400 MHz, $CDCl_3$) 6.66 (1H, s, ^{Ar}CH), 6.54 (1H, s, ^{Ar}CH), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.71 (2H, t, *J* = 6.7, OCH_2), 3.14-2.94 (3H, m, NCH, NCH_2CH_2Ar and NCH_2CHCH_3), 2.61 (1H, dd, *J* = 11.7 and 4.0, NCH_2CH_2Ar), 2.58-2.50 (1H, m, NCH_2CH_2Ar), 2.40 (1H, td, *J* = 11.7 and 4.0, NCH_2CH_2Ar), 2.25 (1H, app d, *J* = 11.1, $CHCH_2CH$), 2.01 (1H, t, *J* = 11.0 Hz, NCH_2CHCH_3), 1.99–1.80 (2H, m, $CHCH_2CH_2OH$ and $CHCH_2CH_3$), 1.69-1.63 (1H, m, $CHCH_2CH_3$), 1.60-1.38 (3H, m, $CHCH_2CH_2OH$, CH_2OH and $CHCH_2CH_3$), 1.30-1.24 (1H, m, $CHCH_2CH_2OH$), 1.18-1.08 (1H, m, $CHCH_2CH$), 0.89 (3H, t, *J* = 7.3 CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 147.3 ($^{Ar}COCH_3$), 147.1 ($^{Ar}COCH_3$), 130.6 (^{Ar}C), 127.2 (^{Ar}C), 111.6 (^{Ar}CH), 108.1 (^{Ar}CH), 61.2 (OCH_2), 57.5 (NCH), 55.9 ($^{Ar}OCH_3$), 55.8 ($^{Ar}OCH_3$), 54.2 (NCH_2CH_2Ar), 52.4 (NCH_2CH), 36.9 ($CHCH_2CH$), 40.7 (CH), 35.7 ($CHCH_2CH_2OH$), 32.5 (CH), 32.4 (NCH_2CH_2Ar), 25.1 ($CHCH_2CH_3$), 12.1 ($CHCH_2CH_3$); *m/z* (CI) 321 (20%), 320 (MH^+, 100); HRMS $C_{19}H_{30}NO_3$ (MH^+) requires 320.2220, found 320.2223.

Methyl 4-(2-(2-bromoallyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)butanoate (381)

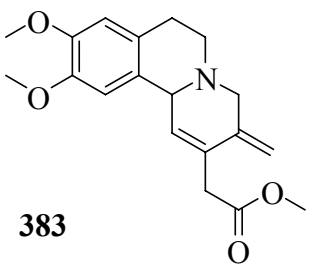


To a stirred solution of methyl (*E*)-4-(2-(2-bromoallyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate **358** (0.410 g, 1.0 mmol) and methanol (0.93 mL, 23.10 mmol) in THF (10 mL) at r.t. was added a solution of samarium(II) iodide (23.63 mL, 1.0 M, 2.36 mmol) in THF. The resulting solution was stirred at r.t. for 1 h, during which time the dark blue colour faded to green. The reaction was incomplete as indicated by LCMS analysis and a further portion of samarium(II) iodide (23.63 mL, 1.0 M, 2.36 mmol) in THF was added and the solution was stirred at r.t. for a further 3 h, during which time the dark blue colour faded to a pale blue solution. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (75 mL), extracted with EtOAc (2 × 75 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated to afford the title compound **381** as a yellow oil (0.303 g, 73%); ν_{max} (thin film) /cm^{-1} 2997 (w), 2946 (m), 2834 (w), 1720 (s), 1656 (w), 1515 (s); δ_H (400 MHz, $CDCl_3$) 6.47 (1H, s, $^{Ar}C\underline{H}$), 6.44 (1H, s, $^{Ar}C\underline{H}$), 5.79 (1H, app d, *J* = 1.2, C(Br)=C$\underline{H}_2$), 5.49 (1H, s, C(Br)=C$\underline{H}_2$), 3.77 (3H, s, OC$\underline{H}_3$), 3.76 (3H, s, OC$\underline{H}_3$), 3.57 (3H, s, $CO_2C\underline{H}_3$), 3.46 (1H, app dd, *J* = 7.5 and 4.5, NC$\underline{H}$), 3.29 (1H, s, NC$\underline{H}_2$C(Br)=CH_2), 3.13 (1H, app ddd, *J* = 14.0, 9.6 and 3.5, NC$\underline{H}_2CH_2$Ar), 2.76-2.65 (2H, m, $NCH_2C\underline{H}_2$Ar and NC$\underline{H}_2CH_2$Ar), 2.46-2.39 (1H, m, $NCH_2C\underline{H}_2$Ar), 2.27 (2H, t, *J* = 7.1, $C\underline{H}_2CO_2CH_3$), 1.80-1.59 (4H, m, NCHC$\underline{H}_2$ and $NCHCH_2C\underline{H}_2$); δ_C (100 MHz, $CDCl_3$) 173.0 ($\underline{C}O_2CH_3$), 146.5 ($^{Ar}\underline{C}OCH_3$), 146.4 ($^{Ar}\underline{C}OCH_3$), 131.6 ($\underline{C}$(Br)=CH_2), 129.0 ($^{Ar}\underline{C}$), 125.2 ($^{Ar}\underline{C}$), 117.0 (C(Br)=$\underline{C}H_2$), 110.6 ($^{Ar}\underline{C}H$), 109.5 ($^{Ar}\underline{C}H$), 61.0 ($N\underline{C}H_2C$(Br)=CH_2), 59.3 ($N\underline{C}H$), 55.0 ($^{Ar}CO\underline{C}H_3$), 54.8 ($^{Ar}CO\underline{C}H_3$), 50.3 ($CO_2\underline{C}H_3$), 42.3 ($N\underline{C}H_2CH_2$Ar), 34.7 ($\underline{C}H_2$), 32.9 ($\underline{C}H_2CO_2$Me), 22.8 ($NCH_2\underline{C}H_2$Ar), 20.7 ($\underline{C}H_2$); *m/z* (CI, NH_3) 414 (MH^+Br^{81}, 98%), 412 (MH^+Br^{79}, 100), 294 (10). HRMS $C_{19}H_{27}{}^{79}BrNO_4$ (MH+) requires 412.1123, found 412.1120.

Methyl (*E*)-2-(9,10-dimethoxy-3-methylene-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-ylidene)acetate (382) and methyl 2-(9,10-dimethoxy-3-methylene-4,6,7,11b-tetrahydro-3H-pyrido[2,1-a]isoquinolin-2-yl)acetate (383)



382



383

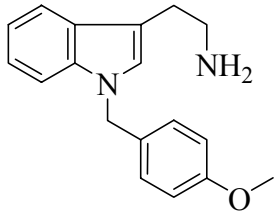
A solution of methyl (*E*)-4-(2-(2-bromoallyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1-yl)but-2-enoate (**358**) (205 mg, 0.5 mmol), palladium(II) acetate (11 mg, 0.05 mmol), triphenylphosphine (26 mg, 0.1 mmol), and *N*,*N*-diisopropylethylamine (0.20 mL, 1.5 mmol) in DMF (5 mL) was evacuated and back-filled with nitrogen (× 3). The solution was then heated to 80 °C for 2 h, during which time black palladium(0) formed. The reaction mixture was cooled to r.t. and diluted with EtOAc (20 mL), then filtered through a pad of Celite to remove the inorganic salts. The filtrate was poured into EtOAc (75mL) and water (25 mL), and the aqueous layer was extracted with EtOAc (3 × 25 mL). The organic layers were combined, washed with water (3 × 25 mL), brine (3 × 25 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (4:1 petrol:EtOAc to EtOAc) to give the title compounds.

Compound **382** was isolated as a yellow oil (59 mg, 36%); ν_{max} (thin film) /cm^{-1} 3050 (m), 2994 (w), 1725 (s), 1420 (m); δ_H (400 MHz, $CDCl_3$) 6.74 (1H, s, $^{Ar}C\underline{H}$), 6.57 (1H, s, $^{Ar}C\underline{H}$), 6.00 (1H, d, *J* = 2.2, C=C(H)CO_2CH_3), 5.25 (1H, s, C=C$\underline{H}_2$), 4.96 (1H, s, C=C$\underline{H}_2$), 4.29 (1H, dd, *J* = 15.6 and 3.2, NCHC$\underline{H}_2$C), 3.87 (3H, s, $^{Ar}OC\underline{H}_3$), 3.83 (3H, s, $^{Ar}OC\underline{H}_3$), 3.72 (3H, s, $CO_2C\underline{H}_3$), 3.54 (1H, d, *J* = 12.9, NC$\underline{H}_2$C=CH_2), 3.44 (1H, dd, *J* = 10.5 and 2.9, NC$\underline{H}$), 3.22 (1H, d, *J* = 12.9, NC$\underline{H}_2$C=CH_2), 3.09-2.99 (2H, m, NC$\underline{H}_2CH_2$Ar and $NCH_2C\underline{H}_2$Ar), 2.72-2.66 (1H, m, $NCH_2C\underline{H}_2$Ar), 2.56 (1H, dd, *J* = 12.6 and 6.1, NC$\underline{H}_2CH_2$Ar), 2.34 (1H, app, ddd, *J* = 15.6, 11.4 and 2.5, NCHC$\underline{H}_2$C); δ_C (100 MHz, $CDCl_3$) 167.0 ($\underline{C}O_2CH_3$), 156.7 ($\underline{C}$=CH_2), 147.7 ($^{Ar}\underline{C}OCH_3$), 147.4 ($^{Ar}\underline{C}OCH_3$), 144.1 ($\underline{C}$=C(H)CO_2CH_3), 129.2 (^{Ar}C), 126.4 (^{Ar}C), 113.7 (C=C(H)CO_2CH_3), 112.6 (C=CH_2), 111.4 (^{Ar}CH), 108.8 (^{Ar}CH), 61.5 (N$\underline{C}H_2$C=CH_2), 60.8 (N$\underline{C}$H), 56.1 ($^{Ar}O\underline{C}H_3$), 55.9 ($^{Ar}O\underline{C}H_3$), 51.2 ($CO_2\underline{C}H_3$), 50.5 (N$\underline{C}H_2$Ar), 35.0 (NCH$\underline{C}H_2$C), 29.0 ($NCH_2\underline{C}H_2$Ar); *m/z* (CI) 334 (15%), 331 (20), 330 (100, MH^+), 316 (15); HRMS $C_{19}H_{24}NO4$ (MH^+) requires 330.1700, found 330.1705.

Alkene **383** was isolated as a yellow oil (56 mg, 34%); ν_{max} (thin film) /cm^{-1} 3062 (m), 2990 (w), 1738 (s), 1392 (w); δ_H (400 MHz, $CDCl_3$) 6.66 (1H, s, ^{Ar}CH), 6.56 (1H, s,

^{Ar}CH), 5.89 (1H, s, NCHC<u>H</u>=C), 5.02 (1H, s C=C<u>H</u>$_2$), 4.91 (1H, s C=C<u>H</u>$_2$), 4.53 (1H, s NC<u>H</u>), 3.84 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.81 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.72 (1H, dt, *J* = 14.4 and 1.8, NC<u>H</u>$_2$C=CH$_2$), 3.65 (3H, s, CO$_2$C<u>H</u>$_3$), 3.49 (1H, d, *J* = 14.4, NC<u>H</u>$_2$C=CH$_2$), 3.29 (1H, dt, *J* = 15.8 and 1.2, C<u>H</u>$_2$CO$_2$CH$_3$), 3.14 (1H, d, *J* = 15.8, C<u>H</u>$_2$CO$_2$CH$_3$), 2.97-2.78 (3H, m, C<u>H</u>$_2$CH$_2$Ar and NCH$_2$C<u>H</u>$_2$Ar), 2.64 (1H, dt, *J* = 10.9 and 5.4, NC<u>H</u>$_2$CH$_2$Ar); δ_C (100 MHz, CDCl$_3$) 172.0 (<u>C</u>O$_2$CH$_3$), 147.7 (^{Ar}<u>C</u>OCH$_3$), 147.5 (^{Ar}<u>C</u>OCH$_3$), 138.2 (<u>C</u>=CH), 132.1 (NCH<u>C</u>H=C), 129.1 (CH=<u>C</u>CH$_2$CO$_2$CH$_3$), 128.2 (^{Ar}<u>C</u>), 126.7 (^{Ar}<u>C</u>), 111.6 (^{Ar}<u>C</u>H), 109.7 (C=CH$_2$), 109.0 (^{Ar}<u>C</u>H), 59.6 (N<u>C</u>H), 58.9 (N<u>C</u>H$_2$C=CH$_2$), 56.1 (^{Ar}O<u>C</u>H$_3$), 55.9 (^{Ar}O<u>C</u>H$_3$), 52.0 (CO$_2$<u>C</u>H$_3$), 46.7 (N<u>C</u>H$_2$CH$_2$Ar), 38.4 (<u>C</u>H$_2$CO$_2$CH$_3$), 28.9 (NCH$_2$<u>C</u>H$_2$Ar); *m/z* (CI) 347 (35%, MNH$_4^+$), 331 (20), 330 (100, MH$^+$); HRMS $C_{19}H_{24}NO_4$ (MH$^+$) requires 330.1700, found 330.1699.

2-(1-(4-Methoxybenzyl)-1H-indol-3-yl)ethanamine (391)[303]

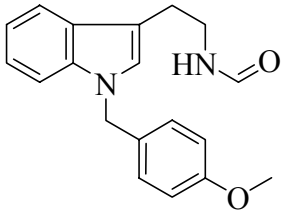


To a stirred solution of 2-(1H-indol-3-yl)ethanamine **388** (10 g, 62.42 mmol), in dimethylacetamide (150 mL) at r.t. was added sodium hydride (2.62 g, 60% dispersion in mineral oil, 65.54 mmol) portionwise, during which time evolution of gas was observed. The solution was stirred at r.t. for 1 h. The resulting suspension was cooled to 0 °C, and 1-(chloromethyl)-4-methoxybenzene (8.6 mL, 62.4 mmol) was added dropwise, following complete addition the resulting solution was warmed to r.t., and stirred for 6 h. The resulting solution was concentrated *in vacuo* to yield a viscous oil. The oil was diluted with water (100 mL) and EtOAc (200 mL), and allowed to stir, the layers were separated and the aqueous layers extracted with EtOAc (2 x 150 mL). The combined organic layer was washed with water (3 x 150 mL), brine (150 mL) and dried over Na_2SO_4, filtered and evaporated to afford a brown oil. The crude product was purified by flash silica chromatography, elution gradient 10% MeOH/NH_3 in DCM to afford 2-2-(1-(4-methoxybenzyl)-1H-indol-3-yl)ethanamine **391** (12.66 g, 72%) as a yellow oil. Rf 0.45 in 10% MeOH/NH_3:DCM; ν_{max} (thin film) /cm^{-1} 2928 (m), 2835 (m), 1611 (m), 1511 (s), 1464 (s), 1440 (w); δ_H (400 MHz, $CDCl_3$) 7.60 (1H, app dt, *J* = 7.9 and 1.0, ^{Ar}C<u>H</u>), 7.27 (1H, d, *J* = 8.1, ^{Ar}C<u>H</u>), 7.16 (1H, dd, *J* = 8.1 and 1.0, ^{Ar}C<u>H</u>), 7.10 (1H, app dd, *J* = 7.9 and 1.0, ^{Ar}C<u>H</u>), 7.05 (2H, app dt, *J* = 8.7 and 2.5, ^{PMB}C<u>H</u>), 6.92 (1H, s, ^{Ar}C<u>H</u>), 6.81 (2H, app dt, *J* = 8.7 and 2.5, ^{PMB}CH), 5.19 (2H, s, ^{PMB}CH$_2$N), 3.75 (3H, s, ^{PMB}COC<u>H</u>$_3$), 3.00 (2H, t, *J* =

6.6, NC$\underline{H}_2$CH$_2^{Ar}$), 2.88 (2H, t, *J* = 6.6, NCH$_2$C$\underline{H}_2^{Ar}$), 1.38 (2H, bs, N$\underline{H}_2$); δ_C (100 MHz, $CDCl_3$) 158.8 ($^{PMB}\underline{C}OCH_3$), 136.5 ($^{Ar}\underline{C}$), 129.5 ($^{Ar}\underline{C}$), 128.1 (2 × $^{PMB}\underline{C}H$), 128.0 ($^{Ar}\underline{C}$), 126.9 ($^{Ar}\underline{C}H$), 121.5 ($^{Ar}\underline{C}H$), 118.9 ($^{Ar}\underline{C}H$), 118.8 ($^{Ar}\underline{C}H$), 113.9 (2 × $^{PMB}\underline{C}H$), 112.5 ($^{Ar}\underline{C}$), 109.9 ($^{Ar}\underline{C}H$), 55.0 ($^{PMB}CO\underline{C}H_3$), 49.1 (N$\underline{C}H_2^{PMB}$), 42.5 (N$\underline{C}H_2CH_2^{Ar}$), 29.4 (NCH$_2\underline{C}H_2^{Ar}$); *m/z* (CI, NH_3) 322 (MMeCNH$^+$, 20%), 281 (MH$^+$, 75), 264 (100).

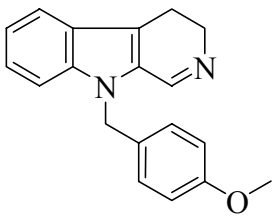
The spectroscopic data is in agreement with reported data.[303]

_N_-(2-(1-(4-Methoxybenzyl)-1H-indol-3-yl)ethyl)formamide (392)



A stirred solution of 2-(1-(4-methoxybenzyl)-1H-indol-3-yl)ethanamine **391** (4.02 g, 14.35 mmol) in ethyl formate (21.03 mL, 258.30 mmol), under nitrogen was heated to reflux for 2 h. Analysis by LCMS indicated incomplete conversion so a further portion of ethyl formate (10.5 mL, 129 mmol) was added and the reaction mixture stirred at reflux overnight. Analysis by LCMS indicated complete conversion, and the solution was concentrated *in vacuo* to yield a viscous oil, of unpurified **392** (4.43 g, quant), which was taken forward to the next step without further purification; δ_H (400 MHz, $CDCl_3$) 7.58 (1H, d, *J* = 7.8, ^{Ar}CH), 7.28 (1H, d, *J* = 8.1, ^{Ar}CH), 7.16 (1H, app td, *J* = 8.1 and 1.0, ^{Ar}CH), 7.10 (1H, app dd, *J* = 8.1 and 1.0, ^{Ar}CH), 7.05 (2H, d, *J* = 8.6, ^{PMB}C$\underline{H}$), 6.92 (1H, s, ^{Ar}CH), 6.81 (2H, d, *J* = 8.6, ^{PMB}C$\underline{H}$), 5.70 (1H, bs, NH), 5.17 (2H, s, ^{PMB}C$\underline{H}_2$N), 3.75 (3H, s, OC$\underline{H}_3$), 3.59 (2H, app q, *J* = 6.6, N$\underline{C}H_2CH_2^{Ar}$), 2.95 (2H, t, *J* = 6.6, NCH$_2$C$\underline{H}_2^{Ar}$); *m/z* (CI, NH_3) 372 (MMeCNNa$^+$, 20%), 331 (MNa$^+$, 45), 309 (MH$^+$, 100), 200 (25).

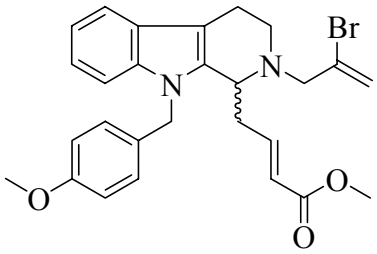
9-(4-Methoxybenzyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (393)



A stirred solution of *N*-(2-(1-(4-methoxybenzyl)-1H-indol-3-yl)ethyl)formamide **392** (4.43 g, 14.4 mmol) in chloroform (5 mL) under nitrogen was cooled to at 0 ºC and stirred for 10 minutes to achieve thermal equilibrium, followed by the slow addition of $POCl_3$ (16.05 mL, 172 mmol). The resulting solution was stirred at 0 ºC for 15 minutes. When the vigorous initial reaction subsided, the mixture was warmed to r.t. and allowed to stir for 3

h. The excess $POCl_3$ was removed *in vacuo*. The resulting oil was taken up into DCM (100 mL) and washed with 2 M aqueous NaOH (100 mL). The aqueous layer was extracted with DCM (100 mL), the combined organic layer was washed with a further portion of 2 M aqueous NaOH (100 mL), brine (100 mL) and dried over Na_2SO_4, filtered and evaporated to afford the title product **393** (4.00 g, 96%) as a fine yellow powder (no further purification was required); ν_{max} (thin film) /cm^{-1} 2974 (m), 2941 (w), 1608 (m), 1406 (m); δ_H (400 MHz, $CDCl_3$) 8.32 (1H, t, *J* = 2.3, HC=N), 7.52 (1H, app dt, *J* = 8.0 and 0.9, ^{Ar}CH), 7.23 (1H, dt, *J* = 8.3 and 0.9, ^{Ar}CH), 7.18 (1H, td, *J* = 8.3 and 1.1, ^{Ar}CH), 7.05 (1H, app ddd, *J* = 8.0, 6.8 and 1.1, ^{Ar}CH), 6.93 (2H, app dt, *J* = 8.7 and 2.5, ^{PMB}CH), 6.72 (2H, app dt, *J* = 8.7 and 2.5, ^{PMB}CH), 5.26 (2H, s, $^{PMB}CH_2N$), 3.82 (2H, td, *J* = 8.6 and 2.3, $NCH_2CH_2^{Ar}$), 3.66 (3H, s, $^{PMB}COCH_3$), 2.82 (2H, t, *J* = 8.6, $NCH_2CH_2^{Ar}$); δ_C (100 MHz, $CDCl_3$) 159.1 ($^{Ar}COCH_3$), 150.2 (HC=N), 137.6 (^{Ar}C), 129.4 (^{Ar}CH), 129.2 (^{Ar}C), 127.6 (2 × ^{PMB}CH), 125.0 (^{Ar}C), 124.5 (^{Ar}CH), 120.2 (^{Ar}CH and ^{Ar}C), 116.1 (^{Ar}C), 114.3 (2 × ^{PMB}CH), 110.4 (^{Ar}CH), 55.3 ($^{PMB}COCH_3$), 48.5 ($NCH_2CH_2^{Ar}$), 46.3 (NCH_2^{PMB}), 29.4 ($NCH_2CH_2^{Ar}$); *m/z* (CI, NH_3) 292 (35%), 291 (MH^+, 100); HRMS $C_{19}H_{19}N_2O$ (MH^+) requires 291.1497, found 291.1493.

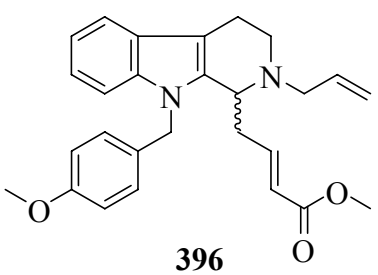
Methyl (*E*)-4-(9-(4-methoxybenzyl)-2-(2-bromoallyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)but-2-enoate (395)



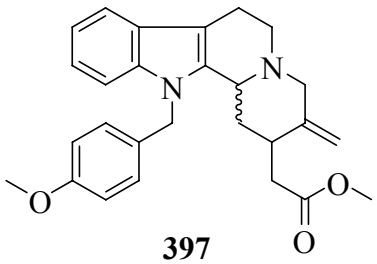
To a stirred solution of 9-(4-methoxybenzyl)-4,9-dihydro-3H-pyrido[3,4-b]indole **393** (4.0 g, 13.78 mmol) in acetonitrile (48.2 mL) at r.t. under nitrogen was added 2,3-dibromoprop-1-ene (2.14 mL, 16.53 mmol). The resulting solution was stirred in the dark for 48 h, during which time the solution turned a dark brown. The crude mixture was evaporated to dryness to afford a dark brown gum. The brown oil was taken up in a further portion of acetonitrile (100 mL), to the resulting solution was added methyl (E)-4-bromobut-2-enoate (4.77 mL, 34.44 mmol) and zinc dust (1.802 g, 27.55 mmol), the solution was stirred at r.t. under nitrogen for 2 days. The reaction mixture was quenched by pouring into a saturated aqueous solution of $NaHCO_3$ (150 mL) and allowed to stir for 30 minutes. The resulting precipitate was removed by filtration, and washed with EtOAc (200 mL), the organic layer was separated and the aqueous layer extracted with EtOAc (2 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to afford a brown oil. The

crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH/NH_3 in DCM. Pure fractions were evaporated to dryness to afford the title compound **395** (1.20 g, 17%) as a yellow oil; ν_{max} (thin film) /cm^{-1} 3585 (w), 3012 (w), 2841 (w), 1730 (s), 1515 (s), 1472 (w); δ_H (400 MHz, $CDCl_3$) 7.53 (1H, app dd, *J* = 7.0 and 1.1, ^{Ar}CH), 7.22 (1H, d, *J* = 7.7, ^{Ar}C<u>H</u>), 7.20-7.09 (3H, m, 2 × ^{Ar}C<u>H</u> and C<u>H</u>=CHCO$_2$Me), 6.84 (2H, d, *J* = 8.8, ^{PMB}C<u>H</u>), 6.77 (2H, d, *J* = 8.8, ^{PMB}C<u>H</u>), 5.82 (1H, dt, *J* = 15.7 and 1.3, CH=C<u>H</u>CO$_2$Me), 5.53 (1H, d, *J* = 1.0, BrC=C<u>H$_2$</u>), 5.42 (1H, s, BrC=C<u>H$_2$</u>), 5.25 (1H, d, *J* = 16.7, NC<u>H$_2$</u>PMB), 5.07 (1H, d, *J* = 16.7, NC<u>H$_2$</u>PMB), 3.74 (3H, s, OC<u>H$_3$</u>), 3.72 (3H, s, OC<u>H$_3$</u>), 3.73-3.70 (1H, m, NC<u>H</u>CH$_2$), 3.38 (1H, d, *J* = 14.7, NC<u>H$_2$</u>BrC), 3.32 (1H, ddd, *J* = 14.3, 11.8 and 5.2, NC<u>H$_2$</u>CH$_2$Ar), 3.21 (1H, d, *J* = 14.7, NC<u>H$_2$</u>BrC), 3.06 (1H, dd, *J* = 14.3 and 5.7, NC<u>H$_2$</u>CH$_2$Ar), 2.91 (1H, app ddd, *J* = 16.8, 11.8 and 6.0, NCH$_2$C<u>H$_2$</u>Ar), 2.68-2.59 (2H, m, NCH$_2$C<u>H$_2$</u>Ar and CHC<u>H$_2$</u>CH=CH), 2.44 (1H, dddd, *J* = 15.3, 7.3, 3.6 and 1.3, CHC<u>H$_2$</u>CH=CH); δ_C (100 MHz, $CDCl_3$) 166.8 (<u>C</u>O$_2$CH$_3$), 159.0 (^{Ar}<u>C</u>), 146.8 (<u>C</u>H=CHCO$_2$CH$_3$), 137.1 (^{Ar}<u>C</u>), 134.8 (^{Ar}<u>C</u>), 131.8 (^{Ar}<u>C</u>), 129.5 (^{Ar}<u>C</u>), 127.1 (2 × ^{PMB}<u>C</u>H), 127.0 (<u>C</u>Br), 122.2 (<u>C</u>HCO$_2$CH$_3$), 121.8 (^{Ar}<u>C</u>H), 119.4 (^{Ar}<u>C</u>H), 118.7 (C(Br)=<u>C</u>H$_2$), 118.3 (^{Ar}<u>C</u>H), 114.3 (2 × ^{PMB}<u>C</u>H), 109.5 (^{Ar}<u>C</u>H), 107.8 (^{Ar}<u>C</u>), 61.4 (N<u>C</u>H), 55.2 (O<u>C</u>H$_3$), 54.7 (O<u>C</u>H$_3$), 51.4 (N<u>C</u>H$_2$Br), 46.2 (N<u>C</u>H$_2$PMB), 42.8 (N<u>C</u>H$_2$CH$_2$Ar), 37.4 (<u>C</u>H$_2$CH=CH), 17.2 (N<u>C</u>H$_2$CH$_2$Ar); *m/z* (CI, NH_3) 511 ($M^{81}BrH^+$, 100%), 509 ($M^{79}BrH^+$, 98), 429 (10); HRMS $C_{27}H_{30}{}^{79}BrN_2O_3$ (MH^+) requires 509.1434, found 509.1430.

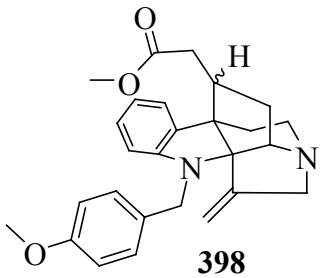
Methyl (*E*)-4-(2-allyl-9-(4-methoxybenzyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)but-2-enoate (396), methyl 2-(12-(4-methoxybenzyl)-3-methylene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (397) and methyl 8-[(4-methoxyphenyl)methyl]-10-methylidene- 8,12- diazapentacyclo[10.3.2.0^{1,9}.0^{2,7}.0^{9,13}] heptadeca- 2(7),3,5-triene-15-carboxylate (398)



396



397



398

A solution of methyl (*E*)-4-(9-(4-methoxybenzyl)-2-(2-bromoallyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)but-2-enoate **395** (1.1 g, 2.2 mmol) in THF (100 mL) was stirred at reflux for 30 minutes, then AIBN (0.035 g, 0.21 mmol) was added. A solution of tributyltin hydride (0.9 mL, 3.5 mmol) and AIBN (0.14 g, 0.9 mmol) in THF (20 mL) was added to

the refluxing solution of the vinyl bromide, over a period of 4 h under nitrogen. Following the complete addition of the tributyltin hydride solution, the reaction mixture was maintained at reflux for a further 2 h, after which the solution was cooled to r.t. The crude reaction mixture was passed through a SCX column, elution gradient 4:1 DCM:MeOH to 4:1 DCM:MeOH/NH_3, the DCM:MeOH/NH_3 fractions were evaporated to afford a yellow oil. The oil was purified by flash silica chromatography, elution gradient 20:1:1 petrol:EtOAc:MeOH/NH_3 to 10:10:1 petrol:EtOAc:MeOH/NH_3. Pure fractions were concentrated *in vacuo* to afford the title compounds.

The direct reduction product **396** was isolated as a yellow gum (33 mg, 3.5%); ν_{max} (thin film) /cm^{-1} 3583 (w), 3008 (w), 2949 (m), 2838 (w), 1722 (s), 1513 (s), 1463 (s); δ_H (400 MHz, $CDCl_3$) 7.54 (1H, app dd, *J* = 6.6 and 1.3, ^{Ar}C<u>H</u>), 7.20 (1H, app dd, *J* = 5.8 and 1.1, ^{Ar}C<u>H</u>), 7.18-7.10 (2H, m, ^{Ar}C<u>H</u>), 7.05 (1H, app dt, *J* = 15.7 and 7.0, C<u>H</u>=CHCO$_2$CH$_3$), 6.85 (2H, app dt, *J* = 8.8 and 2.5, ^{PMB}C<u>H</u>), 6.79 (2H, app dt, *J* = 8.8 and 2.5, ^{PMB}C<u>H</u>), 5.85-5.75 (1H, m, C<u>H</u>=CH$_2$), 5.81 (1H, app dt, *J* = 15.7 and 1.5, CH=C<u>H</u>CO$_2$CH$_3$), 5.22 (1H, d, *J* = 16.7, ^{PMB}CH$_2$), 5.09 (1H, d, *J* = 16.7, ^{PMB}CH$_2$), 5.00 (1H, app dd, *J* = 10.1 and 0.9, CH=C<u>H</u>$_2$), 4.99 (1H, app dd, *J* = 15.8 and 1.3, CH=C<u>H</u>$_2$), 3.81 (1H, dd, *J* = 7.1 and 3.3, NC<u>H</u>), 3.75 (3H, s, ^{PMB}COC<u>H</u>$_3$), 3.73 (3H, s, CO$_2$C<u>H</u>$_3$), 3.27-3.21 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NC<u>H</u>$_2$CH=CH$_2$), 3.10-3.02 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NC<u>H</u>$_2$CH=CH$_2$), 2.96-2.87 (1H, m, NC<u>H</u>$_2$CH$_2^{Ar}$), 2.64-2.55 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NCHC<u>H</u>$_2$CH=CH), 2.45-2.38 (1H, m, NCHC<u>H</u>$_2$CH=CH); δ_C (100 MHz, $CDCl_3$) 166.8 (<u>C</u>=O), 158.8 (^{PMB}<u>C</u>OCH$_3$), 146.9 (<u>C</u>H=CHCO$_2$CH$_3$), 137.0 (<u>C</u>H=CH$_2$), 136.3 (^{Ar}<u>C</u>), 134.9 (^{Ar}<u>C</u>), 129.5 (^{Ar}<u>C</u>), 127.1 (2 × ^{PMB}<u>C</u>H), 127.0 (^{Ar}<u>C</u>), 121.9 (CH=<u>C</u>HCO$_2$CH$_3$), 121.6 (^{Ar}<u>C</u>H), 119.2 (^{Ar}<u>C</u>H), 118.2 (^{Ar}<u>C</u>H), 117.5 (CH=<u>C</u>H$_2$), 114.1 (2 × ^{PMB}<u>C</u>H), 109.5 (^{Ar}<u>C</u>H), 107.7 (^{Ar}<u>C</u>), 56.0 (N<u>C</u>H$_2$CH$_2^{Ar}$), 55.2 (^{PMB}CO<u>C</u>H$_3$), 53.7 (N<u>C</u>H), 51.4 (CO$_2$<u>C</u>H$_3$), 46.2 (N<u>C</u>H$_2^{PMB}$), 42.9 (N<u>C</u>H$_2$CH=CH$_2$), 37.2 (<u>C</u>H$_2$CH=CH), 16.9 (NCH$_2$<u>C</u>H$_2^{Ar}$); *m/z* (CI) 432 (25%), 431 (MH, 100); HRMS (CI, MH^+) calcd for $C_{27}H_{31}N_2O_3$ 431.2329, found 431.2323.

The 6-*exo* cyclisation product **397** was isolated as a yellow gum (0.435 g, 46%) as a 1.6:1 mixture of diastereoisomers; ν_{max} (thin film) /cm^{-1} 2966 (s), 2810 (m), 1733 (s), 1612 (w), 1512 (s); δ_H (400 MHz, $CDCl_3$) (major diastereoisomer) 7.52-7.48 (1H, m, ^{Ar}C<u>H</u>), 7.13-7.06 (3H, m, ^{Ar}C<u>H</u>), 6.89 (2H, d, *J* = 8.7, ^{PMB}C<u>H</u>), 6.78 (2H, d, *J* = 8.7, ^{PMB}C<u>H</u>), 5.26 (1H, d, *J* = 16.9, NC<u>H</u>$_2$PMB), 5.17 (1H, d, *J* = 16.9, NC<u>H</u>$_2$PMB), 4.88 (1H, s, C=C<u>H</u>$_2$), 4.72 (1H, app d, *J* = 1.6, C=C<u>H</u>$_2$), 4.03 (1H, dd, *J* = 12.0 and 3.0 NC<u>H</u>), 3.74 (3H, s, ^{PMB}OC<u>H</u>$_3$), 3.60 (1H, d, *J* = 13.5, NC<u>H</u>$_2$C=CH$_2$), 3.55 (3H, s, CO$_2$C<u>H</u>$_3$), 3.43 (1H, d, *J* = 13.5, NC<u>H</u>$_2$C=CH$_2$), 3.13-3.07 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 2.93-2.86 (2H, m,

$NCH_2C\underline{H}_2Ar$), 2.78-2.70 (2H, m, $C\underline{H}CH_2CO_2CH_3$ and $NC\underline{H}_2CH_2Ar$), 2.63 (1H, dd, J = 15.6 and 6.1, $CHC\underline{H}_2CO_2CH_3$), 2.17 (1H, dd, J = 15.6 and 7.9, $CHC\underline{H}_2CO_2CH_3$), 1.94 (1H, dq, J = 12.0 and 3.0, $NCHC\underline{H}_2CH$), 1.50 (1H, app q, J = 12.0, $NCHC\underline{H}_2CH$); δ_C (100 MHz, $CDCl_3$ (minor diastereoisomer) 172.9 ($\underline{C}O_2CH_3$), 158.8 ($^{PMB}\underline{C}OCH_3$), 144.7 ($\underline{C}=CH_2$), 137.4 ($^{Ar}\underline{C}$), 136.5 ($^{Ar}\underline{C}$), 129.6 ($^{Ar}\underline{C}$), 127.1 (2 × $^{PMB}\underline{C}H$), 127.1 ($^{PMB}\underline{C}$), 121.4 ($^{Ar}\underline{C}H$), 119.3 ($^{Ar}\underline{C}H$), 118.3 ($^{Ar}\underline{C}H$), 114.2 (2 × $^{PMB}\underline{C}H$), 109.7 ($^{Ar}\underline{C}H$), 108.1 ($^{Ar}\underline{C}$), 107.0 ($C=\underline{C}H_2$), 62.7 ($N\underline{C}H_2C=CH_2$), 55.9 ($N\underline{C}H$), 55.3 ($^{Ar}O\underline{C}H_3$), 51.6 ($CO_2\underline{C}H_3$), 46.6 ($N\underline{C}H_2PMB$), 46.4 ($N\underline{C}H_2CH_2Ar$), 37.8 ($\underline{C}HCH_2CO_2CH_3$), 36.9 ($CH\underline{C}H_2CO_2CH_3$), 35.7 ($NCH\underline{C}H_2CH$), 22.2 ($NCH_2\underline{C}H_2Ar$); *m/z* (CI, NH_3) 432 (25%), 431 (MH^+, 100); HRMS $C_{27}H_{31}N_2O_3$ (MH^+) requires 431.2329, found 431.2337.

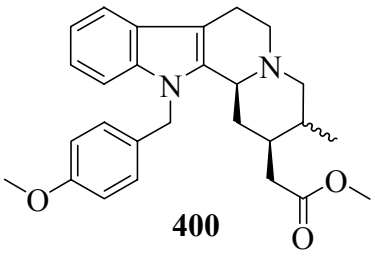
The minor diastereoisomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 5.27 (1H, d, J = 17.0, $NC\underline{H}_2PMB$), 5.13 (1H, d, J = 17.0, $NC\underline{H}_2PMB$), 4.89 (1H, s, $C=C\underline{H}_2$), 4.85 (1H, s, $C=C\underline{H}_2$), 3.74 (3H, s, $^{PMB}OC\underline{H}_3$), 3.58 (3H, s, $CO_2C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 172.5 ($\underline{C}O_2CH_3$), 158.8 ($^{PMB}\underline{C}OCH_3$), 143.5 ($\underline{C}=CH_2$), 137.6 ($^{Ar}\underline{C}$), 136.5 ($^{Ar}\underline{C}$), 129.8 ($^{Ar}\underline{C}$), 127.1 (2 × $^{PMB}\underline{C}H$), 127.0 ($^{PMB}\underline{C}$), 121.4 ($^{Ar}\underline{C}H$), 119.4 ($^{Ar}\underline{C}H$), 118.2 ($^{Ar}\underline{C}H$), 114.2 (2 × $^{PMB}\underline{C}H$), 111.8 ($C=\underline{C}H_2$), 109.7 ($^{Ar}\underline{C}H$), 108.4 ($^{Ar}\underline{C}$), 57.6 ($N\underline{C}H_2C=CH_2$), 55.3 ($N\underline{C}H$), 55.2 ($^{Ar}O\underline{C}H_3$), 51.0 ($CO_2\underline{C}H_3$), 46.8 ($N\underline{C}H_2PMB$), 46.4 ($N\underline{C}H_2CH_2Ar$), 38.4 ($\underline{C}HCH_2CO_2CH_3$), 36.7 ($CH\underline{C}H_2CO_2CH_3$), 33.0 ($NCH\underline{C}H_2CH$), 22.0 ($NCH_2\underline{C}H_2Ar$).

The 5-*exo*/5-*exo* cyclisation product **398** was isolated as a yellow gum (113 mg, 12%) as a 1:1 mixture of partially separable diastereoisomers; ν_{max} (thin film) /cm^{-1} 2949 (m), 2903 (m), 1734 (s), 1613 (w), 1513 (m); δ_H (400 MHz, $CDCl_3$) 7.22 (2H, dt, J = 8.5 and 2.9, $^{PMB}C\underline{H}$), 7.06 (1H td, J = 7.7 and 1.3, $^{Ar}C\underline{H}$), 6.85 (2H, dt, J = 8.5 and 2.9, $^{PMB}C\underline{H}$), 6.88-6.83 (1H, m, $^{Ar}C\underline{H}$), 6.66 (1H, td, J = 7.7 and 0.8, $^{Ar}C\underline{H}$), 6.50 (1H, d, J = 7.7, $^{Ar}C\underline{H}$), 4.89 (1H, dd, J = 1.6 and 0.4, $C=C\underline{H}_2$), 4.43 (1H, dd, J = 1.9 and 0.8, $C=C\underline{H}_2$), 4.34 (1H, d, J = 14.5, $NC\underline{H}_2PMB$), 4.03 (1H, d, J = 14.5, $NC\underline{H}_2PMB$), 3.79 (3H, s, $OC\underline{H}_3$), 3.56 (1H, d, J = 15.5, $NC\underline{H}_2C=CH_2$), 3.48 (3H, s, $OC\underline{H}_3$), 3.24 (1H, d, J = 15.5, $NC\underline{H}_2C=CH_2$), 3.21-3.12 (1H, m, $NC\underline{H}_2CH_2$), 3.10 (1H, d, J = 5.0, $NCC\underline{H}N$), 2.74 (1H, dd, J = 14.5 and 6.0, $NC\underline{H}_2CH_2$), 2.66-2.57 (1H, m, $C\underline{H}CH_2CO_2CH_3$), 2.36 (1H, dd, J = 14.5 and 9.0, $CHC\underline{H}_2CH$), 2.14 (1H, dd, J = 12.6 and 6.0, $NCH_2C\underline{H}_2$), 2.07 (1H, dd, J = 16.1 and 7.6, $CHC\underline{H}_2CO_2CH_3$), 1.96 (1H, dd, J = 16.1 and 7.6, $CHC\underline{H}_2CO_2CH_3$), 1.88 (1H, dd, J = 12.6 and 5.0, $NCH_2C\underline{H}_2$), 1.55 (1H, dt, J = 14.5 and 5.0, $CHC\underline{H}_2CH$); δ_C (100 MHz, $CDCl_3$) 173.8 ($\underline{C}O_2CH_3$), 158.8 ($^{PMB}\underline{C}OCH_3$), 151.9 ($\underline{C}=CH_2$), 145.6 ($^{Ar}\underline{C}$), 131.0 ($^{Ar}\underline{C}$), 130.8 ($^{PMB}\underline{C}$), 129.3 (2 × $^{PMB}\underline{C}H$), 128.1 ($^{Ar}\underline{C}H$), 124.3 ($^{Ar}\underline{C}H$), 117.6 ($^{Ar}\underline{C}H$), 113.9 (2 × $^{PMB}\underline{C}H$), 106.1 ($^{Ar}\underline{C}H$), 104.1 ($C=\underline{C}H_2$), 90.5 ($N\underline{C}CHN$), 70.1 ($NC\underline{C}HN$), 60.4

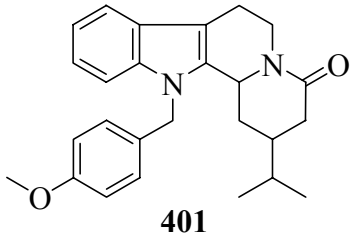
($\underline{C}CHCH_2CO_2CH_3$), 58.7 ($N\underline{C}H_2C=CH_2$), 55.2 ($^{PMB}O\underline{C}H_3$), 51.3 ($CO_2\underline{C}H_3$), 48.7 ($N\underline{C}H_2PMB$), 47.4 ($N\underline{C}H_2CH_2$), 44.3 ($\underline{C}HCH_2CO_2CH_3$), 39.2 ($CH\underline{C}H_2CO_2CH_3$), 34.4 ($CH\underline{C}H_2CH$), 32.8 ($NCH_2\underline{C}H_2$); *m/z* (CI, NH_3) 432 (25%), 431 (MH^+, 100); HRMS $C_{27}H_{31}N_2O_3$, (MH^+) requires 431.2329, found 431.2324.

The other diastereoisomer was identified by the following key peaks; δ_H (400 MHz, $CDCl_3$) 6.61 (1H, td, *J* = 7.6 and 0.8, $^{Ar}C\underline{H}$), 6.41 (1H, d, *J* = 7.7, $^{Ar}C\underline{H}$), 4.90 (1H, m, $C=C\underline{H}_2$), 4.62 (1H, dd, *J* = 2.0 and 0.6, $C=C\underline{H}_2$), 4.39 (1H, d, *J* = 15.2, $NC\underline{H}_2PMB$), 4.09 (1H, d, *J* = 15.2, $NC\underline{H}_2PMB$), 3.78 (3H, s, $OC\underline{H}_3$), 3.60 (3H, s, $OC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 173.2 ($\underline{C}O_2CH_3$), 158.7 ($^{PMB}\underline{C}OCH_3$), 149.8 ($\underline{C}=CH_2$), 145.7 ($^{Ar}\underline{C}$), 133.0 ($^{Ar}\underline{C}$), 130.9 ($^{PMB}\underline{C}$), 129.3 (2 × $^{PMB}\underline{C}H$), 127.8 ($^{Ar}\underline{C}H$), 121.3 ($^{Ar}\underline{C}H$), 117.0 ($^{Ar}\underline{C}H$), 113.8 (2 × $^{PMB}\underline{C}H$), 106.3 ($^{Ar}\underline{C}H$), 104.3 ($C=CH_2$), 90.9 ($N\underline{C}CHN$), 69.3 ($NC\underline{C}HN$), 59.6 ($\underline{C}CHCH_2CO_2CH_3$), 59.3 ($N\underline{C}H_2C=CH_2$), 55.2 ($^{PMB}O\underline{C}H_3$), 51.5 ($CO_2\underline{C}H_3$), 48.0 ($N\underline{C}H_2PMB$), 47.2 ($N\underline{C}H_2CH_2$), 44.9 ($\underline{C}HCH_2CO_2CH_3$), 39.2 ($CH\underline{C}H_2CO_2CH_3$), 34.2 ($CH\underline{C}H_2CH$), 32.2 ($NCH_2\underline{C}H_2$).

Methyl 2-((2*R,12b*S**)-12-(4-methoxybenzyl)-1,2,3,4,6,7,12,12b-octahydro-3-methylindolo[2,3-a]quinolizin-2-yl)acetate (400) and 2-isopropyl-12-(4-methoxybenzyl)-1,2,3,6,7,12b-hexahydroindolo[2,3-a]quinolizin-4(12H)-one (401)**



400



401

A stirred solution of methyl 2-(12-(4-methoxybenzyl)-3-methylene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (**397**) (86 mg, 0.2 mmol) and $Pd(OH)_2/C$ (30 mg) in MeOH:EtOAc (5:5 mL) was evacuated and back-filled with nitrogen (× 3) then hydrogen (× 2). The solution was then stirred under 1 bar hydrogen at r.t. for 4 h, after which time the reaction mixture was filtered through a plug of Celite (EtOAc) and the solvent was evaporated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 10 to 20% MeOH/NH_3 in DCM. Pure fractions were evaporated to dryness to afford the title compounds.

The hydrogenation product **400** was isolated as a yellow gum (41 mg, 48%) as a 1:1 ratio of separable diastereoisomers; ν_{max} (thin film) /cm^{-1} 2950 (m), 2905 (m), 1733 (s), 1613 (w), 1513 (s); δ_H (400 MHz, $CDCl_3$) 7.53-7.47 (1H, m, ^{Ar}CH), 7.12-7.07 (3H, m, ^{Ar}CH), 6.93 (2H, d, *J* = 8.7, ^{PMB}CH), 6.87 (2H, d, *J* = 8.7, ^{PMB}CH), 5.26 (1H, d, *J* = 17.1, NCH_2PMB), 5.17 (1H, d, *J* = 17.1, NCH_2PMB), 3.76 (3H, s, $^{Ar}OCH_3$), 3.53 (3H, s,

CO_2CH_3), 3.33 (1H, dd, *J* = 11.4 and 1.5, NC<u>H</u>), 3.02-2.90 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NCH$_2$C<u>H</u>$_2$Ar), 2.83 (1H, dd, *J* = 11.6 and 2.0, NC<u>H</u>$_2$CH), 2.76 (1H, dd, *J* = 11.6 and 3.0, NC<u>H</u>$_2$CH), 2.73-2.57 (2H, m, NC<u>H</u>$_2$CH$_2$Ar and NCH$_2$C<u>H</u>$_2$Ar), 2.23-2.15 (2H, m, C<u>H</u>CH$_2$CO$_2$CH$_3$ and CHC<u>H</u>$_2$CO$_2$CH$_3$), 2.08-2.02 (1H, m, CHC<u>H</u>$_2$CO$_2$CH$_3$), 1.87-1.78 (2H, m, NCHC<u>H</u>$_2$ and C<u>H</u>CH$_3$), 1.38 (1H, dd, *J* = 12.5 and 11.4, NCHC<u>H</u>$_2$), 1.01 (3H, d, *J* = 7.0, CHC<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 173.3 (<u>C</u>O$_2$CH$_3$), 158.7 (^{PMB}<u>C</u>OCH$_3$), 138.1 (^{Ar}<u>C</u>), 136.7 (^{Ar}<u>C</u>), 129.9 (^{PMB}<u>C</u>), 127.2 (2 × ^{PMB}<u>C</u>H), 127.1 (^{Ar}<u>C</u>), 121.4 (^{Ar}<u>C</u>H), 119.3 (^{Ar}<u>C</u>H), 118.1 (^{Ar}<u>C</u>H), 114.0 (2 × ^{PMB}<u>C</u>H), 109.7 (^{Ar}<u>C</u>H), 62.8 (N<u>C</u>H$_2$CH), 60.2 (N<u>C</u>H), 55.3 (^{Ar}OC<u>H</u>$_3$), 52.5 (N<u>C</u>H$_2$CH$_2$Ar), 51.4 (CO$_2$<u>C</u>H$_3$), 47.5 (N<u>C</u>H$_2$PMB), 38.4 (CH<u>C</u>H$_2$CO$_2$CH$_3$), 36.8 (<u>C</u>HCH$_2$CO$_2$CH$_3$), 32.1 (<u>C</u>HCH$_3$), 31.9 (NCH<u>C</u>H$_2$), 22.7 (NCH$_2$<u>C</u>H$_2$Ar), 13.4 (CH<u>C</u>H$_3$); *m/z* (CI, NH_3) 434 (25%), 433 (100, MH^+); HRMS $C_{27}H_{33}N_2O_3$ (MH^+) requires 433.2486, found 433.2487.

The other diastereoisomer was identified by the following peaks; δ_H (400 MHz, $CDCl_3$) 7.52-7.47 (1H, m, ^{Ar}C<u>H</u>), 7.10-7.06 (3H, m, ^{Ar}C<u>H</u>), 6.89 (2H, d, *J* = 8.7, ^{PMB}C<u>H</u>), 6.77 (2H, d, *J* = 8.7, ^{PMB}C<u>H</u>), 5.26 (1H, d, *J* = 17.0, NC<u>H</u>$_2$PMB), 5.14 (1H, d, *J* = 17.0, NC<u>H</u>$_2$PMB), 3.74 (3H, s, ^{Ar}OC<u>H</u>$_3$), 3.56 (1H, d, *J* = 9.8, NC<u>H</u>), 3.46 (3H, s, CO$_2$C<u>H</u>$_3$), 3.13 (1H, dt, *J* = 11.2 and 5.5, NC<u>H</u>$_2$CH$_2$Ar), 3.00 (1H dd *J* = 12.6 and 3.8, NC<u>H</u>$_2$CH), 2.99-2.91 (1H, m, NCH$_2$C<u>H</u>$_2$Ar), 2.86-2.76 (1H, m, NCH$_2$C<u>H</u>$_2$Ar), 2.69 (1H, ddd, *J* = 11.2, 6.8, 4.6, NC<u>H</u>$_2$CH$_2$Ar), 2.52 (1H, dd, *J* = 15.2 and 3.7, CHC<u>H</u>$_2$COCH$_3$), 2.45 (1H, dd, *J* = 12.6 and 10.8, NC<u>H</u>$_2$CH), 2.04-1.92 (2H, m, CHC<u>H</u>$_2$CO$_2$CH$_3$ and NCHC<u>H</u>$_2$CH), 1.70-1.58 (2H, m, C<u>H</u>CH$_3$ and C<u>H</u>CH$_2$CO$_2$CH$_3$), 1.35 (1H, dd, *J* = 13.1 and 11.4, NCHC<u>H</u>$_2$CH), 0.86 (3H, d, *J* = 6.1, CHC<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 173.4 (<u>C</u>O$_2$CH$_3$), 158.7 (^{PMB}<u>C</u>OCH$_3$), 137.8 (^{Ar}<u>C</u>), 136.7 (^{Ar}<u>C</u>), 129.7 (^{PMB}<u>C</u>), 127.2 (2 × ^{PMB}<u>C</u>H), 121.4 (^{Ar}<u>C</u>H), 119.3 (^{Ar}<u>C</u>H), 118.2 (^{Ar}<u>C</u>H), 114.1 (2 × ^{PMB}<u>C</u>H), 109.7 (^{Ar}<u>C</u>H), 108.2 (^{Ar}<u>C</u>), 63.1 (N<u>C</u>H$_2$CH), 57.8 (N<u>C</u>H), 55.3 (^{Ar}O<u>C</u>H$_3$), 51.4 (CO$_2$<u>C</u>H$_3$), 49.3 (N<u>C</u>H$_2$CH$_2$Ar), 47.1 (N<u>C</u>H$_2$PMB), 40.2 (<u>C</u>HCH$_2$CO$_2$CH$_3$), 38.4 (CH<u>C</u>H$_2$CO$_2$CH$_3$), 34.8 (NCH<u>C</u>H$_2$CH), 33.1 (<u>C</u>HCH$_3$), 22.4 (NCH$_2$<u>C</u>H$_2$Ar), 16.7 (CH<u>C</u>H$_3$).

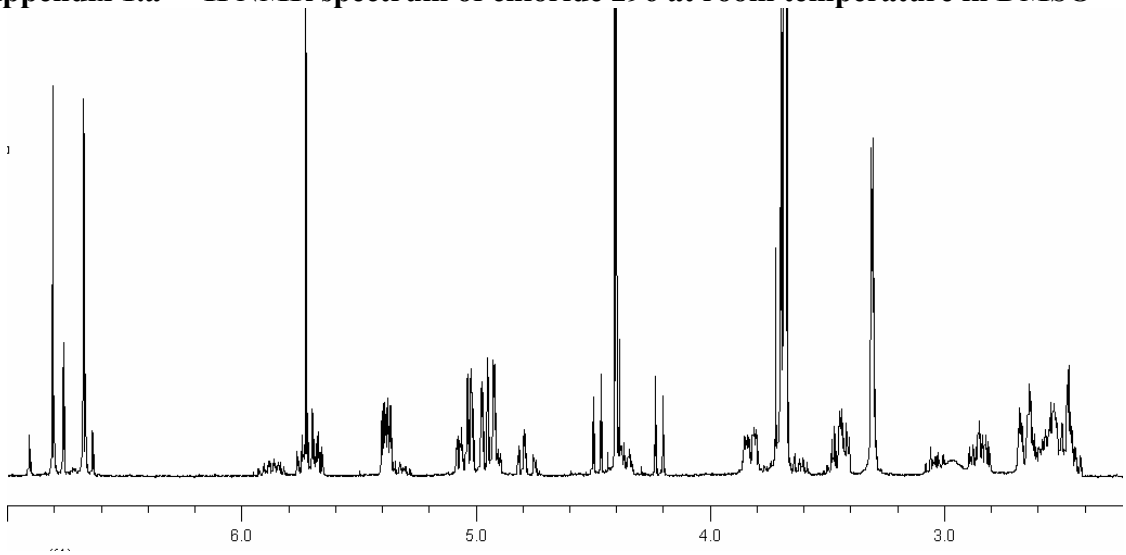
The cyclic amide **401** was isolated as a yellow gum (19 mg, 24%) as a single diastereoisomer; ν_{max} (thin film) /cm^{-1} 2953 (m), 2912 (m), 1688 (s), 1610 (w), 1515 (m); δ_H (400 MHz, $CDCl_3$) 7.53 (1H, dd, *J* = 6.3 and 1.6, ^{Ar}C<u>H</u>), 7.20-7.12 (3H, m, ^{Ar}C<u>H</u>), 6.88 (2H, d, *J* = 8.5, ^{PMB}C<u>H</u>), 6.80 (2H, d, *J* = 8.5, ^{PMB}C<u>H</u>), 5.30 (1H, d, *J* = 17.2, NC<u>H</u>$_2$PMB), 5.23 (1H, d, *J* = 17.2, NC<u>H</u>$_2$PMB), 5.01-4.94 (1H, m, NC<u>H</u>$_2$CH$_2$Ar), 4.69 (1H, dd, *J* = 8.9 and 5.3, NC<u>H</u>), 3.75 (3H, s, ^{PMB}OC<u>H</u>$_3$), 2.92-2.70 (3H, m, NC<u>H</u>$_2$CH$_2$Ar and NCH$_2$C<u>H</u>$_2$Ar), 2.45 (1H, dd, *J* = 16.2 and 5.3, NC(O)C<u>H</u>$_2$CH), 2.26 (1H, dd, *J* = 16.2 and 9.0, NC(O)C<u>H</u>$_2$CH), 2.03 (1H, dt, *J* = 14.2 and 5.3, NCHC<u>H</u>$_2$), 1.81 (1H, ddd, *J* = 14.2, 8.9 and 5.2, NCHC<u>H</u>$_2$), 1.64-1.53 (1H, m, C<u>H</u>CH(CH$_3$)$_2$), 1.46-1.38 (1H, m, <u>CH</u>(CH$_3$)$_2$), 0.81 (3H,

d, J = 6.6, CH(C<u>H</u>$_3$)$_2$), 0.76 (1H, d, J = 6.6, CH(C<u>H</u>$_3$)$_2$); δ_C (100 MHz, $CDCl_3$) 171.5 (N<u>C</u>(O)CH$_2$), 158.9 (^{PMB}<u>C</u>OCH$_3$), 138.0 (^{Ar}<u>C</u>), 134.6 (^{Ar}<u>C</u>), 129.1 (^{PMB}<u>C</u>), 126.8 (2 × ^{PMB}<u>C</u>H), 126.4 (^{Ar}C), 122.1 (^{Ar}CH), 119.7 (^{Ar}CH), 118.3 (^{Ar}CH), 114.2 (2 × ^{PMB}CH), 110.9 (^{Ar}<u>C</u>), 109.6 (^{Ar}<u>C</u>H), 55.2 (^{PMB}O<u>C</u>H$_3$), 51.2 (N<u>C</u>H), 47.1 (NCH$_2$PMB), 40.4 (N<u>CH$_2$</u>CH$_2$Ar), 36.0 (<u>C</u>HCH(CH$_3$)$_2$), 35.8 (NC(O)<u>CH$_2$</u>CH), 33.2 (NCH<u>C</u>H$_2$), 30.8 (<u>C</u>H(CH$_3$)$_2$), 21.2 (NCH$_2$<u>C</u>H$_2$Ar), 19.8 (CH(<u>C</u>H$_3$)$_2$), 19.7 (CH(<u>C</u>H$_3$)$_2$); *m/z* (CI) 404 (25%), 403 (100, MH$^+$), 399 (30), 289 (45); HRMS $C_{26}H_{31}N_2O_2$ (MH$^+$) requires 403.2380, found 403.2376.

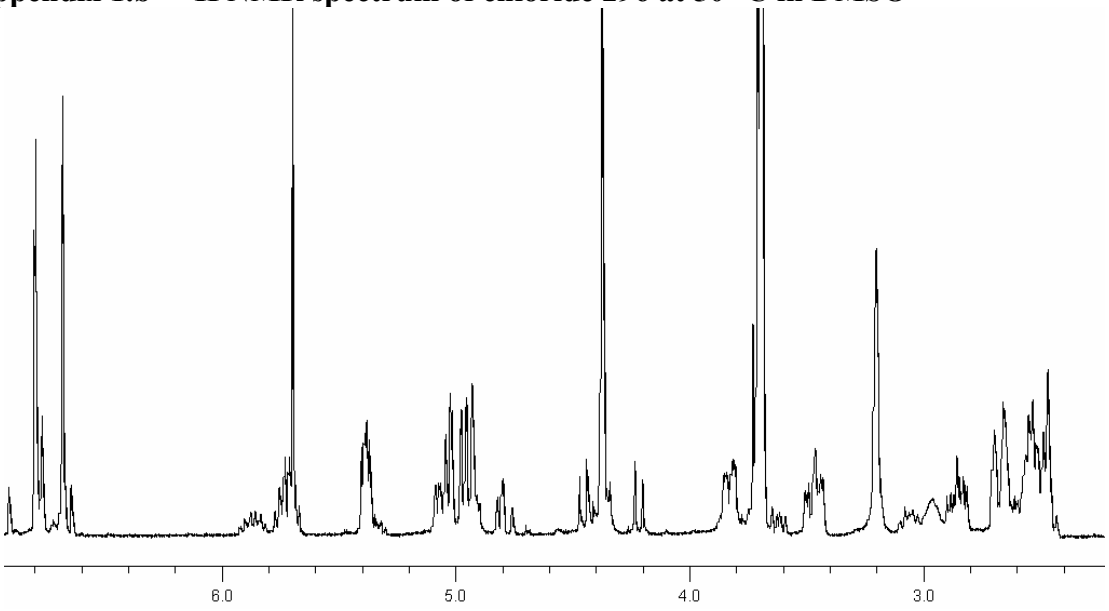
Chapter 8 – Appendices

Appendix 1 – V.T. ^{1}H NMR spectra of chloride 296

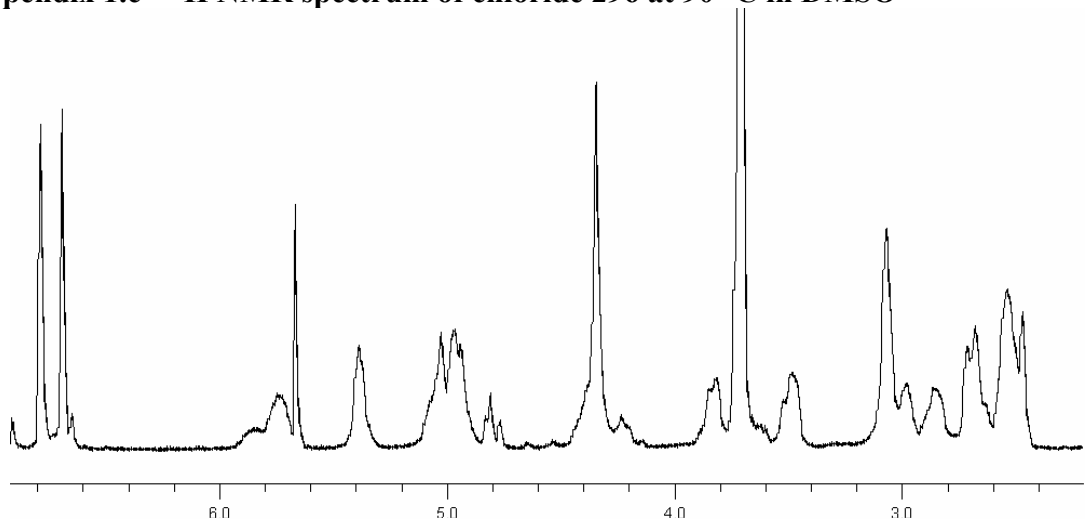
Appendix 1.a – ^{1}H NMR spectrum of chloride 296 at room temperature in DMSO



Appendix 1.b – ^{1}H NMR spectrum of chloride 296 at 50 °C in DMSO

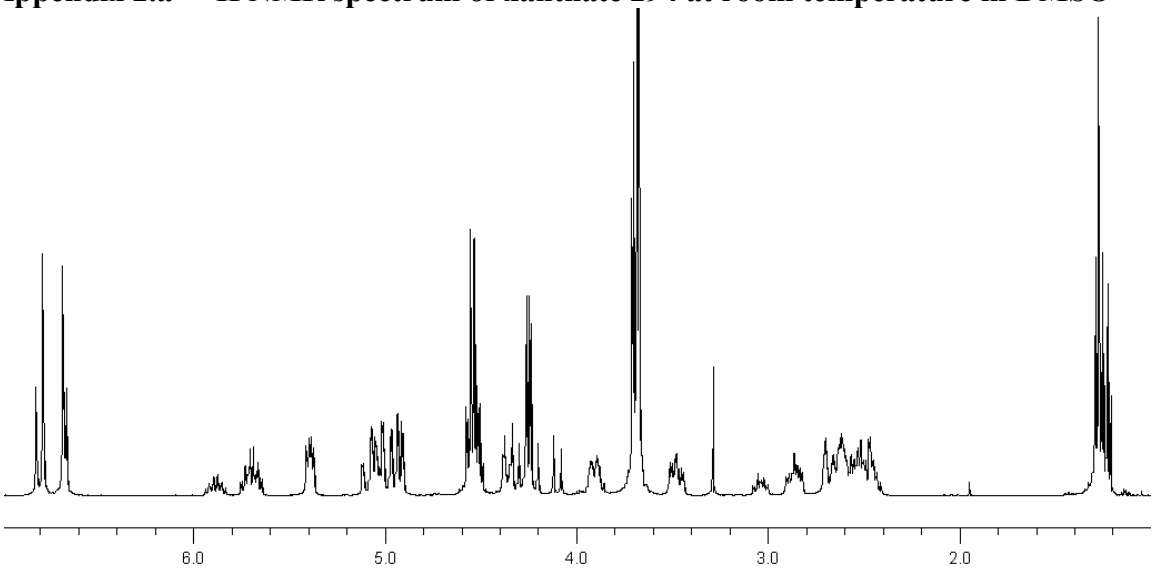


Appendix 1.c – ^{1}H NMR spectrum of chloride 296 at 90 °C in DMSO

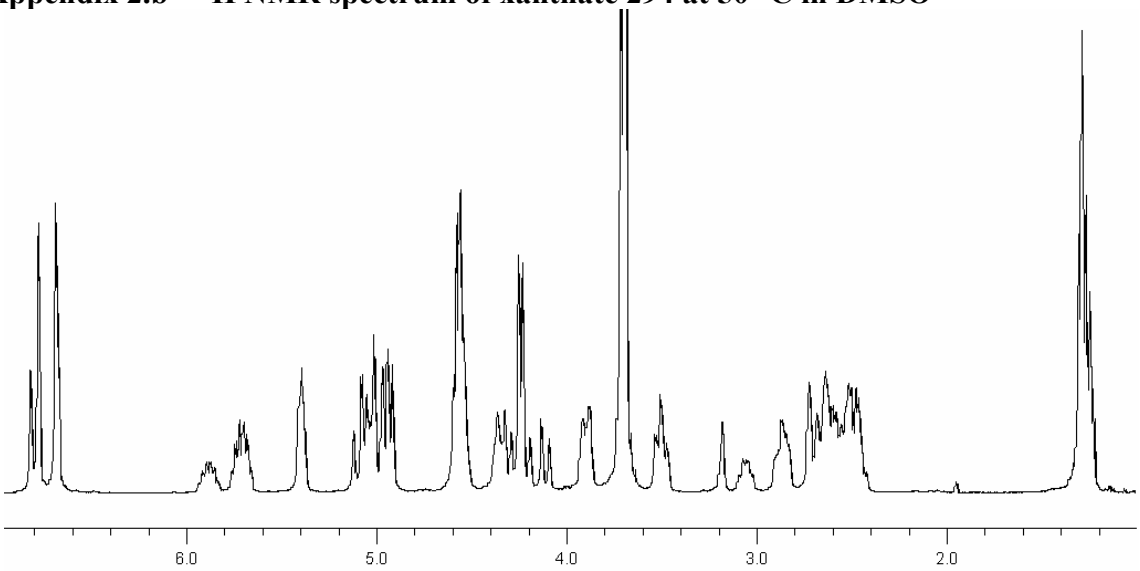


Appendix 2 – V.T. ^{1}H NMR spectra of xanthate 294

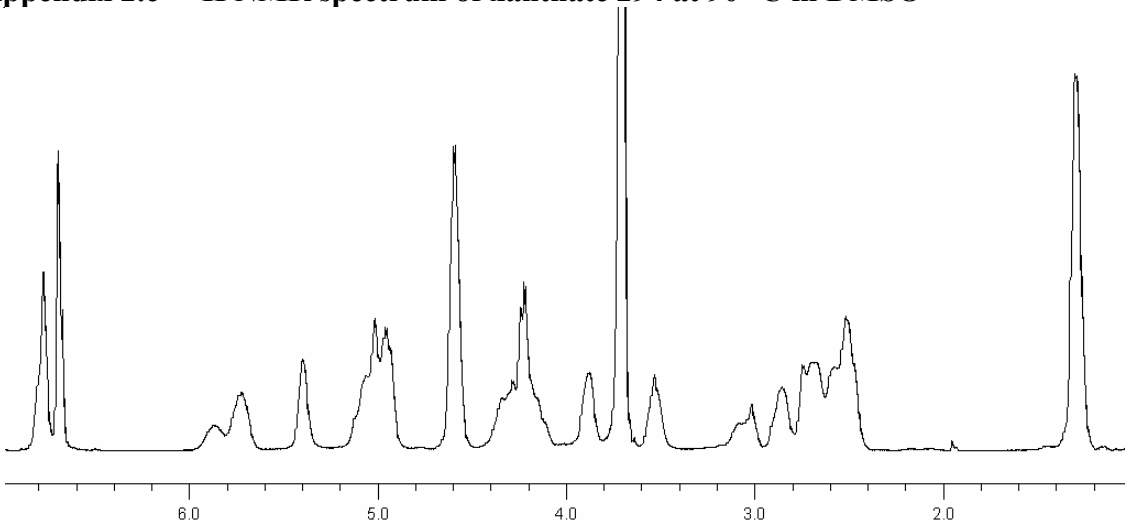
Appendix 2.a – ^{1}H NMR spectrum of xanthate 294 at room temperature in DMSO



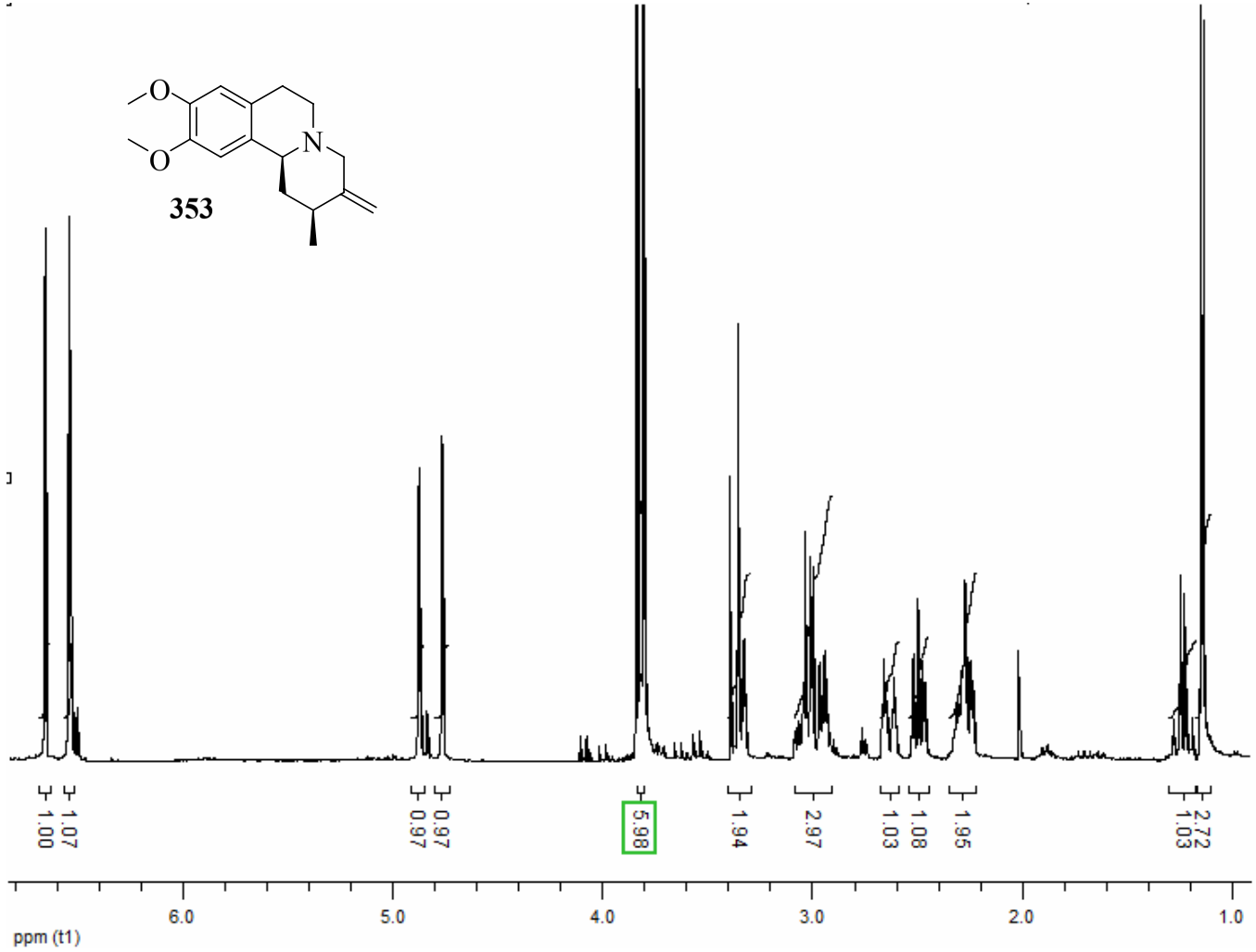
Appendix 2.b – ^{1}H NMR spectrum of xanthate 294 at 50 °C in DMSO



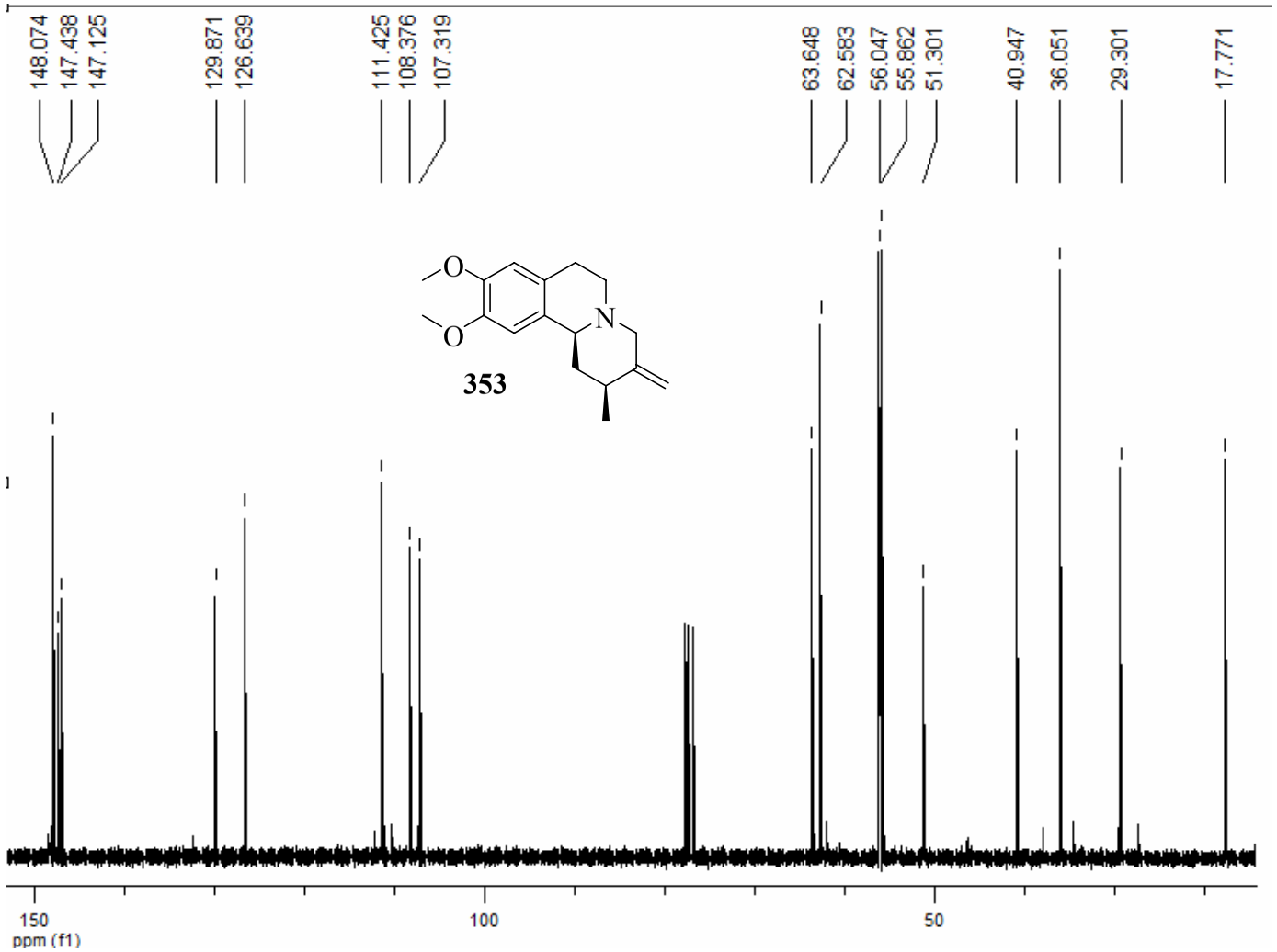
Appendix 2.c – ^{1}H NMR spectrum of xanthate 294 at 90 °C in DMSO



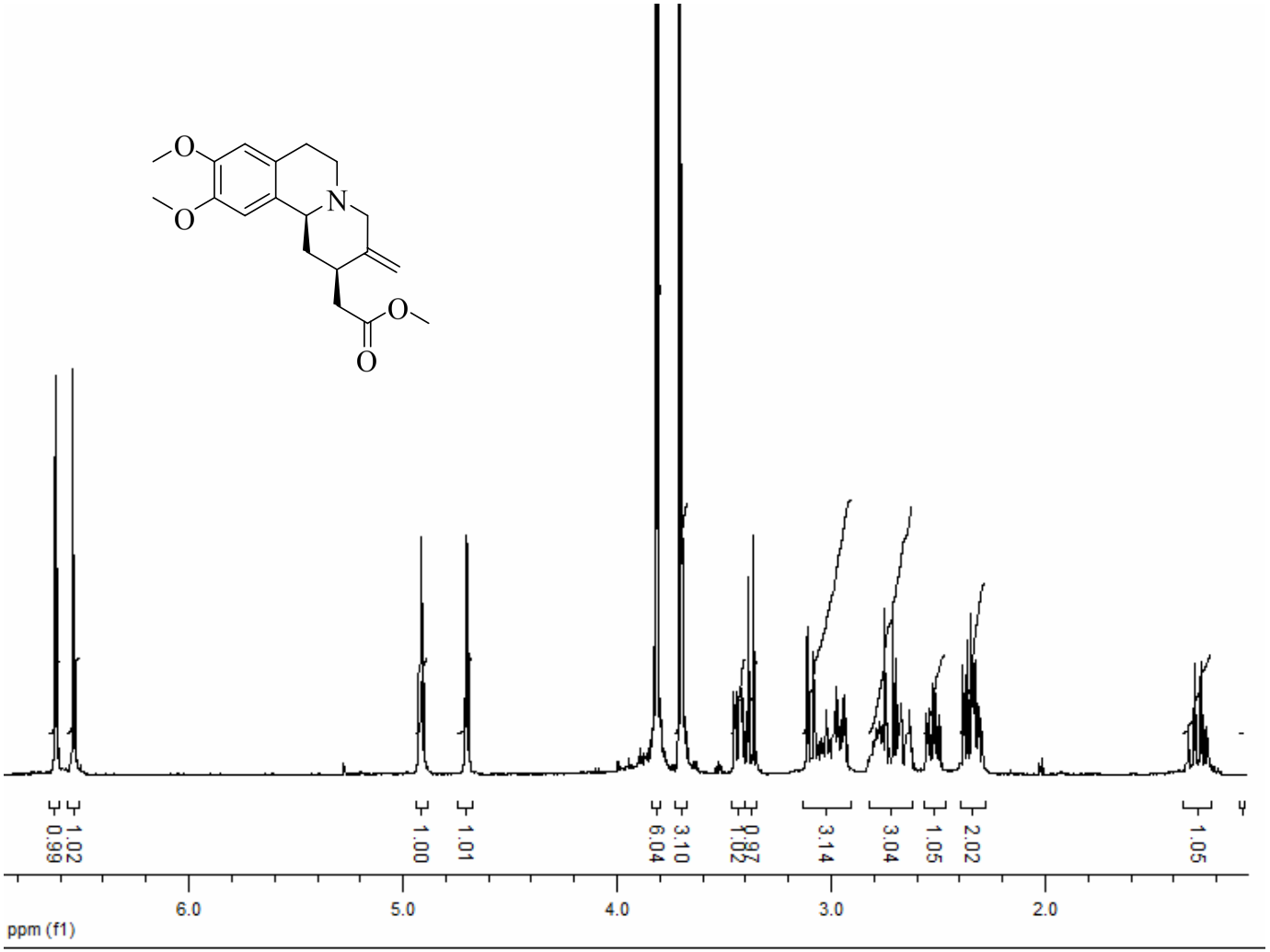
Appendix 3.a - ^{1}H NMR spectrum of 353



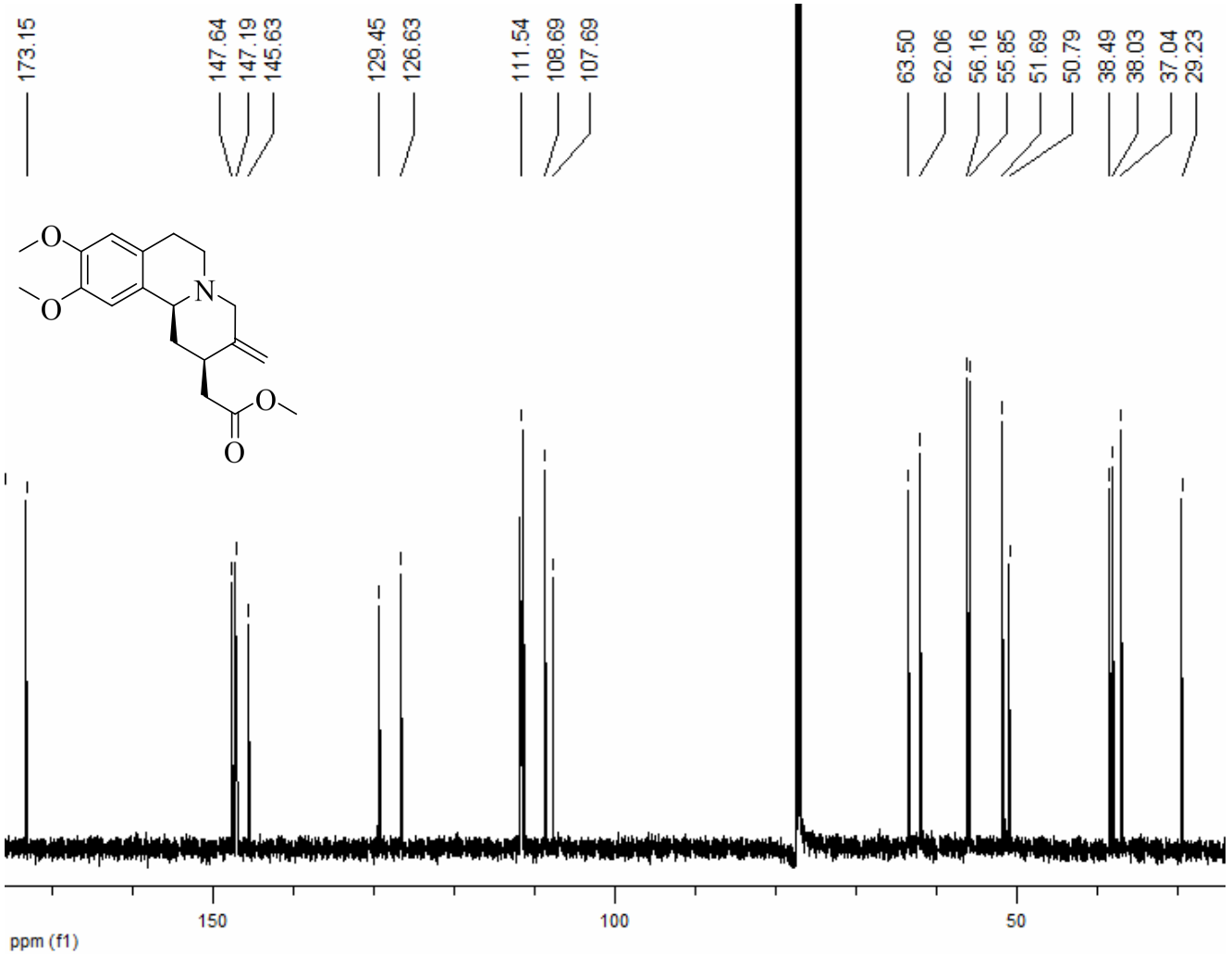
Appendix 3.b - ^{13}C NMR spectrum of 353



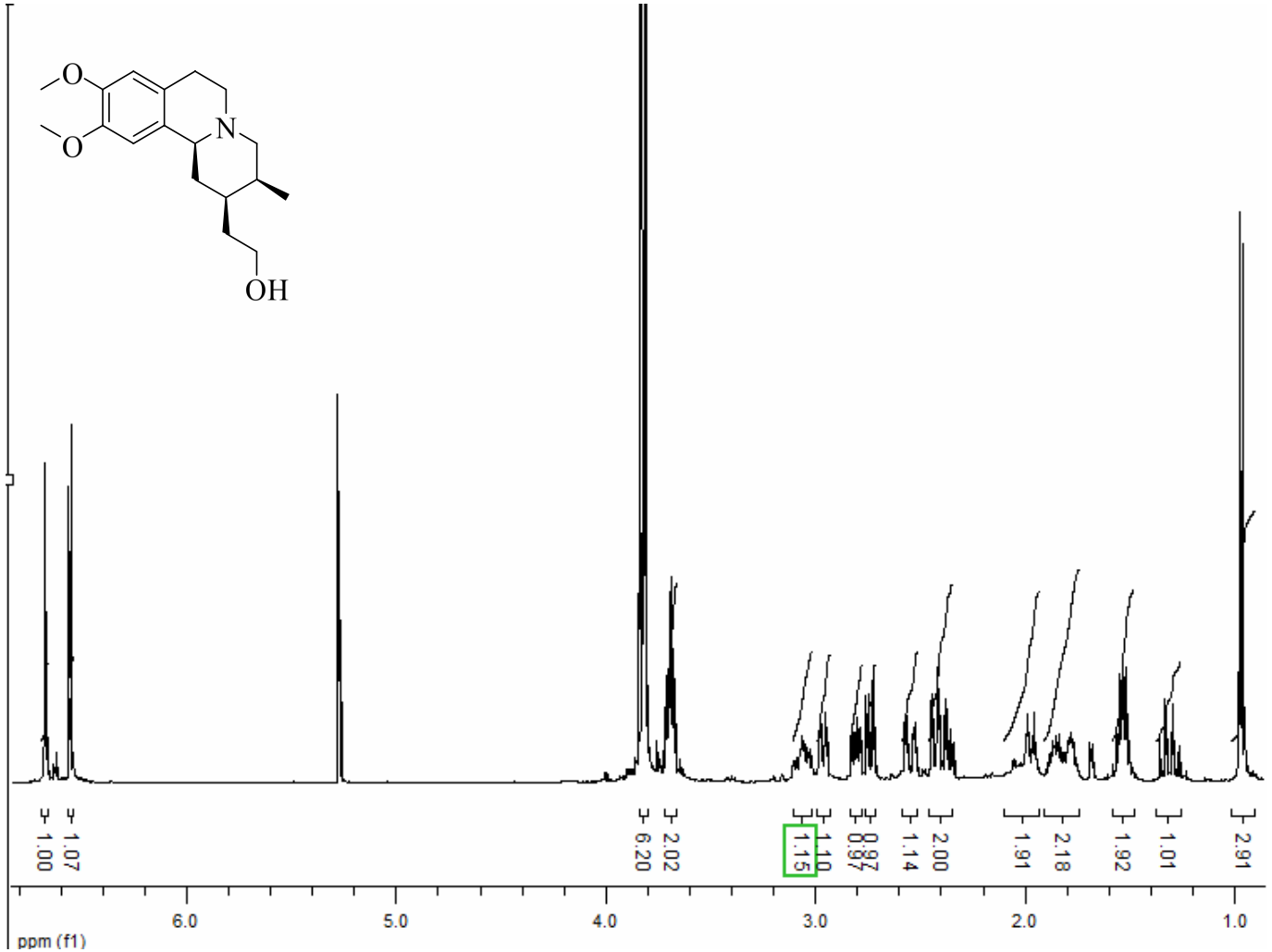
Appendix 4.a - ^{1}H NMR spectrum of 359



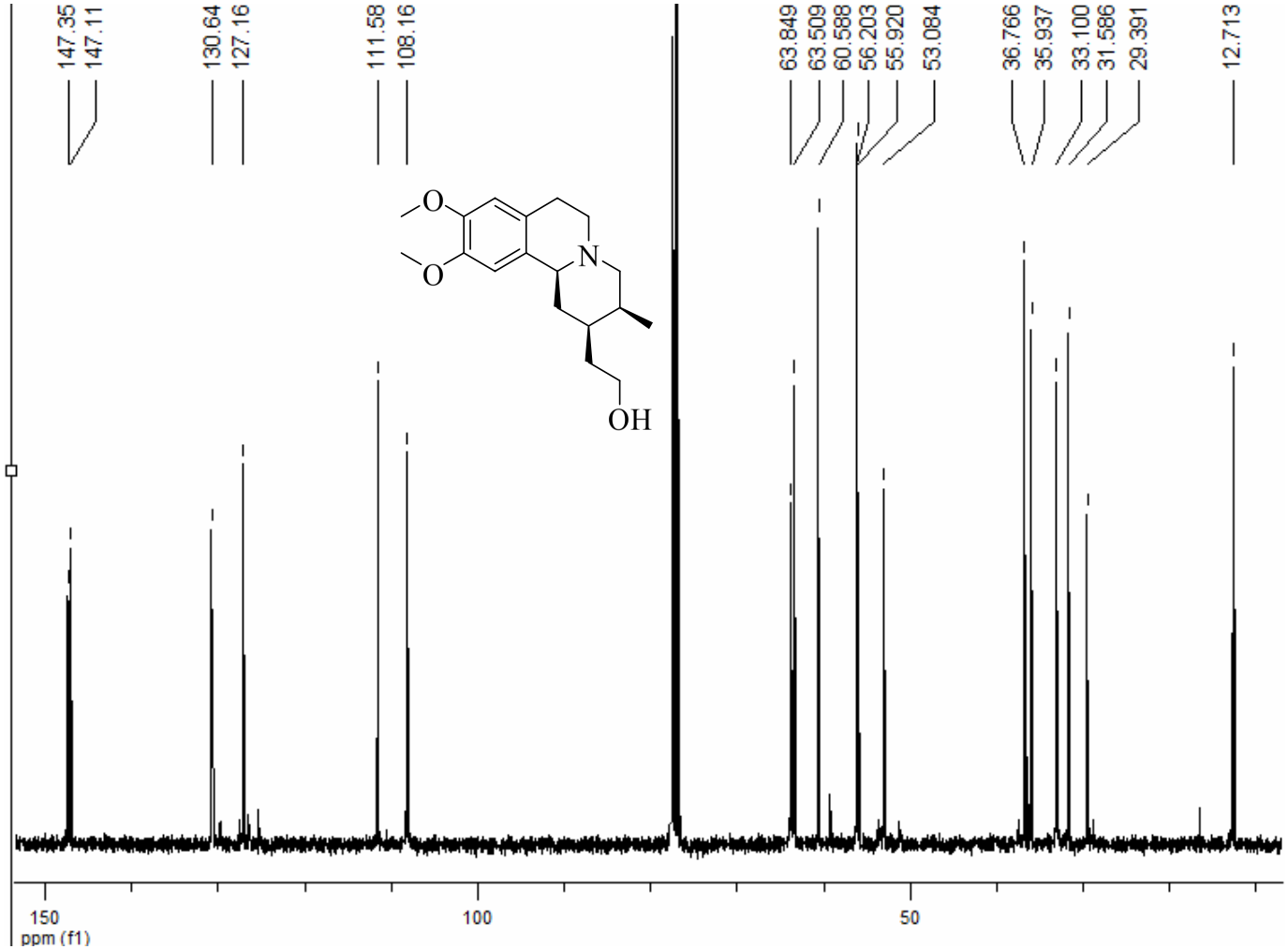
Appendix 4.b - ^{13}C NMR spectrum of 359



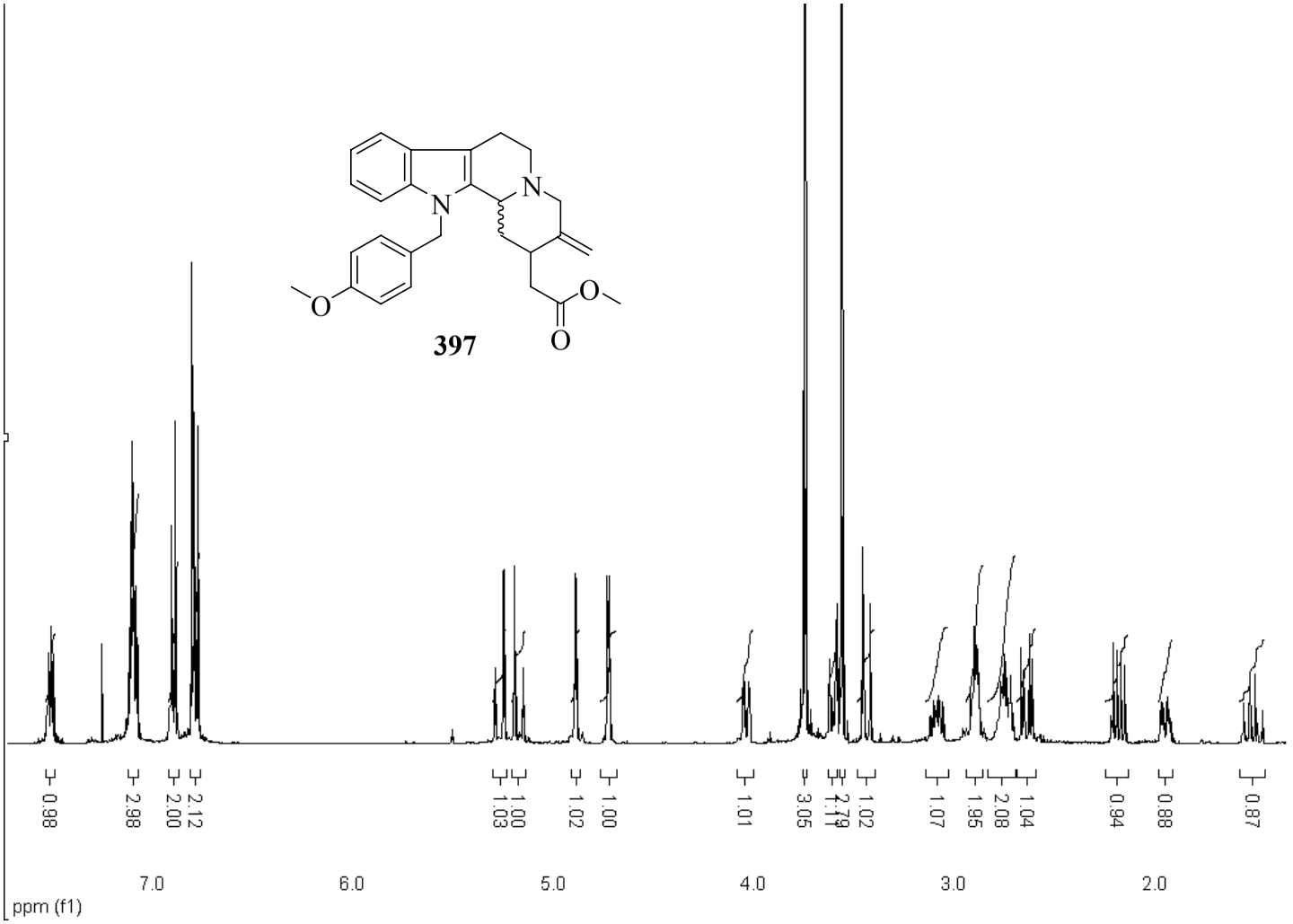
Appendix 5.a - ^{1}H NMR spectrum of 342-b ((±)-des-methyl-epi-protoemetinol)



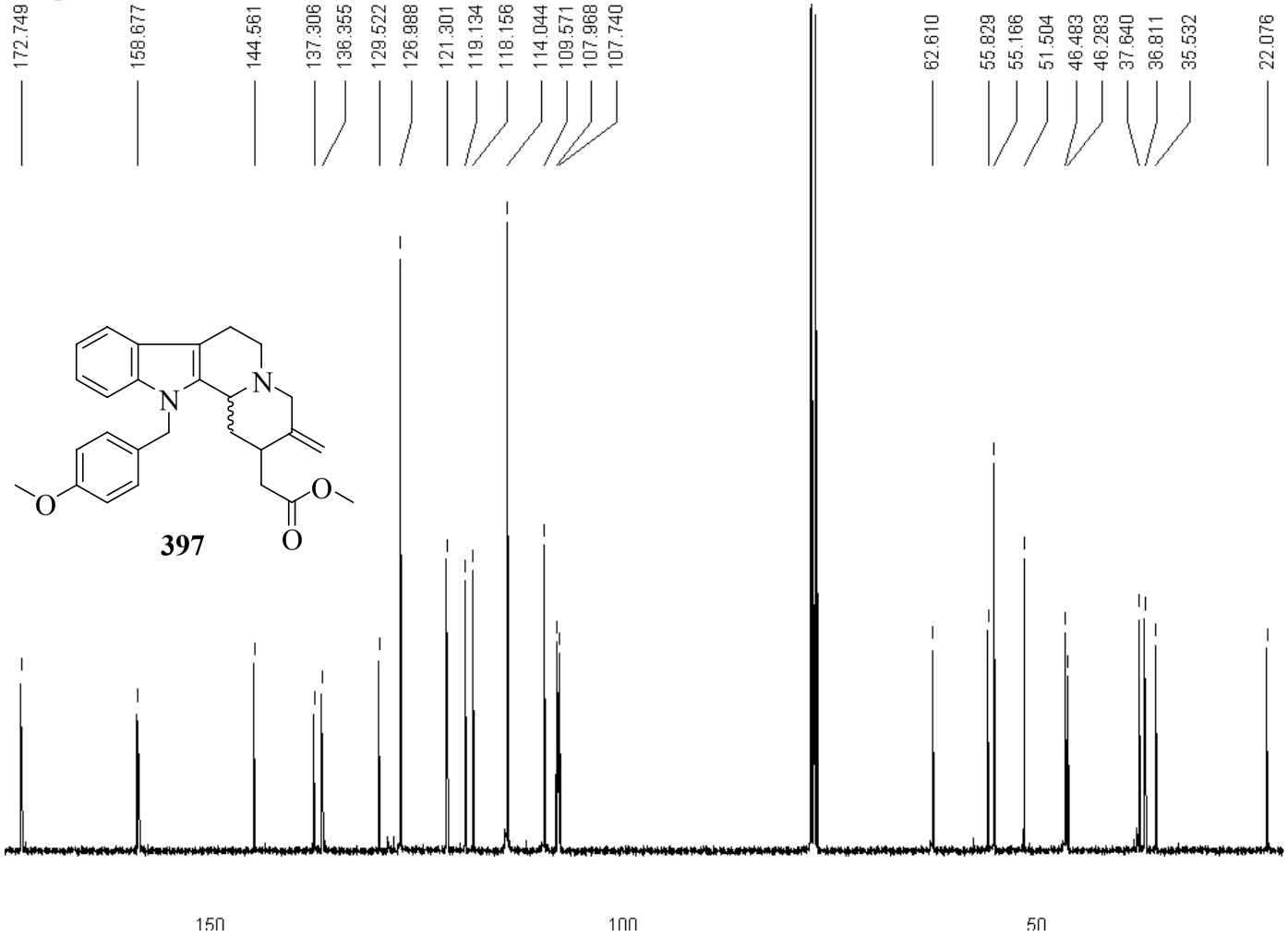
Appendix 5.b - ^{13}C NMR spectrum of 342-b ((±)-des-methyl-epi-protoemetinol)



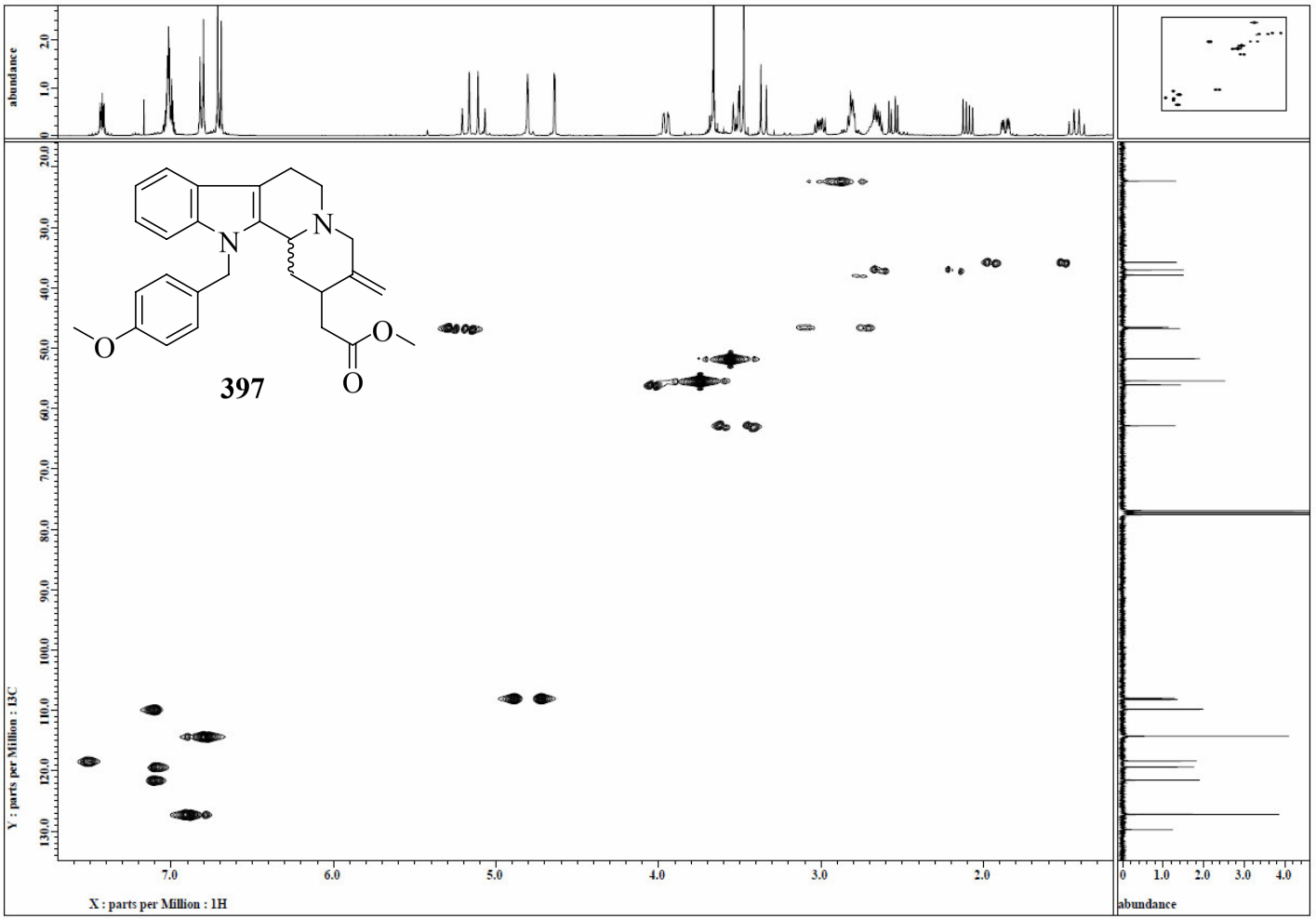
Appendix 6.a - ^{1}H NMR spectrum of 397



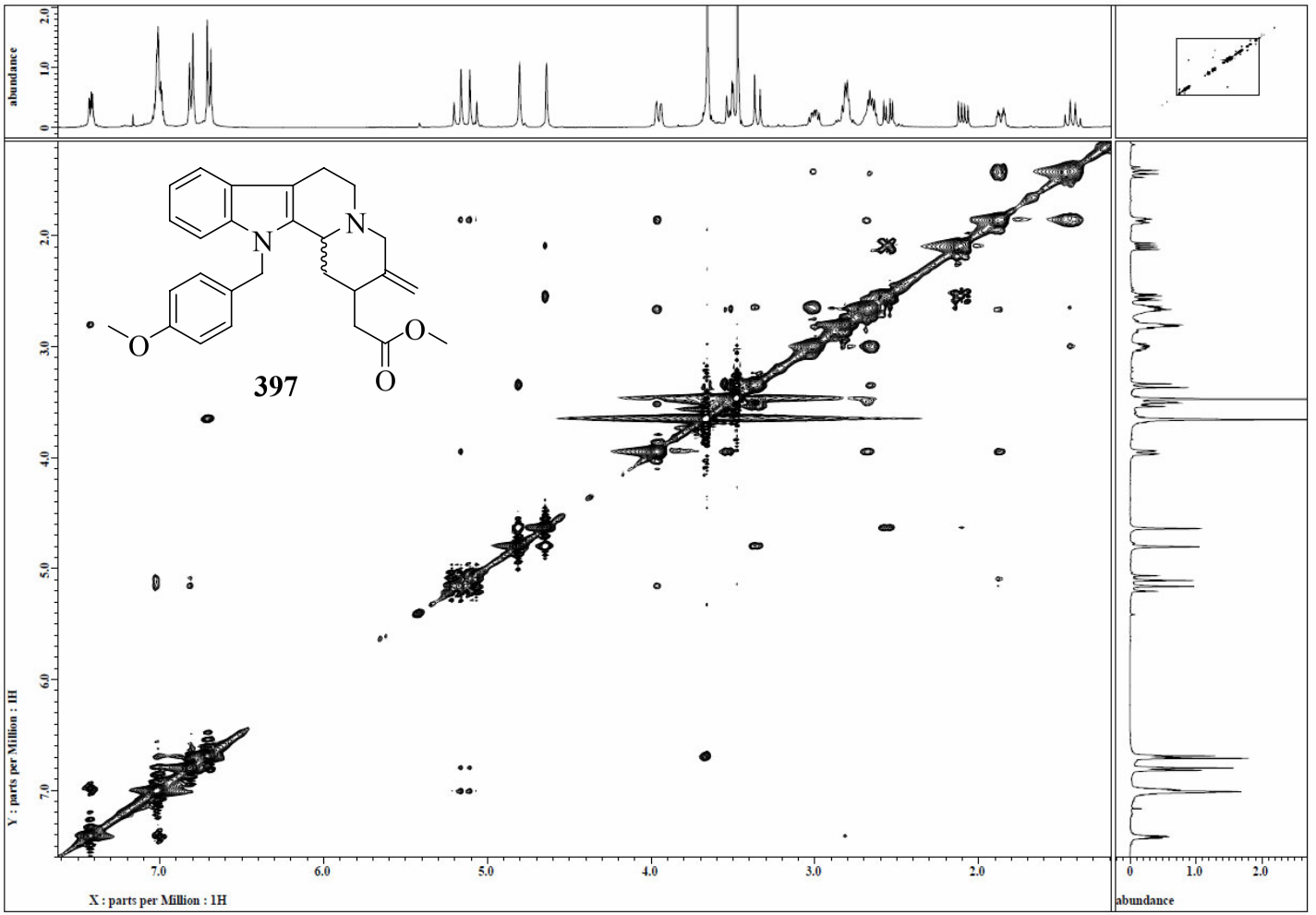
Appendix 6.b - ^{13}C NMR spectrum of 397



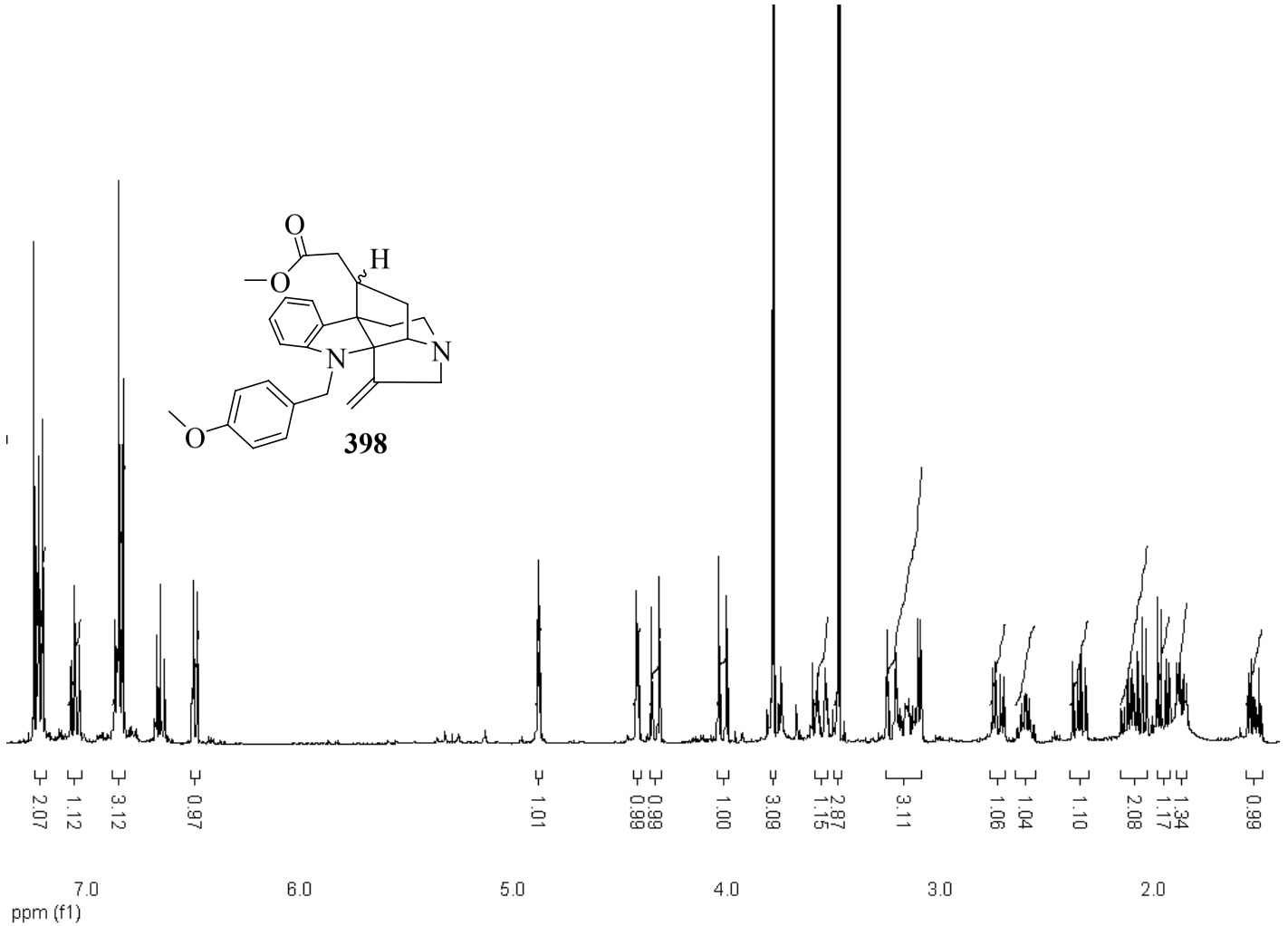
Appendix 6.c – HSQC NMR spectrum of 397



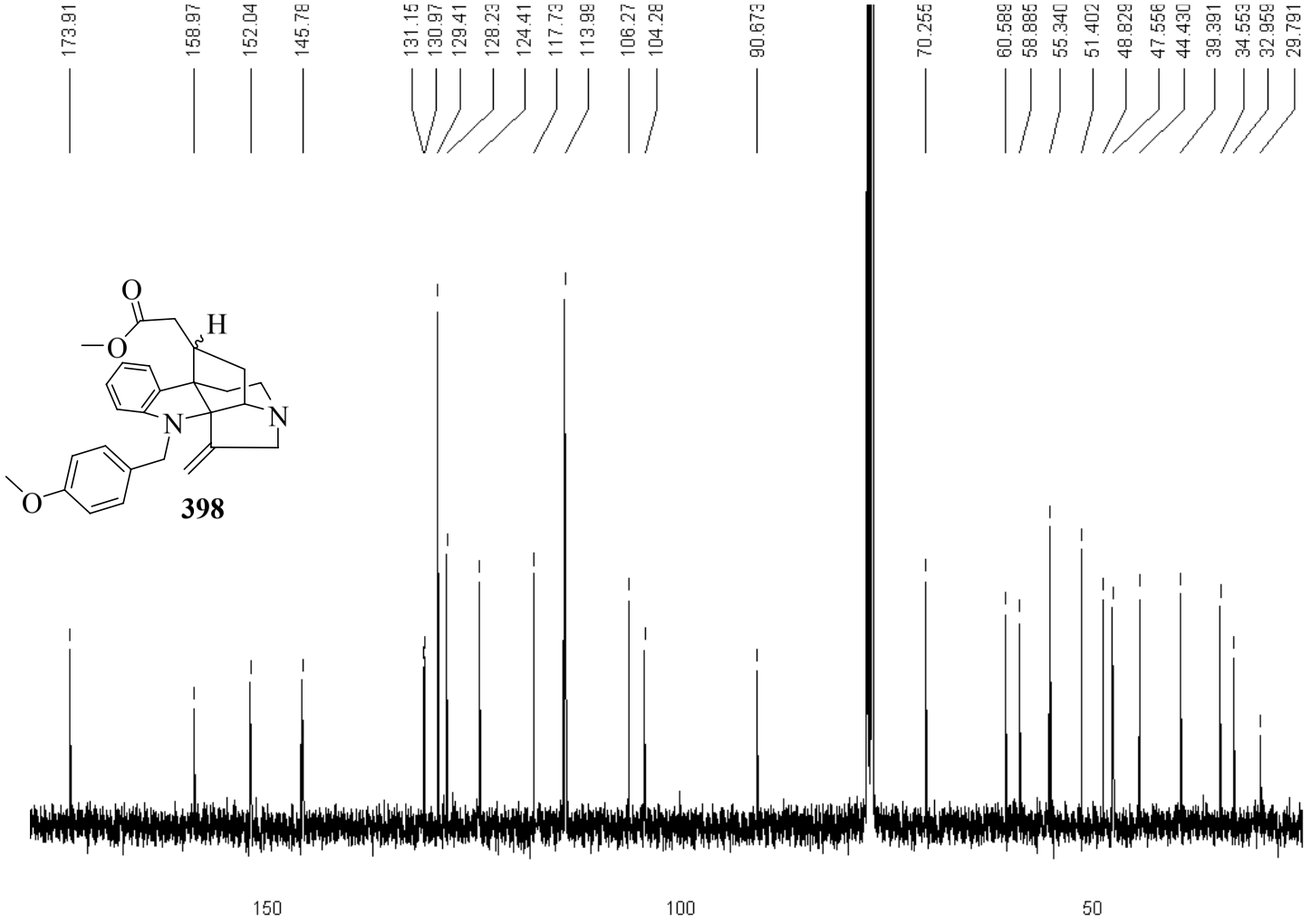
Appendix 6.d – NOESY NMR spectrum of 397



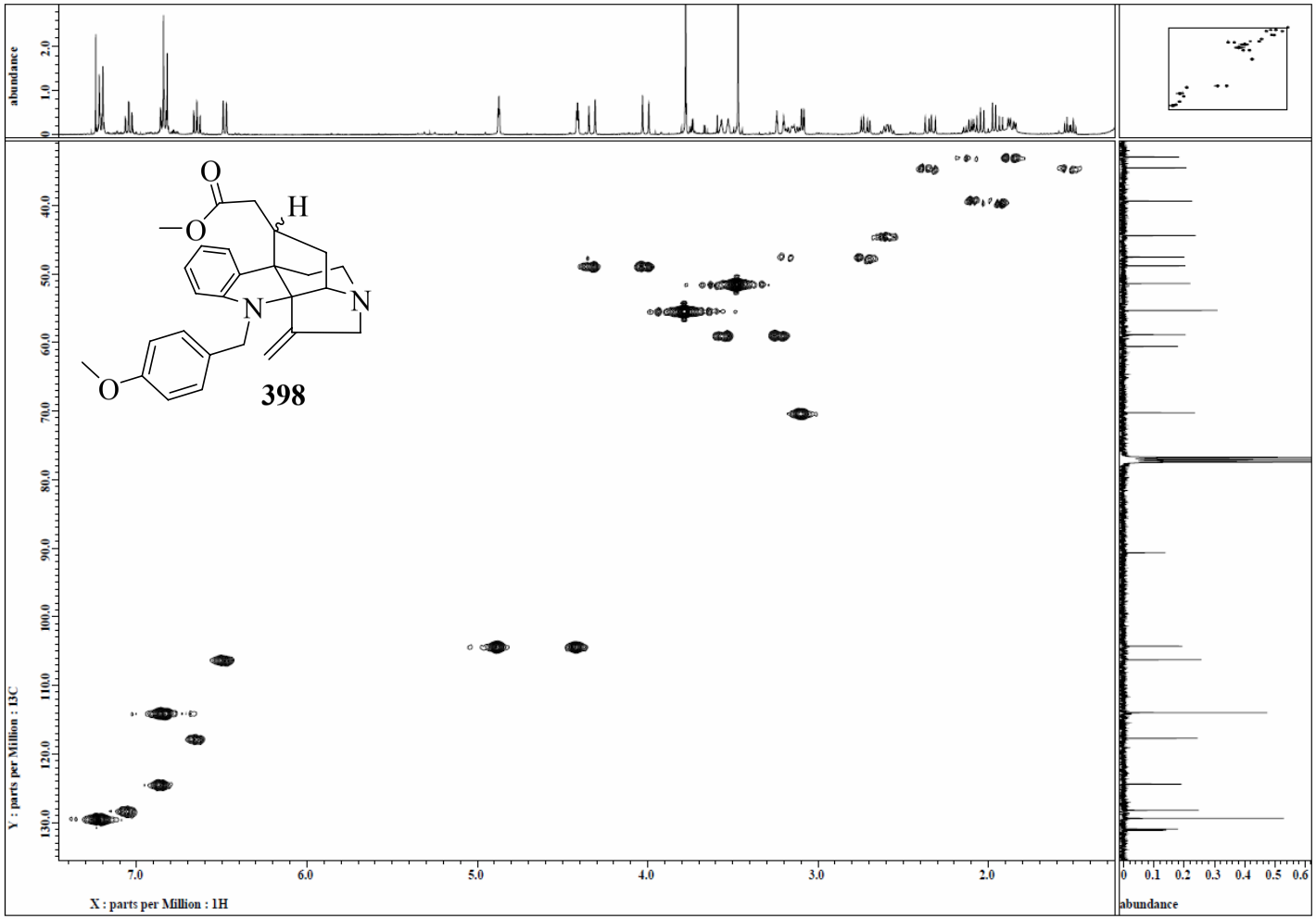
Appendix 7.a - ^{1}H NMR spectrum of 398



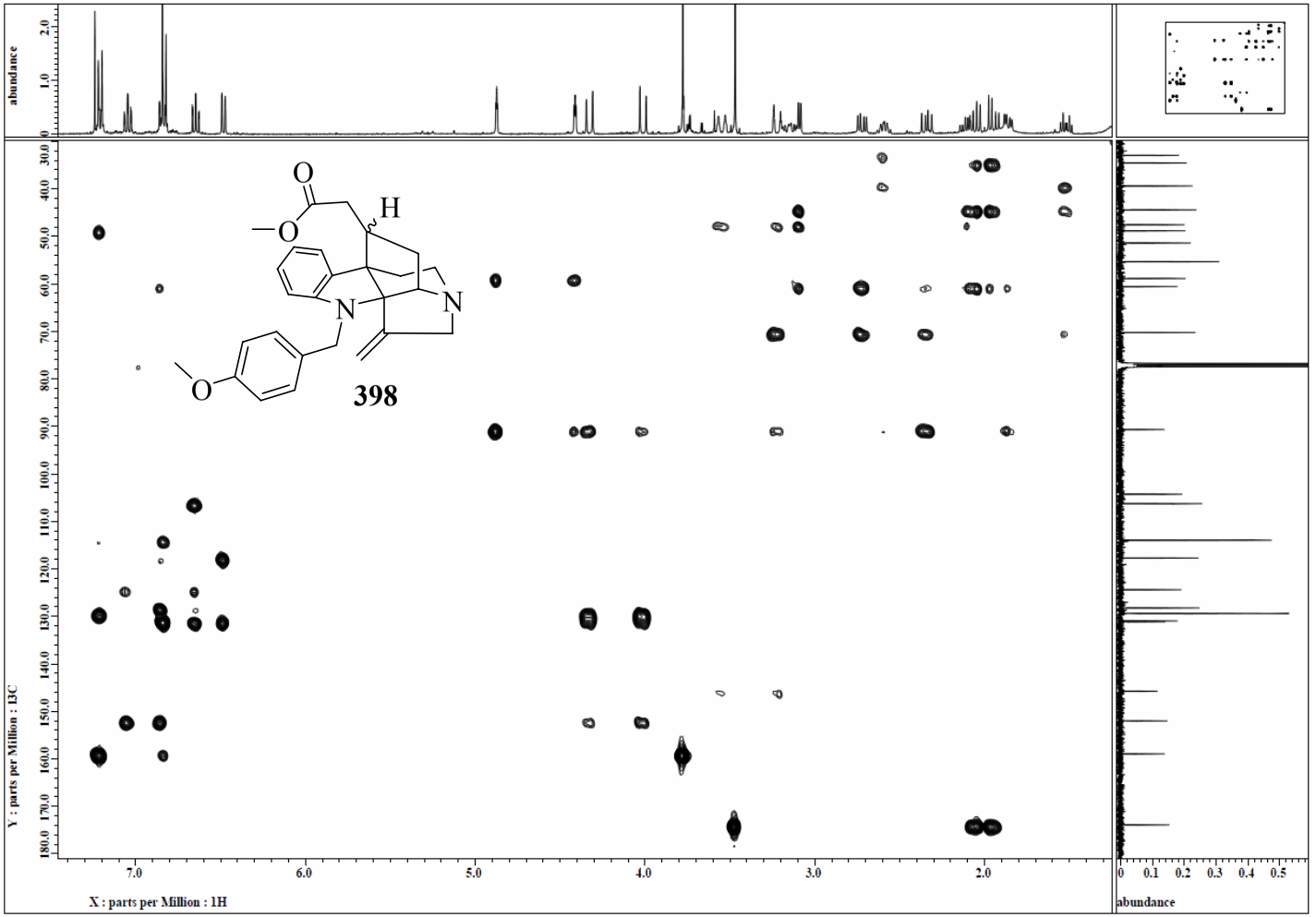
Appendix 7.b - ^{13}C NMR spectrum of 398



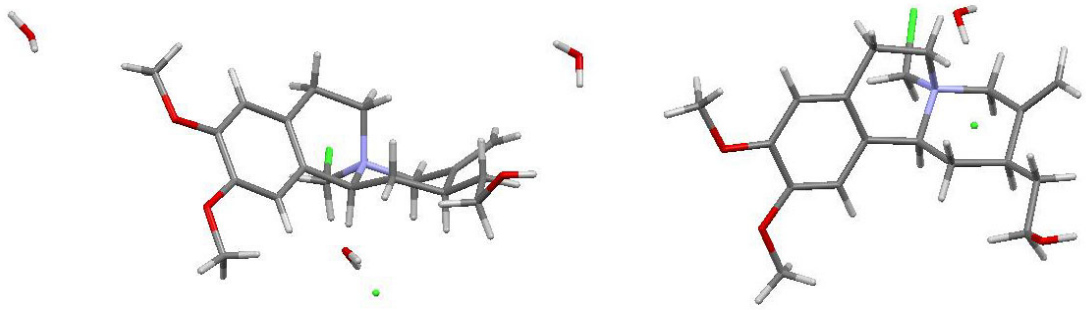
Appendix 7.c – HSQC NMR spectrum of 398



Appendix 7.d – HMBC NMR spectrum of 398



Appendix 6 - X-ray crystal structure of the dichloromethane salt, 363



(original in colour)

Table 1. Crystal data and structure refinement for afp0901m.

Identification code	afp0901m	
Empirical formula	C19 H31 Cl2 N O5	
Formula weight	424.35	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.4632(5) Å	α= 88.3650(10)°.
	b = 8.5839(6) Å	β= 89.6750(10)°.
	c = 15.8706(10) Å	γ = 61.7150(10)°.
Volume	1014.84(11) $Å^3$	
Z	2	
Density (calculated)	1.389 Mg/m^3	
Absorption coefficient	0.350 mm^{-1}	
F(000)	452	
Crystal size	0.28 x 0.20 x 0.12 mm^3	
Theta range for data collection	2.57 to 30.02°.	
Index ranges	-11<=h<=11, -11<=k<=12, -21<=l<=22	
Reflections collected	15393	
Independent reflections	5779 [R(int) = 0.0167]	
Completeness to theta = 30.02°	97.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.959 and 0.861	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5779 / 0 / 266	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0348, wR2 = 0.0924	
R indices (all data)	R1 = 0.0391, wR2 = 0.0960	

Largest diff. peak and hole 0.501 and -0.215 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for afp0901m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-2676(2)	3482(2)	536(1)	20(1)
C(2)	-662(1)	2793(2)	461(1)	16(1)
C(3)	83(1)	3725(1)	1017(1)	14(1)
C(4)	2062(1)	3092(1)	884(1)	14(1)
C(5)	2881(1)	3860(1)	1469(1)	15(1)
C(6)	663(1)	4147(1)	2572(1)	13(1)
C(7)	-204(1)	3434(1)	1956(1)	15(1)
C(8)	3660(1)	1479(1)	2570(1)	16(1)
C(9)	3528(2)	1022(2)	3492(1)	19(1)
C(10)	1707(1)	2134(1)	3877(1)	15(1)
C(11)	416(1)	3646(1)	3466(1)	14(1)
C(12)	-1238(1)	4705(1)	3850(1)	15(1)
C(13)	-1597(1)	4249(1)	4642(1)	15(1)
C(14)	-287(1)	2708(1)	5070(1)	16(1)
C(15)	1341(1)	1678(1)	4685(1)	16(1)
C(16)	3075(2)	1973(2)	303(1)	20(1)
C(17)	-4498(2)	6760(2)	4652(1)	19(1)
C(18)	561(2)	887(2)	6326(1)	24(1)
C(19)	3283(1)	4468(1)	2938(1)	16(1)
Cl(1)	5645(1)	3595(1)	2917(1)	23(1)
N(1)	2659(1)	3455(1)	2391(1)	13(1)
O(1)	-3189(1)	2231(1)	230(1)	24(1)
O(2)	-3160(1)	5190(1)	5068(1)	18(1)
O(3)	-769(1)	2369(1)	5849(1)	21(1)
Cl(2)	7641(1)	1709(1)	8288(1)	22(1)
O(4)	8066(2)	9569(2)	1526(1)	30(1)
O(5)	6538(1)	7466(1)	2235(1)	32(1)

Table 3. Bond lengths [Å] and angles [°] for afp0901m.

C(1)-O(1)	1.4324(14)
C(1)-C(2)	1.5215(15)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.5294(14)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.5113(14)
C(3)-C(7)	1.5406(14)
C(3)-H(3A)	1.0000
C(4)-C(16)	1.3305(15)
C(4)-C(5)	1.5012(14)
C(5)-N(1)	1.5248(13)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(11)	1.5128(14)
C(6)-C(7)	1.5289(14)
C(6)-N(1)	1.5306(13)
C(6)-H(6)	1.0000
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-N(1)	1.5136(13)
C(8)-C(9)	1.5211(15)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.5128(15)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.3855(15)
C(10)-C(15)	1.4059(14)
C(11)-C(12)	1.4048(14)
C(12)-C(13)	1.3812(14)
C(12)-H(12)	0.9500
C(13)-O(2)	1.3661(12)
C(13)-C(14)	1.4170(15)
C(14)-O(3)	1.3653(13)
C(14)-C(15)	1.3855(15)
C(15)-H(15)	0.9500
C(16)-H(16A)	0.9500

C(16)-H(16B)	0.9500
C(17)-O(2)	1.4300(13)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-O(3)	1.4335(14)
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-N(1)	1.5069(13)
C(19)-Cl(1)	1.7717(11)
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900
O(1)-H(1)	0.85(2)
O(4)-H(4A)	0.80(2)
O(4)-H(4B)	0.79(2)
O(5)-H(5C)	0.87(3)
O(5)-H(5D)	0.82(2)

O(1)-C(1)-C(2)	111.13(9)
O(1)-C(1)-H(1A)	109.4
C(2)-C(1)-H(1A)	109.4
O(1)-C(1)-H(1B)	109.4
C(2)-C(1)-H(1B)	109.4
H(1A)-C(1)-H(1B)	108.0
C(1)-C(2)-C(3)	114.29(9)
C(1)-C(2)-H(2A)	108.7
C(3)-C(2)-H(2A)	108.7
C(1)-C(2)-H(2B)	108.7
C(3)-C(2)-H(2B)	108.7
H(2A)-C(2)-H(2B)	107.6
C(4)-C(3)-C(2)	112.86(9)
C(4)-C(3)-C(7)	108.21(8)
C(2)-C(3)-C(7)	110.50(8)
C(4)-C(3)-H(3A)	108.4
C(2)-C(3)-H(3A)	108.4
C(7)-C(3)-H(3A)	108.4
C(16)-C(4)-C(5)	119.61(10)
C(16)-C(4)-C(3)	125.86(10)
C(5)-C(4)-C(3)	114.52(9)
C(4)-C(5)-N(1)	111.79(8)

C(4)-C(5)-H(5A)	109.3
N(1)-C(5)-H(5A)	109.3
C(4)-C(5)-H(5B)	109.3
N(1)-C(5)-H(5B)	109.3
H(5A)-C(5)-H(5B)	107.9
C(11)-C(6)-C(7)	109.69(8)
C(11)-C(6)-N(1)	110.13(8)
C(7)-C(6)-N(1)	111.70(8)
C(11)-C(6)-H(6)	108.4
C(7)-C(6)-H(6)	108.4
N(1)-C(6)-H(6)	108.4
C(6)-C(7)-C(3)	114.93(8)
C(6)-C(7)-H(7A)	108.5
C(3)-C(7)-H(7A)	108.5
C(6)-C(7)-H(7B)	108.5
C(3)-C(7)-H(7B)	108.5
H(7A)-C(7)-H(7B)	107.5
N(1)-C(8)-C(9)	111.73(8)
N(1)-C(8)-H(8A)	109.3
C(9)-C(8)-H(8A)	109.3
N(1)-C(8)-H(8B)	109.3
C(9)-C(8)-H(8B)	109.3
H(8A)-C(8)-H(8B)	107.9
C(10)-C(9)-C(8)	114.30(9)
C(10)-C(9)-H(9A)	108.7
C(8)-C(9)-H(9A)	108.7
C(10)-C(9)-H(9B)	108.7
C(8)-C(9)-H(9B)	108.7
H(9A)-C(9)-H(9B)	107.6
C(11)-C(10)-C(15)	119.08(10)
C(11)-C(10)-C(9)	121.29(9)
C(15)-C(10)-C(9)	119.55(9)
C(10)-C(11)-C(12)	120.48(9)
C(10)-C(11)-C(6)	121.96(9)
C(12)-C(11)-C(6)	117.40(9)
C(13)-C(12)-C(11)	120.30(10)
C(13)-C(12)-H(12)	119.9
C(11)-C(12)-H(12)	119.9
O(2)-C(13)-C(12)	124.73(10)
O(2)-C(13)-C(14)	115.49(9)
C(12)-C(13)-C(14)	119.79(10)

O(3)-C(14)-C(15)	125.31(10)
O(3)-C(14)-C(13)	115.38(9)
C(15)-C(14)-C(13)	119.31(9)
C(14)-C(15)-C(10)	121.04(10)
C(14)-C(15)-H(15)	119.5
C(10)-C(15)-H(15)	119.5
C(4)-C(16)-H(16A)	120.0
C(4)-C(16)-H(16B)	120.0
H(16A)-C(16)-H(16B)	120.0
O(2)-C(17)-H(17A)	109.5
O(2)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
O(2)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
O(3)-C(18)-H(18A)	109.5
O(3)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
O(3)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
N(1)-C(19)-Cl(1)	112.04(7)
N(1)-C(19)-H(19A)	109.2
Cl(1)-C(19)-H(19A)	109.2
N(1)-C(19)-H(19B)	109.2
Cl(1)-C(19)-H(19B)	109.2
H(19A)-C(19)-H(19B)	107.9
C(19)-N(1)-C(8)	112.85(8)
C(19)-N(1)-C(5)	108.65(8)
C(8)-N(1)-C(5)	110.07(8)
C(19)-N(1)-C(6)	106.63(8)
C(8)-N(1)-C(6)	109.42(8)
C(5)-N(1)-C(6)	109.11(8)
C(1)-O(1)-H(1)	108.7(13)
C(13)-O(2)-C(17)	116.59(8)
C(14)-O(3)-C(18)	117.12(9)
H(4A)-O(4)-H(4B)	105(2)
H(5C)-O(5)-H(5D)	111(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for afp0901m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	16(1)	30(1)	19(1)	-3(1)	0(1)	-14(1)
C(2)	16(1)	23(1)	13(1)	-2(1)	0(1)	-12(1)
C(3)	14(1)	17(1)	13(1)	-1(1)	0(1)	-8(1)
C(4)	15(1)	18(1)	13(1)	0(1)	0(1)	-10(1)
C(5)	17(1)	20(1)	11(1)	-2(1)	2(1)	-12(1)
C(6)	12(1)	15(1)	13(1)	-1(1)	1(1)	-6(1)
C(7)	14(1)	19(1)	13(1)	-1(1)	1(1)	-9(1)
C(8)	15(1)	14(1)	16(1)	-1(1)	2(1)	-5(1)
C(9)	16(1)	18(1)	16(1)	1(1)	1(1)	-4(1)
C(10)	15(1)	17(1)	14(1)	-2(1)	1(1)	-8(1)
C(11)	14(1)	17(1)	12(1)	-1(1)	1(1)	-8(1)
C(12)	14(1)	17(1)	13(1)	-1(1)	0(1)	-8(1)
C(13)	14(1)	17(1)	14(1)	-3(1)	1(1)	-8(1)
C(14)	18(1)	19(1)	12(1)	-1(1)	1(1)	-10(1)
C(15)	17(1)	16(1)	15(1)	1(1)	-1(1)	-8(1)
C(16)	16(1)	26(1)	21(1)	-7(1)	3(1)	-12(1)
C(17)	16(1)	20(1)	19(1)	-1(1)	1(1)	-6(1)
C(18)	26(1)	26(1)	16(1)	6(1)	-1(1)	-10(1)
C(19)	16(1)	19(1)	16(1)	-4(1)	1(1)	-10(1)
Cl(1)	18(1)	33(1)	22(1)	-6(1)	1(1)	-15(1)
N(1)	14(1)	15(1)	12(1)	-2(1)	1(1)	-8(1)
O(1)	25(1)	38(1)	19(1)	-3(1)	0(1)	-24(1)
O(2)	15(1)	21(1)	15(1)	0(1)	3(1)	-6(1)
O(3)	22(1)	23(1)	14(1)	3(1)	3(1)	-8(1)
Cl(2)	27(1)	21(1)	21(1)	0(1)	0(1)	-14(1)
O(4)	32(1)	41(1)	25(1)	3(1)	-1(1)	-23(1)
O(5)	26(1)	26(1)	39(1)	8(1)	-5(1)	-9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for afp0901m.

	x	y	z	U(eq)
H(1A)	-3028	3717	1134	24
H(1B)	-3317	4611	209	24
H(2A)	-381	2929	-134	19
H(2B)	-42	1513	612	19
H(3A)	-581	5023	878	17
H(5A)	2306	5159	1372	18
H(5B)	4174	3369	1345	18
H(6)	44	5467	2511	16
H(7A)	-1510	4006	2063	17
H(7B)	283	2148	2072	17
H(8A)	4938	1023	2422	19
H(8B)	3158	890	2213	19
H(9A)	3822	-239	3544	22
H(9B)	4439	1167	3820	22
H(12)	-2114	5740	3563	18
H(15)	2224	647	4972	20
H(16A)	4308	1664	260	24
H(16B)	2564	1482	-70	24
H(17A)	-4031	7600	4560	29
H(17B)	-5570	7297	5004	29
H(17C)	-4808	6459	4109	29
H(18A)	953	-191	6004	36
H(18B)	46	758	6861	36
H(18C)	1591	1081	6438	36
H(19A)	2902	4427	3525	19
H(19B)	2706	5722	2741	19
H(1)	-2910(30)	2060(30)	-285(13)	43(5)
H(4A)	7800(30)	10230(30)	1125(14)	49(6)
H(4B)	9100(30)	9250(30)	1594(14)	49(6)
H(5C)	5520(30)	7630(30)	2028(15)	65(7)
H(5D)	6910(30)	8050(30)	1964(13)	49(6)

Table 6. Torsion angles [°] for afp0901m.

O(1)-C(1)-C(2)-C(3)	-161.24(9)
C(1)-C(2)-C(3)-C(4)	-176.19(9)
C(1)-C(2)-C(3)-C(7)	62.49(12)
C(2)-C(3)-C(4)-C(16)	5.97(15)
C(7)-C(3)-C(4)-C(16)	128.57(12)
C(2)-C(3)-C(4)-C(5)	-175.02(9)
C(7)-C(3)-C(4)-C(5)	-52.42(11)
C(16)-C(4)-C(5)-N(1)	-122.61(11)
C(3)-C(4)-C(5)-N(1)	58.31(12)
C(11)-C(6)-C(7)-C(3)	-175.32(8)
N(1)-C(6)-C(7)-C(3)	-52.92(11)
C(4)-C(3)-C(7)-C(6)	49.94(12)
C(2)-C(3)-C(7)-C(6)	173.97(9)
N(1)-C(8)-C(9)-C(10)	39.36(13)
C(8)-C(9)-C(10)-C(11)	-12.07(15)
C(8)-C(9)-C(10)-C(15)	171.09(10)
C(15)-C(10)-C(11)-C(12)	-0.26(16)
C(9)-C(10)-C(11)-C(12)	-177.13(10)
C(15)-C(10)-C(11)-C(6)	-175.54(10)
C(9)-C(10)-C(11)-C(6)	7.60(16)
C(7)-C(6)-C(11)-C(10)	93.96(12)
N(1)-C(6)-C(11)-C(10)	-29.36(13)
C(7)-C(6)-C(11)-C(12)	-81.45(11)
N(1)-C(6)-C(11)-C(12)	155.22(9)
C(10)-C(11)-C(12)-C(13)	-0.06(16)
C(6)-C(11)-C(12)-C(13)	175.43(9)
C(11)-C(12)-C(13)-O(2)	179.94(10)
C(11)-C(12)-C(13)-C(14)	0.20(16)
O(2)-C(13)-C(14)-O(3)	0.28(14)
C(12)-C(13)-C(14)-O(3)	-179.96(9)
O(2)-C(13)-C(14)-C(15)	-179.78(9)
C(12)-C(13)-C(14)-C(15)	-0.01(16)
O(3)-C(14)-C(15)-C(10)	179.63(10)
C(13)-C(14)-C(15)-C(10)	-0.31(16)
C(11)-C(10)-C(15)-C(14)	0.45(16)
C(9)-C(10)-C(15)-C(14)	177.37(10)
Cl(1)-C(19)-N(1)-C(8)	51.15(10)
Cl(1)-C(19)-N(1)-C(5)	-71.21(9)
Cl(1)-C(19)-N(1)-C(6)	171.31(7)

C(9)-C(8)-N(1)-C(19)	56.37(11)
C(9)-C(8)-N(1)-C(5)	177.94(8)
C(9)-C(8)-N(1)-C(6)	-62.17(11)
C(4)-C(5)-N(1)-C(19)	-172.42(8)
C(4)-C(5)-N(1)-C(8)	63.54(11)
C(4)-C(5)-N(1)-C(6)	-56.54(11)
C(11)-C(6)-N(1)-C(19)	-66.85(10)
C(7)-C(6)-N(1)-C(19)	171.00(8)
C(11)-C(6)-N(1)-C(8)	55.49(10)
C(7)-C(6)-N(1)-C(8)	-66.65(10)
C(11)-C(6)-N(1)-C(5)	175.97(8)
C(7)-C(6)-N(1)-C(5)	53.83(11)
C(12)-C(13)-O(2)-C(17)	-0.30(15)
C(14)-C(13)-O(2)-C(17)	179.45(9)
C(15)-C(14)-O(3)-C(18)	3.98(16)
C(13)-C(14)-O(3)-C(18)	-176.08(10)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for afp0901m [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(5)-H(5D)...O(4)	0.82(2)	2.07(2)	2.8772(16)	168(2)
O(5)-H(5C)...Cl(2)#1	0.87(3)	2.51(3)	3.3647(12)	169(2)
O(4)-H(4B)...Cl(2)#2	0.79(2)	2.49(2)	3.2727(12)	176(2)
O(4)-H(4A)...O(1)#3	0.80(2)	2.05(2)	2.8346(15)	170(2)
O(1)-H(1)...Cl(2)#4	0.85(2)	2.31(2)	3.1539(10)	176.2(18)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1 #2 -x+2,-y+1,-z+1 #3 x+1,y+1,z

#4 x-1,y,z-1

Chapter 9 – References

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